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Jessica van Nies

Early Identification of Rheumatoid Arthritis



Early identification of rheumatoid arthritis

Jessica van Nies



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Promotores:

Prof. dr. A.H.M. van der Helm-van Mil

Prof. dr. T.W.J. Huizinga

Leden promotiecommissie:

Prof. dr. D.M.F.M. van der Heijde

Prof. dr. R.E.M. Toes

Prof. dr. A.E.R.C.H. Boonen

MUMC, Universiteit Maastricht

Dr. E. Brouwer

UMCG, Universiteit Groningen

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CHAPTER 1

Introduction

INTRODUCTION

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is predominantly characterized by symmetrical synovitis of the small joints of hands and feet. However, every joint with synovial lining can be affected.¹

In addition to synovitis, after prolonged inflammation extra articular manifestations can also arise such as several pulmonary diseases, ocular diseases, cutaneous manifestations like rheumatoid nodules and cardiovascular diseases. However some of these extra articular manifestations occur only rarely these days, thanks to better treatment outcomes.² The prevalence of RA in European and North American countries is about 0.5-1.0 percent with an incidence of 20-50 new cases per 100.000 persons each year.³ Women are affected two to three times more often than men. Though RA can occur at any age in adults, the majority of patients are middle aged at disease onset.

Synovitis on the inside of the joints expresses itself on the outside of the body by typical joint swelling (arthritis). RA patients may also experience tender joints, stiffness in and around joints particularly in the morning, limitations of movement and fatigue.

To date, the pathogenesis of RA is still being unravelled. Genetic and environmental factors (e.g. smoking) both play a role in the onset and the course of RA.⁴ In the seventies and eighties of the twentieth century, the most important genetic risk factors for development of RA were identified, which are several *HLA-DRB1* alleles.^{5,6} Later on, more susceptibility Single Nucleotide Polymorphisms (SNPs) in Caucasian RA-patients were identified via candidate gene approaches as well as genome-wide associations studies (GWAS).⁽⁴⁾ Two of these susceptibility SNPs will be discussed in the current thesis, namely *PTPN22* and *TRAF1-C5*.^{7,8}

If RA is untreated, it can lead to considerable joint destruction, even resulting in disability in certain patients. However, the disease course may differ in patients individually from being mild and non-destructive to rapid and destructive.⁹

Auto-Antibodies

Several antibodies in RA have been found, the best known are rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). As RF has been the most 'classic' autoantibody in RA. RF is not only found in RA patients but also in patients with other autoimmune diseases, infectious diseases and even in healthy individuals. The sensitivity and

the specificity of RF for RA are about 69% and 85% respectively. This indicates that not all patients that are positive for RF will develop RA.¹⁰ In early RA patients the prevalence of RF is about 60 percent.¹¹⁻¹³

ACPA, on the other hand, is more specific for RA (sensitivity ~67% and specificity of ~95%) and is thought to play an important role in the pathogenesis of the disease.⁽¹⁰⁾ The prevalence of ACPA in early RA is about 50%.¹¹⁻¹³ Interestingly, there is an overlap in the presence of antibodies in RA patients. This means that most patients that are tested positive on the presence of ACPA are also positive on the presence of RF.

The presence of RF as well as ACPA can precede the clinical phase of RA. This was found by Nielen et al; they investigated patients with RA that had been blood donor prior to their disease and they matched them with controls.¹⁴ Interestingly, RF and ACPA was present in half of these RA patients with a median of 4.5 years before they even experienced symptoms.

Classification of RA

The term 'rheumatoid arthritis' was first presented by Alfred Garrod in 1859.¹⁵ The diagnosis RA is made by a physician based on a combination of certain characteristics (e.g. presence of auto-antibodies) and symptoms (e.g. morning stiffness, symmetrical joint swelling, tenderness of joints) a patient has. However, this may result in a heterogeneous group of patients. For research purposes, the goal is to apply the findings on a group-level. To achieve that, a more homogenous group of patients is required.

Therefore, classification criteria were established. Most frequently used are the revised 1958 ARA-criteria, the revised 1987 ACR criteria and lastly the 2010 ACR-EULAR criteria for RA.¹⁶⁻¹⁸ The approach in formulating the criteria have changed over time: for the 1958 ARA-criteria, data was used from 332 North American cases, for the 1987-ACR criteria 262 patients with RA and 262 control subjects with rheumatic diseases other than RA (non-RA) were used, whilst for the 2010 ACR-EULAR criteria data was used from 2000 European and North American cases with early arthritis (UA+RA). In 1958 criteria for diagnostic classification (developed in 1956 consisting of 11 criteria) were revised since more strict criteria, specificity and simplicity were demanded. Thus a group of 'classical RA' was added in addition to 'definite RA', 'probable RA' and 'possible RA'. Whereas in 1987, the aims were to develop a new set of criteria with fewer criteria (in total 7 criteria), again to be more specific than the old ones and a stricter definition for RA instead of the broad spectrum of diseases identified by the revised 1958-ARA criteria. Moreover, the aim of the latest criteria was to identify patients earlier in the disease course, thereby allowing the inclusion of patients at an earlier stage in clinical trials,

preferably before the development of any structural damage. In clinical practice these classification criteria can be used as guidelines to establish the diagnosis of RA but these criteria are not mandatory. In this thesis patients are classified by the 1987 ACR or the 2010 ACR-EULAR criteria for RA.

Table 1. Different classification criteria for RA

Revised ARA 1958 criteria	Revised ACR 1987 criteria	ACR/EULAR 2010 criteria
1. Morning stiffness	1. Morning stiffness (at least one hour)	1. Joint involvement (0-5) • One medium to large joint (0) • Two to ten medium-to-large joints (1) • One to three small joints (large joints not counted) (2) • Four to ten small joints (large joints not counted) • More than ten joints (at least one small joint) (5)
2. Swelling of a joint	2. Arthritis in three or more joints	2. Negative RF and negative ACPA (0) • Low positive RF or low positive ACPA (2) • High positive RF or high positive ACPA (3)
3. Swelling of another joint	3. Arthritis of the hand joints (1 or more swollen joints)	3. Acute phase reactants (0-1) - Normal CRP and normal ESR (0) - Abnormal CRP or abnormal ESR (1)
4. Pain on movement or tenderness in a joint	4. Symmetrical arthritis	4. Duration of symptoms (0-1) • less than 6 weeks (0) • 6 weeks or more (1)
5. Symmetric swelling	5. Rheumatoid nodules	
6. Rheumatoid nodule	6. Serum rheumatoid factor	
7. Rheumatoid factor	7. Radiographic changes (erosions)	
8. Radiographic changes		
9. Mucin clot		
10. Synovial biopsy		
11. Nodule biopsy		
Classical RA: 7/11 Definite RA: 5/11 Probable RA: 3/11 *Criteria 1-5 continues for at least 6 weeks Possible RA: 2/11 *joint symptoms at least 3 weeks	Four of seven criteria must be present. The first four criteria must have been present for at least 6 weeks.	Points are shown in parentheses. The cut point for RA is six or more points. Patients can also be classified as having RA if they have: (a) typical erosions, (b) longstanding disease previously satisfying the classification criteria

Treatment and treatment strategy

Over the last fifty years the treatment options as well as the approach has changed dramatically. In the 1970s it was common to start with non-steroidal anti-inflammatory drugs (NSAIDs). Strikingly, disease-modifying anti-rheumatic drug (DMARD) therapy was at the time only initiated after radiographic damage had been demonstrated. Interestingly, during the nineties DMARD-therapy was also called SAARD-therapy, which stands for slow-acting anti-rheumatic drug.¹⁹ This term is rarely used nowadays. Several

conventional DMARDs were available, such as anti-malarials (hydroxychloroquine), sulphasalazine, oral gold, intramuscular gold, azathioprine and methotrexate. After NSAIDs had failed, DMARD-therapy was started and preferably one that was least toxic. At the time a so-called pyramid approach was applied, this means that when the disease activity was not sufficiently suppressed another DMARD was added.

However, at the end of the twentieth century treatment strategies changed. DMARD-therapy was started much earlier in the disease course and combination therapy was often started. Several clinical trials such as the COBRA and BeSt-trial showed that initiation of combination therapy including corticosteroids in an early phase of RA led to less joint destruction.^{20,21}

Besides conventional DMARDs another type of DMARD was added to the market, namely 'biologics'. These are drugs that are genetically engineered, by using human genes in non-human cell cultures to produce a biologic agent. Patients who use biologics are more prone to infections (such as tuberculosis) and use of biologics involves high costs. Therefore, the use of biologics is preferably restricted to patients who failed on two or more conventional DMARDs. However, exceptions can be made.²²

In the current thesis we made use of a large inception cohort (the Leiden Early Arthritis Clinic), which included early RA patients.¹¹ In this EAC-cohort the change in treatment and the change in strategy is reflected. RA patients that were included between 1993-1995 were initially treated with NSAIDs and if there was persistent disease a DMARD was added, in most cases after a median of 5 months and generally within 2 years' time.²³ Between 1996-1998 RA patients were initially treated with hydroxychloroquine and sulphasalazine and patients included after 1999 and onwards were promptly treated with methotrexate or sulphasalazine as monotherapy.

Early recognition and the window of opportunity

It has become apparent that initiating aggressive treatment early in RA is associated with less joint damage. Therefore, the aim is to start the treatment of RA patients as soon as possible. To achieve early initiation of DMARD-therapy it is necessary that patients become under the care of rheumatologists shortly after symptoms arise.

The speed with which patients see a rheumatologist will differ between countries due to access to the organisation of medical and rheumatologic care (e.g. distance) and the way in which healthcare is organised.²⁴ For example, in the Netherlands healthcare is organised in such a manner that general practitioners (GP) control access to medical specialists like rheumatologists.

First of all, a patient must feel the urge to seek medical attention due to his symptoms. Secondly, in case of our Dutch system, a GP must recognize the compilation of symptoms and physical examination as a potential rheumatologic disorder and refer to a rheumatologic clinic as quickly as possible. In 2011 in the Netherlands, a total of 295 per 1000 male persons and 325 per 1000 female persons visited their GP because of musculoskeletal symptoms. Of these visits 5 per 1000 male persons and 6 per 1000 female persons were registered under the diagnosis 'Rheumatoid arthritis'. It needs to be mentioned, however, that this includes patients that were newly diagnosed as well as patients already diagnosed with RA.²⁵

Aside from the fact that treatment should be initiated early, it has been suggested that treatment should even be initiated in the so-called therapeutic 'window of opportunity'.^{26,27} Although this concept is not yet fully understood, this window is said to represent a very early phase of the disease in which therapeutic modification is more successful, presumably because of not fully matured disease processes. This window has been suggested to encompass the first 12 weeks after symptom onset.

In a recent research in the Netherlands it was observed that the total delay in RA patients [time between symptom onset and first visit to a rheumatologist] was 18.4 weeks (median) and the GP-delay was the main contributor with two-thirds of the total delay. It is worth noting that only 31% of the RA patients were seen within 12 weeks' time after symptom onset.²⁸

Disease severity: joint damage and disease persistence

There are several ways to study the severity of RA. One could question what is meant by the term 'severity', because physicians and patients are likely to interpret this differently. For a patient it may be important that his or her daily activities aren't impaired, that he or she experiences less pain, fatigue and stiffness and that he or she prefers to use less medication. However, the latter can also be the other way around: some patients may feel anxious to taper medications because they fear for a relapse.

On the other hand, rheumatologists typically prefer to use 'objective' methods to characterize the disease, for example by monitoring inflammatory markers such as the erythrocyte sedimentation rate, the C-reactive protein and presence of erosive joint visualized on X-rays. Rheumatologists will, during a physical examination, also take into account the number of swollen and tender joints. Newer techniques are nowadays applied in assessing disease severity – either in clinical practice or for research purposes – such as ultrasound and magnetic resonance imaging (MRI) of hands and feet. In the current thesis, though, the main focus is on joint damage on X-rays and the opposite of disease persistence. Damage on X-rays is quantified by the Sharp-van der

Heijde scoring method.²⁹ In this method 44 joints of the hands and feet are evaluated on their joint space width and presence of erosions. The maximum attainable score is 448, with a range of 0-4 for joint space narrowing and 0-5 for erosions in the hands and 0-10 for erosions in the feet. In this thesis damage on X-rays was evaluated cross-sectional on a single time point as well as longitudinal to study joint damage progression over time.

The main aim of treatment in RA is to achieve remission: this has not only become an attainable goal in clinical studies and trials, but in clinical practice as well. Remission as outcome has been studied extensively over the years. However, there is heterogeneity in the definition of remission. For example a disease activity score (DAS)-28 <2.6 or DAS-28 >1.6 and the ACR remission introduced by Pinals et al. have been used.³⁰ In 2011 new remission criteria were proposed by the ACR/EULAR for clinical trials namely a Boolean-based definition and an Index-based definition.³¹ It can be argued that these forms of 'remission' are merely a 'state' which is achieved in the disease course since these definitions of remission can be achieved while under treatment and also allow presence of minor (subclinical) inflammation (e.g, 1 swollen joint, increased ESR).

Therefore, in my view, the ultimate treatment goal is to achieve DMARD-free sustained remission. DMARD-free sustained remission in the current thesis was defined as the sustained absence of arthritis after discontinuation of DMARD-therapy, including biologics and corticosteroids for the entire follow-up and during at least one year.³² DMARD-free sustained remission can be seen as the opposite of disease persistency and is the closest proxy to a 'cure' in RA.

Mortality in RA

Mortality is the most undesirable outcome in any disease and has been studied extensively over the years. Even though this outcome is definite, predictors of mortality give clues for therapeutic interventions since these predictors are often predictors for other long-term outcomes.³³

Previously, RA has been associated with increased death rates compared to the general population (1.2-1.3 in inception cohorts and 1.6-1.7 in non-inception cohorts).³³ In addition, it has been observed that the incidence mortality rates (IMR) in RA decrease over time, with an estimated pooled IMR from 4.7/100 persons-years for studies before 1970 to 2.0/100 person-years for studies started after 1985. This resulted in a relative decrease of 2.6% per year between 1955 and 1995.³⁴ These observations are based on early RA cohorts that were initiated between 1955-1995, thus before more stringent, early and aggressive treatments were introduced.

Significant predictors for early death that have been found in many RA cohorts are increasing age, male sex, comorbidities, patients and physician global estimates and a

poor functional status (assessed by physical measures and patient questionnaires).³³ Poor functional status can be reflected among others by various radiographic scores, ESR, CRP or rheumatoid factor.

The major causes of death in RA are cardiovascular diseases (CVD), cancer and infections with percentages similar to the general population. The proportions of cardiovascular deaths may not be higher than their peers, but RA patients die at an earlier age of CVD.³³ RA is associated with CVD, the risk of developing CVD is approximately 2-3 times higher than the general population.³⁵ Especially accelerated atherosclerosis has been observed in RA patients, which may precede major cardiovascular events. This accelerated atherosclerosis can not only be explained by traditional CVD-risk factors being more present in RA patients such as hypertension, hyperlipidemia, diabetes and smoking^{36,37} but also by ongoing inflammation.

Aim and outline of this thesis

There were four main aims of this thesis:

1. To improve early recognition of arthritis.
2. To investigate if a so-called 'therapeutic window of opportunity' is present in RA.
3. To investigate diagnostic and prognostic markers in arthralgia, early arthritis and RA patients.
4. To identify predictors for mortality and compare survival of RA patients with the general Dutch population.

This thesis is divided into four parts.

In **Part I** the efficacy of two early arthritis recognition clinics was evaluated as well as the reasons for arthralgia patients to seek medical help. As described above, the median delay of RA patients with which they are seen by a rheumatologists after symptom onset in the Netherlands was 18.4 weeks.²⁸ Two-third of this delay was contributed by the GP. This underlines, in combination with previous data on the wait-and-see approach, that GPs may have difficulties recognising arthritis of the small joints of the hands and feet.³⁸ To diminish the GP-delay a new initiative was set up at two academic hospitals in Leiden and Groningen (The Netherlands): The early arthritis recognition clinic (EARC). Instead of applying the wait-and-see approach, GPs could send their patients to an EARC in case they were unsure about the presence of arthritis. This clinic was held twice a week and patients did not need to make an appointment. At the EARC, after the patient filled out a small questionnaire on symptoms and reasons to seek medical advice, an experienced rheumatologists briefly examined the patient by performing a full joint

examination. In case arthritis was present the patients returned to the outpatient clinic within approximately 1 week for a full examination including additional laboratory test, X-rays and initiation of appropriate treatment.

In **chapter 2** the efficacy of the clinic after 1 year was evaluated. The GP-delay was the main outcome followed by the total delay. Early arthritis patients from early arthritis clinics (EACs) were used as control group. In **chapter 3** the reasons for arthralgia patients to seek medical help were studied. Among others, patients were divided into two groups; patients who sought medical help shortly after symptom onset and patients who sought medical help rather late. Finally, a partial least square regression analysis was performed to assess whether certain variables (symptom characteristics, motivations/variables regarding the ability to work) frequently clustered together in the same arthralgia patients.

In **part II** the aim was to investigate whether a therapeutic window of opportunity is present in RA indeed. Many previous studies on RA demonstrated that early treatment initiation leads to a more beneficial outcome.^{39,40} It needs to be taken into consideration that an 'early' start can be interpreted differently over the years, for example within 2 years after diagnosis of RA until initiation within a couple of weeks after diagnosis. Thus the following question was whether RA patients in which treatment was initiated shortly after symptom onset also had a more beneficial outcome than RA patients with a prolonged symptom duration. Since many studies included symptom duration as covariate in their analysis in **chapter 4** a systematic literature review on all such studies was performed to assess whether a short symptom duration at treatment initiation was associated with a favourable disease outcome. Subsequently, it was demonstrated that a prolonged symptom duration was associated with severe radiographic progression and a lower chance on DMARD-free sustained remission, the latter by performing a meta-analysis. These results led to the following question: is this association a linear one according to 'the-earlier-the-better principle' or does a specific time-frame exists in which the disease is more susceptible to treatment referring to a 'window of opportunity'. This question was addressed in **chapter 5** by investigating the shape of the association of symptom duration with DMARD-free sustained remission (opposite of disease persistence) in two large early RA cohorts.

In **part III** several disease symptoms, characteristics and classification criteria are investigated for their diagnostic or prognostic value in arthralgia, early arthritis and RA patients. In **chapter 6** a well-known disease characteristic (morning stiffness) that is frequently assessed in clinical practice was evaluated for its diagnostic abilities in three arthralgia cohorts and two early arthritis cohorts and its prognostic abilities in two early

RA cohorts. Current research on morning stiffness showed associations with impaired functional ability in the morning, effects on quality of life and work loss.^{41,42} In addition, it has been mentioned that morning stiffness is a poor discriminator between RA and other rheumatologic disorders.^{43,44} However, these observations are based on studies with a small sample size. In **chapter 7** it was investigated whether an SNP located in the region of the protein tyrosine phosphatase non-receptor 22 (*PTPN22*) was associated with radiological damage in RA patients as well as in a subset of ACPA positive RA patients derived from two cohorts. This region encodes a negative regulator of T-cell activation and is an important risk factor for RA susceptibility in ACPA-positive patients.⁴⁵ In **chapter 8** another frequently assessed disease characteristic (baseline erosions) was studied more in-depth. Baseline erosions, visualized by X-rays, have been used for decades in classification criteria for RA and have been associated as a predictor for further radiographic damage.^{16,17,46} However, mechanisms leading to baseline erosions as a predictor for further joint damage have not been thoroughly explored. Therefore, this question was addressed by performing mediation analyses in early RA patients with radiological data over 7-years of follow-up and subsequently regression analyses in early RA patients with baseline radiographs and MRI-data. As mentioned above, various classification criteria for RA have been developed. The most recent classification criteria for RA, the 2010 ACR-EULAR criteria, are considered to be more sensitive but less specific for RA.⁴⁷ It has become apparent that the phenotype of '2010 RA' patients is milder than the phenotype of patients classified according to the 1987 criteria for RA. Long-term outcomes between these two classification criteria were lacking. Therefore, in **chapter 9** joint damage progression over 7-years and DMARD-free sustained remission over 10-years of follow-up was compared between patients classified according to the 1987 and 2010 criteria for RA.

In **part IV**, risk factors and predictors for mortality in RA are described and comparisons are made between RA patients and the general Dutch population. TRAF1-C5 is another susceptibility allele for RA but also has been associated with other autoimmune diseases, a variant rs3761847 has been studied in relation to mortality in RA. An increased mortality risk for the susceptible genotype GG was observed compared to the non-susceptible AA genotype (hazard ratio 3.96 95% confidence interval 1.24-12.6).⁴⁸ Also, RA patients carrying GG homozygotes had increased rates for the causes of death cancer and infections but not for CVD. Since these patients had a median disease duration of 10 years, CVD related deaths earlier in the disease may have been missed. Therefore, in **chapter 10**, the association between TRAF1/C5 locus and mortality including causes of death was further explored in a cohort of early RA patients. Since an association of TRAF1/C5 may not be restricted to RA, also a large cohort of non-RA patients was analysed.

Rheumatoid factor and ACPA have been associated with less favourable outcomes in RA such as joint damage. In the newly developed criteria for RA both ACPA and rheumatoid factor play an important role, not only by their presence but also their titre.¹⁸ Regarding mortality in early arthritis as well as RA, very few studies are available investigating solely the role of antibodies. Therefore, in **chapter 11**, the presence of antibodies as well as their titre was studied in two large cohorts of early arthritis patients. As is described above, treatment strategies changed dramatically over time. In **chapter 12**, we investigated whether these changes in treatment strategies were also reflected by changes in mortality rates in RA patients. Analyses were performed within three groups of RA patients according to different treatment strategies that were applied and also mortality rates were compared with the general Dutch population. **Chapter 13** provides a summary and discussion of the results which are provided in this thesis.

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PART I

Early recognition of arthritis



CHAPTER 2

Improved early identification of arthritis: evaluating the efficacy of Early Arthritis *Recognition Clinics*

Jessica A.B. van Nies, Elisabeth Brouwer, Floris A. van Gaalen,
Cornelia F. Allaart, Tom W.J. Huizinga, Marcel D. Posthumus,
Annette H.M. van der Helm-van Mil

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ABSTRACT

Objective

Only 31% of Dutch rheumatoid arthritis (RA)-patients visit a rheumatologist within 12 weeks after symptom onset; this is mainly due to delay at the level of the general practitioner (GP). In order to reduce delay of GPs in identifying early arthritis, we initiated an Early Arthritis *Recognition* Clinic (EARC).

Methods

EARCs were initiated at the Leiden and Groningen University Medical Centers. At this EARC, patients filled in a questionnaire about their symptoms, followed by a short visit with only a full joint examination by an experienced rheumatologist. If arthritis was present the patient got an appointment the same week at the regular outpatient clinic. The main outcome parameter was the GP-delay; the secondary outcome parameter was the total delay. In both centers, patients included in early arthritis clinics that had arrived via regular referrals served as control group.

Results

Four hundred patients visited the Leiden EARC and 212 patients the Groningen EARC. Arthritis was detected in 42% and 49% respectively. The median GP-delay for these arthritis patients was 2.0 (0.4-7.3) and 2.0 (0.4-10.0) weeks and the median total delay 8.6 (3.6-22.3) and 10.6 (3.1-30.8) weeks respectively. At these two clinics 59% and 51% of all arthritis patients and 65% and 53% of the patients that were subsequently diagnosed with undifferentiated arthritis or RA were seen within 12 weeks after symptom onset. In the Leiden and Groningen control groups that arrived via regular referrals, only 32% and 38% were seen within 12 weeks time.

Conclusions

The EARC increased the early identification of arthritis and RA.

INTRODUCTION

Data of multiple observational cohorts and clinical trials indicate that early initiation of aggressive treatment in rheumatoid arthritis (RA) patients results in a better outcome.^{1,2} RA-patients that were treated very early in the disease course more often developed remission and had less joint damage.^{3,4} This so-called 'window of opportunity' for treatment is estimated to encompass about the first 12 weeks after symptom onset.^{5,6} Therefore, recognizing arthritis within the first 12 weeks after symptom onset is essential.⁷

We recently observed that only 31% of Dutch RA-patients visit a rheumatologist within 12 weeks after symptom onset.⁸ In the Dutch system, general practitioners (GPs) control the access to specialists such as rheumatologists. We also observed that delay at the level of the GP was the main contributor to the total delay, as it encompassed about two-third of the total delay of 18.4 weeks (median).⁸ This observation is in line with Dutch data revealing that GPs have difficulties in recognizing arthritis of small joints and that in case of doubt they apply a 'wait-and-see' approach.⁹ The distribution between patient delay and GP-delay may be different between countries or settings. Nonetheless, a recent study in 10 centres across Europe showed that there is a substantial delay between symptom onset and the first visit to the rheumatologic outpatient clinic, with the median total delay ranging between 16 and 38 weeks.¹⁰ Also, in a recently initiated immediate access clinic in Vienna the median symptom duration at first visit of RA-patients was 9 months.¹¹

We aimed to increase the proportion of arthritis and RA-patients that is identified within the first 12 weeks after symptom onset. Given the local situation, we particularly aimed at decreasing the GP-delay. To this end we initiated Early Arthritis *Recognition* Clinics (EARC) at two university medical centres in the Netherlands. GPs were advised to send any patient for which they were doubtful about the presence of arthritis to the EARC, instead of applying a 'wait-and-see' approach. At the EARC patients were, during a short visit, screened on the presence of arthritis by physical examination by experienced rheumatologists. This study investigated the efficacy of the EARC to decrease the GP-delay and consequently reduce the total delay in identifying arthritis.

PATIENTS AND METHODS

Early Arthritis *Recognition* Clinic (EARC)

This clinic started in September 2010 in Leiden and in October 2010 in Groningen, the Netherlands. Before we started, there was an educational campaign among regional GPs in Leiden and Groningen, focusing on the importance and the methods of identifying arthritis and the purpose of the EARC. The campaign included articles in GP-oriented

journals, lectures and discussions at periodic trainings of GPs and correspondence to GPs. No campaign was held at the level of the general public. GPs were advised to send any patients for which they had a clinical suspicion of arthritis but were doubtful of the presence of arthritis to the EARC, instead of applying a 'wait-and-see' approach. There were no formal inclusion or exclusion criteria. All patients that visited the EARC during the first 15 months were included in this study. The EARC is held 2 times a week. Patients, referred by their GPs, can visit the EARC without making an appointment. A referral letter is not required, though was generally provided by the GPs. This screening clinic has no waiting list. The EARC, a screening clinic aiming to improve early detection of arthritis, is different from the Leiden Early Arthritis Clinics (EAC) that includes and follows patients with , by a rheumatologist confirmed, early arthritis. Thus the subgroup of arthritis patients identified at the EARC can subsequently be included in the EAC. The Leiden University Medical Center is the only referral center in a health care region of ~400 000 inhabitants in the western part of the Netherlands. The University Medical Center of Groningen is situated in the northern part of the Netherlands and is one of two referral centers in a health care region of ~700 000 inhabitants. The University Medical Center of Groningen also has an EAC that includes patients suspected of having arthritis. In both areas patients had equal access to a GP. In the area of Leiden there was one full-time equivalent GP available per 2400 inhabitants and in the area of Groningen this was one per 2383 inhabitants.¹²

At the EARC patients complete a questionnaire about their joint symptoms, their reasons for seeking medical help and a HAQ (for further details see ¹³). Hereafter, they are seen by an experienced rheumatologist who performs a full joint examination. In case arthritis is present, patients visit the general outpatient clinic, within 1 week time for further examinations, inclusion in the EAC after informed consent and appropriate treatment.¹⁴

Outcome

The main outcome that is relevant for determining the efficacy of the EARC was the GP-delay. Secondary outcomes were the total delay and the proportion of patients that had a total delay of less than 12 weeks. The total delay was defined as the period between the by patient reported symptom onset and the first visit to the rheumatologic outpatient clinic. It is composed of the patient delay and GP-delay. The GP-delay was defined as the time between the first visit to the GP and the first visit to a rheumatologist. As the EARC has no waiting list, it mainly represents the time the GP takes to refer a patient to the rheumatologist.

In order to evaluate the efficacy of the EARC two comparisons were made. The first was between EARC patients and patients that were included in the Leiden and Groningen Early Arthritis Clinics and had arrived by regular referrals at the same time period as the

EARC was present. This comparison may be relevant since an educational campaign was held and a reduction in delay may be attributable to both education and the EARC itself. If, hypothetically speaking, the GP-delay would mainly be affected by the educational campaign – and not by the EARC – the GP-delay of patients that came via regular referrals might also decrease. Alternatively, if the EARC would be the most effective strategy, it was hypothesized that the GP-delay of the patients that visited the EARC would be shorter than the GP-delay of patients that came via regular referrals. The second comparison was a historical comparison and could only be applied to the Leiden dataset. The GP-delay and total delay in early arthritis and early RA-patients included between 1993 and 2006 in the Leiden EAC and thus before the institution of the EARC⁸ were compared to the EARC data. For a full overview of patients studied please see figure 1.

The outcomes were assessed for all early arthritis patients and for patients that were diagnosed as undifferentiated arthritis (UA) or RA at the subsequent regular outpatient clinic visit. RA was classified using the 2010 ACR/EULAR classification criteria.¹⁵

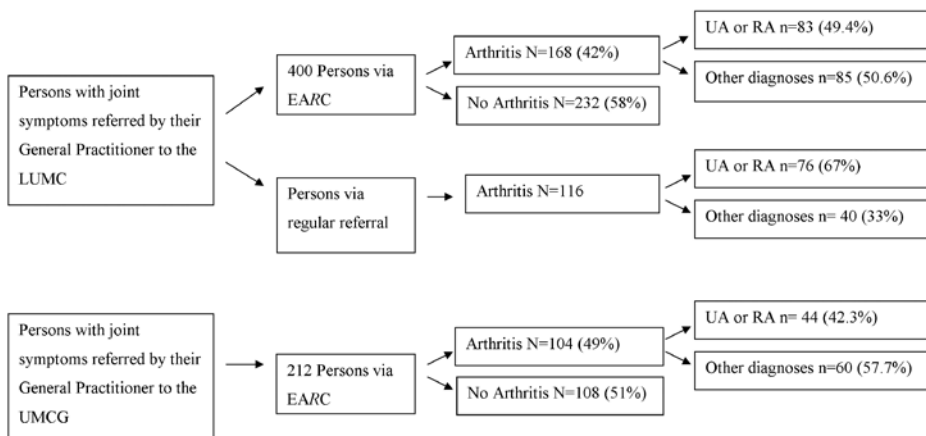


Figure 1. Flowchart of patients with joint symptoms who were screened at the Leiden and Groningen Early Arthritis Recognition Clinics (EARCs) during the first 15 months.

Legend Figure 1. With regard to the control group, presented are the number of patients that were included in the Early Arthritis Clinics of both centers and that arrived via regular referrals. The total numbers of patients who visited the outpatient clinic of the LUMC or UMCG have not been counted. LUMC, Leiden University Medical Center, UMCG, University Medical Center of Groningen. Rheumatoid arthritis (RA) is classified according to the 2010 criteria at the first regular outpatient clinic visit. Since it is in this very early disease phase often challenging to definitely discern between undifferentiated arthritis (UA) and RA, these two patient-sets were analysed together.

Statistical analysis

Comparisons were made using the χ^2 test, Student t-test or Mann-Whitney U-test as applicable. SPSS software V.17.0 was used. p values less than 0.05 were considered significant.

RESULTS

Baseline characteristics

During the first 15 months, 400 patients visited the Leiden EARC and 212 patients the Groningen EARC. Arthritis was observed via physical examination in 168 (42%) patients screened in Leiden and in 104 patients (49%) screened in Groningen. The baseline characteristics are presented in table 1. The diagnoses made during the first regular outpatient clinic visit were: RA (Leiden 14.3%, Groningen 9.6%), UA (Leiden 35.1%, Groningen 32.7%), inflammatory osteoarthritis (Leiden 18.5%, Groningen 26.9%), crystal-induced arthritis (Leiden 7.8%, Groningen 5.8%), psoriatic arthritis (PsA) or spondyloarthritis (SpA) (Leiden 4.2%, Groningen 6.7%) and other diagnoses (Leiden 20.1 %, Groningen 18.3 %).

In order to make comparisons, patients included in the Early Arthritis Clinics, that had arrived via regular referrals were studied (n=116 and n=147 respectively, table 1). These patients had the following diagnoses: RA (Leiden 33.6%, Groningen 17.0%), UA (Leiden 33.6%, Groningen 11.6%), PsA or SpA (Leiden 15.5%, Groningen 5.4%), inflammatory osteoarthritis (Leiden 8.6%, Groningen 18.4%) and crystal arthritis (Leiden 2.6%, Groningen 10.9%), other diagnoses (Leiden 6.8%, Groningen 36.4%).

Dates on symptom onset were missing for 5 and 14 arthritis patients in Leiden and Groningen EARCs respectively and dates on the first visit to the GP were not available for 18 and 9 patients respectively. For the control groups, dates on symptom onset were missing for 1 and 34 patients in Leiden and Groningen and dates on the first GP visit were not available in 27 and 55 patients respectively.

The Groningen control group was used for comparisons on all early arthritis patients but considered too small for sub-analyses on UA-patients and RA-patients (only 19 UA-patients and RA-patients had complete data).

GP-delay of early arthritis patients

When evaluating all patients screened at the EARCs, the median GP-delay was 2.0 (0.4-8.4) weeks in Leiden and 2.3 (0.6-9.1) weeks in Groningen. Since the aim was to more frequently identify arthritis at an early stage, the delay of patients with arthritis was studied more extensively (figure 2A). In the Leiden EARC arthritis patients, the median

GP-delay was 2.0 (0.4-7.3) weeks in contrast to 9.4 (5.9-23.2) weeks in the Leiden arthritis patients who arrived at our clinic via regular referrals. Thus indicating a difference of about 7.4 weeks, $p < 0.001$. The median GP-delay of early arthritis patients identified via the EARC was also considerably lower than the historical GP-delay which was 8.0 (2.7-18.4) weeks.⁽⁸⁾ The median GP-delay in the Groningen EARC arthritis patients was 2.0 (0.4-10.0) weeks which was comparable to the Leiden EARC data, and lower than the GP-delay of the patients that arrived via regular referrals in Groningen which was 3.9 (2.6-12.8) weeks ($p < 0.001$). The GP-delay was rather stable during the study period (see online supplementary figure S1).

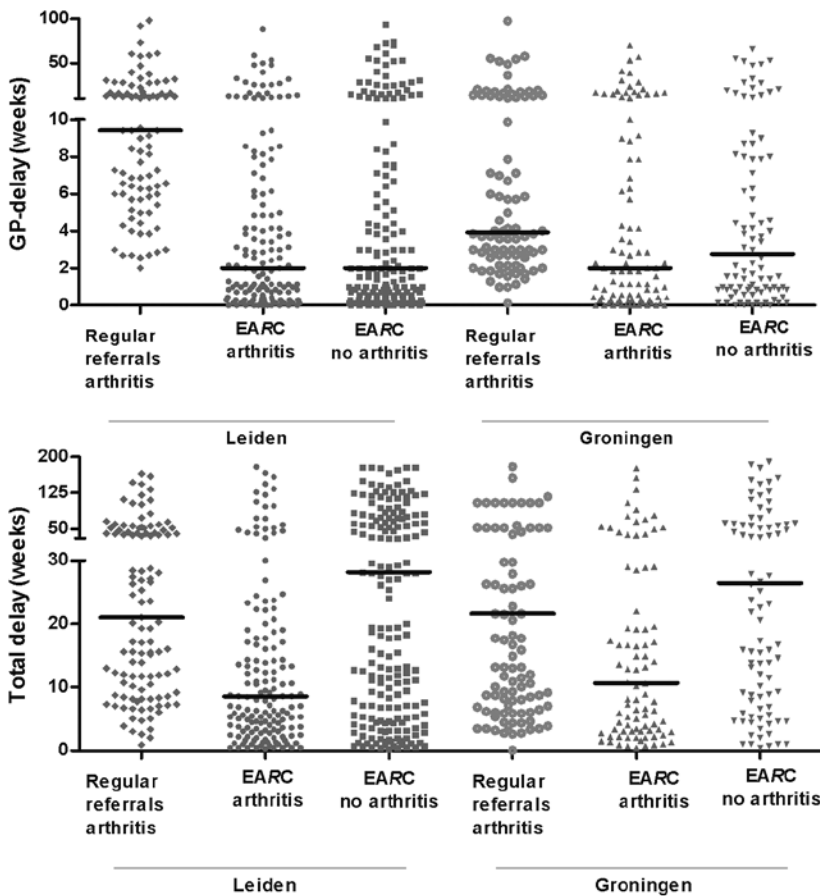


Figure 2. General practitioner-delay (A) and total delay (B) of patients with arthritis and without arthritis screened at the Leiden and Groningen EARC.

Legend Figure 2. The delays of the patients that arrived via regular referrals were presented as well. Each data point represents a single patient; the black horizontal lines show the median.; In (A) 22 data points are out of range (arthritis $n=8$, no arthritis $n=14$). In (B) 93 data points are out of range (arthritis $n=44$, no arthritis $n=49$).

Table 1. Baseline characteristics of the patients visiting the Leiden and Groningen EARC, separated for patients with and without arthritis. Characteristics of patients that were included in the Leiden and Groningen Early Arthritis Clinic and that had arrived via regular referrals are also presented.

	EARC Leiden		Regular referrals Leiden	
	All patients n=400	No Arthritis n= 232	Arthritis n=168	n= 116
Female, n (%)	293 (73.3)	181 (78.0)*	112 (66.7)*	66 (56.9)
Age, years, mean±SD	51.3±16.1	50.3±15.2	52.6±17.3	52.4±16.0
Gradual onset complaints, n (%)	257 (64.3)	153 (65.9)	104 (61.9)	61 (52.6)
Morning stiffness, minutes	15 (10-60)	15 (10-60)	25 (10-60)	40 (10-60)
HAQ (0-3)	0.75 (0.25-1.25)	0.63 (0.25-1.13)*	0.75(0.38-1.38)*	0.75 (0.38-1.25)
TJC ‡	8 (4-18)	9 (5-19.8)	7.5 (3-15)	5 (2-6)
SJC, mean±SD	-	-	3±5	4±5
ESR, mm/hour †	-	-	11 (6-13)	15.5 (6-36)
ACPA positive, n (%) †	-	-	14 (10.0%)	26 (23.0%)
RF, positive, n (%) †	-	-	23 (16.3%)	32 (28.8)

Table 1. Continued

	EARC Groningen			Regular referrals Groningen
	All patients n=212	No Arthritis n=108	Arthritis n=104	
Female, n (%)	133 (62.7)	68 (63.0)	65 (62.5)	92 (62.6)
Age, years, mean±SD	49.4±16.5	48.1±16.1	50.7±16.9	52.1±16.9
Gradually onset complaints, n (%)	137 (64.6)	76 (70.4)	61 (58.7)	88 (59.9)
Morning Stiffness, minutes	30 (10-60)	30 (10-60)	30 (15-90)	15 (0-60)
HAQ (0-3)	0.63 (0.25-1.13)	0.63 (0.25-1.00)*	0.75 (0.38-1.38)*	-
TJC [†]	9 (3-16)	10 (5-18)*	6.5 (2.25-14.75)*	1 (0-5)
SJC, mean±SD	-	-	3±3	2±4
ESR, mm/hour [†]	-	-	14 (7-24)	15 (8-30)
ACPA positive, n (%) [‡]	-	-	10 (11.6%)	27 (18.4%)
RF, positive, n (%) [‡]	-	-	20 (22.2%)	47 (32.0)

Unless otherwise stated values are median (IQR).

* p< 0.05

[†] These variables were collected at the first regular outpatient clinic visit and therefore absent for the patients that at the EARC had no arthritis.

[‡] The TJC in the EARC is as reported by the patients and the TJC of the patients that arrived via regular referrals is assessed by the rheumatologist.

In the two Leiden and two Groningen data-sets, baseline characteristic between arthritis patients with and without information on the dates of symptom onset or the dates on first GP-visit were not significantly different (data not shown).

EARC, Early Arthritis *Recognition* Clinic; HAQ, Health Assessment Questionnaire; SJC, Swollen Joint Count; ESR, Erythrocyte Sedimentation Rate; ACPA, Anti-Citrullinated Protein

Antibody; RF, Rheumatoid Factor; TJC, Tender Joint Count.

GP-delay in UA and RA

The GP-delay of arthritis patients with different diagnoses is depicted in figure 3A. Evaluation of the Leiden EARC patients (n=83) that at baseline were diagnosed with UA or RA revealed a median GP-delay of 2.1 (0.7-8.1) weeks. The median GP-delay of the UA-patients or RA-patients (n=76) that were referred regularly during the same period as the EARC existed was 9.4 (6.0-15.8) weeks, which was significantly longer than that of UA-patients or RA-patients that arrived via the EARC ($P<0.001$). Our historical data on RA-patients also showed a longer median GP-delay (11.8 weeks).⁸ The median GP-delay in the UA-patients or RA-patients identified via the EARC in Groningen (n=44) was similar to that in the Leiden EARC, namely 2.9 (0.5-16.4) weeks.

Total delay of early arthritis patients

In all patients screened at the EARC, the median total delay was 14.0 (4.6-76.6) and 16.5 (4.8-60.9) weeks in Leiden and Groningen respectively. Evaluating all arthritis patients, the median total delay in Leiden was 8.6 (3.6-22.3) weeks which was considerably lower than arthritis patients that came via regular referral during the same period as the EARC was running, where the median total delay was 21.0 (9.6-52.1) weeks, $p<0.001$ (figure 2B). The total delay of 8.6 weeks was also lower than that of the historical data where the median total delay was 13.7 (5.7-28.5) weeks.⁸ The median total delay of arthritis patients identified in the Groningen EARC was quite similar (10.6 weeks, IQR 3.1-30.8 weeks) to that of Leiden EARC early arthritis patients (figure 2B) and much lower than that of regular referral patients from Groningen (21.6 weeks IQR 8.1-104.3, $p<0.001$).

Total delay in UA and RA

The total delay per diagnosis is shown in figure 3B. When studying the Leiden EARC patients that were diagnosed with UA or RA at the first regular outpatient clinic visit, the total delay was 7.6 (3.5-23.8) weeks. This was considerably lower than the total delay of UA-patients and RA-patients that were referred by regular routes, which was 19.3 (9.4-40.3) weeks. Our historical data also showed a longer median total delay in RA-patients namely, 18.4 (10.4-35.0) weeks.⁸ Together, these results are indicative of a substantial decrease in total delay of UA-patients and RA-patients that were identified via the EARC. UA-patients and RA-patients from the Groningen EARC had a median total delay of 10.4 (3.5-20.4) weeks.

Proportion of patients seen < 12 weeks after symptom onset

The proportion of patients that visited the rheumatologist within 12 weeks after symptom onset was evaluated as well. The percentages of all early arthritis patients that were identified via the EARC were 59 and 51 in Leiden and Groningen respectively. In contrast, 32% and 38% respectively of early arthritis patients that came via regular referrals were seen within 12 weeks, and therefore showed lower percentages than the EARC groups ($p<0.001$ and $p=0.074$) (See figure 4A-D).

This analysis was repeated among the patients classified with UA or RA that came via the Leiden and Groningen EARC, 65% and 53% respectively arrived <12 weeks after symptom onset. Only Leiden, but not Groningen, UA and RA-patients that arrived via regular referrals were available for comparison, showing a much lower percentage (36%) of patients that was identified <12 weeks' time (see figure 4E,F). Historically, 31% of RA-patients visited rheumatologists within 12 weeks' time.⁸ Altogether, the percentage of UA-patients and RA-patients that was identified within the first three months after symptom onset has almost doubled when using the EARC.

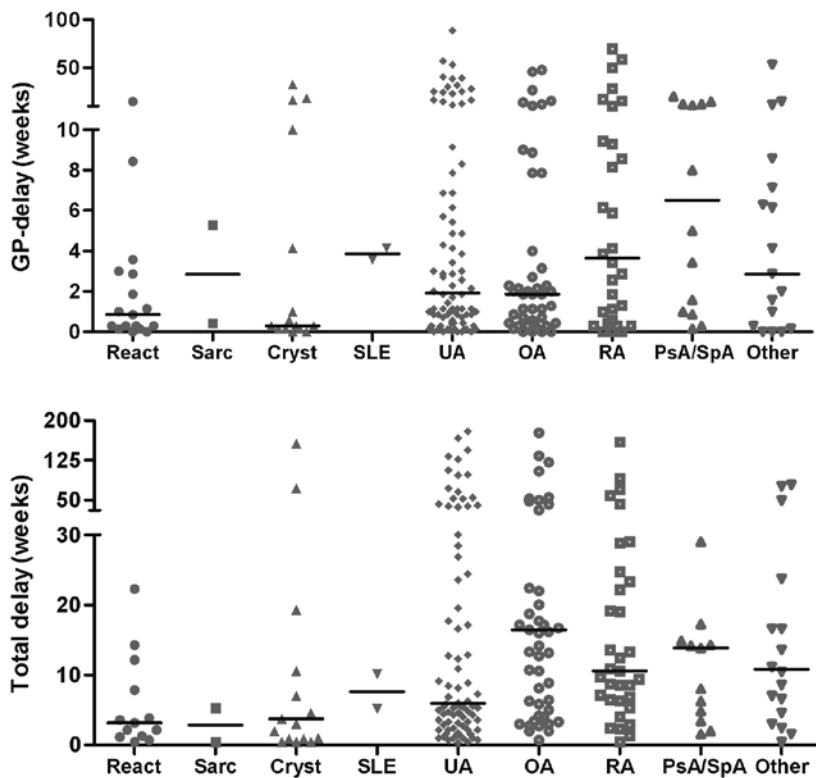


Figure 3. General practitioner-delay (A) and total delay (B) of the patients screened with arthritis at the Early Arthritis Recognition Clinic (EARC) according to the diagnosis made by the rheumatologists at the first regular outpatient clinic visit.

Legend Figure 3. Patients from the Leiden and Groningen EARC were combined in one figure. Each data point represents a single patient; the black horizontal lines show the median. In (A) three data points are out of range. In (B) 15 data points are out of range. React, reactive arthritis viral and bacterial; Sarc, Sarcoidosis; Cryst, Crystal arthritis; SLE, systemic lupus erythematosus; UA, undifferentiated arthritis; OA, osteoarthritis; RA, rheumatoid arthritis 2010 criteria; PsA/SpA, psoriatic arthritis/spondyloarthritis; Other, Other diagnosis.

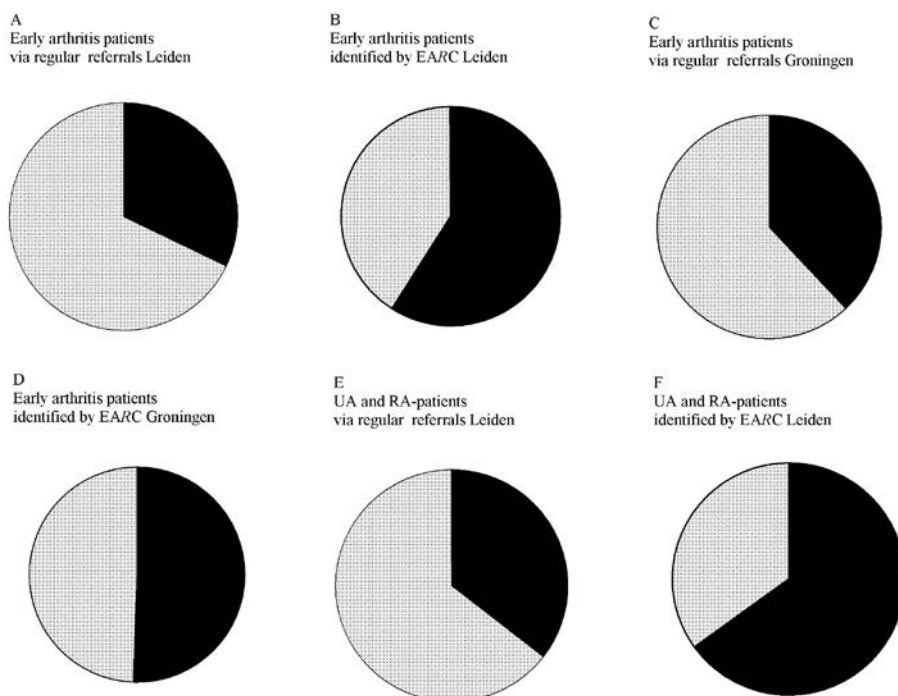


Figure 4. Proportion of Leiden and Groningen early arthritis patients (A-D) and Leiden UA and rheumatoid arthritis-patients (E, F) that at first presentation at the rheumatologists had symptoms for less than 12 weeks.

Legend figure 4. Black: proportion seen by a rheumatologist < 12 weeks after symptom onset. Grey: proportion seen by a rheumatologist > 12 weeks after symptom onset. The proportion of patients seen within 12 weeks was A: 32%, B: 57%, C: 37%, D: 51%, E: 36% and F: 62%.

DISCUSSION

Early initiation of treatment of RA is associated with a higher chance of achieving remission and less progressive joint destruction.^{3,4,8} Early start of treatment requires early identification of arthritis and of RA.⁷ A recent study across Europe in RA-patients revealed that the median period between first symptoms and first visit to the rheumatologist is considerable and that the proportion of patients seen within 12 weeks after symptom onset ranged between 8% and 42%.¹⁰

In our setting, delay in referral by GPs was the main contributor to the total delay.⁸ To reduce this delay we initiated an EARC. The present study, which evaluated the efficacy of this screening clinic, revealed that the GP-delay decreased from about eight weeks to about two weeks in arthritis patients. Furthermore, the proportion of patients that was

identified with UA or RA within the first 3 months of the disease has doubled. Based on these results we conclude that the EARC strategy significantly decreases the delay in recognizing arthritis and RA.

Throughout Europe several other strategies were developed to recognize arthritis at an early stage or to increase awareness of arthritis symptoms. For example in Vienna the 'Rheuma-bus'-initiative was launched and, more recently, an Immediate Access Clinic was established. Elsewhere, triage systems and the effectiveness of education of GPs were evaluated.^{11,16-19} A difference with some of these initiatives is that the present EARC focuses particularly on decreasing the GP-delay in referring arthritis patients.

This new referral strategy was initiated at two different places that are situated 200 km apart in the Netherlands. Strength of the current study is that the GP-delay and total delay of arthritis patients at both places were comparable.

In order to evaluate the efficacy of the EARC two comparisons were made. Both have drawbacks. The comparison with delay data obtained before the initiation of the EARC is informative. Nevertheless, although the delay durations were stable between 1993 and 2006⁸, differences in delay durations with those of the patients screened at the EARC in 2010 and 2011 may have other reasons than the EARC itself. A limitation of the comparison between EARC arthritis patients and arthritis patients that came via regular referrals is that the motivations of the GP to send to the EARC or to use the regular referral route were not evaluated. In this study referral strategies were not randomized and none of the control groups yielded perfect comparability. Nonetheless, in both control groups the delays observed were longer than those of the arthritis patients identified by the EARC.

Another shortcoming is that we depended on patients' memory for collecting the dates of symptom onset and of first visits to the GPs. A study in patients with acute heart disease showed a good agreement at the aggregate level between self-reported delay and delay data obtained by structured interviews, suggesting that this way of collecting data is acceptable.²⁰ Nonetheless, patients with symptoms for a relatively short time period may be more precise in indicating the exact dates than patients that experience symptoms for years.

When evaluating the length of the delay in relation to the diagnoses, it is evident that diseases characterized by an acute severe onset such as sarcoidosis and reactive arthritis had the lowest delay (figure 3), and patients diagnosed with RA, UA, PsA or SpA had the longest delay. This observation is in line with our previous findings.⁸

The EARC aims to decrease the GP-delay as this is the main contributor to the total delay in the Netherlands.⁸ Recent UK studies revealed that patient delay was most the most important factor here.^{21,22} The EARC did not address the level of delay that is caused by the patients themselves. Hence the applicability of an EARC should be regarded in the context of the local setting.

We did not calculate whether the initiation of an EARC is cost-effective. Given that almost one out of two patients screened had arthritis and that the costs of screening by physical examination are low (5-10 minutes per rheumatologist per patient), it may well be cost effective. Most important is to determine prospectively whether the group of RA-patients identified via the EARC indeed has a better long-term outcome than the group of RA-patients that was identified at our clinic via regular referrals. Longer follow-up of these two groups is therefore required.

Altogether, EARCs were initiated at two different places and the first results of these EARCs consistently showed that this initiative importantly increased the early identification of arthritis and RA.

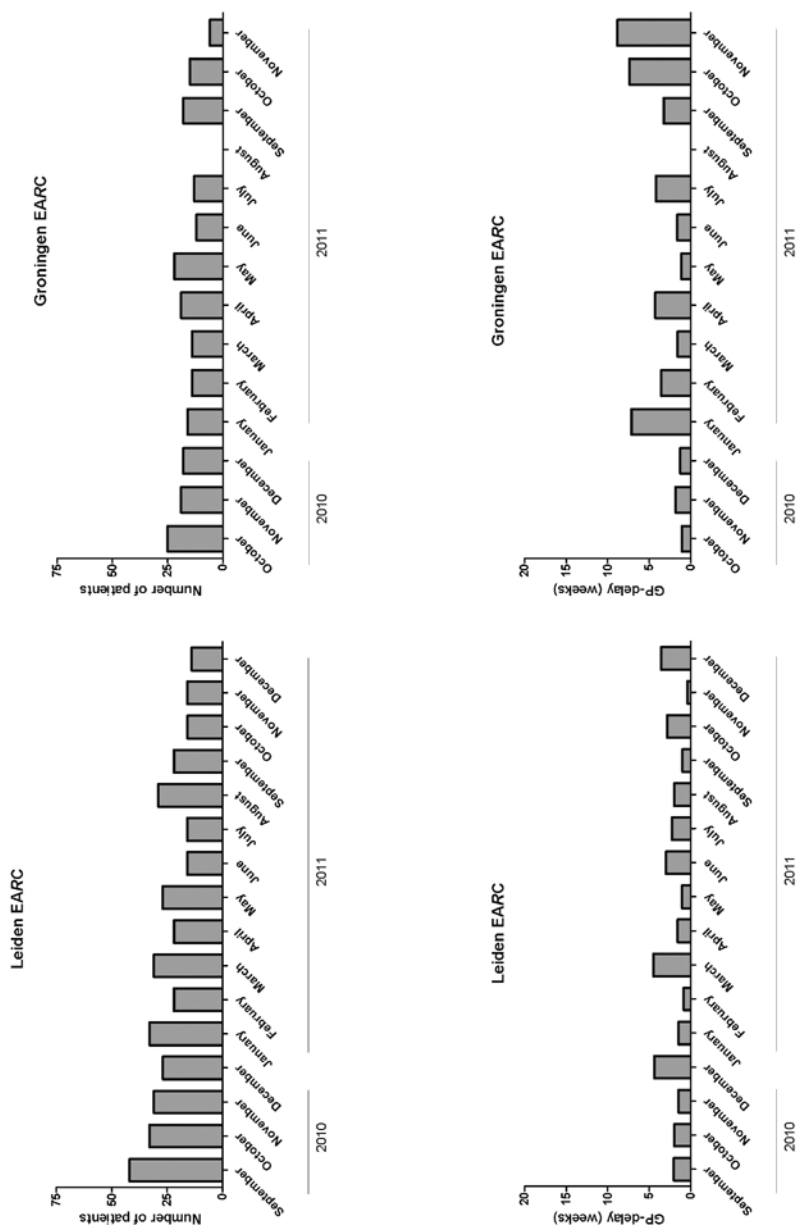
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SUPPLEMENTARY DATA

Supplementary Figure 1.





CHAPTER 3

Reasons for medical help-seeking behaviour of patients with recent- onset arthralgia

Jessica A.B. van Nies, Elisabeth Brouwer, Diederik P.C. de Rooy,
Floris A. van Gaalen, Tom W.J. Huizinga, Marcel D. Posthumus,
Annette H.M. van der Helm-van Mil

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ABSTRACT

Objective

Patient delay in seeking medical help may cause suboptimal use of the therapeutic window in rheumatoid arthritis. We aimed to assess the motivations and the urgency with which patients with arthralgia seek medical help.

Methods

612 patients with arthralgia – visiting two Dutch Early Arthritis Recognition Clinics – were studied. Patients filled out a questionnaire with questions on their symptoms and their reasons for seeking medical help. Comparisons were made for patients with short or prolonged patient delay, patients with and without arthritis, age and gender.

Results

The median symptom duration was 4 weeks. A prolonged delay in seeking help was associated with a gradual onset of symptoms (78%) and the perception that symptoms would not be serious or would go away (16% and 48%, respectively). Arthralgia patients who promptly sought medical help more often had an acute onset of symptoms and more frequently reported impairments at work or in daily functioning than patients who postponed seeking help (all $p < 0.005$). Patients with and without arthritis generally had similar reasons for seeking help. The proportion of patients who had a prolonged patient delay was comparable between male and female subjects and between age categories. Particularly younger patients postponed seeking help because they thought their symptoms would disappear spontaneously.

Conclusion

This large-scale study observed several reasons and symptom characteristics influencing the help-seeking behaviour of persons with arthralgia. These data can be helpful to define strategies aiming at early identification of arthritis.

INTRODUCTION

Data of multiple observational cohorts and clinical trials indicate that treatment initiation in the first 3 months of rheumatoid arthritis (RA) is particularly effective at controlling arthritis and results in a better outcome.¹⁻⁶ To allow early treatment initiation, it is required that arthritis is recognized at a very early stage.⁷ The time between symptom onset and the first visit to the rheumatologist is composed of several components, such as delay on part of the patient in seeking medical help at symptom onset, delay in referral by the general practitioner (GP) and delay in getting access to rheumatologic care.⁸ This study evaluated reasons of patients with arthralgia for seeking medical help in the primary healthcare. Understanding the motivations leading to a delay in seeking medical help is required when considering targeted health interventions (directed at early recognition of arthritis) on the level of the general public.

A recent study across Europe showed that the contribution of the patient delay to the total delay in RA varies from place to place. For instance, in Heraklion and Birmingham the median patient delay was 30 weeks and 12 weeks, respectively, whereas in Vienna, Berlin and Warsaw the patient delay was relatively short (median 2-6 weeks).⁹ In a recent Dutch study a median patient delay of 3.3 weeks was observed.¹⁰ Cultural differences or differences in design or the access to the healthcare system might contribute to the observed variations in patient delay.^{8,11}

The help-seeking behaviour of RA-patients has been studied before and was recently summarized.¹² Former studies had relatively small sample sizes (on average 30 patients per study, minimum 3, maximum 120 patients) and studied patients classified with RA who had variable disease durations (1-15 years). None of the previous studies evaluated drivers or barriers for seeking help at the stage of arthralgia.¹² The present large-scale study was conducted to assess the reasons why patients with arthralgia seek medical help and to determine the readiness with which they seek medical help.

PATIENTS AND METHODS

Arthralgia patients

We studied patients with arthralgia who were referred to one of our two Early Arthritis Recognition Clinics (EARC). These clinics were initiated in September 2010 in Leiden and in October 2010 in Groningen, The Netherlands. These outpatient clinics aim to decrease the GP delay.¹³ Our observation that in the Netherlands, GP delay contributed for two-thirds to the total delay and GPs frequently 'wait-and-see' in case they are unsure about the presence of arthritis, which prompted us to initiate the EARC.¹⁰ For further details on the design of the EARC, please see 13. At the EARC, patients were asked to

fill out a questionnaire with questions on their symptoms, their functioning, and their reasons for seeking medical help. Subsequently, they were screened for the presence of arthritis by physical examination by experienced rheumatologists. In case of arthritis observed by physical examination (this was found in 44.4 % of cases), patients visited the general outpatient clinic within 1 week for further examinations (such as laboratory and radiological evaluations) and appropriate treatment.¹⁴ All arthralgia patients who were seen in our EARCs during the first 15 months were included.

Questionnaire

The questionnaire consisted of questions about several items. First, there were questions about the characteristics of the symptoms (pain, swelling or stiffness of joints experienced by the patient), the acuteness of onset, the distribution of the symptoms and the presence of morning stiffness. The dates of symptom onset (reported by the patient) and of the first visit to the GP were determined. Second, there were questions related to work absenteeism, presenteeism (reduced functioning while being at work) and the presence of impairments in daily functioning. Patients filled out a Health Assessment Questionnaire (HAQ). Finally, motivations for seeking medical help or postponing seeking medical help were evaluated. Patients were asked to indicate whether one or more reasons (presented in a list) were applicable to them; multiple answers were allowed (for the questions see online supplementary table 1). The questionnaire was completed by the patients without interference from the rheumatologist.

The patient delay was defined as the period between symptom onset and the first visit to the GP. This delay is a composite of delay on the part of the patient in seeking medical help by a GP and the time a patient has to wait to see his/her GP after an appointment is made. In the Dutch healthcare system patients have direct access to GPs, so the latter part of this delay is negligible. Of all 612 patients, 125 patients did not report the first visit to the GP, so the duration of the patient delay could not be determined. Patients without data on the first GP visit were older (55.8 vs 49.2 years), less often had arthritis (32% versus 48%), less often had acute onset of symptoms (16% vs 37%) and had a significantly longer total delay (median 167 vs 12 weeks) than patients who did report the date of their first GP visit. Out of all patients with arthritis (n=272), there were 40 patients who did not report a date on the first GP visit. These patients were older (58 vs 51 years) and had a longer total delay (144 vs 8 weeks) than arthritis patients who did report the date of the first GP visit.

Statistical Analyses

We started with an analysis of all arthralgia patients' data. Subsequently, analyses were repeated for patients with short and prolonged patient delay, patients with and without arthritis and for gender and age categories (<40, 40-60 and >60 years).

Comparisons were made using the χ^2 test, Student t test or Mann-Whitney U test and Kruskal-Wallis test as applicable.

Then we studied whether certain symptom characteristics and reasons for seeking medical help frequently occurred together. This was done at the variable level using the variable reduction technique Partial Least Squares regression (PLS). PLS combines variables that frequently occur together in the so-called latent factors. Age, gender, symptom characteristics, work-related questions and reasons for seeking help were included in the PLS as independent variables; the patient delay (short/prolonged) was entered as dependant variable. Identified latent factors were plotted to look for clustering. To perform PLS, the relevant SPSS extension packages were downloaded from the official SPSS website. SPSS software V.17.0 was used. p Values <0.05 were considered significant.

RESULTS

Arthralgia patients

In total, 612 patients with arthralgia were evaluated; arthritis was observed in 272 patients (44.4%). Baseline characteristics are presented in table 1. The median patient delay was 4.1 (0.9-17.14) weeks. Overall, 24% of the patients were absent from work due to their symptoms and 61.7% of the patients experienced impairments in daily functioning (table 2). Frequently mentioned motivations to seek medical help were worsening of symptoms (66%) and impairments in daily functioning (35%). A frequent reason to postpone seeking medical help was the thought that symptoms would go away by themselves (39%) (table 3). Only 14% of the patients with arthralgia were concerned about having joint inflammation and knew that, in that case, they had to act quickly (table 3). The reasons for seeking medical help or postponing seeking medical help did not differ between the centres (data not shown). Therefore, we combined the datasets from both EARCs for this study.

Table 1. Baseline characteristics of all arthralgia patients as well as separated for short and prolonged patient delay and for patients with and without arthritis.

	All arthralgia patients N=612	Patient delay		Arthritis at examination	
		< 4 weeks N=242	> 4 weeks N=245	Present N=272	Absent N= 340
Female (n (%))	426 (69.6)	157 (64.9)	174 (71.0)	177 (65.1)	249 (73.2)*
Age, years, mean±SD	50.6 (16.3)	49.5 (17.0)	49.1 (15.5)	51.9 (17.1)	49.6 (15.5)
Gradual onset symptoms, n(%)	394 (64.4)	103 (42.6)	192 (78.4)*	165 (60.7)	229 (67.4)
Morning stiffness, minutes	20 (10-60)	17.5 (10-60)	30 (10-60)	30 (12.5-60)	15 (10-60)*
Patient Reported TJC	8 (4-12)	6 (2-14.25)	9 (4.25-18)*	7 (3-15)	9 (5-19)*
HAQ (0-3)	0.63 (0.25-1.13)	0.75 (0.38-1.25)	0.5 (0.25-0.88)*	0.75 (0.38-1.38)	0.63 (0.25-1.13)*
Arthritis at examination, n(%)	272 (44.4)	137 (56.6)	95 (38.8)*		

Unless otherwise stated values are median (IQR).

Missing values for patients with PD<4weeks and patients with PD>4 weeks: onset complaints n=5 and n=5, duration mornings stiffness n=116 and n=84, self-reported TJC n=0 and n=1, and HAQ n=27 and n=19. Missing values for arthritis patients and patients without arthritis: onset complaints n=6 and n=10, duration mornings stiffness n=115 and n=134, self-reported TJC n=0 and n=1, and HAQ n=30 and n=24.

*p Value< 0.05

HAQ, Health Assessment Questionnaire; PD, patient delay; TJC, tender joint count 68.

Comparisons for short versus prolonged patient delay

Subsequently, patients with a short or prolonged patient delay were studied separately. Categorization into 'short delay' and 'prolonged delay' was done using the median symptom duration at evaluation (4 weeks) as cut-off. Patients with a short patient delay more often experienced a sudden onset of symptoms than patients with prolonged delay ($p<0.05$ table 1). They also had a higher Health Assessment Questionnaire score, were more frequently absent from work (36% vs 14.4%, $p<0.001$), had more often functional impairment at work (70% vs 56%, $p=0.006$) as well as impairments in daily functioning (71% vs 54%, $p=0.001$). Furthermore, arthralgia patients with a short delay more frequently mentioned suddenly occurring symptoms and functional impairments as important reasons for rapidly seeking medical help (48% vs 18% and 41% vs 29% respectively, $p <0.05$, table 3). Patients with a prolonged patient delay postponed seeking medical help because they thought the symptoms would go away by themselves or that the symptoms did not indicate anything serious. In all, 69% of the patients with a prolonged delay sought medical help because the symptoms were getting worse (table 3).

Table 2. Frequency of absenteeism, impairment in work or in functioning in all arthralgia patients as well as separated for short and prolonged patient delay and for patients with and without arthritis.

	All arthralgia patients N=612	Patient delay		Arthritis at examination	
		< 4 weeks N=242	> 4 weeks N=245	Present N=272	Absent N= 340
Do you have a (paid) job (% yes)	64.3	67.1	65.0	64.1	64.5
If so, have you missed work/have you been absent from work due to your symptoms? (% yes)	23.9	36.3	14.4*	28.2	20.7
If so, did you have functional impairment at work due to your symptoms? (% yes)	63.1	69.7	55.6*	67.4	60.1
Have you been impaired in your daily functioning due to your symptoms?(% yes)	61.7	71.1	53.6*	66.3	58.3

*p Value<0.05

Table 3. Frequency of reasons for seeking medical help in all arthralgia patients and subsequently for short versus prolonged patient delay and patients with and without arthritis.

	All arthralgia patients N=612	Patient delay		Arthritis at examination	
		< 4 weeks N=242	> 4 weeks N=245	Present N=272	Absent N= 340
Reasons for seeking medical help; Because...					
The symptoms suddenly occurred	27.9	47.5	18.0*	34.2	22.9*
The symptoms were getting worse	65.7	60.3	69.4*	64.7	66.5
More symptoms occurred	37.4	29.3	39.2*	35.7	38.8
I worried about what could be wrong	42.0	43.8	43.3	43.8	40.6
I worried I might have had a joint inflammation	36.1	36.4	33.9	34.9	37.1
I worried I might have had a joint inflammation and I heard/read that you have to act quickly	14.4	14.0	13.9	14.0	14.7
Due to my symptoms, I was unable to do things	35.1	40.9	28.6*	37.5	33.2
I wanted to ask for a painkiller	15.8	16.9	12.2	16.2	15.6
My family/friends thought I should go	22.2	22.3	21.6	26.1	19.1*
Reasons for postponing seeking medical help; Because...					
I was unable to go sooner	2.0	2.9	2.0	1.8	2.1
I wanted to wait and see	43.0	39.7	47.3	41.2	44.4
The doctor could not see me sooner	1.1	1.2	1.6	1.1	1.2
It seemed like it was getting better	7.5	4.1	11.4*	7.0	7.9
I thought it would go away by itself	39.4	32.6	48.2*	37.9	40.6
I thought nothing could be done about it	6.4	1.7	7.3*	5.5	7.1
I thought it I wouldn't be taken seriously	3.4	0.8	3.7*	3.3	3.5
It didn't seem serious	12.4	7.0	16.3*	11.4	13.2
I was afraid it might have been serious	2.6	1.7	3.7	3.3	2.1
I asked somebody else to look at it first	3.9	1.7	4.1	3.3	4.4

Data are expressed as %.

*p Value< 0.05.

Comparisons between patients with and without arthritis

The median patient delay in the arthralgia patients who also had arthritis was 2.6 (0.7-9.0) weeks and 5.9 (1.1-27.9) weeks in the patients without arthritis ($p<0.001$) (table 2). Generally speaking, the reasons of patients with and without arthritis were not different, though patients with arthritis were more often motivated to seek medical help because they experienced symptoms that occurred suddenly (34% vs 23%, $p<0.05$) and, interestingly, also because they were more often advised to do so by family or friends (26% vs 19%, $p<0.05$, table 3).

Comparisons between female and male subjects

Overall, 70% of the arthralgia patients were female subjects. The median patient delay was 3.1 (0.9-12.9) weeks in male subjects and 4.3 (1.0-19.6) weeks in female subjects (not statistically significant). More male than female subjects were absent from their work due to the symptoms (31% vs 21%, $p=0.033$, table 4). Female subjects more often reported occurrence of new symptoms (41% vs 29%, $p=0.005$) and worsening of symptoms (69% vs 58%, $p=0.015$) as reasons for seeking medical help. Male subjects were more often concerned about the cause of the complaints (49% vs 39%, $p=0.034$, table 5). There were no differences in reasons for postponing seeking medical help.

Comparisons between different age categories

Patients with arthralgia were divided into three age categories based on the distribution of the raw data (not shown) as follows: <40 years (26%), 40-60 years (44%) and > 60 years (30%). The median duration between symptom onset and first visit to the GP was 4.0 (1.1-12.6), 4.3 (1.0-21.9) and 3.3 (0.4-15.1) weeks, respectively. Patients in the youngest age category more frequently sought medical help because they experienced suddenly occurring symptoms (table 5). They were also more encouraged by family and friends to seek medical help (32.9% vs 17.4% and 20.1%, $p=0.001$). Patients in the oldest age category more often mentioned the wish for asking a painkiller as reason for seeking medical help. With regard to reasons for postponing seeking medical help, arthralgia patients in the youngest age category more often thought that the symptoms would go away by themselves (51.3% vs 39.3% and 29.3%, $p<0.001$).

Table 4. Frequency of absenteeism, impairment in work or in functioning in female and male patients and in patients in different age-categories.

	Gender	Age categories		
		Female	Male	
		N=426	N=186	N=158
			N=270	N=184
Do you have a (paid) job (% yes)		64.6	63.5	83.9
If so, have you missed work/have you been absent from work due to your symptoms? (% yes)		21.0	30.8*	22.9
If so, did you have functional impairment at work due to your symptoms? (% yes)		64.5	59.5	64.2
Have you been impaired in your daily functioning due to your symptoms? (% yes)		61.6	62.1	65.9
			62.6	53.5

*p Value< 0.05.

Clustering of variables

We subsequently questioned whether some symptom characteristics, motivations or variables concerning the ability to work frequently occurred together, thus clustering in the same arthralgia patients. A data reduction method, PLS regression analysis, was applied to this end. Two latent factors were found that together accounted for 33% of the observed variation (see online supplementary table 2). In figure 1, the individual patient scores on these factors were plotted against each other. Two clusters were observed. A group of patients was found who were characterized by a short patient delay, a sudden onset of symptoms, functional impairments and absenteeism. The other group consisted mainly of patients with a prolonged patient delay, a gradual onset of symptoms and no absenteeism.

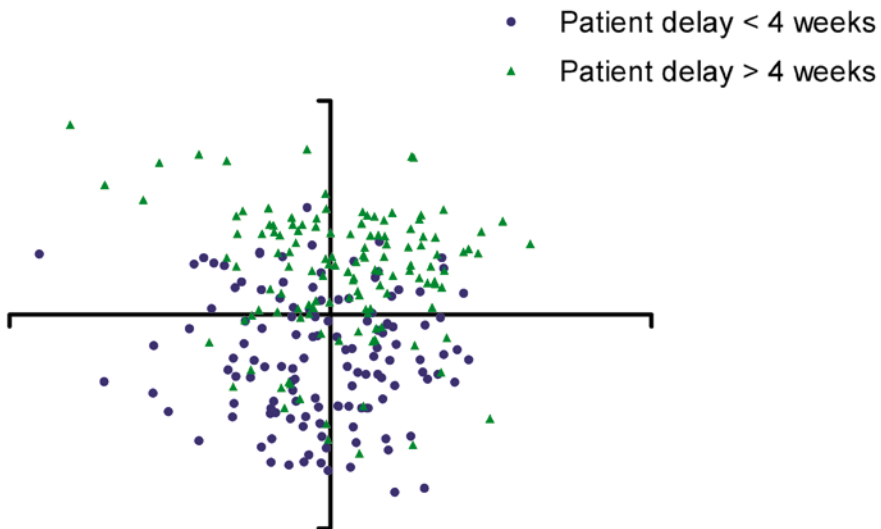


Figure 1. Clustering of variables in arthralgia patients related to help-seeking behaviour.

Legend figure 1. In this plot each dot indicates a single person. Latent factor scores indicate how strongly each factor is represented in each patient. Patients with a patient delay <4 weeks are blue, whereas patients with a patient delay >4 weeks are green. The first latent factor is plotted on the y-axis, and the second latent factor is plotted on the x-axis. A group of patients (below $y=0$) was found who mostly had a short patient delay, had more often a sudden symptom onset, more functional impairments and were more often absent of work. The other group (above $y=0$) consisted mainly of patients with a prolonged patient delay, a gradual onset of symptoms and less absent from work.

Table 5. Frequency of reasons for seeking medical help in female and male patients and in patients in different age categories.

	Gender		Age categories		
	Female N=426	Male N=186	<40 years N=158	40-60 years N=270	>60 years N=184
Reasons for seeking medical help; Because...					
The symptoms suddenly occurred	25.8	32.8	35.4	24.1	27.2*
The symptoms were getting worse	68.8	58.6*	69.0	66.3	62.0
More symptoms occurred	41.1	29.0*	36.7	43.0	29.9*
I worried about what could be wrong	39.2	48.4*	48.1	45.2	32.1*
I worried I might have had a joint inflammation	35.2	38.2	32.9	35.6	39.7
I worried I might have had a joint inflammation and I heard/read that you have to act quickly	13.1	17.2	12.7	13.7	16.8
Due to my symptoms, I was unable to do things	35.9	33.3	38.0	35.6	32.1
I wanted to ask for a painkiller	15.5	16.7	10.8	14.8	21.7*
My family/friends thought I should go	23.0	20.4	32.9	17.4	20.1*
Reasons for postponing seeking medical help; Because...					
I was unable to go sooner	1.4	3.2	3.2	1.9	1.1
I wanted to wait and see	43.7	41.4	53.8	43.7	32.6*
The doctor could not see me sooner	1.2	1.1	2.5	0.7	0.5
It seemed like it was getting better	6.3	10.2	7.0	8.5	6.5
I thought it would go away by itself	39.2	39.8	51.3	39.3	29.3*
I thought nothing could be done about it	7.3	4.3	3.2	6.3	9.2
I thought it I wouldn't be taken seriously	4.2	1.6	3.2	3.3	3.8
It didn't seem serious	12.4	12.4	18.4	11.5	8.7*
I was afraid it might have been serious	3.3	1.1	2.5	1.1	4.9*
I asked somebody else to look at it first	4.2	3.2	1.9	4.8	4.3

Data are expressed as %.

*p Values< 0.05.

DISCUSSION

This study aimed to assess reasons of persons with arthralgia for seeking medical help. For early recognition of arthritis, it is required that such patients seek timely medical help. Comprehension on the symptoms or reasons that motivate persons with arthralgia to seek or postpone seeking medical help is crucial. It may be helpful in developing intervention strategies for public health. In the present study, 612 patients with arthralgia for whom the GP was unsure of the presence of arthritis were evaluated. The median duration between symptom onset and seeking help with the GP was relatively short (4 weeks) and was comparable with the patient delay that we observed recently in early RA patients who visited our early arthritis clinic.¹⁰ Despite the short patient delay on a group level, several symptom characteristics and reasons were associated with the readiness of seeking medical help. Most importantly, prolonged delay in seeking help was associated with a gradual onset of symptoms and the perception that symptoms were not serious and would go away by themselves. Arthralgia patients who rapidly sought medical help more often did so because symptoms suddenly occurred, because they had functional impairments and because they were absent from work due to their symptoms.

Musculoskeletal problems are very common among the general population.^{15,16} A large population-based survey (3664 respondents) on musculoskeletal pain in the Netherlands showed that only about half of the persons consulted a health professional.¹⁶ This is consistent with a report on an Austria's initiative, the 'Rheuma-bus'; here they found that about 40% of persons with musculoskeletal complaints never contacted a physician.¹⁷ The present study focused on patients who did seek medical help, although with differences in the readiness to do so. The present study is the first to evaluate patients with arthralgia instead of patients who are identified with RA. However, our study was not designed to identify the motivations of patients with musculoskeletal pain that did not seek medical help.

The present study has several strengths. The patients studied had symptoms for (on average) a relatively short period. This indicates that the arthritis patients included in the present study were studied at a very early disease stage, earlier than has been studied thus far. The short symptom duration may also have reduced possible recall bias. Another strength of this study is the sample size, which is considerably larger than other studies on this subject⁹ and also allowed for performing subanalyses.

Interestingly, the reasons for seeking medical help of patients with and without arthritis were not evidently different. It is noteworthy that in all subcategories studied, about two-thirds of the patients reported impairments in daily functioning as well as functional impairments at work. In about half of these patients (35%), these functional impairments were mentioned as a reason for seeking medical help.

This study also has limitations. A limitation is that we did not use a validated questionnaire since such a questionnaire on this topic does not yet exist. It is reassuring that some of the findings of the present study are in line with previous, smaller studies. For instance, the association between impairment in daily functioning and a short patient delay has been observed before.^{11,18-20} At present, a questionnaire is being developed and validated that will assess reasons for delay in RA patients as well as in inflammatory arthritis patients.²¹ It would be very interesting to use this questionnaire in arthralgia patients as well. Arthralgia patients were not asked about their socio-economic status and educational level. This might also be considered a limitation.

Importantly, only 14% of all arthralgia patients were aware that, in the presence of arthritis, it is relevant to act quickly. A lack of knowledge on arthritis and RA has also been observed previously in patients diagnosed with RA in the UK and Canada.^{11,19,20} This might call the need for public health intervention strategies. When designing such strategies, the results of the present large-scale study may be helpful. A gradual onset of arthralgia and the perception that these symptoms were not serious and would go away by themselves were the main reasons for waiting for seeking medical help. Based on these results, in particular at places where patient delay is an important contributor to the total delay, it may be relevant to inform the general public about the type of symptoms of arthralgia for which medical help should be sought immediately.

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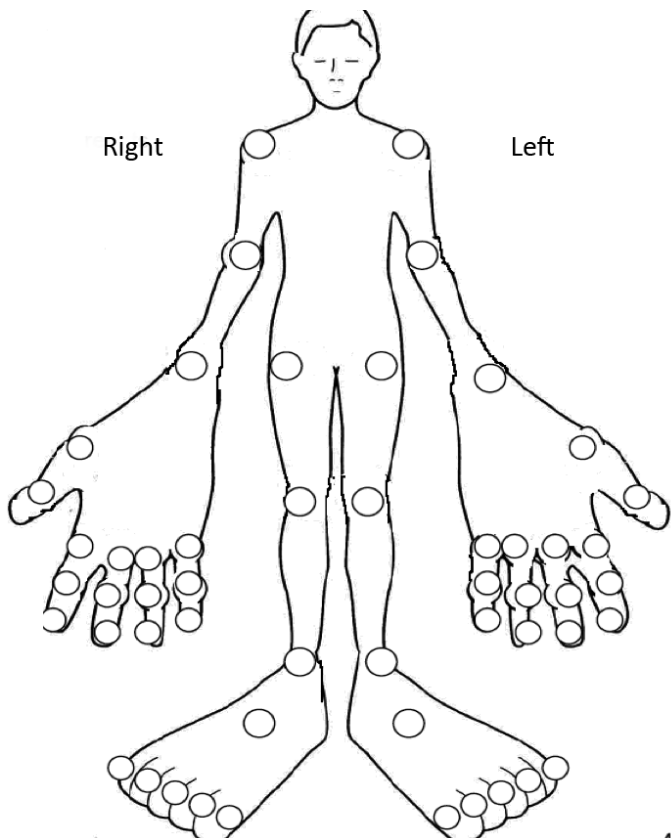
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SUPPLEMENTARY DATA

Supplementary Table 1. Overview of the EARC Questionnaire

In an accompanying letter with the questionnaire it was explained that the questions concerned joint pain or swelling. Subsequently patients were asked to fill out the following questions. Patients finally also filled in a HAQ, which is not presented here. The layout presented here is the different from the original questionnaire.

Symptom-related questions	Possible answers	
When did the symptoms first occur?	...-...-....	(date)
When did you first visit your GP regarding your joint symptoms?	...-...-....	(date)
Did the symptoms appear suddenly or gradually?	suddenly	gradually
Do you experience stiffness when you get up in the morning?	no	yes; in minutes? ...
Please indicate in the manikin which joints are bothering you (by filling in the circles).		



Work-related questions	Possible answers	
Do you have a (paid) job?	no	yes
If so, have you missed work/have you been absent from work due to your symptoms?	no	yes
If so, did you have functional impairment at work due to your symptoms?	no	yes
Have you been impaired in your daily functioning due to your symptoms?	no	yes

Why did you visit your family doctor/ general physician?

(Multiple answers are possible. There are no "right" or "wrong" answers.)

*patients could tick the box below

The symptoms suddenly occurred	☐
The symptoms were getting worse	☐
More symptoms occurred	☐
I worried about what could be wrong	☐
I worried I might have had a joint inflammation	☐
I worried I might have had an inflammation in my joint and	☐
I heard/read that you have to act quickly	☐
Due to my symptoms, I was unable to do things	☐
I wanted to ask for a painkiller	☐
My family/friends thought I should go	☐

If you did not immediately visit your family doctor/general physician, why did you wait?

(Multiple answers are possible. There are no "right" or "wrong" answers.)

*patients could tick the box below

I was unable to go sooner	☐
I wanted to wait and see	☐
The doctor could not see me sooner	☐
It seemed like it was getting better	☐
I thought it would go away by itself	☐
I thought nothing could be done about it	☐
I thought it I wouldn't be taken seriously	☐
It didn't seem serious	☐
I was afraid it might have been serious	☐
I asked somebody else to look at it first	☐

Supplementary Table 2. Overview of major variables in the two latent factors of the Partial Least Square regression analysis.

Variable	Latent factor	
	1	2
Baseline characteristics		
Onset of symptoms (Acute)	2.496	2.413
Questionnaires		
If so, are you absent of work due to your symptoms?	1.629	1.579
Do you have impairment in daily functioning?	1.241	1.198
Of sudden onset of symptoms	2.632	2.547
New symptoms kept coming		1.020
I thought the complaints would pass	1.327	1.282
It didn't seem to be anything serious	1.123	1.084
I was afraid it would be something grave	1.111	1.078

Legend supplementary table 2. Two latent factors in the Partial Least Square regression analysis were found that together accounted for 33% of the observed variation. Presented are the most important variables that contributed to this extent. Latent factors > 0.6 are generally considered relevant.

PART II

A therapeutic window of opportunity
in rheumatoid arthritis



CHAPTER 4

What is the evidence for the
presence of a therapeutic window of
opportunity in rheumatoid arthritis?
A systematic literature review

Jessica A.B. van Nies, Annemarie Krabben, Jan W. Schoones,
Tom W.J. Huizinga, Margreet Kloppenburg, Annette H.M. van
der Helm-van Mil

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ABSTRACT

Objective

Initiation of DMARD-therapy in the 'window of opportunity' is thought to result in a more effective modification of the processes underlying rheumatoid arthritis (RA). We questioned whether this effect is true or hyped and performed a systematic literature review.

Methods

Medical literature databases up to June 2012 were systematically reviewed for cohort studies and randomised controlled trials reporting outcome data of early RA in relation with symptom duration at treatment initiation. The quality of these studies was assessed by two independent reviewers using a criteria scoring system of 15 items. Studies were dichotomised with the median score (79%) as cut-off. Best-evidence synthesis was applied to determine the level of evidence per outcome category. A meta-analysis was performed on the studies reporting on achieving DMARD-free sustained remission (the reverse of disease persistency).

Results

Out of 836 screened articles, 18 fulfilled the selection criteria and were not duplicates. Ten were scored as high quality. remission (various definitions) and radiographic progression were frequently studied outcomes. There was strong evidence for an association between symptom duration and radiographic progression. A meta-analysis on datasets evaluating DMARD-free sustained remission showed that symptom duration was independently associated with such remission; HR 0.989 (95% CI 0.983 to 0.995) per week increase in symptom duration. A moderate level of evidence was observed for other remission outcomes.

Conclusions

Even when heterogeneity of patients is taken into account, prolonged symptom duration is associated with radiographic progression and a lower chance on DMARD-free sustained remission. These data may support the presence of a 'window of opportunity'.

INTRODUCTION

Delay in initiating treatment after the diagnosis rheumatoid arthritis (RA) has been established is associated with progression of joint damage.¹ Recently it has been suggested that it is important to initiate treatment even earlier, in the so-called therapeutic ‘window of opportunity’.² Although not yet fully understood, this window is said to represent a very early phase in the disease in which therapeutic disease modification is more successful, presumably because of not fully matured underlying disease processes. The thought is that intervention in this period may hamper disease progression in such a way that chronicity is reduced. In case such a period is present, this has important consequences for the care of RA, as using this period will reduce the burden of the disease and may, for instance, reduce the number of patients who ultimately require biologics. If a period in which the disease is more susceptible to disease modifying drugs truly exists, efforts resulting in identification of a very early stage of RA may also be cost effective. However, the question arises; does it really exist? One reason for advocating an absence of this particular window is citation bias, assuming that positive studies are preferentially cited and those with negative results neglected. Since many studies have included symptom duration as covariate in their analysis, it is relevant to systematically review all such studies in order to assess whether short symptom duration at treatment initiation is associated with less progression of the disease. It has also been suggested that the window of opportunity encompasses the first 12 weeks after symptom onset.^{3, 4} A difficulty here is that the definition of symptom onset is highly variable between studies⁵; it can relate to the start of symptoms or the start of swelling, and be self-reported by patients or recorded by physicians. Such differences yield incompatibility between studies with regard to the timeframe that was assessed, and preclude performing an extensive meta-analysis. We therefore aimed to perform a qualitative systematic literature review, focusing on two outcomes of early RA; achieving remission and the severity of radiographic joint damage progression.

METHODS

Identification of studies

To identify studies investigating the relationship between symptom duration and the outcome of RA, we searched with the assistance of a medical librarian (JS) in medical literature databases (MEDLINE (OVID-version), PubMed, Embase (OVID_version), Web of Science, CochraneLibrary, CINAHL, Academic Search Premier and ScienceDirect) up to June 2012. Central terms in our analysis were ‘RA’ and ‘symptom duration’, for a detailed overview of the search per database, please see online supplementary file 2. Additional articles were searched in the reference lists of identified articles or via expert opinion.

Inclusion and exclusion criteria

Selection of titles, abstract and articles was performed independently by two reviewers (JABvN and AHMvdH-vM). In case of disagreement, consensus was reached after discussion. First, all retrieved titles were screened, subsequently, abstracts were retrieved for detailed review and, finally, full text articles were read and screened on our inclusion/exclusion criteria. Included studies fulfilled the following criteria: (1) patients with RA were studied, (2) patients were prescribed DMARDs, allowing to evaluate the time period before treatment initiation, (3) patients had early disease; symptom duration (period between symptom onset and start of treatment) was recorded and <2 years, (4) patients were followed prospectively and follow-up was ≥ 1 year and (5) symptom duration was part of the analyses on disease outcome. Animal studies, studies with patients <18 years, reviews, conference) abstracts, letters to the editor, case reports, case series and studies in languages other than English were excluded.

Data extraction

A standardised form was used to extract information about the following data: (1) study population (population size, setting and time period of the study, symptom duration, age and gender), (2) follow-up period, (3) outcomes (joint damage progression, remission or other outcomes), (4) effect estimates.

Methodological quality assessment

The quality of each included paper was reviewed by two reviewers independently (JABvN and AHMvdHvM) using a maximum of 15 criteria (see online supplementary table S1), which were based on previous systematic reviews in the field of musculoskeletal disorders.^{6,7} The criteria were adapted for our research question of symptom duration. When a criterion was met in the article, a '1' was given, otherwise a '0'. A '0' was also given when no information was given about the specific criterion mentioned in the article. In case of differences in ranking, a consensus was agreed after discussion. The maximum score (100%) for each study was based only on the items that were applicable for that study design (randomised controlled trial with radiographic outcome 15, and 14 without, observational cohort with radiographic outcome 14, and 13 without). Total scores per study were calculated as the percentage of maximum obtainable scores.

Rating level of evidence

Because the studies obtained were heterogeneous with regard to the reported effect estimates, a pooled-effect estimate could not be calculated (except for a meta-analysis on the outcome achieving DMARD-free sustained remission). Therefore, we performed a best-evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group.⁸ This is a method to summarise evidence in observational studies if the population, outcomes and data analyses are heterogenic. It

consists of five levels of evidence (table 1). A study was considered to be of high quality (HQ) if the total quality score was $\geq 79\%$ (which is the median of the quality scores obtained in this study).

Table 1. Best evidence synthesis used in this article

Strong	Generally consistent findings ($\geq 75\%$) in multiple high quality longitudinal studies.
Moderate	Generally consistent findings ($\geq 75\%$) in multiple low quality longitudinal studies and/or positive findings in one high quality longitudinal study.
Limited	Findings in one or more low quality longitudinal studies
Conflicting	Inconsistent findings among multiple longitudinal studies.
No evidence	No longitudinal studies, either observational cohorts or RCTs, could be found.

RCT, randomised controlled trial.

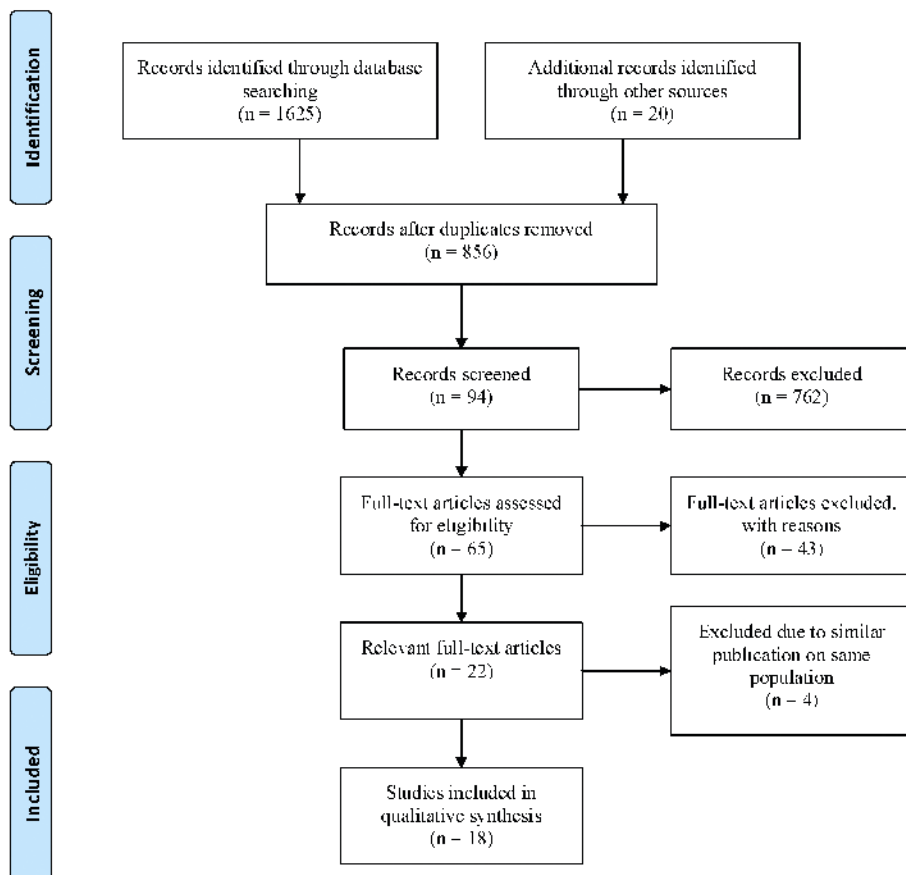


Figure 1. Overview of literature research.

Methodological quality assessment

The two reviewers scored 249 items in total and agreed on 234 items (94%, table 2), the 16 disagreements were resolved in consensus (see online supplementary table S1). The median quality score was 79% (mean 72.7%, range 43–100%). Consequently, articles with scores $\geq 79\%$ were ranked as HQ. Low-quality (LQ) studies frequently missed points on the following items: description of the source population and information on the accurateness of determined outcomes. Additionally, few studies assessed the presence and consequences of lost to follow-up.^{9, 10, 16, 21–22, 30} Finally, of all included studies, information on the definition of symptom onset was provided in only 28%.^{9, 10, 16, 21, 30}

Study characteristics

The characteristics of the 18 included studies are shown in table 3. The majority of the patients were female and, generally, patients were aged >50 years. In all studies, RA was classified according to the 1987 American College of Rheumatology (ACR) classification criteria, except for one study that used the diagnosis of the rheumatologist.²² The number of patients included varied between 40 and 895. Frequencies of symptom duration were reported in different ways; mean $\pm$ SD, median (IQR) or percentages (table 3). Various outcome measured were assessed; the majority related to radiographic joint damage or remission, though actual measures were variable. Progression of radiographic joint destruction was measured using the Larsen score (n=4), the Sharp–van der Heijde score (SHS) (n=4), the Sharp score (n=1) or the presence/absence of erosiveness (n=1). Remission was defined as a state after treatment (eg, Disease activity score (DAS)-28 <1.6 , DAS-28 <2.6 , DAS-44 <1.6 , ACR-remission (n=1, n=2, n=1 and n=2, respectively)), or as the resolution of disease persistency, which is DMARD-free sustained remission (n=3). This latter outcome was defined as sustained absence of synovitis for at least 1 year after cessation of DMARD-therapy, and of all outcomes studies the closest approximation of ‘cure’. Three studies had included analyses on changes in functional ability using the health assessment questionnaire (HAQ).

Table 2. Overview of selected papers

First author, year of publication ^(ref)	N	Quality score (%)	Outcome	Association between shorter symptom duration and outcome
<i>Radiographic joint damage</i>				
Jansen, 2001 ⁽¹⁶⁾	130	79	SHS	S
Lukas, 2011 ⁽²²⁾	661	86	SHS	S
Nell, 2004 ⁽²⁴⁾	40	86	Larsen	S
Van der Linden, 2010 ⁽²¹⁾	598	100	SHS	S
Weng, 2010 ⁽³⁰⁾	233	85	Sharp	NS
Bosello, 2011 ⁽¹²⁾	121	50	Larsen or SHS	S
Dixey, 2004 ⁽¹³⁾	866	64	Larsen	S
Kaufmann, 2003 ⁽¹⁸⁾	54	43	Larsen	NS
Pascual-Ramos, 2009 ⁽²⁵⁾	72	43	Erosive(yes/no)	NS
Sanmarti, 2003 ⁽²⁷⁾	60	57	Larsen	S
<i>DMARD-free sustained remission</i>				
De Rooy, 2011 ⁽¹⁰⁾ *	676	86	DMARD-free sustained remission	S
Van der Woude, 2009 ^{(9)*} (ERAS)	895	86	DMARD-free sustained remission	S
Van der Woude, 2012 ^{(11)*} (BeSt)	508	79	DMARD-free sustained remission	NS
<i>Other outcomes in RA</i>				
Jayakumar, 2012 ⁽¹⁷⁾ +	704	85	DAS-28 <1.6†	S
Möttönen, 2002 ⁽²³⁾	199	87	ACR remission	S/NS\$
Nell, 2004 ⁽²⁴⁾	40	86	DAS-28 <2.6† ΔHAQ	S
Weng, 2010 ⁽³⁰⁾	233	85	DAS-44 <1.6† ΔHAQ score	S
				NS

Table 2. Continued

First author, year of publication ^(ref)	N	Quality score (%)	Outcome	Association between shorter symptom duration and outcome
Bosello, 2011 ⁽¹²⁾ ¶	121	47	ACR remission	S
Gremese, 2012 ⁽¹⁴⁾	481	69	DAS-2.8 <2.6‡	S
Hodkinson, 2012 ⁽¹⁵⁾	171	54	low SDAI	NS
Soderlin, 2011 ⁽²⁸⁾	180	69	EULAR response ΔHAQ	S
				S

Definitions:

- ☐ Scored as High quality study
- ☐ Scores as Low quality study

High quality study ≥ 79% (which is the median of all quality scores)

*Van de Woude 2009 reported on the Leiden EAC and the ERAS; since the Leiden EAC data were represented by the De Rooy article, only the ERAS data of this article were used. Similarly, only the BeSt data were used of the Van der Woude *et al.* 2012 article.

† Jayakumar *et al.* and van der Woude 2009 *et al.* report on the same cohort however other outcomes were applied.

‡ DAS remission is defined as a state, thus an absolute DAS at a specific time point after treatment.

§Two groups were studied, in the single therapy group a significant association with symptom duration was found, in contrast to the combination therapy group.

*This cohort is also part of the three cohorts of Gremese *et al.* but different outcomes were used, namely ACR remission and erosiveness in the Bosello *et al.* article and DAS-2.8<2.6 in the Gremese *et al.* article.

ACR, American College of Rheumatology; DAS, Disease activity score; EAC, early arthritis clinic; ERAS, Early Rheumatoid Arthritis Study group; Erosive (yes/no), erosive disease present or absent; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; NS, Not statistically significant Trend: almost statistically significant. RA, Rheumatoid Arthritis; S, statistically significant; SHS, Sharp—van der Heijde score.

Radiographic joint damage in RA

Five HQ studies evaluated joint damage as outcome. Four of these (75%) demonstrated that shorter symptom duration was associated with less radiographic progression over time.^{16, 21, 22, 24} This implies that the evidence on the association between symptom duration and joint damage progression is strong. One HQ study showed the opposite, this study included a severe subset of patients with RA (>6 swollen joints, >9 tender joints, 90% anti-citrullinated protein antibody (ACPA) positivity) and compared patients with RA with symptom duration of <5 and >5 months at treatment initiation; the patients with RA who started >5 months of symptoms had a better outcome.³⁰ Three of the four HQ studies that reported a beneficial effect of early initiation of treatment had divided patients in groups with symptoms of <3 and >3 months, and observed that patients with symptoms <3 months at start of treatment developed less severe joint damage. Lukas et al²² reported a mean SHS progression of 0.8 vs 1.7 units after 1 year, respectively ($p=0.033$), Nell et al²⁴ showed a mean Larson progression of 3.6 vs 14.7 after 3 years ($p<0.05$) and Van der Linden et al²¹ reported a 1.3-fold higher rate of joint destruction during 6 years follow-up in patients with RA with a symptom duration of >3 months ($p<0.001$). In three of the six LQ studies,^{12, 13, 27} a significant association was also observed between shorter symptom duration and less radiographic progression. Two LQ studies showed the same trend in the data, but statistical significance was not achieved (table 3).^{18, 25}

DMARD-free sustained remission in RA

Three HQ studies assessed DMARD-free sustained remission in patients with RA. With the permission of the authors, the raw data were used to perform a meta-analysis.⁹⁻¹¹ First, a meta-analysis of the univariable association between symptom duration and achieving DMARD-free sustained remission was performed, showing a significant beneficial effect of a shorter symptom duration (HR on DMARD-free sustained remission 0.990 (95% CI 0.984 to 0.996) per week increase in symptom duration figure 2A). Then analyses were adjusted for age, gender and applied treatment, as these variables possibly modify the effect. This revealed an almost unchanged association between symptom duration and DMARD-free sustained remission (figure 2B). Certain levels of inflammation markers or auto-antibodies are a reflection of disease severity, and are also associated with the chance of achieving DMARD-free sustained remission. Therefore, analyses were finally adjusted for age, gender, treatment, erythrocyte sedimentation rate (ESR) and presence of rheumatoid factor (RF) (anti-cyclic citrullinated peptide (CCP) was not available in all cohorts). The adjustment factors in the latter analyses allowed differentiating between effects of patient characteristics and of symptom duration on DMARD-free sustained remission. Also, this analysis revealed that symptom duration was independently associated with DMARD-free sustained remission; each week increase in symptom duration decreased the chance of achieving DMARD-free sustained remission (HR 0.989,

95% CI 0.982 to 0.995, $p < 0.001$, figure 2C). Assuming a linear correlation with time in the early disease stage, the HR for achieving DMARD-free sustained remission in case of 12 weeks symptom duration at treatment initiation is 0.88.

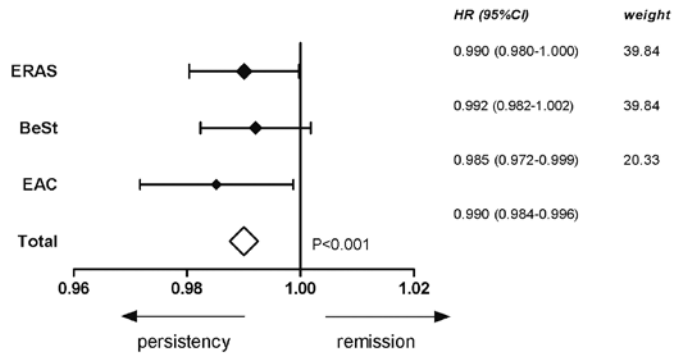
Other outcomes in RA

Eight studies reported other outcomes which were collected during DMARD-therapy. Five of these eight studies showed a significant association between shorter symptom duration and increased frequency of remission.^{12, 14, 17, 24} Of the four HQ studies, one study did not observe a significant association with symptom duration,³⁰ two studies found a significant association,^{17, 24} and one study assessed two cohorts of differently treated patients, showing a significant association in one but not in the other patient group.²³ Based on these findings, the evidence for an association between symptom duration and these remission outcomes in RA is moderate. Three of the eight studies had also assessed changes in HAQ scores. Two studies (1 HQ and LQ) reported that shorter symptom duration was associated with a higher improvement in HAQ scores.^{24, 28}

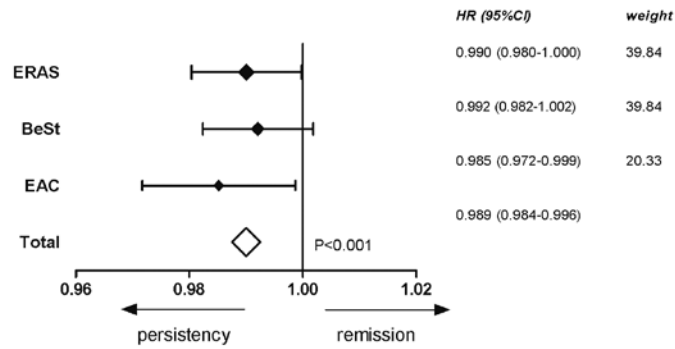
Legend figure 2.

(A) Univariable analysis on symptom duration, heterogeneity $p = 0.72$, $I^2 = 0.0$. (B) Multivariable analysis on symptom duration, adjusted for age, gender and treatment, heterogeneity $p = 0.72$, $I^2 = 0.0$. (C) Multivariable analysis on symptom duration, adjusted for age, gender, treatment, rheumatoid factor and ESR, heterogeneity $p = 0.70$, $I^2 = 0.0$. The follow-up durations studied were similar as in the articles, 10 years for Early Rheumatoid Arthritis Study group (ERAS), 5 years for BeSt and 10 years for the Leiden early arthritis clinic. The number of patients with RA included in these three datasets with complete data for current analysis were $n = 892$, $n = 507$ and $n = 505$, respectively. De Rooy; in the original article: the term persistency was used; in the meta-analysis we used the reverse, namely 'DMARD-free sustained remission' A decreased chance on achieving a DMARD-free sustained remission is equal to an increased chance on arthritis persistency.

2A



2B



2C

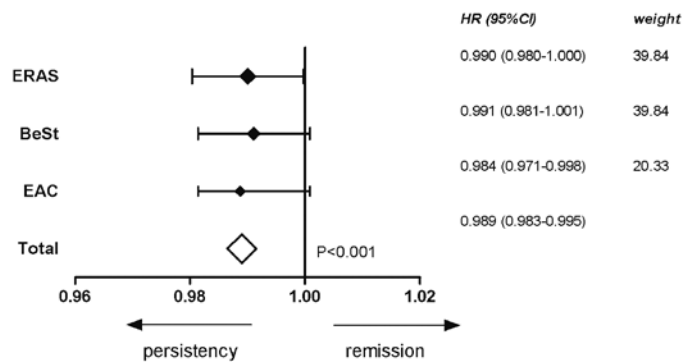


Figure 2. Meta-analysis on the association between symptom duration (in weeks) and achieving DMARD-free sustained remission over time in rheumatoid arthritis (RA).

Table 3. Extended overview of selected articles.

First author, year publication ^{ref}	Study design	●Population ● Location	N	Age, years <i>mean±SD</i> or <i>median (IQR)</i>	Female (%)	Symptom duration (months) <i>mean±SD</i> or <i>median(IQR)</i>
Bosello, 2011 ¹²	OC	1987+ RA ,Italy	121	53.6±13.3	76	5.7±3.5
Dixey, 2004 ¹³	OC	1987+RA, UK (ERAS)	866	<45:24% 45-60: 40% >60:36%	66	6 (4-11)
De Rooy, 2010 ⁹	OC	1987+ RA, Netherlands (EAC Leiden)	676	56.4±15.7	67.9	6.1±5.2
Gremese, 2012 ¹⁴	OC (3 cohorts combined)	1987+ and 2010+ RA patients, Italy	481	54.4±12.0	74.4	6.4±3.3
Hodkinson, 2012 ¹⁵	OC	1987+ RA, South-Africa	171	47.1±12.4	81.9	11.7±7.1
Jansen, 2001 ¹⁶	OC	1987+ RA, Netherlands	130	65(21-86)	67	3 (0-24)
Jayakumar, 2012 ¹⁷	OC	1987+ RA ,UK (ERAS)	704	55 (45-64)	65.6	7 (4-12)
Kaufmann, 2003 ¹⁸	OC	1987+ RA, Germany	54	56 (30-38)	83.3	<6months: 27 (50%)
Lukas, 2011 ²²	OC	RA according to the rheumatologist, France (ESPOIR)	661	48.6±12.1	77.2	<3months 32% >3months 68%
Mötönen, 2002 ²³	RCT	1987+ RA, Finland (FIN-RACo)	165	mean age varied 46-50 years between the arms	62	Combination arm: 6 (4-9) Single arm: 7(4-11)

Definition symptom onset	Outcome of relevance	Adjustment factors	Relevant results
NR	● Radiographic joint damage (defined ≥ 1 unit increase in of SHS/Larson erosions score) after 1 year FU ● ACR remission	● Sex, erosive disease, HAQ ● Sex, RF, ACPA, ESR, SJC	● Not having 'VERA' predictor of erosiveness at 12 months, OR 2.4 (95%CI 1.1-5.6) ● 'VERA' predictor for ACR remission, OR 5.3 (95% CI 2.1-13.0).
NR	Radiographic outcome at 3 years (by Larson score; cut off median erosions score and the worst quartile	none	Symptom duration (weeks) on radiographic outcome, OR 1.86 (95%CI 1.30-2.66).
Onset of joint symptoms reported by the patient	Arthritis persistency (the reverse of DMARD-free sustained remission)	Age, sex, inclusion-period (as proxy for treatment strategy)	Symptom duration (weeks) OR 1.011 on arthritis persistency (95% CI 1.002, 1.019), $p=0.012$
NR	DAS-28 (<2.6) remission at 12 months FU	DAS-28, HAQ, ACPA, erosions, DMARDs within 3months	'VERA' on DAS-28 remission, OR 2.03 (95% CI 1.15;3.30)
NR	Low disease activity (LDA) at 12 months ($SDAI \leq 11$) versus moderate/high disease activity (MDA/HAD; $SDAI \geq 11$)	none	LDA symptom duration 9.9 ± 6.9 months versus MDA/HDA 11.7 ± 6.8 months. (mean $\pm$ SD) Not significant (p -value unknown).
Onset of persistent pain and swelling reported by the patient	Delta radiographic damage at 1 year (by SHS).	none	Symptom duration was correlated with radiographic progression ($p < 0.005$)
NR	Sustained remission DAS-28 < 1.6 after 5 years FU	Sex, TJC, treatment and many other baseline variables	Symptom duration < 6 months OR 3.15 (95% CI 1.03; 10.0, $p=0.046$)
NR	Radiographic progression defined by yearly increase of Larsen score ≥ 5.8	Age, sex, RF, HLA-DR4 SE, erosions, ESR and CRP	Symptom duration (>6 months) on severe radiographic progression OR=1.05, p -value=0.826
Onset of swollen joints reported by the patient	Radiographic progression after 1 year of follow-up (by delta SHS units)	DAS-28, RF, involvement > 3 joint groups, CRP, ACPA, treatment (propensity score)	Symptom duration < 3 months versus > 3 months: Estimated marginal means 0.8 units (SEM 0.37) versus 1.7 units (SEM 0.19), $p=0.033$.
NR	ACR remission at 2 years FU (fatigue and duration criteria excluded)	age, sex, SE, RF and number of other ACR1987 criteria fulfilled	Estimated proportion of remission in: - the single treatment group for symptom duration 0-4 months ~36% vs. > 4 months ~10%, $P=0.010$ - the combination treatment group symptom duration 0-4 months ~43% vs. > 4 months ~40%, $p=0.83$

Table 3. Continued

First author, year publication ^{ref}	Study design	●Population ● Location	N	Age, years <i>mean±SD</i> or <i>median (IQR)</i>	Female (%)	Symptom duration (months) <i>mean±SD</i> or <i>median(IQR)</i>
Nell, 2004 ²⁴	OC	1987+ RA, Austria	40	54 (25-80)	75	VERA 3 (2-4) LERA 12 (9-30)
Pascual-Ramos, 2009 ²⁵	OC	1987+ RA, Mexico	72	NR	NR	Erosive 4.9±2.9 And non-erosive dise 6.5±1.8
Sanmarti, 2003 ²⁷	OC	1987+ RA, Spain	60	52.2±15.7	78.3	9.5±6.5
Soderlin, 2011 ²⁸	OC	1987+ RA, Sweden (BARFOT)	180	58±15	68	5.8±12
Van der Linden, 2010 ²¹	OC	1987+ RA, Netherlands (EAC Leiden)	598	56.8±15.8	67.7	4.2 (2.4-8.1)
van der Woude, 2009 ⁹	OC	1987+ RA, UK (ERAS)	895	52±13	69	8.3±6
Van der Woude, 2012 ¹¹	RCT	1987+ RA, Netherlands (BeSt Trial)	508	54±13.7	68	5.3 (3.2-12.2)
Weng, 2010 ³⁰	OC	1987+ RA, USA and Mexico	233	50±13	77	5.7 (0.6-15.9)

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; DAS, Disease activity score; EAC, early arthritis clinic; ERAS, Early Rheumatoid Arthritis Study group; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FU, follow-up; HAQ, Health assessment questionnaire; HDA, high disease activity; LERA, late early rheumatoid arthritis;

Definition symptom onset	Outcome of relevance	Adjustment factors	Relevant results
NR	● Radiographic progression (delta Larsen score) ● DAS-28 improvement/remission (<2.6) ● HAQ improvement All outcomes after 3 years FU	None	● VERA patients had an increase of 3.6±6.5 units compared to an increase of 14.7±9.9 Larson units in LERA, $p<0.05$. (mean±SD) ● DAS <2.6 was obtained in 50% of VERA and 15% of the LERA patients ($p<0.05$). ● Change in HAQ score: VERA -0.7±0.7 (-78%), LERA -0.4±0.6 (-44%), $p<0.05$.
NR	Joint damage (erosive disease yes/no) at 1 year FU	None	Symptom duration (months) on erosive disease OR 1.16 (95% CI 0.97-1.4), $p=0.11$
NR	Radiographic progression at 1 year (Larson Score; progression defined as >2 units)	All baseline variables with $P<0.15$ in univariable analysis	Multivariable; symptom duration n(months) OR 1.15 (95% CI 1.03-1.28), $p<0.05$
NR	● 1 year good-EULAR response ● mean Δ HAQ change at 1 year	Age, sex, smoking, RF, HAQ, treatment, DAS-28	● Patients with a good/moderate EULAR response in case of symptom duration <12 wks 81%, 13-24 weeks 82% and 25-52 wks 76%, $p=0.03$. ● HAQ and symptom duration: correlation coefficient=0.12, $p=0.0001$
Onset of joint symptom reported by the patient	SHS progression over 6 years based on yearly made X-rays	Age, sex, inclusion-period (as proxy for treatment strategy)	Patients with symptom duration >12 weeks have a 1.34-fold higher progression ratio than patients with symptom duration <12 wks, over a period of 6 years ($p=0.001$).
NR	DMARD-free sustained remission	All baseline variables with $P<0.10$ univariable analysis	● Multivariable; Symptom duration on achieving DMARD-free remission, HR 0.94 (0.89-0.99), $p=0.029$.
NR	DMARD-free Sustained remission	Age, sex, DAS-44, ACPA	● Symptom duration on achieving DMARD-free sustained remission, OR 0.99 (95% CI 0.98, 1.00), $p=0.099$.
First appearance of joint symptoms leading to diagnosis of RA	● Annual progression rate by total Sharp over 2 years. ● DAS-44<1.6 over 2 years ● Change in HAQ over 2 years	None	'Early' patients (<150 days symptom duration) versus 'late' patients (>150 days symptom duration at baseline) ● Total Sharp, units per year 3.13±6.49 versus 1.69±4.43, $p=0.3$ ● 2 yr DAS 44< 1.6: 25% vs 25%, NS (p NR) ● Delta HAQ -0.61±0.57 versus -0.42±0.68 NS (p NR)

NS, Not statistically significant Trend: almost statistically significant; NR, not reported; OC, observational cohort; RCT, randomised controlled trial; RF, rheumatoid factor; SHS, Sharp-van der Heijde Score; TJC, tender joint count; VERA, very early rheumatoid arthritis.

DISCUSSION

At present, early identification of RA and early start of DMARD therapy have become important targets in the treatment of RA. Despite the current focus on the early phases of the disease, we questioned whether very early intervention with the disease is indeed more effective with regard to modifying the disease outcome, or that positive findings are overemphasised in current thinking. We performed a systematic literature review to address this question. We identified strong evidence for an association between shorter symptom duration and less severe radiographic joint damage in patients with early RA. Furthermore a meta-analysis on the outcome DMARD-free sustained remission demonstrated that prolonged symptom duration is independently associated with a decreased chance on this remission; in case of symptom duration of 12 weeks (the suggested period of the window of opportunity) at treatment initiation the HR on remission was 0.88. At present, a DMARD-free sustained remission is the closest available proxy of 'cure' of RA; this outcome is presumably most suited to evaluate whether an early period in which the disease is most susceptible to treatment exists. Current data supports the presence of a 'window of opportunity' effect.

This study, however, has limitations. First, this study addressed possible citation bias but not publication bias. Another major limitation is that heterogeneity in the definition of symptom onset, and consequently differences in time periods studied, prohibited us from performing a meta-analysis on all 18 selected studies. There were also large differences in study designs and study outcomes. A qualitative review was performed instead. Strengths of the current approach are that two independent readers scored all the articles, that criteria for evaluation of the quality were in line with those of previous studies,^{6,7} and that predefined and stringent qualitative levels of evidence⁸ were used to summarise the data (strong evidence was defined as $\geq 75\%$ of the HQ studies reporting an effect in the same direction). With this approach, we tried to optimise the accuracy of this systematic qualitative literature review. An important drawback of a systematic literature review is that by simply counting the number of positive and negative studies, the sample sizes and power of the individual studies was ignored. Hence, studies with a tendency in the data that were underpowered to obtain a significant result were considered equally negative as studies with true negative findings. With a qualitative systematic literature review, the data can also not be presented in a funnel plot because an overall effect size cannot be generated.

The fact that a systematic literature review and meta-analysis may result in a slightly different answer is illustrated here with the data on achieving DMARD-free sustained remission. Three HQ studies were found. Two studies^{9, 10} were significant; the third¹¹ was not significant but showed a tendency towards an effect of symptom duration on

remission (HR 0.99 (95% CI 0.98 to 1.00), $p=0.099$ in multivariable analysis). Given the predefined levels of evidence (table 1), two out of three positive studies would result in the conclusion that there is a moderate level of evidence for an association between symptom duration and DMARD-free sustained remission. However, in the meta-analyses there was a consistent and independent association between symptom duration and DMARD-free sustained remission.

Another difficulty when interpreting the results of the present study is the fact that different studies had included different adjustment factors in the analyses (see table 3). Not adjusting for patient and disease characteristics and treatment effects may potentially result in findings that are not driven by symptom duration but by the association of these factors with disease outcome. In 12 of the total 18 studies, 11 of the 14 positive studies, and seven of the 10 HQ-studies adjustments for patient and disease characteristics were applied, though not exactly the same factors. Four of the 10 HQ studies applied adjustments for differences in treatment. Furthermore, Mottönen et al²³ observed a significant association in the single therapy group but not in the combination therapy group. In the meta-analyses on DMARD-free sustained remission, the association between symptom duration and disease outcome was independent of patient characteristics (age, gender), disease characteristics (ESR as marker of inflammation and RF as marker of autoantibody positivity) and the applied treatment strategies. The drugs used in the studies that applied adjustments for treatment were conventional DMARDs^{10, 17, 21, 23, 28} and/or biologics.^{14, 22}

Some studies evaluated symptom duration and had divided patients in groups of, for example, symptoms for >5 and <5 months,^{17, 18, 30} meaning that patients in both groups had passed the period of the 'window of opportunity' that was previously defined as the first 12 weeks.

Our formulated inclusion and exclusion criteria resulted in a selection of studied articles. A large proportion of screened articles was not included in this review because of not fulfilling the inclusion criteria. Some studies investigated patients with early (poly) arthritis, but not specifically RA, and were, therefore, not included.^{31, 32} Several of the excluded studies did show that patients with RA with shorter symptom duration had a better outcome. For example, Green et al³³ reported on disease persistency after 6 months in inflammatory patients with polyarthritis treated with corticosteroids, and observed that patients with symptom duration <12 weeks more often achieved remission. This study had 6 months of follow-up and did not fulfil our inclusion criteria of ≥1 year of follow-up. The latter was also the case for the study of Saevardottir et al³⁴ on the SWEFOT trial, observing that prolonged symptom duration was associated with a lower chance on achieving a good EULAR response after 3–4 months methotrexate

treatment. Several papers were excluded because the period between diagnosis and treatment onset was studied but not the period between symptom duration and treatment onset,^{35–39} or because the patients studied had symptoms >2 years.^{40–42} We acknowledge that the maximum of 2 years symptom duration as definition of early RA is arbitrary, though given our study question, we decided to focus on early RA.

In conclusion, the present systematic literature review observed that in early patients with RA who were mostly treated with conventional DMARDs, there is strong evidence that prolonged symptom duration is associated with severe joint damage progression. Additionally, a meta-analysis on achieving DMARD-free sustained remission observed an independent association for symptom duration. These results, therefore, support the notion of the presence of a ‘window of opportunity’. The details of the time frame (evaluation of when the window ‘opens’ and ‘closes’) are left to be explored in the near future. Many studies using uniform definitions of symptom onset are required to this end; definitions for standardised durations were recently proposed.⁵

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SUPPLEMENTARY DATA

Supplementary table 1. Results of the study quality assessment scores in alphabetical order of first Author. (1: present, 0: absent or no information) Scores solved by discussion are in italics.

Author, year (Ref)	Criteria															Total score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Bosello, 2011(12)	0	1	0	0	1	N/A	0	0	1	0	1	1	1	1	0	7/14=50%
Dixey, 2004 (13)	1	1	1	1	1	N/A	0	0	1	0	0	1	1	1	0	9/14=64%
De Rooy, 2010 (9)	1	1	1	1	1	N/A	0	1	1	1	1	1	1	1	0	12/14=86%
Gremese, 2012 (14)	1	1	1	0	1	N/A	0	0	1	N/A	0	1	1	1	1	9/13=69%
Hodkinson, 2012 (15)	1	1	0	0	1	N/A	0	0	1	N/A	0	1	1	1	0	7/13=54%
Jansen, 2001 (16)	1	1	1	0	1	N/A	1	1	1	1	0	1	1	1	0	11/14=79%
Jayakumar, 2012 (17)	1	1	1	1	1	N/A	0	0	1	N/A	1	1	1	1	1	11/13=85%
Kaufmann, 2003 (18)	0	1	0	1	0	N/A	0	0	1	1	0	0	1	1	0	6/14=43%
Lukas, 2011 (22)	1	1	1	0	1	N/A	1	1	1	1	1	0	1	1	1	12/14=86%
Mötönen, 2002 (23)	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	13/15=87%
Nell, 2004 (24)	1	1	1	1	1	N/A	1	0	1	1	1	1	1	1	0	12/14=86%
Pascual-Ramos, 2009 (25)	0	1	1	0	1	N/A	0	0	0	0	0	1	1	1	0	6/14=43%
Sanmarti, 2003 (27)	1	1	0	0	1	N/A	0	0	1	0	1	1	1	1	0	8/14=57%
Soderlin, 2011 (28)	1	1	1	0	1	N/A	0	0	1	N/A	0	1	1	1	1	9/13=69%
Van der Linden, 2010 (21)	1	1	1	1	1	N/A	1	1	1	1	1	1	1	1	1	14/14=100%
van der Woude, 2009 (9)	1	1	1	1	1	N/A	1	0	1	1	1	1	1	1	0	12/14=86%
Van der Woude, 2012 (11)	1	1	1	1	1	1	0	0	1	N/A	1	1	1	1	0	11/14=79%
Weng, 2010(30)	1	1	1	0	1	N/A	0	1	1	1	1	1	1	1	0	12/14=86%

Supplemental file 2. Methodological quality assessment form and search criteria per database.

OC: observation cohort study. RCT: randomized-controlled trial studies:

Paper:		
Reader:		
Item	Criteria	Applicable for:
1	<u>Definition of study population</u> Sufficient description of characteristics of study groups <i>A '1' is given when a paper describes at least setting and time period of the study, ages of patients (and its range) and man:woman ratio</i>	OC /RCT
2	<u>Definition of diagnosis</u> RA diagnosis was according to the 1987 ACR or 2010 ACR/EULAR classification criteria .	OC /RCT
3	<u>Selection bias</u> Clear description of selection of study subjects. <i>When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.</i>	OC/ RCT
4	<u>Follow-up</u> Follow up time $\geq$ 2 years for RA patients. <i>More than 2 years was seen as an acceptable follow up duration to assess RA outcome (such as sustained DMARD-free or radiographic progression).</i>	OC/ RCT
5	Organization of follow-up <i>A '1' was given if there was a structured follow-up applied. So not only on patients request.</i>	OC/ RCT
6	Participation rate $\geq$ 80% for study groups <i>80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.</i>	RCT
7	No differences in lost to follow-up (in both groups). <i>Including (quantative and qualitative) information on completers and non-completers</i>	OC/RCT
8	<u>Assessment of symptom duration</u> <i>Symptom onset is clearly defined as symptoms such as pain or swelling reported by the patient or swelling observed by the physician/rheumatologist.</i>	OC/ RCT

Item	Criteria	Applicable for:
9	<u>Assessment of the outcome: valid measures of disease activity , joint-damage or remission</u> <i>For disease activity; DAS-28, DAS 44 or SDAI. For (radiologic) joint-damage measures; SHS, LARSON score or RAMRIS. For Remission; DMARD-free remission defined by the rheumatologist and the DMARD-free remission period should be given</i>	OC/ RCT
10	Radiologic outcome assessment was blinded to clinical data (at least treatment and symptom duration) <i>A '1' is given if the observers were blinded to the intervention and symptom duration when for example scoring the radiographs.</i>	OC/ RCT
11	Outcome measure was assessed reproducibly <i>For example A '1' is given if an ICC/Kappa is provided concerning radiographic outcomes. Or if internal or external validation is provided in relation to prediction rules. In case of remission; if DMARD-free period is given or if (DAS)remission was still present in the follow-up visit at the rheumatologist.</i>	OC/ RCT
12	<u>Analysis and Data Presentation</u> Frequencies of symptom duration was given	OC/ RCT
13	Frequencies of important outcomes studied were given	OC/ RCT
14	Appropriate analysis techniques with estimates were used	OC/ /RCT
15	Adjusted for at least age and gender and treatment strategy/arm.	OC/ RCT
	TOTAL QUALITY RATE	With radiographic outcome; OC .../14 RCT .../15 Without radiographic outcome; OC .../13 RCT .../14

Overview of the search per database.

Total d.d. 11-5-2012: 836 references, extracted from the following databases:

- MEDLINE (OVID): 452
- PubMed: 164, of which 14 unique
- Embase: 606 (of which 164 meeting abstracts): 297 unique
- Web of Science: 278, of which 54 unique
- COCHRANE: 18, of which 1 unique
- CINAHL: 46, of which 13 unique
- Academic Search Premier: 51, of which 5 unique
- ScienceDirect: 10, of which 0 unique

PubMed

(rheumatoid arthritis OR "rheumatoid arthritis" OR "Arthritis, Rheumatoid"[Mesh:noexp] OR rheumatoid OR arthritis[tiab] OR arthritic) AND ("symptom duration" OR "complaint duration" OR ((symptom*[ti] OR complaint*[ti]) AND duration*[ti]) OR ((symptom*[ti] OR complaint*[ti]) AND "Time Factors"[mesh]))

MEDLINE (OVID-version)

(rheumatoid arthritis.mp OR "rheumatoid arthritis".mp OR Arthritis, Rheumatoid/ OR rheumatoid.mp OR arthritis.ti,ab OR arthritic.mp) AND ("symptom duration".mp OR "complaint duration".mp OR ((symptom*.ti OR complaint*.ti) AND duration*.ti) OR ((symptom*.ti OR complaint*.ti) AND exp Time Factors/) OR (symptom* **ADJ6** duration*).mp OR (complaint* **ADJ6** duration*).mp)

Embase (OVID-version)

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Web of Science

(TS=(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid) OR TI=arthriti*) AND (TS=("symptom duration" OR "complaint duration") OR TI=((symptom* OR complaint*) AND duration*) OR TS=((symptom* **NEAR/5** duration*) OR (complaint* **NEAR/5** duration*)))

Cochrane Library

(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint")

CINAHL

(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint")

Academic Search Premier

(rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint")

A. ScienceDirect

TITLE-ABSTR-KEY((rheumatoid arthritis OR "rheumatoid arthritis" OR rheumatoid OR arthriti*) AND ("symptom duration" OR "complaint duration" OR "duration of symptoms" OR "duration of symptom" OR "duration of complaints" OR "duration of complaint"))



CHAPTER 5

Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden Early Arthritis Clinic and ESPOIR cohorts

Jessica A.B van Nies, Roula Tsonaka, Cécile Gaujoux-Viala,
Bruno Fautrel, Annette H.M van der Helm-van Mil

ABSTRACT

Background

A prolonged symptom or disease duration at treatment initiation is associated with unfavourable outcomes in rheumatoid arthritis (RA). It is unknown whether this relation is linear, referring to a common ‘the-earlier-the-better principle’, or whether a transient time frame in which the disease is more susceptible to treatment exists, referring to a ‘window of opportunity’. To elucidate this, we evaluated the shape of the associations of symptom duration with persistence of RA.

Methods

Patients with 1987 RA treated with disease modifying antirheumatic drugs (DMARDs) in the Leiden Early Arthritis Clinic (EAC, n=738) and Evaluation et Suivi de POLyarthrites Indifférenciées Récentes (ESPOIR) (n=533) were studied. Cox proportional hazards regression models using natural cubic splines were performed; the log-HR on DMARD-free sustained remission (the opposite of RA persistence) during 5-year follow-up was plotted against symptom duration. Discrimination was measured using time-dependent receiver operator characteristic curves. Subanalyses were performed stratified for the DMARDs used (methotrexate or other conventional DMARDs) and for anticitrullinated peptide antibody (ACPA).

Results

11.5% (85/738) and 5.4% (29/533) of EAC and ESPOIR RA patients achieved DMARD-free sustained remission. In both cohorts and all analyses, the curves depicting the log-HRs on remission in relation to symptom duration were not linear. The symptom duration with optimal discriminative ability was 14.9 weeks (95% CI 12.3 to 16.0; area under the curve (AUC) 0.61) in the EAC and 19.1 weeks (95% CI 12.3 to 28.0; AUC 0.59) in ESPOIR. For ACPA-positive RA, this was 11.4 weeks (95% CI 7.7 to 19.0; AUC 0.56) and for ACPA-negative RA 15.0 weeks (95% CI 9.7 to 20.3; AUC 0.56).

Conclusions

The association between symptom duration and RA persistence is not linear, suggesting the presence of a confined period in which RA is more susceptible to treatment

INTRODUCTION

Many studies within rheumatoid arthritis (RA) have shown that a prolonged disease duration or symptom duration at treatment initiation is unfavourable. It is associated with more severe radiographic joint destruction, a higher need of orthopaedic surgery, a higher mortality rate and a lower chance to achieve disease modifying antirheumatic drug (DMARD)-free sustained remission.^{1–5} The shape of the association between the risk on an unfavourable disease course and the symptom duration at treatment start, however, is not known.

Two profiles may possibly explain the mentioned observations. First, a transient window during which outcomes can be more effectively modulated by therapy may be present. This refers to the ‘window of opportunity’ hypothesis and implies that whenever certain master-switches (crucial processes) have turned on or off the responsiveness to treatment is reduced. A small observational study aiming to evaluate the optimal time point of DMARD introduction showed that patients with a median disease duration of 3 months achieved lower disease activity score (DAS) scores and less radiographic damage than patients with a median disease duration of 12 months at first DMARD initiation.⁶ Two larger cohort studies observed that patients with symptom durations ≤ 12 weeks developed less joint destruction^{2, 7} and achieved DMARD-free sustained remission more often² than patients with symptom durations > 12 weeks. Although these observations may support the presence of a temporary window of opportunity, it has never been shown that after a certain symptom duration the effect of initiated treatment starts to diminish.

The alternative explanation of the association between the time till intervention and the outcome of RA relates to the ‘the-earlier-the-better’ principle that is universally valid in the context of the initiation of treatment for many diseases.⁸ With regard to RA, it can be presumed that the total inflammatory load at the time of treatment onset is related to the disease outcome. Since the total inflammatory load is the product of the severity and the duration of inflammation, a linear association between the symptom duration and the outcome of RA can be hypothesised. Then the effect of early intervention is not confined to a very early window. In 1995, a randomised clinical trial in recent onset RA patients was published;⁹ patients started treatment with auranofin directly or after a delay of 8 months. The early treatment group had better outcomes and this effect was maintained after 5-year follow-up. A similar trial was performed using hydroxychloroquine and similar findings were obtained.¹⁰ The timing of intervention in most patients in both arms of both studies was considerably later than < 3 months of symptom onset and still early treatment initiation was beneficial. Therefore, the advantageous effect of early treatment might not be restricted to a very early and temporary time frame.

Furthermore, the difference in outcome observed in cohort studies comparing patients with < or ≥ 3 months symptoms^{2,6,7} can also be found in case symptom duration is linearly associated with the outcome. Moreover, a recent study evaluating symptom duration on a continuous scale using regular cox regression, thus assuming that every increase in symptom duration is equally deleterious and hence assuming linearity, also observed significant associations for symptom duration.¹

Altogether, these studies do not allow differentiating between a linear effect and a window of opportunity. This study, therefore, set out to elucidate the shape of the relationship between the symptom duration at treatment initiation and the risk on a persistent course of RA. Persistence was defined as the absence of DMARD-free sustained remission; of possible disease outcomes, this outcome is the closest available proxy of cure of RA. We studied RA patients treated with conventional DMARDs that were included in two early arthritis cohorts. Symptom duration was kept continuous. The cox regression model applied did not assume a particular form of the relationship and the model that fitted the data best was presented.

METHODS

Patients

RA patients were classified according to the 1987 American College of Rheumatology (ACR) criteria and derived from the Leiden Early Arthritis Clinic (EAC) and the French Evaluation et Suivi de POLyarthrites Indifférenciées Récentes (ESPOIR) cohort.

The EAC is an inception cohort that started in 1993 and has been described previously.¹¹ Inclusion took place when arthritis was confirmed by physical examination and symptom duration was <2 years. At study entry, patients used no DMARDs or glucocorticoids. For the current research question, RA patients who were promptly treated with DMARD therapy after inclusion were selected. Between 1996 and 2011, this concerned 802 RA patients; 738 of these had information on dates of symptom onset and were studied. The 63 patients without this information and the 738 studied patients did not differ in baseline characteristics (data not shown). Information on the initiated DMARDs is presented in table 1. None of the patients included in the years 1993–1995 were evaluated, as initial therapy concerned nonsteroidal anti-inflammatory drugs (NSAIDs) but not DMARDs.

ESPOIR is a longitudinal cohort including patients with RA or a suspicion to develop RA from 14 rheumatology centres in France.¹² Patients had to be aged 18–70 years and have ≥ 2 swollen joints for >6 weeks and <6 months. Out of the 813 RA patients included between 2002 and 2005, 533 were treated with DMARDs and studied here.

In both cohorts, patients filled in questionnaires at baseline, joint counts were performed and laboratory evaluations done. The yearly follow-up visits included clinical, laboratory and radiographic evaluations.

Symptom onset in EAC and ESPOIR was delineated identically and defined as the first musculoskeletal symptom (either being pain or swelling) relevant to the current presentation.¹³ The symptom duration was defined as the duration between this patient reported symptom onset and inclusion and was determined by subtraction of dates, expressed in weeks.

Outcome

The main outcome was DMARD-free sustained remission; this is the opposite of disease persistence and was defined as the sustained absence of arthritis (absence of swelling by physical examination) after discontinuation of DMARD therapy, including biologics and glucocorticoids (systemic and intra-articular), for the entire period of follow-up (at least 1 year, up to 5 years). In the EAC, all medical files were explored until 5 April 2012. In ESPOIR, all structured visits in the database were reviewed.

Subanalyses

Because it is not known whether treatment with different DMARDs differently affects the associations between symptom duration and the log-hazard on DMARD-free sustained remission, analyses were stratified for the use of methotrexate (the current first-line therapy) and other conventional DMARDs. Further, since the biological pathway of development of anticitrullinated peptide antibody (ACPA)-positive and ACPA-negative RA is different, and ACPA-positive RA patients achieve DMARD-free sustained remission less often than ACPA-negative patients, it is possible that the associations between symptom duration and the log-hazard on DMARD-free sustained remission differ for ACPA-positive and ACPA-negative RA. Analyses were therefore also stratified for ACPA. Finally, we assessed the shape of the association of symptom duration with other outcomes. Although the outcome DMARD-free sustained remission (and its counterpart RA persistence) most closely fits with the window-of-opportunity hypothesis, DMARD-free sustained remission is achieved infrequently and for clinical daily practice other outcomes are relevant as well. The first alternative outcome was radiological joint destruction. The time between baseline and achieving a certain progression in joint destruction was assessed; two cut-offs were chosen rather arbitrarily and applied in the EAC in 485 RA patients who were included between 1996 and 2006 with scored radiographs (by one experienced reader with an intraclass observer correlation coefficients of 0.91): a delta increase of 5 and 15 Sharp- van der Heijde Score (SHS) points. The other outcome was time till sustained remission irrespective of DMARD therapy. Sustained remission was derived from the ESPOIR database and defined as

the sustained absence of swollen joints count ($=0$) for at least 1 year irrespective of DMARD therapy and subsequently absence of swollen joints for the entire follow-up (the maximal follow-up was 5 years).

Statistics

Cox proportional hazards regression models using natural cubic splines were used to model the effect of the symptom duration on time to DMARD-free sustained remission.^{14, 15} The use of cubic spline functions allows investigation of the shape of the effect; in contrast to regular cox regression, it does not assume linearity. HRs generally have a non-linear relationship with covariates; this is not the case for log-HRs. Therefore, the log-HR for increasing symptom duration values was plotted based on the model that fitted the data best. Time-dependent receiver operator characteristic (ROC) curves were used to evaluate the discriminative capability of symptom duration; the optimal cut-off value for symptom duration was determined using Youden's index (optimal sensitivity+specificity-1). All analyses were done in the statistical software R;¹⁶ in particular, the R-packages survival and survival ROC were used.^{17, 18}

RESULTS

Symptom duration in relation to log-HR on DMARD-free sustained remission

Characteristics of the RA patients are presented in table 1. The median symptom duration at inclusion was 18.7 weeks (IQR 9.3–35.3) in the EAC and 21.3 weeks (IQR 13.4–33.5) in ESPOIR. In all, 67% and 76% of the patients started treatment with methotrexate; the majority of the remaining patients were treated with sulfasalazine or hydroxychloroquine. During 5-year follow-up, DMARD-free sustained remission was obtained in 11.5% (85/738) and 5.4% (29/533) in the EAC and ESPOIR, respectively.

First, the log-HR on DMARD-free sustained remission (the opposite of RA persistence) during 5-year follow-up was plotted against the symptom duration in the EAC (figure 1A). The log-HRs were negative, indicating a decreased chance on DMARD-free sustained remission, which equals an increased chance on disease persistence. The curve was not linear and the steepness changed at a point in time (figure 1A). For RA patients included in ESPOIR, a non-linear profile was also observed; after an almost linear start, the curve flattened towards an almost horizontal line (figure 1B). In order to comprehend the HRs more easily, the profile plotting the HR on DMARD-free sustained remission against symptom duration is presented as well (figure 1C, D).

Time integrated ROC curves

To evaluate the discriminative capability of symptom duration, time-dependent ROC curves were constructed with DMARD-free sustained remission as outcome. In both

cohorts, the areas under the ROC curves were rather low: 0.61 in EAC and 0.59 in ESPOIR (figure 1E, F). These low values reduced the certainty with which the optimum of the ROC curve can be identified. The symptom duration with the best discrimination of patients with DMARD-free sustained remission from patients with persistent disease was 14.9 weeks (95% CI 12.3 to 16.0) in the EAC. Similarly, the symptom duration with best combination of sensitivity and specificity was 19.1 weeks (95% CI 12.3 to 28.0) in ESPOIR.

Table 1. Characteristics of the RA patients studied

	EAC n=738	ESPOIR n=533
Age, years, mean±SD	57.2±15.7	48.8±11.9
Gender, n(%)	484 (65.6)	404 (75.8)
Symptom duration at first visit, weeks, median(IQR)	18.7 (9.3-35.3)	21.3 (13.4-33.5)
SJC, median(IQR)	8.0 (4.0-13.5)	7.0 (4.0-12.0)
RF positive, n (%)	430 (58.7)	309 (58.0)
ACPA positive, n (%)	370 (52.4)	268 (50.3)
ESR, mm/h, median(IQR)	31.0 (17.0-50.0)	24.0 (12.0-44.5)
Initiated DMARD, n (%)		
Methotrexate	563 (76.3)	357 (67.0)
Sulfasalazine	100 (13.6)	62 (11.6)
Hydroxychloroquine	63 (8.5)	64 (12.0)
Leflunomide	-	30 (5.6)
Other DMARDs*	12 (1.6)	20 (3.8)

Missing data were as follows: in the EAC, SJC n=17, RF n=5, ACPA n=37, ESR n=6; in ESPOIR, ESR n=5.

*Including glucocorticoids.

ACPA, anticitrullinated peptide antibody; DMARD, disease modifying antirheumatic

drug; EAC, Early Arthritis Clinic; ESPOIR, Evaluation et Suivi de POLyarthrites

Indifférenciées Récentes; ESR, erythrocyte sedimentation rate; RA, rheumatoid

arthritis; RF, rheumatoid factor; SJC, swollen joint count

Subanalyses on initiated DMARD

To evaluate the influence of treatment on the relation between the log-hazard on DMARD-free sustained remission and symptom duration, analyses on 5-year follow-up data were repeated for patients treated with methotrexate and patients treated with other conventional DMARDs separately. In both groups of patients in both cohorts, the profiles of the association between symptom duration and DMARD-free sustained remission were not linear (figure 2). The optimum symptom duration (determined using ROCs) in the EAC was 14.4 weeks (95% CI 10.3 to 46.3; area under the curve (AUC) 0.61) for methotrexate users and 18.3 weeks (95% CI 10.7 to 39.9; AUC 0.60) for patients treated with other DMARDs. In ESPOIR, this was 19.1 weeks (95% CI 7.0 to 168.3; AUC

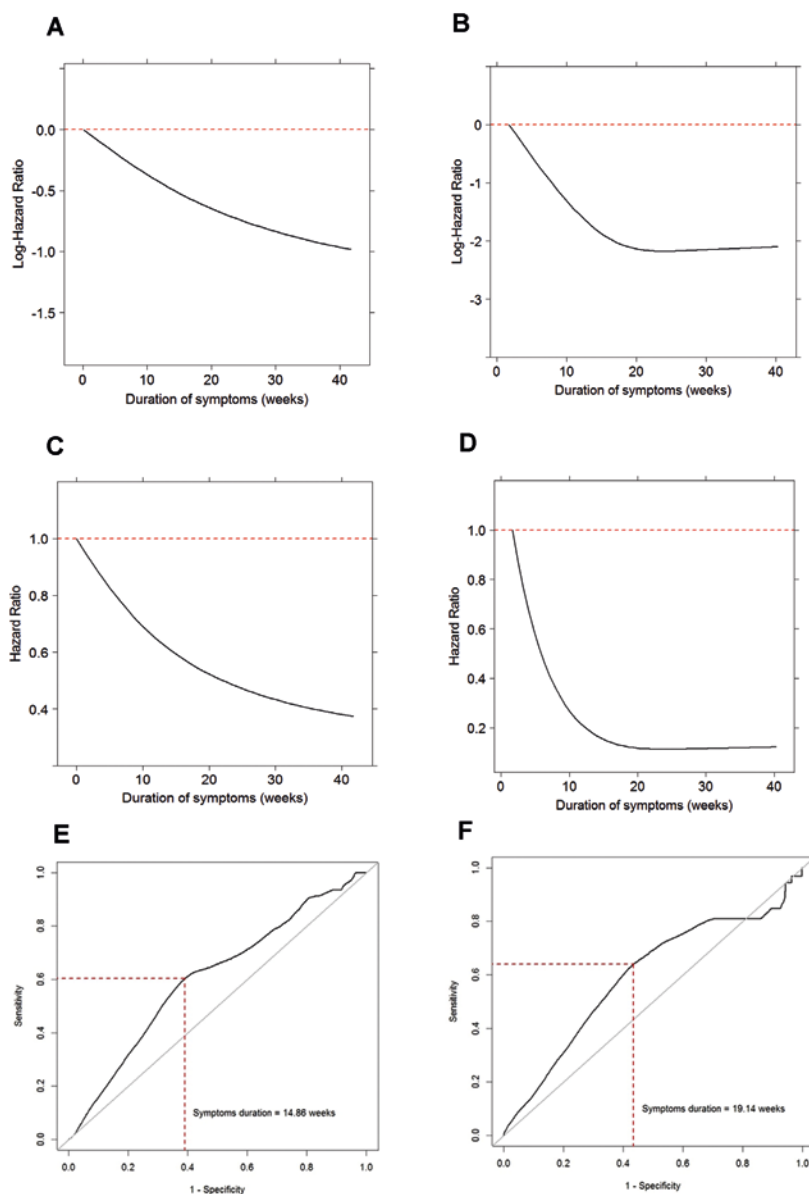


Figure 1. Symptom duration in relation to the log-hazard (A and B) and HR (C and D) on DMARD-free sustained remission in rheumatoid arthritis patients in the EAC (A and C) and Evaluation et Suivi de POLyarthrites Indifférenciées Récentes (ESPOIR) (B and D) and the HR in the EAC (C) and ESPOIR (D) during 5-year follow-up. Time-dependent receiver operator characteristic curves of symptom duration with DMARD-free sustained remission as outcome in the EAC (E) and ESPOIR (F). (E and F) The symptom duration with the best discriminative ability was determined using Youden's index. DMARD, disease modifying antirheumatic drug; EAC, Early Arthritis Clinic.

Subanalyses on ACPA

Because ACPA-positive and ACPA-negative RA differ in the processes underlying disease development and disease outcomes, analyses were also stratified for ACPA. In the EAC, $n=67$ (19.9%) of ACPA-negative RA patients achieved DMARD-free sustained remission during 5 years and $n=13$ (3.5%) of ACPA-positive RA patients. Also here, the curves plotting the log-HRs on DMARD-free sustained remission against symptom duration were not linear (data not shown). The optimum symptom duration was 11.4 weeks (95% CI 7.7 to 79.0; AUC 0.56) for ACPA-positive RA patients and 15.0 weeks (95% CI 9.7 to 48.7; AUC 0.56, see online supplementary figure S2) for ACPA-negative RA patients. In ESPOIR, only $n=3$ (1.1%) ACPA-positive patients obtained DMARD-free sustained remission, prohibiting stratified analyses in this cohort.

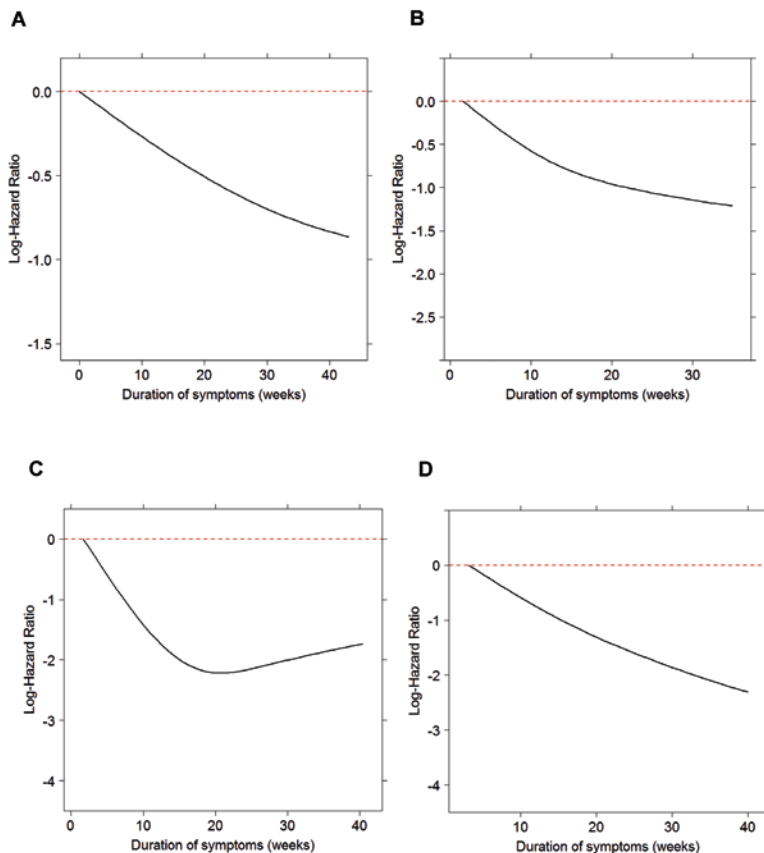


Figure 2. Symptom duration in relation to the log-hazard on DMARD-free sustained remission during 5-year follow-up in rheumatoid arthritis patients treated with methotrexate (A and C) or other conventional DMARDs (B, D) in the Leiden EAC (A and B) and Evaluation et Suivi de POLyarthrites Indifférenciées Récentes (ESPOIR) (C and D). DMARD, disease modifying antirheumatic drug; EAC, Early Arthritis Clinic.

Subanalyses using other outcomes

Although the outcome DMARD-free remission fits most closely to the window of opportunity hypothesis, the shape of the association between symptom duration and other outcomes was evaluated as well. First, the time till a certain level of radiographic progression was achieved (an increase of 5 and 15 SHS points from baseline onwards, respectively) was assessed. These outcomes were obtained in 294 (61%) and 148 (31%) of the RA patients after a median follow-up of 3 (IQR 1–5) and 5 (4–5) years, respectively. The cox regression analyses using these outcomes also showed non-linear curves (figure 3A, B). Sustained remission was studied as well, although this outcome might reflect an individual patient's susceptibility to certain treatments in addition to changes in underlying disease mechanisms. Sustained remission was obtained in 212 (40%) patients. The profile was not linear here also; after an almost linear start, the steepness of the curve changed substantially at a certain point in time (figure 3C).

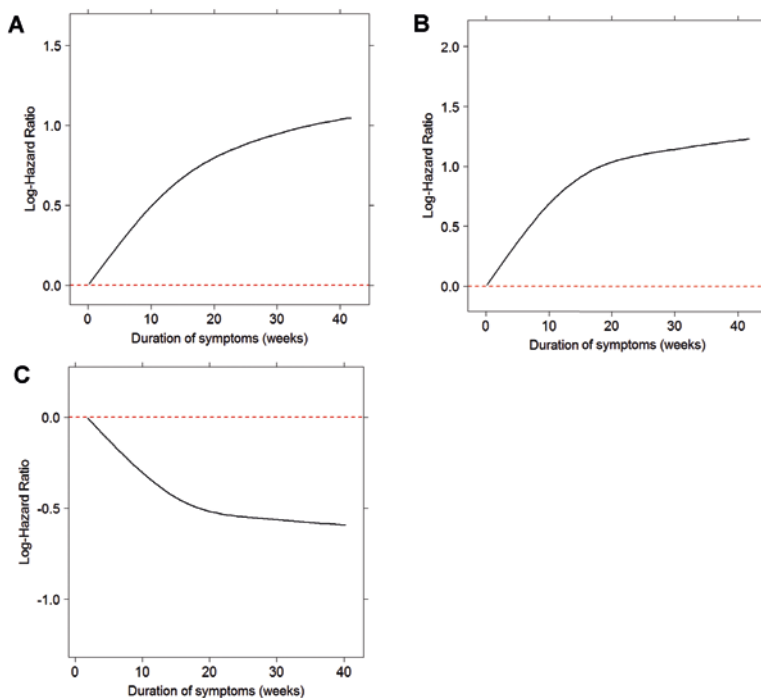


Figure 3. Symptom duration in relation to the log-hazard on an increase in SHS scores of 5 (A) and 15 (B) from inclusion onwards in the Leiden EAC and the log-hazard on sustained remission irrespective of DMARD therapy (C) in Evaluation et Suivi de POLyarthrites Indifférenciées Récentes (ESPOIR), all assessed during 5-year follow-up in rheumatoid arthritis patients. Achievement of an increase of SHS of 5 and 15 points is an unfavourable outcome and therefore the log-HRs were above 0. Sustained remission, in contrast, is a favourable outcome and therefore the HRs were below 0. DMARD, disease modifying antirheumatic drug; EAC, Early Arthritis Clinic.

DISCUSSION

During the last two decades, many studies have observed that the time to intervention is associated with the efficacy of this intervention. A window of opportunity for therapeutic interventions, a time frame within which there is a disproportionate response to therapy resulting in long-term sustained benefits, is proposed to be present. The concept of this window was first hypothesised in the early 1990s.¹⁹ The studies available on this subject have either compared 'early' versus 'late' or analysed the duration as a continuous variable presuming that every increase in units of time was equally deleterious.^{1-3, 6, 20} Although both type of studies reported inverse associations between time to intervention and disease outcomes, the issue is still open whether there truly is an early period when RA patients respond to intervention in a fundamentally different way than they would if therapy was delayed.²¹ This caveat prompted us to study the shape of the association between log-HRs on achieving DMARD-free sustained remission (absence of RA persistence) and symptom duration in RA patients treated with conventional DMARDs. The patients studied were included in ESPOIR and the Leiden EAC; previous studies on these cohorts have already shown that a prolonged symptom association was statistically significantly associated with an unfavourable course of RA.^{2,7} We here applied methodology that allowed elucidating the shape of the relationship. We observed a non-linear association; the log-hazard on DMARD-free sustained remission decreased after a certain symptom duration. These data suggest that a confined period in which the disease is more susceptible to treatment is present indeed.

The duration of the window is unknown. In 1991, the window was supposed to endure 2 years²² and at present it is considered to be the first 3 months. However, these suggestions are based on expert opinion rather than on scientific data. Although the cut-off of 3 months or 12 weeks is often referred to,^{8, 23, 24} we did not find literature with data supporting this time-point. Several studies compared patients with symptoms for < or ≥3 months,^{2, 6, 7} but a rationale for this categorisation was not provided and it is unknown whether results would have been even stronger when another cut-off was chosen. In the present data, the steepness of the curve plotting the log-HR against symptom duration diminished around 15–20 weeks after symptom onset (figure 1). It cannot be concluded that the window 'is closed' after this period, but the data of the present cohorts clearly showed that the hazard on remission was less after this period, and so possibly it 'starts to close' at this point in time. In other words, we do not suggest that DMARD treatment after a certain window is futile, but that initiating a DMARD in this particular window might yield a better outcome. In case a patient is identified after this period has passed, DMARD therapy should certainly not be withheld.

The symptom duration with the optimum discriminative ability of disease persistence was estimated at 14.9 weeks in the EAC and 19.1 weeks in ESPOIR. The time point at which the curve plotting the log-HR against symptom duration started to flatten does not necessarily coincide with the symptom duration with the best Youden's index determined using an ROC. Nonetheless, in the present data both time indications were roughly similar. Importantly, the time estimation obtained using the ROC curves should be interpreted with care. First, because the ROC curves were relatively flat and the AUCs low, making the identification of a single time point less reliable compared with ROC curves with high AUCs. This uncertainty is reflected by the broad CIs. Second, the exact dates at which patients started to take DMARDs were not known in all patients (in the EAC, these data were incomplete; in ESPOIR, the median duration between inclusion and DMARD start was 1.4 weeks). We therefore performed the analyses defining symptom duration as the period between symptom onset and the first visit. Consequently, the obtained time estimation may be too 'narrow'. Third, the time indications are obtained on group level and may not be identical in every individual patient with RA. Because of these limitations, we cannot give definite answers on the length of the window of opportunity. Still, the observed results on symptom duration are rather consistent, which suggests some validity of these results.

The validity of the results on non-linear associations of symptom duration with the course of RA are strengthened by the finding that non-linear curves were also observed for radiographic progression and sustained remission. The curves on DMARD-free sustained remission of the EAC and ESPOIR cohort were not completely similar as the change in steepness was more profound in the results of the ESPOIR cohort. Nevertheless, when evaluating the results of both cohorts and the different outcomes, the general picture is that the association of symptom duration with the chance of either a favourable outcome (remission) or unfavourable outcome (joint damage) is not linear.

This study has limitations. It has been noted previously that studies evaluating the symptom or disease duration should indicate precisely how symptom onset or disease onset is defined in order to allow comparisons between studies.¹³ In both cohorts, the onset of symptoms was defined identically as the first symptoms noticed by patients themselves. The fact that the symptom start was reported by patients may have induced some heterogeneity due to inter-individual differences in symptom awareness or symptom recollection.²⁵ Another issue is that we evaluated data of longitudinal observational cohort studies. These data reflect the daily care of patients and decisions to start and stop DMARDs were left to the patients and rheumatologists and not protocolised. In ESPOIR, mainly in the first years of its existence, quitting DMARD therapy was uncommon. Consequently, the observed frequency of DMARD-free sustained remission may be underestimated. Finally, whether DMARD-free sustained remission was

achieved was determined slightly differently in the cohorts. In the EAC, all medical files were checked to ensure that DMARD-free sustained remission was present. In ESPOIR, the data of the structured visits with yearly intervals were studied. It is possible that more patients included in ESPOIR would have achieved DMARD-free sustained remission when all information present in medical files was evaluated. Though, differences in common practice on discontinuing DMARD therapy might be the most important cause for the higher frequency of DMARD-free sustained remission in the EAC than in ESPOIR. It is not known which DMARD is most effective in taking advantage of the early, treatment susceptible, disease period. None of the patients studied were treated with biologics as first therapy. Since methotrexate is the treatment of first choice according to European league against rheumatism (EULAR) recommendations,²⁶ patients treated with methotrexate were studied in detail. The results of this subanalysis were in line with the results of the total group. Although it is known that methotrexate therapy reduces the severity of radiographic progression,^{27,28} thus far evidence demonstrating that methotrexate is able to increase the chance on DMARD-free sustained remission when initiated early is absent. Current data therefore add importantly to the conception of methotrexate being disease modifying.²⁶

The biological mechanisms underlying the concept of the window of opportunity are unclear. Pathophysiologically, ACPA-positive and ACPA-negative RA are considered to be different subsets of RA. Analyses stratified for ACPA were possible in one cohort and revealed a slightly shorter window in ACPA-positive than in ACPA-negative patients (11.4 vs 15.0 weeks). Because the CIs were broad, no definite conclusions can be drawn on these comparisons, though the tendency in the data may lead to the speculation that the presence of ACPA is related to a master-switch leading to an earlier closing of the window.

Present guidelines on the treatment of RA contain indications on the time ideally elapsed until access to rheumatological care is obtained or treatment is started.^{26,29} More studies are required to determine what is 'in time' or 'too late' for specific groups of RA patients. In conclusion, the present study demonstrated that the HRs on DMARD-free sustained remission decreased considerably before a certain time point. This study is the first providing strongly suggestive evidence that a confined period in which RA is more susceptible to treatment exists. Further proof might be obtained by performing clinical trials in patients with symptoms of very recent onset randomising for direct or delayed treatment. However, given the present knowledge this may be considered unethical.

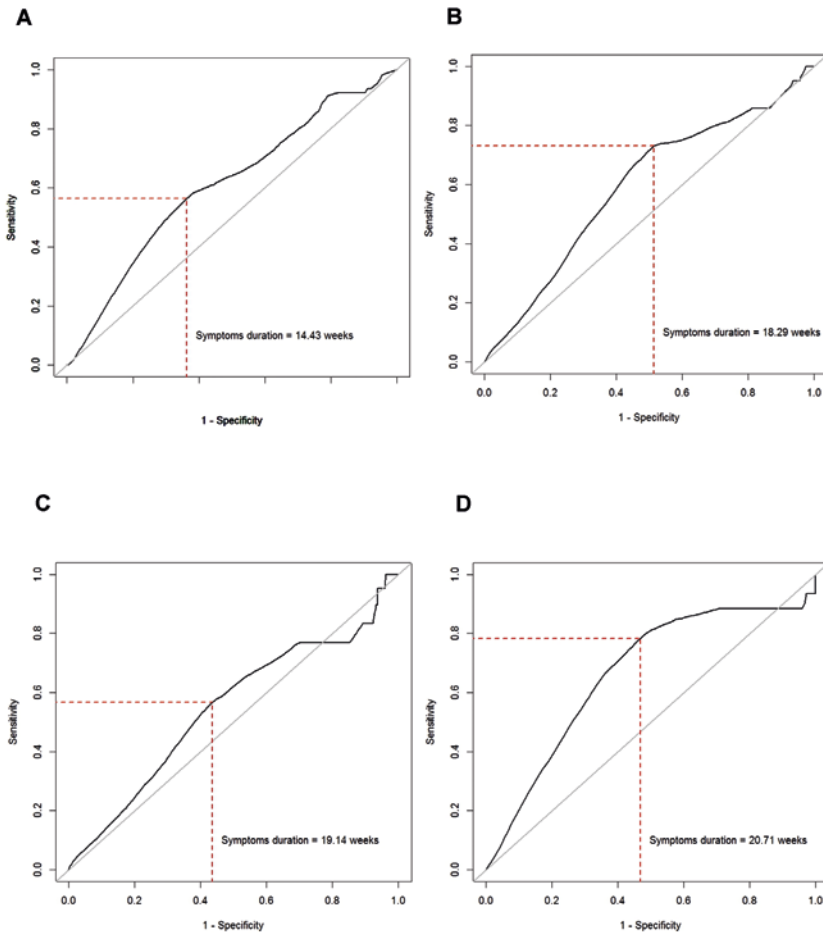
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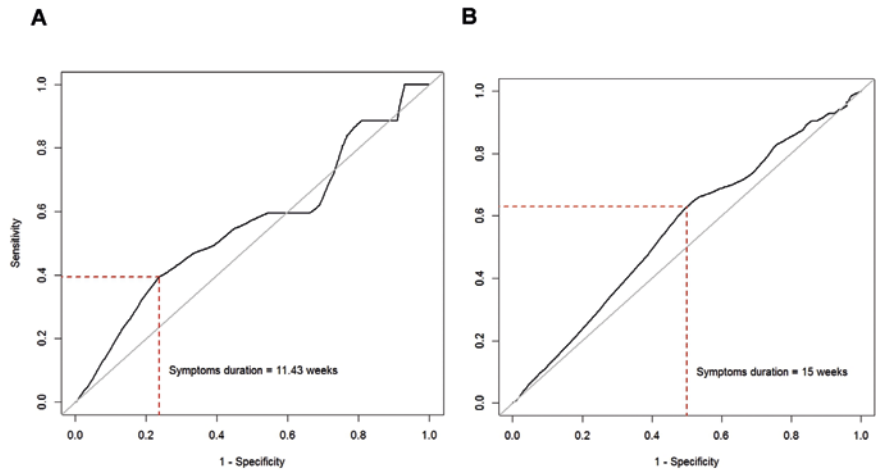
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SUPPLEMENTARY DATA



Supplementary Figure 1. Time-dependent receiver-operator-characteristic curves of symptom duration with DMARD-free sustained remission during 5-year follow-up as outcome for methotrexate users (A,C) and patients using other conventional DMARDs (B,D) in the EAC (A,B) and ESPOIR (C,D); the symptom duration with the best discriminative ability was determined using Youden's index.



Supplementary Figure 2. Time-dependent receiver-operator-characteristic curves of symptom duration with DMARD-free sustained remission during 5-year follow-up as outcome for ACPA-positive (A) and ACPA-negative (B) RA-patients in the EAC.

PART III

Diagnostic and prognostic value of
disease symptoms, characteristics
and classification criteria in
arthralgia, early arthritis and RA
patients



CHAPTER 6

Reappraisal of the diagnostic and prognostic value of morning stiffness in arthralgia and early arthritis: results from the Groningen EARC, Leiden EARC, ESPOIR, Leiden EAC and REACH

Jessica A.B. van Nies, Celina Alves, Audrey L.S. Radix-Bloemen, Cécile Gaujoux-Viala, Tom W.J. Huizinga, Johanna M.W. Hazes, Elisabeth Brouwer, Bruno Fautrel, Annette H.M. van der Helm-van Mil

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ABSTRACT

Introduction

Morning stiffness is assessed daily in the diagnostic process of arthralgia and arthritis, but large-scale studies on the discriminative ability are absent. This study explored the diagnostic value of morning stiffness in 5,202 arthralgia and arthritis patients and the prognostic value in early rheumatoid arthritis (RA).

Methods

In arthralgia patients referred to the Early Arthritis Recognition Clinics (EARC) of Leiden ($n = 807$) and Groningen ($n = 481$) or included in the Rotterdam Early Arthritis Cohort (REACH) study ($n = 353$), the associations (cross-sectional analyses) between morning stiffness and presence of arthritis at physical examination were studied. In early arthritis patients, included in the Leiden Early Arthritis Clinic (EAC) ($n = 2,748$) and Evaluation et Suivi de POLyarthrites Indifférenciées Récentes (ESPOIR) ($n = 813$), associations with fulfilling the 2010-RA criteria after one year were assessed. In 2010-RA patients included in the EAC ($n = 1,140$) and ESPOIR ($n = 677$), association with the long-term outcomes of disease-modifying antirheumatic drug (DMARD)-free sustained remission and radiological progression were determined. Morning stiffness was defined as a duration ≥ 60 minutes; sensitivity analyses were performed for other definitions.

Results

In arthralgia, morning stiffness (≥ 60 minutes) associated with the presence of arthritis; Leiden EARC odds ratio (OR) 1.49 (95% CI 1.001 to 2.20), Groningen EARC OR 2.21 (1.33 to 3.69) and REACH OR 1.55 (0.97 to 2.47) but the areas under the receiver operating characteristic curve (AUCs) were low (0.52, 0.57, 0.54). In early arthritis, morning stiffness was associated with 2010-RA independent of other predictors (Leiden EAC OR 1.72 (95% CI 1.31 to 2.25, AUC 0.68), ESPOIR OR 1.68 (1.03 to 2.74, AUC 0.64)). Duration of ≥ 30 minutes provided optimal discrimination for RA in early arthritis. Morning stiffness was not associated with radiological progression or DMARD-free sustained remission.

Conclusions

Morning stiffness in arthralgia and early arthritis is associated with arthritis and RA respectively. This supports the incorporation of morning stiffness in the diagnostic process.

INTRODUCTION

Morning stiffness is common in patients with rheumatoid arthritis (RA); it affects the ability to function in the morning ¹, the quality of life and is associated with work loss ². Presence of morning stiffness, together with fatigue, are often mentioned as one of the first symptoms of RA. Therefore, morning stiffness is usually assessed in the diagnostic process of patients presenting with arthralgia or arthritis ³.

The scientific data on the diagnostic value of this symptom are surprisingly scanty. In the literature, it has been mentioned that morning stiffness is a poor discriminator between RA and other rheumatologic disorders ^{4,5}. However, these conclusions are predominantly based on two studies, with relatively small sample sizes. The first study compared 93 RA patients and 46 patients with non-inflammatory joint diseases [4]. The second study compared 31 RA patients with 23 systemic lupus erythematosus (SLE) patients and 34 osteoarthritis (OA) patients ⁵. It has also been suggested that morning stiffness is commonly present in the general population and not specific for RA ^{6,7}. This notion is also based on only two studies. A large study revealed a prevalence of morning stiffness of 37% when defined as stiffness of ≥ 15 minutes; this definition is generally not considered as typical for RA ⁶. The other study originated from the early 1950s and reported morning stiffness in 19% of persons without RA, but a definition of morning stiffness was not provided ⁷. Altogether, there is not much evidence on the diagnostic value of morning stiffness. It is also not part of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA, whereas it had been included in the 1958 American Rheumatism Association (ARA) criteria and the 1987 ACR criteria for RA ⁸⁻¹⁰. Because of the paradox of the lack of large-scale studies focusing on morning stiffness, and the use of morning stiffness in daily practice by rheumatologists and general practitioners, we set out to study the diagnostic value of morning stiffness in arthralgia and early arthritis by studying different European datasets and cohorts. The basic aim to this study was to evaluate the diagnostic value of morning stiffness. Because the diagnostic value is dependent on the patient population in which a test is performed, we studied the discriminative ability of morning stiffness in two situations. First, in cross-sectional analyses on patients with arthralgia, the association between morning stiffness and the presence of arthritis at physical examination was studied. This information is relevant for general practitioners (GPs) and other physicians who encounter patients with joint symptoms in their practices and who have limited experience in joint examination. Second, in early arthritis, the ability of morning stiffness to discriminate patients with RA from other early arthritis patients was assessed.

Although it is known that morning stiffness is associated with the disease activity¹¹, functional disability¹² and work loss² in RA, it is undetermined whether morning stiffness at first presentation is a risk factor for a more severe disease reflected by structural damage or disease persistence. To evaluate this, associations with radiographic progression and achieving DMARD-free sustained remission (the absence of disease persistence) were assessed in two longitudinal cohort studies.

METHODS

Patients

All datasets and cohorts used are described in more detail elsewhere¹³⁻¹⁶.

In short, the arthralgia patients were referred to the Early Arthritis *Recognition* Clinics (EARC) from Leiden and Groningen (the Netherlands) or included in the Rotterdam Early Arthritis Cohort (REACH) (the Netherlands). The EARCs were initiated to reduce referral delay by GPs. It was observed that the GP delay contributed to two-thirds of the total delay between symptom onset and first visit to a rheumatologist in the Netherlands and that GPs frequently applied a 'wait and-see' approach if they were unsure of the presence of arthritis. Therefore, GPs were instructed to refer to the EARC if they were undecided. The EARCs are early access clinics in which experienced rheumatologists screen patients on the presence of arthritis by physical examination; no laboratory investigations are done^{13,17}. The studied arthralgia patients visited the Leiden EARC between September 2010 and August 2013 and the Groningen EARC between October 2010 and January 2014. The EARC is primarily part of our care. Patients visiting the EARCs were not subjected to procedures that were done for scientific purposes, such as blood taking for biobanking. Therefore, in line with the Dutch law 'Wet medisch- wetenschappelijk onderzoek met mensen' (translated as 'the law on medical and scientific research involving people'), patients were not asked to sign an informed consent form.

The REACH study is an inception cohort that was initiated in the Rotterdam area, the Netherlands, in 2004. Inclusion required either pain or loss of movement in ≥ 2 joints or >1 swollen joint and ≥ 2 of the following items: unable to clench a fist in the morning, pain when shaking someone's hand, pins and needles in the fingers, difficulties wearing rings or shoes, a family history of RA, morning stiffness >1 hour, unexplained fatigue, all <1 year¹⁴. The patients studied here were referred with joint symptoms by GPs between 2004 and 2009 and the presence of arthritis was assessed at the first visit. REACH was approved by the ethics committees of all three participating hospitals (Erasmus MC University Medical Center Rotterdam, Sint Franciscus Gasthuis Rotterdam and Maastad Ziekenhuis Rotterdam); all patients gave written informed consent.

The early arthritis patients were included in the Leiden Early Arthritis Clinic (EAC) and the Evaluation et Suivi de POlyarthrites Indifférenciées Récentes (ESPOIR) cohort. The Leiden EAC is a population-based inception cohort that started in 1993. Inclusion required the presence of arthritis of ≥ 1 joint at physical examination and symptom duration < 2 years ¹⁵. The patients studied were included between 1993 and 2011. The EAC was approved by the local Leiden University Medical Center (LUMC) ethics committee, all patients gave informed consent. ESPOIR is a nationwide cohort in which 14 rheumatology centres throughout France collaborate. Early arthritis patients are included if the treating rheumatologists suspected them of having or developing RA. Further, for inclusion patients had to be aged 18 to 70 years and to have ≥ 2 swollen joints for > 6 weeks and < 6 months. Patients studied were included between 2002 and 2005 ¹⁶. ESPOIR was approved by the ethics committee of Montpellier; all patients gave written informed consent. In both the EAC and ESPOIR questionnaires were filled in, joint counts performed and laboratory evaluations done at baseline. Patients were followed prospectively with yearly follow-up visits; these included clinical and laboratory evaluations and radiographs of hands and feet.

Assessment of morning stiffness

In all cohorts the duration of morning stiffness was reported in minutes. In the EARCs, patients answered questionnaires on the presence and duration of morning stiffness (Additional file 1). In the EAC, ESPOIR and REACH the questions on presence and duration of morning stiffness were asked by trained research nurses (Additional file 1). Patients were not asked for specific locations of stiffness. Morning stiffness duration was dichotomized into < 60 and ≥ 60 minutes. Sensitivity analyses were performed with ≥ 30 and ≥ 90 minutes as cutoffs. To evaluate the consistency in results when morning stiffness was assessed differently, analyses on arthritis patients were repeated with the severity of morning stiffness instead of the duration. The severity was assessed using a visual analogue scale (VAS) in 1,959 EAC patients included between 1993 and February 2010 and in all ESPOIR patients. For analyses, the VAS was divided into the three categories; mild 0 to 33 millimeter (mm), moderate 34 to 67 mm and severe 68 to 100 mm. In the arthralgia datasets the severity was not recorded. In all patients studied, morning stiffness was assessed at the first visit, when patients were not treated with disease-modifying antirheumatic drugs (DMARDs).

Outcomes

The outcomes were different in the three parts of this study (Figure 1).

Diagnostic value in arthralgia

In arthralgia patients, the outcome was the presence of arthritis ascertained at physical examination by experienced rheumatologists (assessed at the same visit when morning stiffness was evaluated). In both EARCs, a small proportion of patients (58 and 25) had no evident arthritis but were also not classified as having 'no arthritis' because the rheumatologists suspected these patients of RA development; these patients were excluded from analyses.

Diagnostic value in early arthritis

In early arthritis, we aimed to assess the diagnostic value of morning stiffness and here the outcome was the presence of RA after one year. RA was defined as fulfilling the 2010 ACR/EULAR criteria for RA during the first year. An advantage of the 2010-RA criteria is that morning stiffness is not included, preventing circle reasoning. Since during the first weeks the diagnoses may not yet be definitive, the classification after year one was evaluated. These first two parts evaluated the diagnostic value.

Prognostic value within RA

Third, within 2010-RA patients, the prognostic value was assessed by studying two long-term outcomes. Structural damage was assessed using serial hands and feet radiographs that were scored according to the Sharp/van der Heijde (SHS) method with known time order and blinded to clinical data. In the EAC, radiographs were scored of patients included between 1993 and 2006. The follow-up was seven years in the EAC and three years in ESPOIR. The within-reader intraclass correlation coefficients (ICCs) were 0.91 and 0.87 for two readers in the EAC and 0.97 in ESPOIR. DMARD-free sustained remission, the opposite of disease persistence, was defined as the sustained absence of arthritis after discontinuation of DMARD therapy, including biologics and glucocorticoids (systemic and intra-articular), for the entire period of follow-up, which was at least one year¹⁸. In the EAC, it was assessed by exploring the medical files until 10 years of follow-up. In ESPOIR, it was assessed over five years of follow-up by reviewing the structured visits in the ESPOIR database.

Analyses

Characteristics were compared using Student t tests, Mann–Whitney tests or chi-square tests when appropriate. Associations of morning stiffness in arthralgia and early arthritis were done using logistic regression analyses. All analyses were adjusted for age and gender (although morning stiffness was not correlated with age in arthralgia or early arthritis). In early arthritis further adjustments were made for anti-citrullinated protein antibody (ACPA), rheumatoid factor (RF), swollen joint count (SJC), erythrocyte sedimentation rate (ESR) and symptom duration at baseline. The test characteristics (sensitivity, specificity), positive/negative predictive values (PPV/NPV) and area under

the receiver operating characteristic curve (AUC) were calculated. This curve was used to derive the morning stiffness duration with the optimal discriminative ability (Youden's index). Associations between morning stiffness at baseline and radiographic progression were studied using multivariate normal regression analysis with log-transformed radiographic data as response variable as described elsewhere^{19,20}. Analyses on DMARD-free sustained remission were done by Kaplan-Meier survival curves and Cox proportional hazard regression models with morning stiffness as an independent variable. Analyses on radiographic progression and DMARD-free sustained remission were adjusted for age, gender, ACPA and inclusion period as a proxy for differences in treatment strategy as described elsewhere¹⁷. SPSS version 20.0 was used (IBM Corp, Armonk, NY, USA).

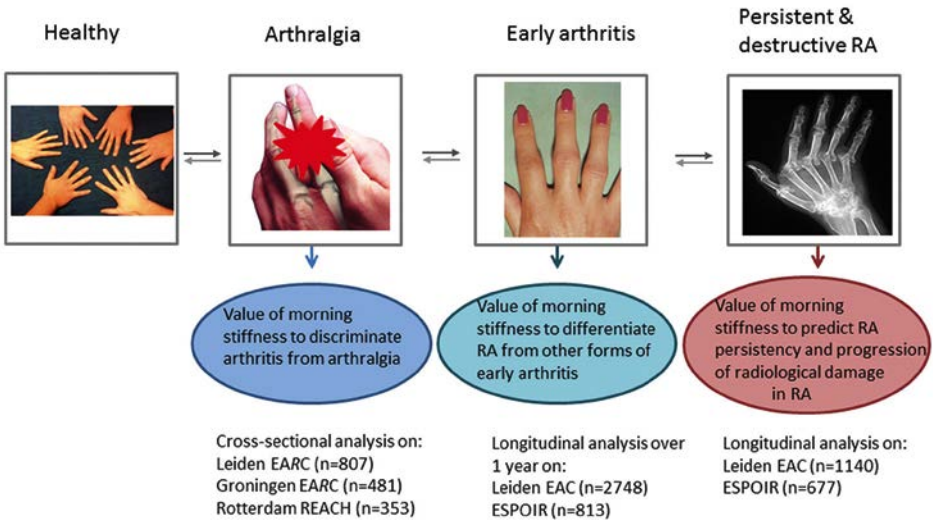


Figure 1. Outline of study questions.

Legend Figure 1. Of the 2010-RA patients in the EAC, radiographs were scored for the patients included between 1993 and 2006 ($n = 636$). Baseline characteristics of RA patients included before or after 2006 were not different. In ESPOIR, radiographic data was available for 659 of 677 RA patients. Here also, baseline characteristics of patients with and without radiographs were not different. EAC, Early Arthritis Clinic; ESPOIR, Evaluation et Suivi de POLyarthrites Indifférenciées Récentes; RA, rheumatoid arthritis.

RESULTS

Table 1. Baseline characteristics of the arthralgia patients

	Leiden EARC			Groningen EARC			REACH		
	All n=807	No Arthritis n=435	Arthritis n=372	All n=481	No Arthritis n=214	Arthritis n=267	All n=353	No Arthritis n=172	Arthritis n=181
Age, mean±SD, years	51.4±16.3	49.6±15.5	53.5±17.0	51.6±16.4	49.0±15.3	53.7±16.9	48.6±14.1	46.7±11.7	50.3±15.9
Female, n (%)	574 (71)	345 (79)	229 (62)	311 (65)	145 (68)	166 (62)	277 (79)	149 (87)	128 (71)
Gradual onset symptoms, n (%)	499 (62)	285 (67)	214 (59)	299 (63)	140 (66)	159 (61)	183 (58)	115 (71)	68 (44)
Morning stiffness, minutes	10 (0-30)	10 (0-30)	10 (0-30)	10 (0-30)	10 (0-30)	15 (0-60)	30 (0-60)	30 (0-60)	30 (0-97)
≥30 minutes, n (%)	210 (30)	106 (28)	104 (32)	146 (36)	55 (30)	91 (40)	185 (53)	87 (52)	98 (54)
≥60 minutes, n (%)	129 (18)	60 (16)	69 (21)	88 (22)	27 (15)	61 (27)	114 (32)	45 (27)	68 (38)
≥90 minutes, n (%)	71 (10)	27 (7)	44 (14)	53 (13)	15 (8)	38 (17)	73 (21)	25 (15)	48 (27)
Tender joint count	7 (2-14)	8 (3-17)	5 (2-13)	9 (4-18)	9 (4-18)	8 (3-18)	7 (3-12)	7 (2-12)	7 (3-11)
Symptom duration, weeks	11.5 (4.0-61.0)	19.3 (6.1-122)	6.9 (2.7-21.6)	18.0 (5.6-64.3)	22.9 (6.9-74.9)	16.6 (4.6-54.9)	1.7 (0.8-3.2)	2.4 (1.2-3.6)	1.3 (0.7-2.3)
<12 weeks symptom duration, n(%)	380 (51)	162 (41)	218 (62)	165 (39)	70 (38)	95 (39)	352(100)	171 (100)	181 (100)

Values are median (Interquartile range) unless indicated otherwise. Missingness per variable as follows; Gradual onset symptoms (defined as start of onset > 1 week) Leiden EARC n=17, Groningen EARC n=8, REACH n=36 ; Morning stiffness Leiden EARC n=101, Groningen EARC n=72 , REACH n=5 ; Tender joint count Groningen EARC n=1; Symptom duration/ <12 weeks symptom duration Leiden EARC n=61, Groningen EARC n=54 REACH n=1. Patients with missing data on morning stiffness duration did not differ significantly from patients with data on morning stiffness (data not shown). EARC, Early Arthritis Recognition Clinic; REACH, Rotterdam Early Arthritis Cohort; SD, standard deviation.

Diagnostic value of morning stiffness in arthralgia

In the Leiden EARC, 807 arthralgia patients were seen, in the Groningen EARC, 481 arthralgia patients and in the REACH, 353 patients were included. Arthritis was observed in 372 (46%), 267 (56%) and 181 (51%) patients respectively. Table 1 presents baseline characteristics. The median (interquartile range (IQR)) duration of morning stiffness was 10 (0 to 30), 10 (0 to 30) and 30 (0 to 60) minutes respectively. The odds ratios (ORs) of morning stiffness (≥ 60 minutes) for the presence on arthritis were 1.49 (95% confidence interval (CI) 1.001 to 2.20), 2.21 (1.33 to 3.69) and 1.55 (0.97 to 2.47) for the Leiden EARC, Groningen EARC and REACH respectively. The specificities ranged between 73 to 85% but the sensitivities were low (21 to 38%). The low sensitivity indicated that the majority of all patients with arthritis did not have morning stiffness for ≥ 60 minutes. The PPVs were 54%, 69% and 60% respectively (Table 2) and all higher than the absolute chances on arthritis without assessing morning stiffness (these were 46%, 56%, 51%). The AUCs were very low (Leiden EARC 0.52, Groningen EARC 0.57, REACH 0.54); therefore, no duration with optimal discriminative ability was ascertained. When morning stiffness was defined as ≥ 90 minutes (present in 10 to 21% of arthralgia patients), the specificity increased to 85 to 93% (Table 2). This indicated that almost all arthralgia patients without arthritis did not have morning stiffness for ≥ 90 minutes.

Table 2. The diagnostic value of morning stiffness (different durations) in arthralgia for the presence of arthritis.

	OR (95%CI) <i>adjusted for age & gender</i>	Sensitivity	Specificity	PPV	NPV
Leiden EARC					
≥ 30 minutes	1.24 (0.89-1.73)	31.9%	72.1%	49.5%	55.2%
≥ 60 minutes	1.49 (1.001-2.20)	21.2%	84.2%	53.5%	55.5%
≥ 90 minutes	1.98 (1.18-3.30)	13.5%	92.9%	62.0%	55.6%
Groningen EARC					
≥ 30 minutes	1.63 (1.07-2.47)	40.3%	70.0%	62.3%	48.7%
≥ 60 minutes	2.21 (1.33-3.69)	27.0%	85.3%	69.3%	48.6%
≥ 90 minutes	2.16 (1.14-4.10)	16.8%	91.8%	71.7%	47.2%
REACH					
≥ 30 minutes	1.07 (0.69-1.65)	54.4%	48.2%	53.0%	50.3%
≥ 60 minutes	1.55 (0.97-2.47)	37.8%	72.6%	59.7%	47.9%
≥ 90 minutes	2.05 (1.18-3.58)	26.7%	85.1%	65.8%	48.0%

OR, odds ratio; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; EARC, Early Arthritis Recognition Clinic; REACH, Rotterdam Early Arthritis Cohort.

Diagnostic value of morning stiffness in early arthritis

A total of 2,748 early arthritis patients were included in the EAC and 813 in ESPOIR. The median duration of morning stiffness at baseline was 30 (0 to 90) and 60 (15 to 120) minutes. Other baseline characteristics are presented in Table S1 in Additional file 1. In total, 42% and 83% of the patients were classified as 2010-RA after year one respectively. Figure 2 shows the duration of morning stiffness per diagnosis of early arthritis patients included in the EAC; the median duration in RA was 60 minutes and longer than that of other early arthritis patients (except for SLE patients). Since ESPOIR included early arthritis patients with a clinical suspicion of RA and not patients with other diagnoses, this figure was not derived for ESPOIR.

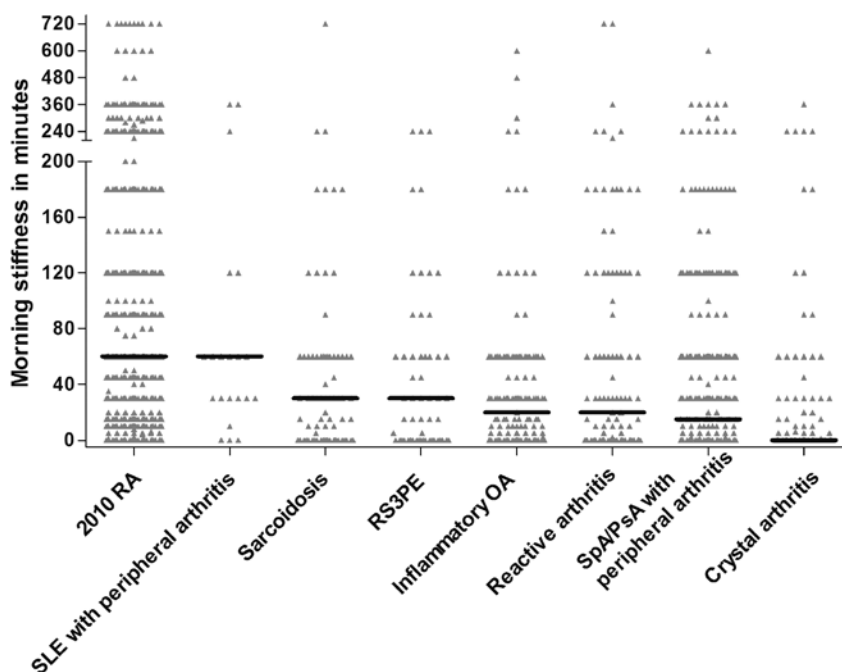


Figure 2. The duration of morning stiffness per diagnosis in the Leiden EAC.

Legend Figure 2. The black horizontal line indicates the median duration. Number of patients per diagnosis after one year of follow-up: 2010-RA n = 1,140, SLE with peripheral arthritis n = 21, sarcoidosis n = 78, RS3PE n = 60, inflammatory arthritis n = 133, reactive arthritis n = 108, SpA/PsA with peripheral arthritis n = 287, crystal arthritis n = 119. Two data points (2010-RA n = 1 and SpA/PsA with peripheral arthritis n = 1) are outside the axis limits. EAC, Early Arthritis Clinic; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; SLE, systemic lupus erythematosus; SpA, spondyloarthritis.

Morning stiffness (≥ 60 minutes) was significantly associated with RA in the EAC (OR 2.92, 95% CI 2.47 to 3.44) and ESPOIR (OR 2.33, 95% CI 1.59 to 3.44), also after additional adjustments for ACPA, RF, SJC, symptom duration and ESR (OR 1.72, 95% CI 1.31 to 2.25 in EAC and OR 1.68, 95% CI 1.03 to 2.74 in ESPOIR). In both cohorts the sensitivity and specificity were around 60%. The PPV was 56.7% in EAC and 88.7% in ESPOIR, these absolute chances were a little higher than the pre-test chances on RA (42% and 83%). When morning stiffness was defined as ≥ 30 or ≥ 90 minutes consistent results were observed (Table 3). The AUCs of the presence of morning stiffness for RA in both cohorts were 0.68 (95% CI 0.66 to 0.70) and 0.64 (95% CI 0.58 to 0.69). The duration with the optimal combination of sensitivity and specificity for RA was 27.5 minutes in the EAC and 25.0 minutes in ESPOIR (Figure 3). Both cohorts also recorded the severity of morning stiffness. In both cohorts morning stiffness duration and severity were correlated (Spearman rho 0.42, $P < 0.001$ in EAC and Spearman rho 0.54, $P < 0.001$ in ESPOIR) Early arthritis patients with moderate severity (VAS 34 to 67 mm) had an OR on RA of 1.87 (95% CI 1.48 to 2.36) and 2.04 (1.32 to 3.17) and the patients in the most severe category (VAS ≥ 68 mm) had ORs of 2.38 (95% CI 1.89 to 3.00) and 2.46 (95% CI 1.53 to 3.96) respectively. Using the VAS, the AUCs were 0.62 (95% CI 0.60 to 0.65) in EAC and 0.62 (95% CI 0.57 to 0.68) in ESPOIR. The AUCs of morning stiffness duration and morning stiffness severity were not statistically significantly different.

Table 3. The diagnostic value of morning stiffness (duration and severity) in early arthritis for classifying RA

	OR (95%CI) <i>adjusted for age & gender</i>	OR (95%CI) <i>adjusted for age, gender, SJC, ACPA, RF, ESR and symptom duration</i>	Sensitivity	Specificity	PPV	NPV
Leiden EAC						
≥ 30 minutes	3.37 (2.83-4.03)	2.22 (1.66-2.96)	77.0%	51.5%	53.5%	75.5%
≥ 60 minutes	2.92 (2.47-3.44)	1.72 (1.31-2.25)	61.2%	66.1%	56.7%	70.1%
≥ 90 minutes	2.44 (2.04-2.92)	1.61 (1.19-2.18)	39.1%	80.3%	59.0%	64.5%
VAS 34-67mm	1.87 (1.48-2.36)	2.10 (1.43-3.09)	56.5%	60.0%	49.1%	66.8%
VAS ≥ 68 mm	2.38 (1.89-3.00)	1.93 (1.32-2.83)	60.7%	61.8%	55.3%	66.8%
ESPOIR						
≥ 30 minutes	2.64 (1.81-3.87)	1.76 (1.07-2.88)	74.2%	47.8%	87.6%	27.1%
≥ 60 minutes	2.33 (1.59-3.44)	1.68 (1.03-2.74)	55.4%	64.7%	88.7%	22.6%
≥ 90 minutes	2.02 (1.28-3.20)	1.64 (0.92-2.92)	32.5%	80.9%	89.4%	19.4%
VAS 34-67mm	2.04 (1.32-3.17)	1.93 (1.10-3.37)	61.0%	56.3%	85.7%	25.1%
VAS 68-100 mm	2.46 (1.53-3.96)	1.65 (0.88-3.11)	57.3%	63.7%	87.6%	25.1%

RA is classified according to the 2010 ACR-EULAR criteria. VAS: (0-100mm). In the analyses of VAS Morning stiffness 3 categories were formed, the reference group was a VAS 0-33 mm. The sensitivity, specificity, PPV and NPV of the VAS morning stiffness were calculated against this reference group.

Prognostic value of morning stiffness in early RA

RA patients reporting morning stiffness (≥ 60 minutes) at baseline did not have more severe radiographic progression (Figure S1A, B in Additional file 1) over time. During 10 years of follow-up, 23% ($n = 257$) of the RA patients in the EAC obtained DMARD-free sustained remission; in ESPOIR this was 10% ($n = 65$) during five years of follow-up. Morning stiffness (≥ 60 minutes) was not associated with achieving remission (Figure S1C, D in Additional file 1). Defining morning stiffness as ≥ 30 or ≥ 90 minutes or using VAS scores did not evidently change the results (Figure S1E-H in Additional file 1). In 128 EAC RA patients that achieved remission (after median 2.4 years) the VAS at inclusion and at time of remission were available; it declined from 52.5 mm at baseline (IQR 25.8 to 75.8) to 13.5 mm (IQR 1.3 to 35.8, $P < 0.005$).

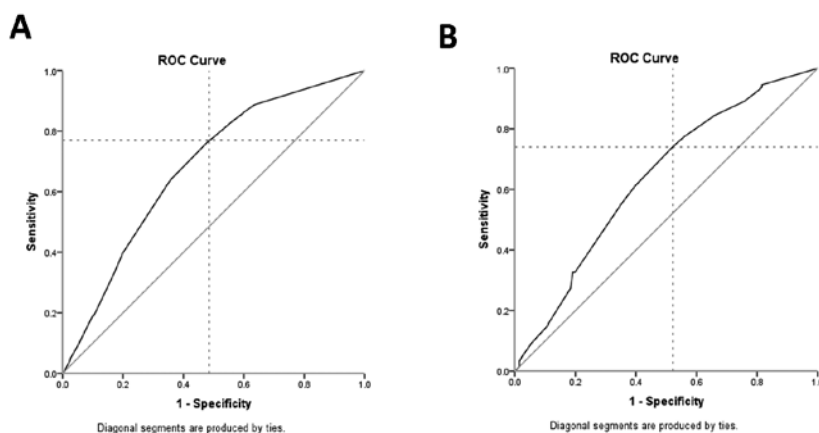


Figure 3. ROC curves on morning stiffness in early arthritis patients of the EAC (A) and ESPOIR (B).

Legend figure 3. The AUCs were 0.68 in the EAC and 0.64 in ESPOIR. In the EAC, the optimal cutoff point (crossing of dashed lines) reflected a sensitivity of 77% and a specificity of 52%; morning stiffness duration at this point was 27.5 minutes. When selecting the point with 80% specificity, the sensitivity was 40% and the morning stiffness duration 67.5 minutes (EAC) and a sensitivity of 33% and a morning stiffness duration 62.5 minutes (ESPOIR). AUC, area under the receiver operating characteristic curve; EAC, Early Arthritis Clinic; ESPOIR, Evaluation et Suivi de Polyarthrites Indifférenciées Récentes.

DISCUSSION

Morning stiffness is one of most commonly evaluated symptoms in the diagnostic process of joint symptoms because its presence is thought to be characteristic for arthritis or RA. Others, however, have doubted the value of morning stiffness in this respect ^{4,5}. The

absence of large-scale studies on the diagnostic value of morning stiffness prompted us to initiate the present study. The subject is timely because of the current focus on early identification of arthritis and RA ^{17,21}. Furthermore, assessing the presence of or duration of morning stiffness is relatively easy, illustrating its potential utility. We aimed to determine the diagnostic and prognostic value of morning stiffness. To this end we performed a comprehensive study in different types of patients. We observed that arthralgia patients with morning stiffness for ≥ 60 minutes more often had arthritis than patients without morning stiffness, but the discriminative ability of this single variable (AUC) was low. Among early arthritis patients, RA patients experienced morning stiffness more frequently. Also here the discriminative ability of morning stiffness alone was moderate. This indicates that evaluation of morning stiffness is helpful in the diagnostic process in clinical practice but that it should be combined with other characteristics for optimal discrimination.

Advantageous in this study is that morning stiffness was evaluated in many arthralgia and early arthritis patients (>5,000 in total) included in several European cohorts. The arthralgia datasets had different inclusion criteria. The studied EARC arthralgia patients were referred by their GPs because they doubted the presence of arthritis. The threshold for referral to the EARCs was low and the GP delays short. ¹³ Although the diagnostic value of morning stiffness of persons with joint symptoms in general practices was not studied, the arthralgia patients studied here represent the subset of arthralgia patients in which GPs were concerned about the presence of arthritis. Patients in REACH had to fulfil several criteria. Presence of morning stiffness was a criterion, explaining the higher median duration of morning stiffness in REACH patients. Despite the differences in patients' selection, the test characteristics of morning stiffness for arthritis in the different arthralgia datasets were comparable, which strengthens the validity of the findings.

The early arthritis cohorts also had different inclusion criteria. ESPOIR included patients that were considered susceptible to have or develop RA, whereas the EAC included all types of early arthritis patients. Consequently, the percentage of patients fulfilling the 2010 criteria at year one and the PPV were higher in ESPOIR than in the EAC and the difference in morning stiffness between RA and non-RA patients was larger in the EAC. Nonetheless, the ORs, AUCs and test characteristics were almost similar between the cohorts, supporting the consistency of the findings.

Emery et al. proposed that the suspicion of RA is increased in the presence of ≥ 3 swollen joints, a positive squeeze test or morning stiffness ≥ 30 minutes. Data supporting the latter recommendation were not published before ³ but the present data support this recommendation as in early arthritis with RA as outcome, the best sensitivity-specificity

combination (sensitivity 74 to 77%, specificity 48 to 52%) was present for morning stiffness enduring ≥ 30 minutes. However, it should be noted that the AUCs were not high and that it remains debatable whether the discriminative ability of ≥ 30 minutes is clearly superior to other durations. In addition, when one should aim for a specificity of 80%, to reduce false positive results, a cutoff of ≥ 60 minutes is required (EAC 67.5 minutes, ESPOIR 62.5 minutes, Figure 3).

The outcome in early arthritis was fulfilling the 2010-RA criteria after one year; generally diagnoses are definite then ²². We did not intend to evaluate the predictive ability of morning stiffness for RA in undifferentiated arthritis as done previously ^{22,23}. We aimed to determine the discriminative ability of morning stiffness in early arthritis for RA and to this end the diagnosis had to be ascertained with as much certainty as possible.

Our findings that morning stiffness is associated with 2010-RA, independent of other characteristics (for example ACPA, RF, SJC, ESR), are in contrast with the absence of morning stiffness in the 2010 criteria ²². This is noteworthy as the cohorts studied here were also included in the first phase of the derivation of the criteria. Several factors may play a role. First, in the derivation process patients with diagnoses other than RA or unclassified arthritis (UA) were excluded, diminishing the contrast between the groups (for comparison we observed a larger difference within the EAC than within ESPOIR). Second, the outcome was methotrexate initiation whereas we here studied fulfilling the 2010 criteria. Furthermore, morning stiffness was missing in 760 out of 3,115 patients included in phase 1 and morning stiffness was assessed differently in the different cohorts (present/absent, $</\geq 1$ hour or some categories on duration) ¹⁰. This heterogeneity in data collection contributed to the fact that morning stiffness was voted out in phase 1 ¹⁰. Nevertheless, the present data reveal that patients with 2010-RA more often suffer with morning stiffness than other early arthritis patients. This association is independent of the variables in the 2010 classification criteria for RA. In our view, the present data suggest that it is helpful to evaluate morning stiffness in addition to the other items of the 2010 criteria. However, we did not intend to refine the 2010 ACR/EULAR criteria for RA. For refinement of existing criteria, a different approach, involving many rheumatologists from Europe and the USA and focusing on reaching consensus, would be required.

Our study in early arthritis assessed morning stiffness in two ways: the questions related to the duration and the severity (on a VAS). It has been reported that such descriptions poorly define the experiences of patients, which encompass temporal patterns, intensities and functional disability in the early morning ^{24,25}. To our knowledge, no validated method is available to evaluate these items. Thus, exploration of such items may increase the diagnostic ability of morning stiffness but were not explored here.

A limitation of our data on the severity of morning stiffness is that VAS data were missing in 19% of EAC RA patients at baseline and in almost 50% of the RA patients who achieved DMARD remission at the time of remission. A previous study on 143 patients reported that morning stiffness severity is more responsive than morning stiffness duration ²⁶. We did not study the responsiveness of morning stiffness but noted that morning stiffness had almost disappeared when DMARD-free sustained remission was achieved. Furthermore, we also did not intend to study in detail whether the severity or the duration of morning stiffness is a better discriminator. Nonetheless, we did observe in early arthritis patients that both measures correlated moderately and that the AUC of morning stiffness severity was not superior to that of morning stiffness duration.

Another limitation of this study is that no longitudinal evaluations on the arthralgia patients were done. Recently, a prediction rule for arthritis development in ACPA positive arthralgia patients was derived and morning stiffness ≥ 1 hour was part of this rule ²⁷. This supports the notion that including morning stiffness in the diagnostic process is valuable. More longitudinal studies on arthralgia patients are needed.

Although the circadian rhythm is associated with nightly activation of the inflammatory processes and elevation of pro-inflammatory cytokines (for example TNF- α and IL-6) ²⁸⁻³⁰, the exact mechanisms causing the stiffness in the early morning are unknown. In addition, the cortisol rhythm might contribute to the increased inflammation at night due to the low nocturnal levels of cortisol ³¹. Despite the association with inflammation, morning stiffness at first presentation of RA was not associated with radiological progression or RA persistence over time. Other studies reported that morning stiffness is associated with functional disability, and work loss and therefore impacts on individual RA patients' lives ^{2,11,12}.

CONCLUSIONS

The additional relevance of present data is that it provides evidence, for the first time on a large study, that incorporating morning stiffness in the diagnostic process of joint symptoms in daily practice is valuable. A duration of morning stiffness of 30 minutes had the best combination of sensitivity and specificity (74 to 77% and 48 to 52% respectively). However, in case one prefers to be specific (specificity $\geq 80\%$) a cutoff duration of 60 minutes is preferable.

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SUPPLEMENTARY DATA

Supplemental Table 1. Baseline characteristics of the early arthritis patients subdivided into 2010-RA and other

	Leiden EAC			ESPOIR		
	all early arthritis n=2748	2010 RA n=1140	Other n=1608	all early arthritis n=813	2010 RA n=677	Other n=136
Age, mean±SD, years	52.1±17.1	55.9±15.9	49.4±17.4	48.1±12.6	48.6±12.3	45.3±13.6
Female, n (%)	1640 (60)	365 (32)	743 (46)	189 (23)	524 (77)	100 (74)
Symptom duration, weeks	14.9 (6.4-31.7)	19.4 (10.0-36.3)	12.0 (4.4-28.3)	21.3 (13.2-30.9)	21.4 (13.4-31.4)	20.0 (12.1-28.8)
Swollen joints	4 (2-9)	8 (4-13)	2 (1-5)	6 (3-10)	7 (4-11)	3 (2-4)
ACPA positive, n (%)	628 (28)	556 (53)	72 (6)	316 (39)	316 (47)	0
RF positive, n (%)	800 (30)	651 (57)	149 (10)	385 (47)	379 (56)	6 (4)
ESR mm/h	25 (11-45)	30 (14-50)	19 (9-41)	22 (12-38)	23 (12-38)	18 (8-36)
Morning stiffness, minutes	30 (0-90)	60 (30-120)	15 (0-60)	60 (15-120)	60 (20-120)	30 (10-60)
≥30 minutes, n (%)	1585 (61)	848 (77)	737 (49)	573 (71)	502 (74)	71 (52)
≥60 minutes, n (%)	1189 (45)	674 (61)	515 (34)	423 (52)	375 (55)	48 (35)
≥90 minutes, n (%)	730 (28)	431 (39)	299 (20)	246 (30)	220 (33)	26 (19)
VAS-MS ≤33mm	699 (36)	232 (26)	467 (44)	231 (29)	173 (26)	58 (43)
VAS-MS 34-67mm	613 (31)	301 (34)	312 (29)	315 (39)	270 (40)	45 (33)
VAS-MS ≥68mm	647 (33)	358 (40)	289 (27)	265 (33)	232 (34)	33 (24)

Median (Interquartile range) unless indicated otherwise. VAS-MS: VAS morning stiffness. Missingness per variable as follows in all early arthritis patients; Symptom duration EAC n=220, Swollen joint (based on 66-Swollen joint count) EAC n=137; ACPA EAC n=506, ESPOIR n=1; RF EAC n=37, ESPOIR n=1; ESR EAC n=21, ESPOIR n=11, morning stiffness EAC n=127, VAS morning stiffness EAC n=532, ESPOIR n=2.

Supplemental Methods. Questions asked on presence mornings stiffness per data-set or cohort

EAC Leiden and Groningen: via self-reported questionnaire

Do you experience stiffness when you get up in the morning?

Answers: no or yes. If so for how many minutes ... ?

REACH study: via research nurse

Do you experience morning stiffness? If yes, for how long?

Leiden EAC: via research nurse

Do you experience in stiffness in your joints in the morning.

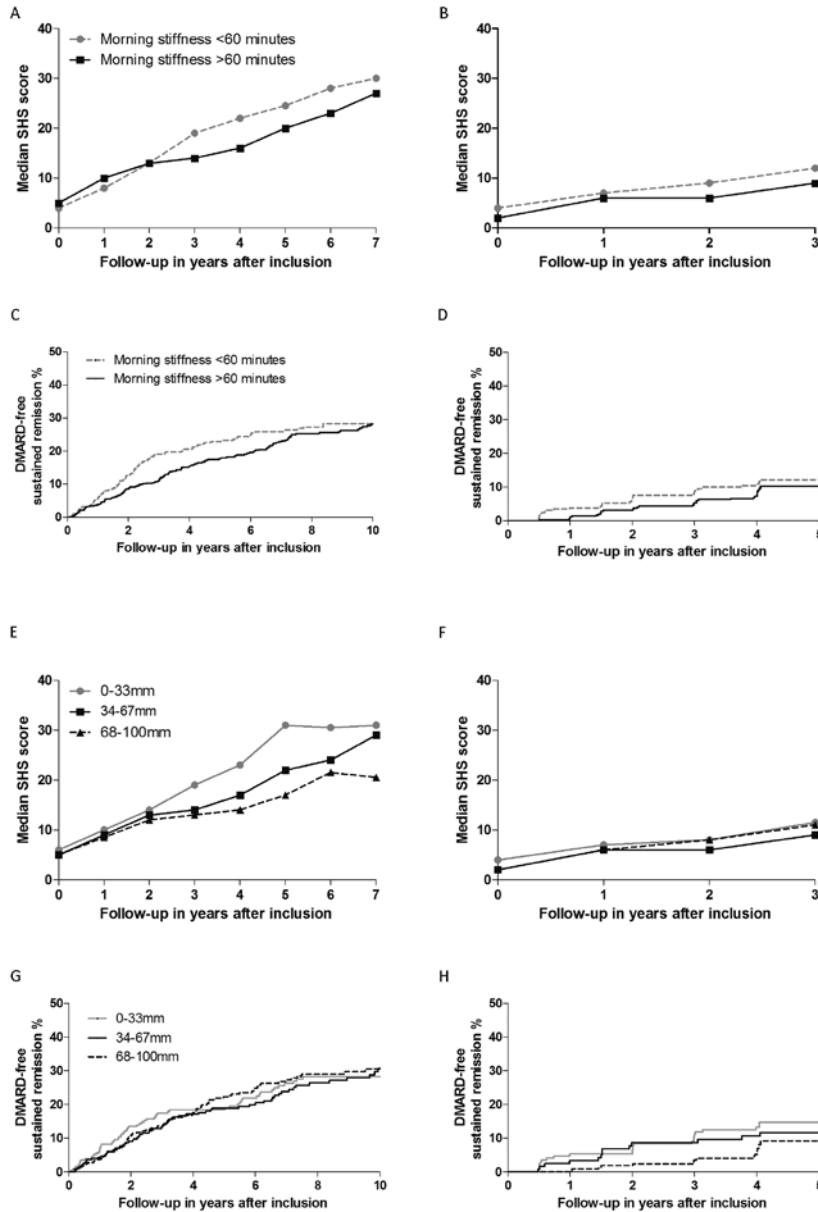
And if so, how long does this stiffness endures?

ESPOIR: via research nurse

Do you experience in stiffness in your joints in the morning.

And if so, how long does this stiffness endures?

Supplementary Figure 1. The severity of joint destruction (A, B, E, F) and the percentage of patients with DMARD-free sustained remission (C, D, G, H) in 2010 RA-patients in Leiden EAC (A, C, E and G) and ESPOIR (B, D, F and H) with the presence (≥ 60 minutes) and absence of mornings stiffness at baseline and VAS morning stiffness.



SHS- Sharp-van der Heijde score (SHS)

A: β 0.98 (95%CI 0.96-1.00) $p=0.054$

B: β 1.05 (95%CI 1.00-1.10) $p=0.076$ The beta of morning stiffness is presented with an interaction with time, indicating the relative difference in progression rate of patients with morning stiffness compared to patients without morning stiffness per year of follow-up.

C: EAC log rank $p=0.21$, HR 0.85 (95%CI 0.65-1.11).

D: ESPOIR log rank $p=0.34$, HR 0.80 (95%CI 0.50-1.29).

E: $\beta_{34-67mm}$ 1.00 (95%CI 0.97-1.03) $p=0.75$, $\beta_{68-100mm}$ 1.01 (95%CI 0.98-1.04) $p=0.48$

F: $\beta_{34-67mm}$ 1.03 (95%CI 0.96-1.10) $p=0.53$, $\beta_{68-100mm}$ 1.02 (95%CI 0.96-1.09) $p=0.45$ VAS morning stiffness of 0-33mm is used as reference group.

G: EAC log rank $p=0.919$, HR_{34-67mm} 0.72 (95%CI 0.49-1.04) HR_{68-100mm} 0.79 (95%CI 0.55-1.12) VAS morning stiffness of 0-33mm is used as reference group

H: HR_{34-67mm} 0.60 (95%CI 0.34-1.06) HR_{68-100mm} 0.52 (95%CI 0.28-0.98) VAS morning stiffness of 0-33mm is used as reference group

Performing similar analyses for the severity of joint destruction when defining morning stiffness as ≥ 30 minutes revealed the following results: EAC β 1.00 (95%CI 0.97-1.03) $p=0.98$, ESPOIR β 1.06 (95%CI 1.00-1.12) $p=0.058$. When morning stiffness was defined as ≥ 90 minutes the results were: EAC β 0.98 (95%CI 0.96-1.00) $p=0.11$, ESPOIR β 1.04 (95%CI 0.99-1.10) $p=0.13$. Sensitivity analyses on DMARD-free sustained remission were as follows with morning stiffness defined as ≥ 30 minutes: log rank $p=0.91$ HR 0.90 (95%CI 0.65-1.23) in EAC and log rank $p=0.65$ HR 0.83 (95%CI 0.349-1.41) in ESPOIR and when morning stiffness was defined as ≥ 90 minutes: log rank $p=0.55$ HR 0.94 (95%CI 0.71-1.23) in EAC and log rank $p=0.23$ HR 0.80 (95%CI 0.47-1.37) in ESPOIR.



CHAPTER 7

The *PTPN22* susceptibility risk variant is not associated with the rate of joint destruction in anti-citrullinated protein antibody-positive rheumatoid arthritis

A missense single-nucleotide polymorphism in the protein tyrosine phosphatase non-receptor 22 (*PTPN22*) gene, which encodes a negative regulator of T-cell activation, is an important genetic risk factor for rheumatoid arthritis (RA) susceptibility.¹ The association of the *PTPN22* susceptibility risk allele and the severity of joint destruction is unclear as a result of contradictory observations.^{2–6} To determine an individual patient's rate of joint destruction accurately, it is required that radiological measurements are collected by means of standard procedures, scored quantitatively and sensitively and are repeated in time. Consequently, differences in used measurements and analysis methods may contribute to the occurrence of contrasting findings. Second, although the effect of *PTPN22* on RA susceptibility is confined to the anti-citrullinated protein antibody (ACPA)-positive group,^{2,6} most studies on *PTPN22* and joint destruction did not analyse the ACPA-positive subset.^{2–5} The present study studied the effect of the *PTPN22* susceptibility risk variant on the rate of joint destruction in two large cohorts of ACPA positive RA patients, using sensitive methods for measurement and analysis.

The first cohort consisted of 593 RA patients from the Leiden Early Arthritis Clinic,⁷ of whom 55% were ACPA-positive. Radiographs were made at baseline and on consecutive years. The radiographs were scored by one experienced scorer. The intraclass observer correlation coefficient was 0.91. The progression in Sharp van der Heijde score (SHS) during 6 years of follow-up was compared between RA patients with and without the risk variant (T allele) of rs6679677, a perfect proxy for rs2476601/C1858T ($r^2=1$), using a repeated measurement analysis. Such analysis takes advantage of the longitudinal, repetitive character of the data and does not exclude patients with incomplete follow-up data, avoiding selection bias. In a linear mixed model with radiological score as response variable, the effect of time was assumed to be linear in the interaction terms. *PTPN22* and its interaction with time were entered in the model, to test whether *PTPN22* T/non-T carriers had different radiological scores over time. Age, gender and inclusion period (a proxy for treatment strategy) were entered in the model to correct for possible confounding effects.⁸

The replication cohort consisted of 397 ACPA-positive RA patients from the North American Rheumatoid Arthritis Consortium with cross-sectional radiological measurements (SHS) and genotypic data of rs2476601. Estimated radiological progression rates per year were compared using the Mann–Whitney test. In this cohort, no corrections were made for age, gender or treatment.

In the first cohort, 69.0% of RA patients were women and the mean age was 56.4 ± 15.8 years. The genotype frequencies (GG/GT/TT) were 462/120/11 (77.9%/20.2%/1.9%). The presence of the T allele (TT+TG genotype) was not associated with a higher rate of radiological joint destruction compared with the absence of this allele (GG genotype)

($p=0.10$ and $p=0.93$, respectively, in ACPA-positive and in all RA patients) (figure 1). In the second cohort, 72.8% of the patients were women and the mean age was 40.8 ± 12.0 years. The genotype frequencies (CC/CT/TT) were 282/105/10 (71%/26%/3%). Again, no significant difference in estimated radiological progression per year was found (median 2.11 Sharp units per year in the CC group vs 2.4 Sharp units per year in the TT+TC group, $p=0.22$). The exclusion of 10 genetic outliers did not change these results.

Using the present Early Arthritis Clinic data, this study had a power of 0.986 to detect a difference of 2.14 SHS scores with a SD of 4.07 (difference in increase in SHS over 6 years) and an α of 0.05; indicating that this study was sufficiently powered to prevent false-negative findings.

In conclusion, this study shows that *PTPN22*, although it predisposes to ACPA-positive RA, is not associated with RA severity measured by the radiological rate of joint destruction, proving a further indication that the contribution of *PTPN22* to RA is primarily found in setting the balance involved in the emergence of ACPA.

A total of 315 ACPA-positive patients had radiographs available. The number of radiographs declined from 303 to 267, 251, 212, 185, 169 and 139, respectively, from baseline to the 6-year follow-up. The available radiographs of the total RA population were in total 593, this declined to 577, 488, 442, 365, 309, 263 and 212, respectively, from baseline to the 6-year follow-up.

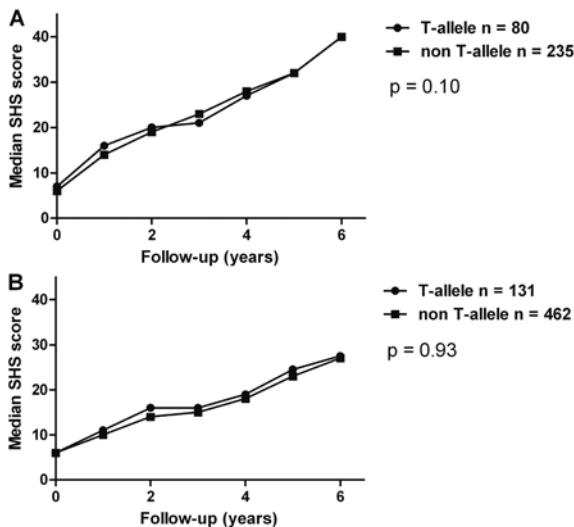


Figure 1. Median Sharp van der Heijde score (SHS) during 6 years of follow-up for patients with and without the T allele of protein tyrosine phosphatase non-receptor 22 (PTPN22) (A) in anti-citrullinated protein antibody-positive rheumatoid arthritis (RA); (B) as well as all RA in the Early Arthritis Clinic.

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CHAPTER 8

Evaluating processes underlying the predictive value of baseline erosions for future radiological damage in early rheumatoid arthritis

Jessica A.B. van Nies, Hanna W. van Steenbergen,
Annemarie Krabben, Wouter Stomp, Tom W.J. Huizinga,
Monique Reijnierse, Annette H.M. van der Helm-van Mil

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ABSTRACT

Objectives

Baseline erosions are characteristic for rheumatoid arthritis (RA) and predictive for a severe disease course. The mechanisms leading to baseline erosions being a strong predictor for radiological progression are unknown. We aimed to increase this understanding by mediation analyses in an observational cohort and a cross-sectional MRI study.

Methods

3256 hands and feet radiographs of 653 early RA patients assessed during 7 years of disease were scored using the Sharp-van der Heijde-method. Mediation models and multivariate regression analyses were used to explore the association between baseline erosions, other predictors and radiological damage over time. 603 joints (MCP2-5 and MTP1-5) of 67 RA patients underwent 1.5 T MRI at baseline. Data on MRI inflammation were compared with clinical inflammation and baseline radiological erosions.

Results

Patients with baseline erosions had, at any point in time during 7 years, 3.45 times more joint damage than patients without erosions ($p < 0.001$, 95% CI 3.00 to 3.98). Baseline erosions were an independent predictor and not a mediator between symptom duration, systemic or local clinical inflammation (erythrocyte sedimentation rate (ESR), swollen joint count (SJC)) or autoantibodies (anti-citrullinated-peptide antibodies, rheumatoid factor) and radiological damage. Subclinical MRI inflammation was studied in relation to erosions, revealing that 83% of the non-swollen joints with baseline erosions had subclinical MRI inflammation compared with 25% of the non-swollen joints without baseline erosions (OR 15.2 95% CI 3.1 to 102.1). The association between MRI inflammation and baseline erosions was independent of symptom duration, ESR, SJC and autoantibodies.

Conclusions

Baseline erosions are a predictor for future joint damage, independent of known predictors as time, autoantibodies or clinical measurable inflammation. Subclinical inflammation is suggested as an underlying mechanism.

INTRODUCTION

Erosions are characteristic for rheumatoid arthritis (RA) and occur in a majority of RA patients during the disease. A proportion of patients have erosions on hands or feet radiographs already at first presentation. For decades, information on the presence of bone erosions is used to classify RA. In the 1958 ARA criteria, radiographic changes typical of RA were part of the criteria; this concerned decalcification of joints that was not confined to hands or feet.¹ Presence of erosions on hand or wrist radiographs was one of the seven 1987 ACR classification criteria.² Here it was not defined what type of erosive lesions or what number of lesions were required for satisfying this criterion. According to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria, RA can be classified in two ways: by scoring six points on the basis of these criteria, or by having RA-specific erosiveness.^{3,4} According to the definition developed by an EULAR task force, RA-specific erosiveness concerns three or more metacarpal phalangeal (MCP), wrist or metatarsophalangeal (MTP) joints with a cortical break.⁴ Altogether, baseline erosions are considered typical for RA and are relevant to classifying RA.

Presence of erosions at first presentation is also a predictor for the further progression of structural damage.^{5,6} It has thus far not been thoroughly explored whether the association between baseline erosions and disease outcome is mediated by associations between other predictors and radiological progression. In a study on 112 RA patients multivariable analyses were performed and it was concluded that the baseline erosion score was the most important prognostic factor for the severity of joint damage after 10 years.⁷ Nonetheless, it remains undetermined whether baseline erosions have a direct relationship with structural damage or that it acts in the path of other risk markers for a severe destructive disease course.

In other words, although it is common practice to screen early arthritis patients for the presence of erosions with hand and foot radiographs, it has to the best of our knowledge not yet been thoroughly explored by what mechanism baseline erosions are associated with the development of further joint damage. Several possible mechanisms can be hypothesized. It is possible that RA patients with erosions at first presentation have a more advanced disease than patients without baseline erosions. This would imply that patients with baseline erosions do not have a more severe disease but they just visit rheumatologists at a later point in time. An alternative explanation is that the presence of baseline erosions is a hallmark of severe disease. Then baseline erosions are expected to be more frequently present in RA patients with high levels of inflammation or in RA patients carrying autoantibodies. Interesting in this respect are the recent observations suggesting that anticitrullinated peptide antibodies (ACPA) themselves stimulate

osteoclast differentiation and bone loss.⁸ Other hypotheses for the method by which baseline erosions reflect a marker for more severe progression may also be proposed.

We aimed to increase the understanding of mechanisms leading to baseline erosions being a strong predictor for structural damage. We addressed this question by evaluating the relationships between different predictors for structural damage using mediation models and multivariate regression analyses. Data of two sets of RA patients were explored to this end: a set of 653 RA patients with radiological follow-up over 7 years of disease and a set of 67 RA patients with baseline radiographs and MRI data.

METHODS

Patients

All RA patients that were studied fulfilled the 2010 ACR/EULAR criteria by scoring six points and were included in the Leiden Early Arthritis Clinic (EAC) Cohort, a large inception cohort that started in 1993.⁹ Inclusion took place when synovitis was confirmed by physical examination and symptom duration was <2 years. At baseline, patients were asked about their joint symptoms and subjected to physical examination, including a 66 swollen joint count (SJC). Blood samples were taken, amongst others, for determination of the erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and ACPA. Follow-up visits occurred yearly. Radiographs of hands and feet were taken at baseline and thereafter annually. Since August 2010, extremity MRI was added to the baseline visit. Two sets of RA patients were extracted from the EAC database. First, in order to evaluate structural damage over 7 years of disease, we studied RA patients consecutively included between 1993 and 2006 (dataset A). Different treatment strategies were used over time. Patients included between 1993 and 1995 were initially treated with non-steroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs were started later after a median of 5 months (and generally within 2 years' time).¹⁰ Patients included between 1996 and 1998 were initially treated with chloroquine or sulfasalazine, and patients included after 1999 were promptly treated with methotrexate or sulfasalazine.¹⁰ In the analyses, the inclusion period was used as a proxy for the applied treatment strategy as described previously.¹¹

The second dataset consisted of consecutive RA patients who underwent extremity MRI during the first visit in addition to the regular baseline visit. These patients were included between 2010 and 2012 (dataset B). In this cross-sectional study, radiographic erosions at baseline were related to MRI findings.

All patients gave informed consent. The study was approved by the local Medical Ethics Committee.

Radiologic measurements

Baseline erosions were defined similar to the 2010 criterion for RA-specific erosiveness.^{4,12} Patients with ≥ 3 erosive small joints were considered 'positive' and patients with 0-2 erosive joints were considered 'baseline erosions negative'.

All radiographs obtained during 7 years in dataset A were scored according to the Sharp-van der Heijde (SHS) method by two readers with known time order and blinded to clinical data. Within-reader intraclass-observer correlation coefficients (ICC) were 0.91 and 0.87 and the between-reader ICC was 0.89. The baseline radiographs of dataset B were SHS scored by one reader (ICC 0.86). In the analyses that were done on joint level, a joint was considered erosive in case of a SHS-erosion score ≥ 1 .

MRI measurements

MRI examinations were performed on a MSK Extreme 1.5 T dedicated extremity scanner (GE, Wisconsin, USA). The recommended RAMRIS imaging set was acquired for the wrist, MCP and MTP joints. See the online supplementary methods for a detailed scanning protocol. Joints were scanned at the most painful, or if indifferent, dominant side. MRIs were scored according to RAMRIS by two readers independently, blinded to clinical data.¹³ The within-reader ICCs for the total RAMRIS score were 0.98 and 0.83; the between-reader ICC was 0.82. For all analyses, the synovitis and bone marrow oedema scores were assessed; the sum was called MRI inflammation. For analyses on joint level, MRI inflammation data on MCP(2-5) and MTP (1-5)-joints were extracted; MRI inflammation data on wrists were not used, as part of the carpal bones assessed with RAMRIS cannot be accurately evaluated on radiographs, prohibiting direct comparisons. For analyses on joint level, MRI inflammation data were categorized. MRI inflammation was considered to be present when both readers scored ≥ 1 for synovitis and/or bone marrow oedema at that joint or bone. An independent third reader was used in case of discordant scores, if 2/3 readers scored ≥ 1 MRI inflammation was considered present. For analyses on patient level the total MRI inflammation score, the sum of all scanned joints, was evaluated.

Analyses

For comparisons between groups, Student t test, Mann-Whitney test or χ^2 - test were used when appropriate. Multivariate normal regression analysis for repeated measurements with radiological damage as response variable was used on log-transformed radiological data as described elsewhere.^{11,14} This model takes advantage of within-patient correlations of serial radiographs and allows inclusion of patients with missing radiographs at certain time-points. All analyses were adjusted for age, gender and treatment strategy. First, the association between baseline erosions and joint damage over time was assessed. Then mediation analyses were performed to

investigate whether baseline erosions acted as a mediator between presumed predictors and structural damage over time. The presumed predictors for structural damage were: symptom duration (in weeks) as representative of the disease duration, presence of the autoantibodies ACPA and RF, the level of systemic inflammation as represented by the ESR and the extend of clinical local inflammation reflected by the SJC. A path diagram was used as described by Baron and Kenny to depict a causal chain (see figure 1).¹⁵ This illustrates the two causal paths that can lead to the outcome; a direct path from the independent to the outcome (c) and an indirect path from the mediator to the outcome (b). Finally, a path exists from the independent to the mediator (a). To test for mediation three regression analyses need to be performed.¹⁵ (1) Regress the mediator on the independent variable (a); the independent should significantly affect the mediator. (2) Regress the dependent (outcome) on the independent variable (c); the independent variable should significantly affect the outcome. (3) Regress the dependent on both the independent and the mediator. In case of mediation the mediator is significantly associated with the outcome and the effect of the independent variable on the outcome is less than in step 2 (partial mediation) or absent (full mediation). Baseline radiographic and MRI data were analysed by logistic regression. SPSS V.20.0 was used. p Values <0.05 were considered significant.

RESULTS

Baseline characteristics

Of the 653 RA patients studied in dataset A, 53% had baseline erosions (≥ 3 erosive joints). Table 1 presents the baseline characteristics. Overall patients with baseline erosions were older, more often male (36.3% vs 26.1%), more often RF-positive (65.4% vs 55.9%) and had higher ESR (median 39.5 vs 27.0 mm/hr). The median symptom duration was similar in both groups.

Baseline erosions are a predictor for future radiological damage

First baseline erosions were studied in relation to radiological damage over 7 years. This demonstrated that patients with baseline erosions had 3.45 times (95% CI 3.00 to 3.98, $p < 0.001$) more radiological damage at any point in time than patients without baseline erosions.

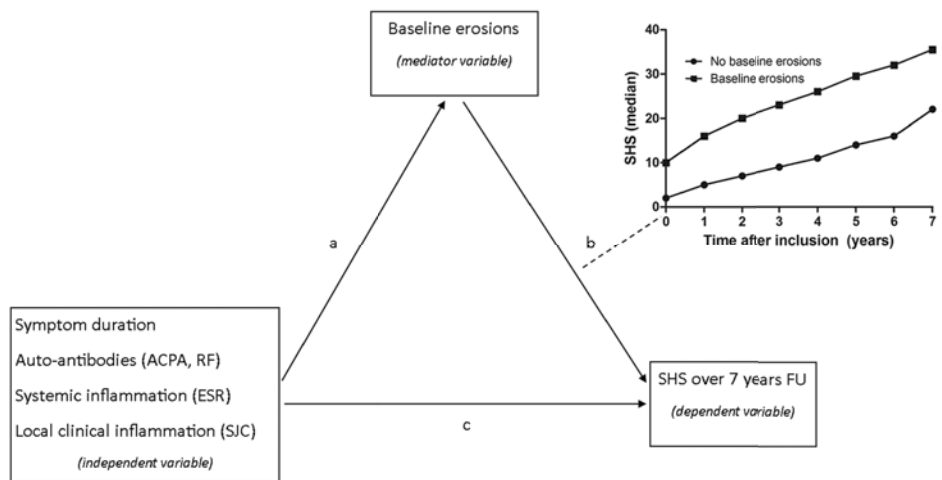


Figure 1. Schematic overview of the causal paths that were studied using mediation models as described by Baron and Kenny.

Legend Figure 1. The diagram illustrates the two causal paths that can lead to the outcome; a direct path from the independent to the outcome (c) and an indirect path from the mediator to the outcome (b). Finally a path exist from the independent to the mediator (a). According to the description of Baron and Kenny, to test for mediation the following three regression analyses need to be performed.¹⁵ (1) Regress the mediator on the independent variable (a); the independent should significantly affect the mediator. (2) Regress the dependent (outcome) on the independent variable (c); also here the independent variable should significantly affect the outcome. (3) Regress the dependent on both the independent and the mediator; in case of mediation the mediator is significantly associated with the outcome and the effect of the independent variable on the outcome is less than in step 2 (partial mediation) or there is no effect at all (full mediation). In this study we tested the following hypothesis; Do baseline erosions act as a mediator in the path of symptom duration, or in the path of autoantibodies (anticitrullinated-peptide antibodies (ACPA) and rheumatoid factor (RF)), or in the path of systemic inflammation (measured using the erythrocyte sedimentation rate), or in the path of local clinical inflammation (measured using the swollen joint count). Suppose baseline erosions act in the path of symptom duration, symptom duration is associated with baseline erosions (a) and with structural damage over 7 years (c) but when baseline erosions and symptom duration are both included in the model, symptom duration is no longer associated with structural damage (full mediation) or the effect size of symptom duration in relation to structural damage over 7 years has diminished (partial mediation). The β for baseline erosions on structural damage over 7 years was 3.45 (95% CI 3.00 to 3.98 $p < 0.001$). Thus patients with baseline erosions had 3.45 times more radiological damage at any point during follow-up than patients without baseline erosions. SHS, Sharp–van der Heijde score.

Table 1. Baseline characteristics of RA patients with and without baseline erosions (dataset A) and of RA patients who underwent an extremity MRI (dataset B).

	All patients (dataset A) n=653	No baseline erosions n=295	Baseline erosions n=344	Patients with MRI (dataset B) n=67
Age, years, mean±SD	57.1±15.9	48.7±14.5	62.7±14.0*	56.7±13.3
Female, n (%)	449 (68.8)	218 (73.9)	219 (63.7)*	41(61.2)
Symptom duration, weeks	19.6 (11.1-37.3)	19.0 (10.7-36.4)	19.8 (11.1-39.9)	17.3 (8.9-34.7)
<12 weeks symptom duration, n (%)	181 (27.7)	86 (29.2)	93 (27.0)	23 (34.3)
ACPA-positive, n (%)	358 (54.8)	150 (50.8)	198 (57.6)	40 (59.7)
RF-positive, n (%)	399 (61.1)	165 (55.9)	225 (65.4)*	42 (62.7)
ESR, mm/h	33 (19.0-54.0)	27.0 (14.0-44.5)	39.5 (23.0-59.3)*	25 (9.0-38.0)
Swollen joint count (66-SJC)	9 (5-15)	9 (5-14)	9 (4-15)	5 (3-10)

Data are presented as median (IQR) unless indicated otherwise.

Baseline erosions are present in case of ≥3 erosive joints.

Missing data in dataset A; Symptom duration n=31, ACPA n=23, ESR n=4, HAQ n=103, baseline radiographs n=14.

*p Value <0.05 for comparison with patients without erosions, analysed with χ^2 -test, Students t test or Mann-Whitney U test where appropriate.

ACPA, anticitrullinated peptide antibodies; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count.

Baseline erosions are not a mediator of symptom duration

We then hypothesized that patients who have baseline erosions are more advanced in their disease and that baseline erosions are a mediator between symptom duration at baseline and radiologic damage over time. Step 1 of the mediation analysis showed no significant association between symptom duration and baseline erosions (table 2). Patients with baseline erosions had symptoms for median 19.8 weeks and patients without erosion for median 19.0 weeks. Thus, baseline erosions did not act as a mediator in the path of symptom duration.

Table 2. Results of the individual steps of the performed mediation analyses

	Effect (OR)	95% CI	P Value
<i>Step 1: (a) baseline erosions (as possible mediator)</i>			
Symptom duration, per week	1.00	1.00-1.01	0.21
ACPA positive	1.24	0.90-1.71	0.18
RF positive	1.49	1.08-2.05	0.015
Systemic inflammation, per mm/hour	1.01	1.01-1.02	<0.001
Local clinical inflammation, per SJ	1.00	0.98-1.02	0.79
	Effect (β)	95% CI	P Value
<i>Step 2;(c) SHS over 7 years of FU (dependent)</i>			
Symptom duration, per week	1.0037	1.0016-1.0060	0.001
ACPA-positive	1.11	1.09-1.14	<0.001
RF-positive	1.08	1.05-1.10	<0.001
Systemic inflammation, per mm/h	1.0004	0.9999-1.0008	0.07
Local clinical inflammation, per SJ	0.9977	0.9963-0.9991	0.001
	Effect (β)	95% CI	p-value
<i>Step 3: (b+c) SHS over 7 years of FU (dependent)</i>			
<i>Each variable together with baseline erosions</i>			
Symptom duration, per week	1.0019	1.0002-1.0037	0.03
Baseline erosions	3.35	2.90-3.87	<0.001
ACPA-positive	1.14	1.12-1.16	<0.001
Baseline erosions	3.35	2.90-3.87	<0.001
RF-positive	1.10	1.07-1.12	<0.001
Baseline erosions	3.39	2.94-3.91	<0.001
Systemic inflammation, per mm/h	1.0005	1.0000-1.0009	0.01
Baseline erosions	3.45	6.40-3.98	<0.001
Local clinical inflammation, per SJ	0.9974	0.9961-0.9988	0.14
Baseline erosions	3.46	3.00-3.99	<0.001

Effects are given per unit increase, for example, per week increase in symptom duration , per unit increase in mm/h and per unit increase in swollen joints.

Steps 1, 2 and 3 are explained in figure 1. In step 1, a logistic regression analysis is performed and in steps 2 and 3 a multivariate normal regression analysis. ACPA, RF, ESR and SJC associated with radiological progression with interaction with time, indicating a more severe progression rate per year of follow-up. For instance, for ACPA the β is 1.11/year and this is equal to a $1.11^7=2.08$ times higher rate of joint destruction over 7 years, which is equal to a 108% increase in rate of joint destruction. Symptom duration and baseline erosions were significantly associated with radiological damage and that effect was constantly present during follow-up. For more methodological information see ref. 11

ACPA, anticitrullinated-peptide antibodies; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SHS, Sharp-van der Heijde score; SJ, swollen joint; SJC, swollen joint count.

Baseline erosions are not a mediator of the presence of RA-related autoantibodies

Since ACPA and RF are associated with severe radiological joint damage, we then speculated that these autoantibodies are associated with baseline erosions and more subsequent joint damage. We therefore sought to determine whether baseline erosions acted as a mediator in the path of ACPA or RF. In step 1, ACPA had no significant effect on baseline erosions, whereas RF was significantly associated with baseline erosions (OR 1.49, 95% CI 1.08 to 2.05, $p=0.02$, table 2). Step 2 showed that RF had a significant effect on radiological damage over 7 years (β 1.08, 95% CI 1.05 to 1.10, $p<0.001$). Finally, RF and baseline erosions both had a significant effect on radiological damage over time in step 3 (β 1.10, 95% CI 1.07 to 2.12, $p<0.001$ and β 3.39, 95% CI 2.94 to 3.91, $p<0.001$ respectively). However, the conditions on mediation did not hold; namely the effect size of RF was not diminished in the analysis of step 3 ($\beta=1.08$ and $\beta=1.10$ respectively) and statistically significant. ACPA was not significantly associated with baseline erosions in step 1, and step 3 revealed that baseline erosions were independently associated with radiological damage when adjusted for ACPA (table 2). Therefore, baseline erosions were not a mediator between RA-related autoantibodies and radiological damage over 7 years.

Baseline erosions are not a mediator of systemic or local clinical inflammation

The next hypothesis was that baseline erosions occurred in patients with high levels of inflammation and that this actually drives the association between baseline erosions and radiological joint damage over time. The ESR and SJs were considered to reflect systemic and local inflammation. In step 1, only a significant effect was found for ESR (OR 1.01 95% CI 1.01 to 1.02, $p<0.001$, table 2) However, in step 2, no significant effect was observed between ESR and long-term structural damage; therefore, the conditions on mediation were not met. Altogether baseline erosions had an effect on radiological joint damage independent of systemic or clinically measured local inflammation.

Baseline erosions independent in multivariate model

Subsequently, all potential predictors for severe joint damage (symptom duration, ACPA, RF, SJC and ESR) were included in a multivariate regression model with radiological damage over 7 years as outcome (table 3). Patients with baseline erosions had 3.23 times more joint damage at any point during follow-up versus patients without baseline erosions (95% CI 2.79 to 3.74, $p<0.001$, figure 1, table 3). Thus presenting with baseline erosions was associated with a worse radiological outcome over time, and this could not be explained by the studied known predictors.

Table 3. The results of a multivariate analysis including nine variables and joint damage over 7 years as outcome.

	Effect (β)	95% CI	p Value
Baseline erosions	3.23	2.79-3.74	<0.001
Symptom duration, per week	1.0023	1.0004-1.0041	0.01
ACPA-positive	1.12	1.09-1.15	<0.001
RF-positive	1.03	1.01 -1.06	0.02
Systemic inflammation (ESR), per mm/h	1.0003	0.9999-1.0007	0.14
Local clinical inflammation (SJC), per SJ	0.9997	0.9983-1.0011	0.68
Age at inclusion	1.022	1.016-1.026	<0.001
Male sex	0.90	0.79-1.01	0.07
Treatment strategy 1	1.09	1.06-1.03	<0.001
Treatment strategy 2	1.06	1.03-1.08	<0.001

Effects are given per unit increase, for example, per week increase in symptom duration , per unit increase in mm/h and per unit increase in swollen joints.

Treatment strategy represents three different inclusion periods in which different treatment strategies were applied. Treatment strategy 1; patients included between 1993 and 1995 were initially treated with non-steroidal anti-inflammatory drugs. Treatment strategy 2; patients included between 1996 and 1998 were initially treated with chloroquine and sulfasalazine. Treatment strategy 3; patients included after 1999 were promptly treated with methotrexate or sulfasalazine, this was used as reference category and therefore not depicted in the table. ACPA, RF, ESR, SJC and treatment strategies 1 and 2 associated with radiological progression with an interaction with time, indicating a more severe progression rate per year of follow-up. For instance, for ACPA the β is 1.12/year and this is equal to a $1.12^7=2.21$ times higher rate of joint destruction over 7 years, which is equal to a 121% increase in rate of joint destruction. Symptom duration, baseline erosions, age and sex were significantly associated with radiological damage and that effect was constantly present over time.

ACPA, anticitrullinated-peptide antibodies; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SJ, swollen joint; SJC, swollen joint count.

Joints with baseline erosions often show subclinical inflammation on MRI

To further explore mechanisms underlying baseline erosions as predictor for future joint damage, we evaluated whether they were associated with subclinical inflammation, which can be visualized by MRI in clinically non-swollen joints. Of the 603 MCP and MTP joints studied, 491 were clinically not swollen. Of these, MRI and radiographic data were available on 485 joints (for technical reasons 6/491 joints could not be evaluated on MRI). Joints with subclinical inflammation (MRI inflammation in clinically non-swollen joints) had radiographic erosions substantially more often compared with joints without subclinical inflammation (83% vs 25%, OR 15.2 95% CI 3.1 to 102.1, table 4).

Table 4. Frequency of subclinical inflammation in 485 clinically non-swollen MCP and MTP joints in relation to the presence of baseline erosions on hand and foot radiographs in 67 RA patients

	Baseline erosions	No baseline erosions	Total
MRI subclinical inflammation	10 (83%)	117 (25%)	127
No MRI subclinical inflammation	2 (17%)	356 (75%)	358
Total	12 (100%)	473(100%)	485

All joints that were assessed with MRI were also depicted on radiographs and scored accordingly. Joints with subclinical inflammation (MRI inflammation in clinically non-swollen joints) had more frequently baseline erosions compared to joints without subclinical inflammation (OR 15.2, 95% CI 3.1 to 102.1).

MCP, metacarpal phalangeal; MTP, metatarsophalangeal; RA, rheumatoid arthritis.

MRI inflammation is independently associated with baseline erosions

Finally, we studied, on patient level, whether MRI inflammation at disease presentation was associated with baseline radiographic erosions independent of other possible predictors for erosions. In a logistic regression analysis with the presence of baseline erosions as outcome, the MRI inflammation score was associated with an increased odds of erosions (OR 1.11 95% CI 1.02 to 1.20) independent of SJC, ESR, ACPA, RF or symptom duration (table 5).

Table 5. Associations with radiographic baseline erosions (≥ 3 erosive joints) as outcome in 67 RA patients that had both radiographic and MRI data at baseline.

	Univariable			Multivariable		
	OR	95% CI	p Value	OR	95% CI	p Value
Age at inclusion, years	1.06	1.01 to -1.10	0.01	1.01	0.91 to 1.11	0.91
Male sex	0.78	0.29 to 2.10	0.63	0.33	0.05 to 2.48	0.28
Symptom duration, weeks	1.01	1.00 to 1.02	0.20	1.02	1.00 to 1.04	0.09
ACPA-positive	0.88	0.33 to 2.35	0.80	0.77	0.05 to 11.6	0.85
RF-positive	0.69	0.26 to 1.87	0.47	0.74	0.08 to 7.04	0.79
Systemic inflammation (ESR)	1.01	0.99 to 1.03	0.19	0.99	0.95 to 1.03	0.54
Local clinical inflammation (SJC)	1.11	1.01 to 1.23	0.03	1.05	0.87 to 1.26	0.63
MRI inflammation score	1.11	1.04 to 1.19	0.001	1.11	1.02 to 1.20	0.02

Both univariable and multivariable analyses were done on patient level. The MRI inflammation score was defined as the sum of the synovitis-score and bone-marrow-oedema score according to RAMRIS. This variable was associated with the presence of baseline erosions, defined as the presence of ≥ 3 erosive small hand or feet joints, as outcome. This association was independent of other predictors including markers of local clinical inflammation (SJC) and systemic inflammation (ESR).

ACPA, anticitrullinated-peptide antibodies; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count.

DISCUSSION

Baseline erosions are used in classification criteria for RA¹⁻³ and are one of the most potent predictors for future joint damage.¹⁶ Surprisingly, thus far no studies thoroughly explored potential mechanisms underlying this association. During the present study, we observed that baseline erosions are not located in the causal path of disease duration (symptom duration), autoantibodies (ACPA, RF) or commonly used markers of inflammation (SJC, ESR). Furthermore, we observed that the large majority of joints presenting with baseline erosions also showed subclinical inflammation. Combined together, these data suggest that subclinical inflammation is relevant for the development of baseline erosions.

Association analyses as performed in the present study provide only an indication of causality. More conclusive evidence on causal relationships can be obtained from animal models where specific proteins can be knocked out or in relation to the current manuscript where inflammation can be induced and subsequent MRIs and radiographs of extremities can reveal the induced changes in joints and bone.¹⁷ In humans, however, such approaches cannot be adopted and mediation models were used as substitute. An advantage of mediation analysis is that known predictors were assessed separately. This yielded a higher certainty to conclude on causal paths than could be obtained from multivariable analysis.

No uniform definition of baseline erosions exist. Previous studies used different definitions, such as any radiological evidence of erosions, a cortical break of $\geq 2\text{mm}$, presence of two or three erosions, or a certain Larsen or SHS score.^{7,18-22} In this study, erosive disease was defined as having ≥ 3 erosive joints, which is the same as the recently proposed definition of RA-specific erosiveness in light of the 2010 ACR/EULAR criteria.⁴ Notably, when applying another cut-off for erosive disease (≥ 2 erosive joints) similar results were obtained (data not shown). A limitation of any definition of erosions visualized with radiographs is that these are depicted only two-dimensionally.

The presence of baseline erosions was not a reflection of a longer symptom duration, suggesting that the duration of processes underlying the disease was similar in patients with and without erosions. Furthermore, differences in inflammation measured using ESR and SJC were insufficient to explain the association between baseline erosions and subsequent damage. No difference was found in the mediation analyses when CRP was used instead of ESR to reflect systemic inflammation (data not shown). In other words, these known risk factors for long-term joint damage (symptom duration, ESR and SJC) did not act via mechanisms that also promote baseline erosions. The biologic processes underlying the association between symptom duration and radiological outcome,²³ which is also called the 'window-of-opportunity' are unknown. Apparently, these processes do not promote baseline erosions. Of note, there might be risk factors for baseline or long-term structural damage that were not assessed in this study.

Intriguingly we observed no significant difference in the percentage of ACPA positivity in patients with and without baseline erosions (58% vs 51%). Because a recent study showed that ACPA itself is capable of activating osteoclast activity, even in the preclinical phase,⁸ we assumed that ACPA-positive patients had more frequent erosions at baseline. The absence of this finding does not imply that ACPA does not activate osteoclasts. Still, radiological visible bone erosions at disease presentation cannot be explained by the effect of ACPA.

We observed that inflammation measured with MRI is associated with the presence of baseline erosions independently of ESR, SJC, ACPA and symptom duration. More importantly, 83% of the non-swollen-joints with baseline erosions had subclinical swelling. These data suggest that previous or still present subclinical inflammation is important to develop baseline erosions and further joint damage. This finding at disease onset is in line with observations of others, showing the relevance of MRI inflammation of RA patients in remission.^{24,25} There are however several limitations. The number of MCP and MTP joints that had baseline erosions in dataset B was small. Furthermore, no long-term radiological outcome data were available of these joints. Thus, although a strong association was observed between subclinical inflammation and baseline erosions (step 1 of the mediation analyses), step 3, revealing that baseline erosions are a mediator in the causal path between subclinical inflammation and future joint damage, could not be evaluated. Nonetheless, despite these limitations, the finding that all but two clinically non-swollen joints with baseline erosions also had subclinical inflammation at MRI is suggestive. Since the MRIs were made at the same time as the radiographs it cannot be excluded that the baseline erosions in the two non-swollen joints without subclinical inflammation were related to previous local inflammation that resolved at the time of disease presentation.

In conclusion, this study is the first to explore mechanisms mediating the association between baseline erosions and future structural damage in early RA by taking advantage of both a large observational cohort and high-quality extremity MRI data. Present data suggest that local subclinical inflammation is relevant. Further studies on the long-term outcome of subclinical inflammation in the early clinical phase and presumably also in the preclinical phase of RA are warranted.

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SUPPLEMENTARY DATA

Supplementary file 1.

MR imaging

MR imaging of the hand (wrist and metacarpophalangeal joints) and forefoot (metatarsophalangeal joints) was performed within two weeks after inclusion, at the most painful side, or in case of completely symmetric symptoms at the dominant side. The presence of clinical arthritis at physical examination of the joints that were scanned was not a prerequisite. Patients with impaired renal function or known hypersensitivity or allergic reactions to contrast media were imaged without contrast administration (n=1).

MR imaging was performed on a MSK-extreme 1.5T extremity MR imaging system (GE, Wisconsin, USA) using a 145mm coil for the foot and a 100mm coil for the hand. The patient was positioned in a chair beside the scanner, with the hand or foot fixed in the coil with cushions.

The forefoot was scanned using a T1-weighted fast spin-echo (FSE) sequence in the axial plane with repetition time (TR) of 650 ms, echo time (TE) 17ms, acquisition matrix, 388×288, echo train length (ETL) 2; and a T2-weighted FSE sequence with frequency selective fat saturation in the axial plane (TR/TE 3000/61.8; acquisition matrix 300×224, ETL7). Due to time constraints, imaging of the foot was limited to pre-contrast sequences only.

In the hand, the following sequences were acquired before contrast injection: T1-weighted FSE sequence in the coronal plane (TR/TE 650/17ms; acquisition matrix 388×88; ETL2); T2-weighted FSE sequence with frequency selective fat saturation in the coronal plane (TR/TE 3000/61.8ms; acquisition matrix, 300×224, ETL7). After intravenous injection of gadolinium contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1 mmol/kg) the following sequences were obtained: T1-weighted FSE sequence with frequency selective fat saturation in the coronal plane (TR/TE 650/17ms, acquisition matrix 364×224, ETL2), T1-weighted FSE sequence with frequency selective fat saturation in the axial plane (TR/TE 570/7 ms; acquisition matrix 320×192; ETL2).

Field-of-view was 100mm for the hand and 140mm for the foot. Coronal sequences had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. All axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm, with 20 slices for the hand and 16 for the foot. Total imaging time was approximately 75 minutes.



CHAPTER 9

Long-term outcome of Rheumatoid Arthritis defined according to the 2010-classification criteria

Jessica A.B. van Nies*, Leonie E. Burgers*, L. Yvonne Ho, Diederik P.C. de Rooy, Tom W.J. Huizinga, Annette H.M. van der Helm-van Mil

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* contributed equally.

ABSTRACT

Objective

The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for rheumatoid arthritis (RA) have been thoroughly studied for the test characteristics but it is unclear whether '2010 RA' has a different phenotype than '1987 RA' when assessing the severity of the disease course. Therefore this study compared two long-term disease outcomes.

Methods

1502 early arthritis patients that had no other diagnoses than RA or undifferentiated arthritis (UA) were studied on fulfilling the 1987 ACR criteria, 2010 criteria or both. The severity of joint damage was studied with yearly radiographs over 7 years. Achieving disease-modifying antirheumatic drug (DMARD)-free sustained remission was assessed over 10-years follow-up. Multivariate normal regression and Cox-proportional hazard regression were used, adjusting for age, gender and treatment.

Results

550 patients fulfilled the 1987 criteria, 788 patients the 2010 criteria and 489 both criteria sets. Patients fulfilling the 2010 criteria developed less severe radiological joint damage ($p=0.023$) and achieved DMARD-free sustained remission more often ($HR=1.18$ ($0.93-1.50$)) than patients fulfilling the 1987 criteria, though the latter was not statistically significant. All 1987 +2010- patients were anti-citrullinated peptide antibody (ACPA)-negative. When also applying the radiologic criterion of the 2010-criteria, half of the 1987+2010- patients became 2010 criteria positive, but results on the long-term outcome remained similar.

Conclusions

'2010 RA' has a milder disease course than '1987 RA'. This may have important implications for basic scientific studies and clinical trials in RA.

INTRODUCTION

Presently rheumatoid arthritis (RA) can be classified according to either the 1987 ACR criteria or the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria. Both sets of criteria are being used and multiple studies have evaluated the performance of the 2010 criteria.¹⁻⁵ A formal meta-analysis on the test characteristic is in progress (personal communication H Radner), but the current impression is that the 2010 criteria, compared to the 1987 criteria, are more sensitive and less specific in classifying RA.¹ It is yet insufficiently clear whether the phenotype of RA is different when the disease is classified according to the 2010 criteria or the 1987 criteria. Several studies observed that some disease characteristics at disease onset of 2010 RA patients were milder than of 1987 RA patients.²⁻⁵ Some authors reported that erosions at baseline and after 2 years are more often present in 1987 RA compared to 2010 RA.^{2,4-6} Together, these data lead to the presumption that RA defined according to the 2010 criteria is milder in nature than that defined according to the 1987 criteria, but there is insufficient data to draw definite conclusions on this matter. Particularly, there are no studies comparing the long-term outcome of RA patients when RA is classified either to the 1987 criteria or the 2010 criteria. The most characteristic hallmarks of RA are progression of joint damage and disease persistence. We aimed to compare these two long-term disease outcomes in relation to the classification of RA and performed the present longitudinal study to this end.

METHODS

Patients

Early arthritis patients included in the Leiden Early Arthritis Clinic Cohort⁷ between 1993 and May 2011 were studied. Inclusion took place when arthritis was confirmed at physical examination and symptom duration was <2 years. At the first visit, patients and rheumatologists completed questionnaires, physical examination was performed, and serum and radiographs were taken. Follow-up visits were performed yearly. For further description, see reference 7. The treatment differed for different inclusion periods. Patients included between 1993 and 1995 were initially treated with NSAIDs, patients included between 1996 and 1998 were initially treated with chloroquine or sulfasalazine and patients included after 1999 were promptly treated with methotrexate or sulfasalazine. The inclusion period was used as a proxy for the applied treatment strategy in the analyses.

Of all 2748 included early arthritis patients, patients that at first visit had a clear diagnosis other than RA or undifferentiated arthritis were excluded (n=839), which is in line with the 2010 criteria. Patients that were treated in randomised clinical trials were

excluded (n=397) as the treatment of these patients was more tightly controlled and the medications used more potent, affecting the disease course. Patients with a follow-up <1 year were also excluded (n=10). Thus, 1502 patients were studied (figure 1A) and classified on fulfilling the 1987 ACR criteria and/or the 2010 ACR/EULAR criteria.

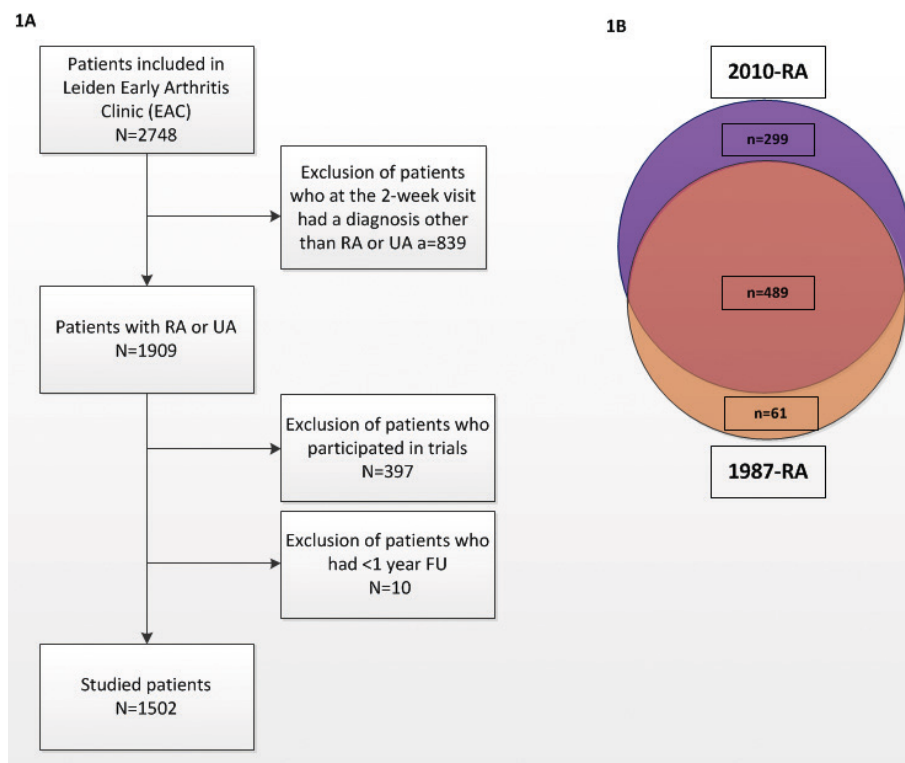


Figure 1. Flowchart of patient selection (A) and number of patients studied that fulfilled the 1987- and/or 2010 classification criteria at baseline (B)

Legend figure 1. (A) The 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria state that these criteria should not be applied in patients that have other diagnoses. For this reason, patients that at the 2-week visit (when the results of laboratory and radiological evaluations were known) had clear rheumatologic diagnoses were excluded. Patients that were treated according to trial protocols were excluded as well, as treatment strategies of these patients differed from the other patients. However, the trial patients were included in a sensitivity analysis. (B) Of the 1502 patients studied, 489 fulfilled both criteria sets for rheumatoid arthritis (RA) at the 2-week visit. 299 patients fulfilled only the 2010-criteria and 61 patients fulfilled only the 1987-criteria. 714 patients fulfilled none of the criteria sets for RA.

Outcome

Two outcome measures were studied. The first was the severity of radiological damage during 7 years of follow-up. Hand and feet x-rays were taken at baseline and yearly thereafter and scored according to the Sharp-van der Heijde method by two readers with known time order, blinded to clinical data. Intraclass-observer correlation coefficients within the readers were 0.91 and 0.87 and between the two readers, it was 0.89.

The second outcome was achieving a disease-modifying antirheumatic drug (DMARD)-free sustained remission during 10 years of follow-up. Remission was defined as the sustained absence of synovitis (by physical examination) after discontinuation of DMARD-therapy. Synovitis had to be absent for the entire period of follow-up and at least during 1 year⁸; in general, these patients were also discharged from the outpatient clinic. Patients that achieved such a remission but relapsed (n=13) were included in the non-remission group. This stringent definition of remission is the best possible outcome of RA as it approximates 'cure'; it is the opposite of disease persistency. Medical files of all patients were studied on remission, and this was determined until the 5 April 2012.

Statistical analyses

Analyses on remission were done using a Cox proportional hazard regression analysis.⁸ Analyses on joint destruction were done using a multivariate normal regression analysis as described previously, including all radiographs in one analysis and taking advantage of serial measurements.⁹ Another advantage is that it allowed to study all patients, also in case of missing radiographs, preventing selection bias that would be induced by a completers-only analysis.¹⁰ All analyses were adjusted for age, gender, and treatment strategy. First the long-term outcomes of patients with RA according to the 1987 criteria and RA according to the 2010 criteria were compared. In this analysis, patients that fulfilled both criteria sets were included in both groups. Subsequently all patients were split in three groups (1987+2010-, 1987-2010+ and 1987+2010+) and analyses repeated. SPSS V.20.0 was used. p Values <0.05 were considered significant.

RESULTS

Baseline characteristics

Of the 1502 patients studied, 550 patients fulfilled the 1987 criteria, 788 patients the 2010 criteria by having ≥ 6 points and 489 patients fulfilled both criteria (figure 1B). Table 1 presents the baseline characteristics. Overall, no large differences were seen between 1987 RA and 2010 RA, but 2010+ patients experienced less morning stiffness than 1987+ patients (median 60 vs 90 min) and had slightly lower C-reactive protein (CRP) levels. When comparing the three subgroups, it was observed that all 1987+2010- patients were anti-citrullinated peptide antibody (ACPA)-negative.

Comparison of 1987 and 2010 RA

RA patients according to the 2010 criteria had less severe radiological joint destruction over 7 years of disease than RA patients classified using the 1987 criteria ($p=0.023$, figure 2A). When evaluating DMARD-free sustained remission, more remission was achieved in 2010+ RA-patients than in 1987+ RA-patients, though this difference was not statistically significant ($HR=1.18(0.93-1.50)$ $p=0.17$, figure 2B).

Subanalyses

Subsequently, the RA patients were stratified in three groups (1987+2010–, 1987–2010+, 1987+2010+) and the analyses were repeated. As presented in figure 2 C,D, 1987+2010+ RA patients developed more severe joint destruction and achieved DMARD-free sustained remission less often than patients fulfilling one criteria set for RA ($p<0.001$ for both outcomes and comparison of three groups). Moreover, when analysing these subgroups in more detail, the severity of joint damage was not different between the 1987+2010+ and 1987+2010– patients ($p=0.35$) but differed between the 1987+2010+ and 1987 –2010+ patients, $p<0.001$, figures 2C,D). Interestingly, 1987 +2010– RA patients achieved DMARD-free sustained remission most frequently. However, this small subgroup contained only ACPA-negative patients. When the analysis was also adjusted for ACPA, this effect was no longer present (figure 2F).

Thus far, the 2010 criteria were applied using the point system. When applying the radiological criterion for RA-specific erosiveness (≥ 3 erosive joints)(11;12) in addition to the point system, 30 of the 61 1987+2010– RA were now 2010-criteria positive. All analyses on joint damage and remission were repeated; this did not influence the results (see online supplementary figures 1 and 2).

Finally, all analyses were repeated including the 397 patients that were treated in clinical trials, yielding similar results as described above (data not shown).

Table 1. Baseline characteristics of patients classified rheumatoid arthritis (RA) according to either the 1987 and/or the 2010- criteria.

Patient characteristic	1987-RA (n=550)	2010-RA (n=788)	1987-/2010+ (n=299)	1987+/2010+ (n=489)	1987+/2010-(n=61)
Age at inclusion, years, mean $\pm$ SD	57.9 $\pm$ 16.2	56.6 $\pm$ 16.4	54.7 $\pm$ 16.4	57.8 $\pm$ 16.2	58.9 $\pm$ 15.8
Female sex	377 (68.5)	536 (68.0)	198 (66.2)	338 (69.1)	39 (63.9)
Symptom duration in weeks, median (IQR)	21.9 (12.7-38.1)	19.9 (10.6-37.3)*	15.0 (5.9-31.3)	22.0 (13.0-40.0)	15.7 (10.8-31.8)
Symptom duration < 12 weeks	120 (23.5)	221 (29.7)*	119 (41.2)	102 (22.4)	18 (33.3)
Swollen joint count of 66 joints, median (IQR)	10.0 (6.0-15.0)	9.0 (4.0-15.0)	4.0 (2.0-10.0)	11.0 (7.0-16.0)	6.0 (4.0-8.0)
Acute onset of symptoms	287 (53.8)	408 (53.5)	159 (55.4)	249 (52.3)	38 (66.7)
Onset of symptoms in small joints	306 (57.0)	443 (57.2)	170 (57.2)	273 (57.1)	33 (55.9)
Symmetric onset of symptoms	377 (74.8)	519 (71.8)	183 (66.8)	336 (74.8)	41 (74.5)
RF positive	307 (55.9)	444 (56.5)	138 (46.3)	306 (62.7)	1 (1.6)
ACPA positive	264 (52.3)	379 (52.1)	115 (41.7)	264 (58.5)	0 (0)
ESR, mm/h, mean $\pm$ SD	41.1 $\pm$ 28.8	38.1 $\pm$ 28.2	32.0 $\pm$ 26.3	42.0 $\pm$ 28.7	34.7 $\pm$ 28.8
CRP, mg/L, median (IQR)	19.0 (8.0-42.8)	16.0 (6.0-37.0)*	12.0 (4.0-26.3)	19.0 (9.0-43.0)	19.0 (6.5-37.0)
Morning stiffness, minutes, median (IQR)	90 (60-180)	60 (30-120)*	30 (10-82.5)	90 (60-180)	90 (60-150)
HAQ (0-3), median (IQR)	1.0 (0.6-1.6)	1.0 (0.5-1.5)	0.8 (0.4-1.4)	1.0 (0.6-1.6)	0.9 (0.6-1.3)
Erosive joints, median (IQR)	3 (1-7)	3 (1-6)	1.5 (0-4)	4 (1-7)	4 (1-6)

Unless indicated otherwise, values are the number (%) of patients.

Some data were missing: for symptom duration (n=48), for acute onset of symptoms (n=29), for symptom onset in small joints (n=15), for symmetric onset of symptoms (n=71), for RF (n=2), for antibodies to citrullinated protein antigen (ACPA) (n=68), for ESR (n=3), for CRP (n=35), for morning stiffness (n=24) and for HAQ (n=138).

*p<0.05 for comparison between 1987-RA and 2010-RA (Student t-test or Mann-Whitney U test as applicable).

ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; RF, rheumatoid factor; SD, standard error.

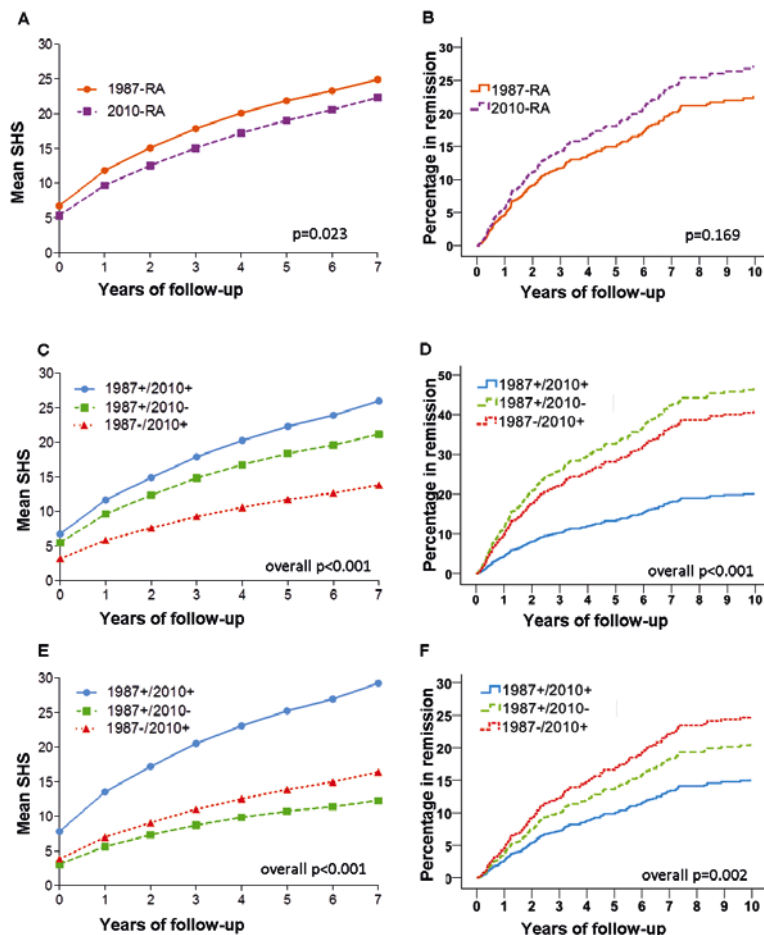


Figure 2. Comparison of long-term outcomes of rheumatoid arthritis (RA) according to fulfilment of the 1987- and/or 2010 classification criteria for RA.

Legend figure 2. All analyses were adjusted for age, gender and treatment. Depicted in (A, C and E) are the predicted (by the multivariate normal regression model) Sharp-van der Heijde scores during 7-years of follow-up. Depicted in (B, D and F) are the percentage of patients achieving disease-modifying anti-rheumatic drug (DMARD)-free sustained remission (A and B) Comparison of patients fulfilling the 1987 criteria and patients fulfilling the 2010 criteria. (C and D) Comparison of patients fulfilling either one or both criteria sets for RA. (E and F) Comparison of patients fulfilling either one or both criteria sets for RA, after also adjusting for the presence of ACPA. (C–F) Presented are the overall p values when comparing three groups. For comparisons of subgroups with the 1987+/2010+ patients as reference the results were for C: 1987+/2010+ vs 1987+/2010- $p=0.35$, 1987+/2010+ vs 1987-/2010+ $p<0.001$. D: 1987+/2010+ vs 1987+/2010- $p<0.001$, 1987+/2010+ vs 1987-/2010+ $p<0.001$. E: 1987+/2010+ vs 1987+/2010- $p=0.14$, 1987+/2010+ vs 1987-/2010+ $p<0.001$. F: 1987+/2010+ vs 1987+/2010- $p=0.21$, 1987+/2010+ vs 1987-/2010+ $p<0.001$.

DISCUSSION

The present study evaluated the long-term outcome of patients classified to the 1987 criteria or the 2010 criteria and observed a statistically significant difference in the severity of joint damage and a non-significant difference with regard to disease persistency. For both outcomes, patients classified as RA using the 2010 criteria had a less severe disease course. Thereby the present data suggest that RA, when using the most recent classification criteria, has become a milder disease.

This observation might fit within the observations that the 2010 classification criteria have a lower specificity than the 1987 criteria and can be positive in patients that later on have other diagnoses (associated with a less destructive course).^{1,5,6,13-15} Alternatively, patients fulfilling the 2010 criteria, in particular, the 1987–2010+ patients, may simply represent a milder set of patients. The milder outcome observed was not due to an earlier diagnosis and earlier treatment initiation, as the 2010 criteria were applied after the follow-up data were obtained.

In our study, we did not observe large differences in baseline characteristics, though the 1987 RA patients experienced more morning stiffness than the 2010 RA patients. This may be a consequence of morning stiffness being part of the 1987 criteria. Adding morning stiffness as an additional adjustment factor to the analyses did not give different results (data not shown); hence the findings done were not driven by this baseline difference. The 2010 criteria were derived with MTX-usage as outcome; by using this outcome, some level of circularity could not be prevented. Advantages of the two outcomes used here is that they are independent of any set of classification criteria, and therefore, do not suffer from circle reasoning.

A limitation is that patients were treated. Ideally, the present study question was evaluated in patients that were not treated over many years, as this completely represents the natural disease course. We excluded patients that were treated in clinical trials and studied only patients treated according to routine care. Nonetheless, the treatment strategies used in these patients had changed over time; therefore analyses were adjusted for these differences in treatment. Importantly, the proportion of 1987+ and 2010+ patients was similar for the different inclusion periods (data not shown). Moreover, including patients who were treated in clinical trials did not influence the findings.

All 1987+2010– patients were ACPA-negative, which is in line with another recent report.¹⁶ When the radiological criterion of the 2010 criteria was also applied, half of this group of patients became 2010-criteria positive. This supports the relevance of the radiological criterion as the frequency of this misclassification reduced.

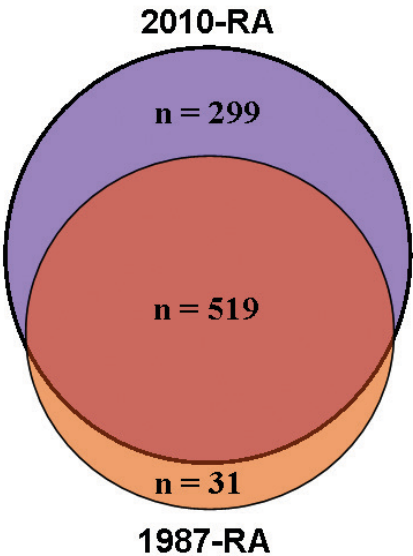
In conclusion, the present longitudinal study showed that RA classified according to the 2010 criteria has less severe joint destruction and is less often persistent than RA classified according to the 1987 criteria. This may have important implications, both for basic scientific studies and randomised clinical trials in RA.

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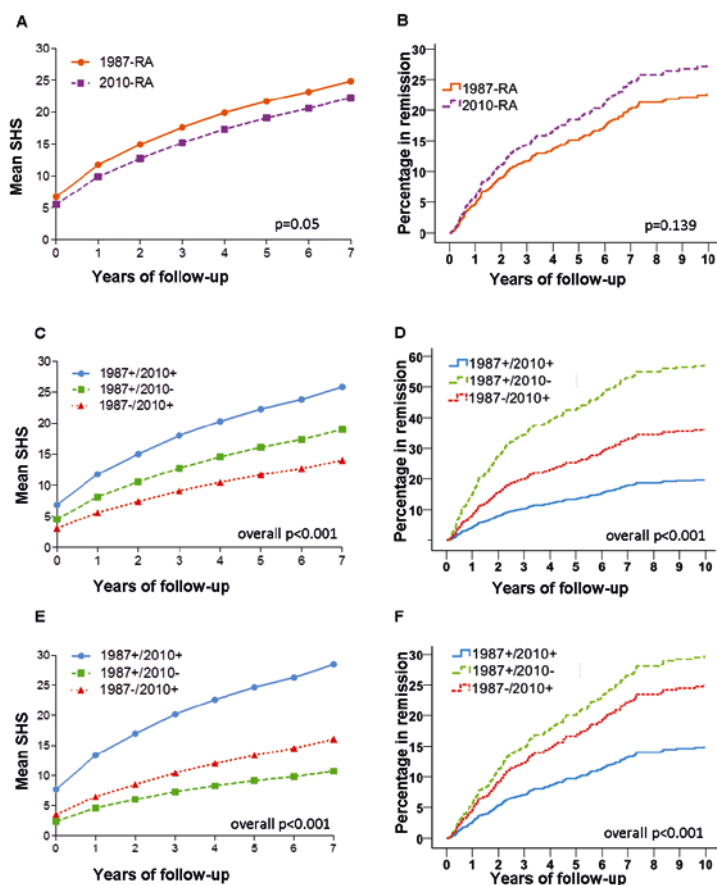
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SUPPLEMENTARY DATA



Supplementary figure 1. Fulfillment of the 1987- and 2010 classification criteria at baseline after application of the radiological criterion of the 2010 criteria in addition to the point system. Of the 1502 included patients, 519 fulfilled both criteria sets for RA. 299 patients fulfilled only the 2010-criteria and 31 patients fulfilled only the 1987-criteria. 714 patients fulfilled none of the criteria sets for RA



Supplemental figure 2. Comparison of long-term outcomes of RA according to fulfillment of the 1987- and/or 2010 classification criteria for RA after applying the erosion criterion.

Legend supplemental figure 2.

All analyses were adjusted for age, gender and treatment. Depicted in A, C and E are the predicted (by the multivariate normal regression model) Sharp-van der Heijde scores during 7-years of follow-up. Depicted in B,D,F are the percentage of patients achieving DMARD-free sustained remission

A-B: Comparison of patients fulfilling the 1987-criteria and patients fulfilling the 2010-criteria.

C-D: Comparison of patients fulfilling either one or both criteria sets for RA.

E-F Comparison of patients fulfilling either one or both criteria sets for RA, after also adjusting for the presence of ACPA.

C,D,E,F; Presented are the overall p-values when comparing three groups. For comparisons of subgroups with the 1987+2010+ patients as reference the results were for;

C: 1987+/2010+ versus 1987+/2010- $p=0.001$, 1987+/2010+ versus 1987-/2010+ $p<0.001$.

D: 1987+/2010+ versus 1987+/2010- $p<0.001$, 1987+/2010+ versus 1987-/2010+ $p<0.001$;

E: 1987+/2010+ versus 1987+/2010- $p=0.08$, 1987+/2010+ versus 1987-/2010+ $p<0.001$.

F: 1987+/2010+ versus 1987+/2010- $p=0.01$, 1987+/2010+ versus 1987-/2010+ $p<0.001$.

PART IV

Mortality in RA



CHAPTER 10

TRAF1/C5 polymorphism is not associated with increased mortality in rheumatoid arthritis: two large longitudinal studies

Jessica A.B. van Nies, Rute B. Marques, Stella Trompet, Zuzana de Jong, Fina A.S. Kurreeman, Rene E.M. Toes, J. Wouter Jukema, Tom WJ Huizinga, Annette H.M. van der Helm-van Mil

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ABSTRACT

Introduction

Recently an association between a genetic variation in *TRAF1/C5* and mortality from sepsis or cancer was found in rheumatoid arthritis (RA). The most prevalent cause of death, cardiovascular disease, may have been missed in that study, since patients were enrolled at an advanced disease stage. Therefore, we used an inception cohort of RA patients to investigate the association between *TRAF1/C5* and cardiovascular mortality, and replicate the findings on all-cause mortality. As *TRAF1/C5* associated mortality may not be restricted to RA, we also studied a large cohort of non-RA patients.

Methods

615 RA patients from the Leiden Early Arthritis Clinic (EAC) (mean follow-up 7.6 years) were genotyped for rs10818488. In addition 5634 persons enrolled in the PROspective Study of Pravastatin in the Elderly at Risk (mean follow-up 3.2 years) were genotyped for rs2416808 ($R^2 > 0.99$ with rs10818488). The life/death status was determined and for the deceased persons the cause of death was ascertained. Cox proportional hazards and regression models were used to assess hazard ratios (HR) and 95% confidence intervals (CI).

Results

Seventy-seven RA patients died. The main death causes in RA patients were cardiovascular diseases (37.7%), cancer (28.6%) and death due to infections (9.1%). No association was observed between the rs10818488 susceptible genotype AA and cardiovascular mortality (HR 1.08 95%CI 0.54 to 2.15) and all-cause mortality (HR 0.81 95%CI 0.27 to 2.43). Similar findings were observed for rs2416808 susceptible genotype GG in the non-RA cohort (HR 0.99; 95%CI 0.79 to 1.25 and HR 0.89; 95%CI 0.64 to 1.25, respectively).

Conclusions

The *TRAF1/C5* region is not associated with an increased mortality risk.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have an increased mortality risk. A recent review, studying data from 84 unique cohorts, showed that mortality rates in RA patients were 1.5 to 1.6 fold higher than in the general population.¹ The attributed causes of death in RA patients are identical to those in the general population,¹ cardiovascular disease being the primary cause of death followed by cancer and infection. Age, sex and most clinical markers that are related to a more severe destructive disease course (among others number of inflamed joints, C reactive protein (CRP) and presence of erosions) are also associated with higher mortality risks.¹

Genetic risk factors for mortality in RA are scarcely investigated. Presence of the human leukocyte antigen (HLA)-DRB1 shared epitope alleles are reported to be associated with an increased mortality and, in particular, mortality related to cardiovascular disease (CVD).²⁻⁴ Although a lot of progress has been made in the field of genetics of RA-susceptibility, the HLA-shared epitope alleles still constitute the most powerful genetic risk factor to developing RA. Well-replicated non-HLA risk factors are *PTPN22*, *TNFAIP3*, and *TRAF1/C5*.⁵⁻⁷ *TRAF1/C5* associated with several autoimmune diseases other than RA such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematodes.^{8,9}

A recent study analyzed the *TRAF1/C5* variant, rs3761847, in relation to mortality in RA and observed an increased mortality risk for the susceptible genotype GG compared with the non-susceptible AA genotype (hazard ratio (HR) = 3.96, 95% confidence interval (CI) = 1.24 to 12.6).¹⁰ Such an observation is relevant because it indicates that genetic factors, such as *TRAF1/C5*, contribute to the increased mortality in RA. The causes of death were also investigated. Intriguingly, no increased death rate for CVD was found among GG homozygotes, whereas increased death rates were found for cancer and infections. As this study enrolled patients with a median disease duration of 10 (range 4 to 18) years, which were subsequently followed up for two to four years, CVD related deaths occurring earlier in the disease course may have been missed. To further explore the association between the *TRAF1/C5* locus and CVD-related mortality in RA, we studied a cohort of 615 early RA patients that were followed from disease onset to 14 years onwards. In addition, we investigated whether the association with all-cause, infectious and cancer-related mortality Panoulas and colleagues observed could be replicated.¹⁰ Finally, as an association between *TRAF1/C5* and mortality may not be restricted to RA patients, we also analysed a large cohort of non-RA patients.

MATERIAL AND METHODS

Early arthritis clinic cohort

The Leiden early arthritis cohort (EAC) is an inception cohort consisting of patients with recent-onset arthritis referred to the Department of Rheumatology of the Leiden University Medical Center from 1993 onwards.¹¹ Patients were included when arthritis was observed by a rheumatologist. For the present study, patients were selected who fulfilled the American College of Rheumatology 1987 revised criteria for RA within the first year of follow up and had DNA samples available ($n = 615$).¹² Written informed consent was obtained from all participants. The study was approved by the appropriate local institutional review board. At inclusion, a physical examination was performed and blood samples were taken to determine CRP, immunoglobulin (Ig) M rheumatoid factor (RF; by ELISA) and anti-cyclic citrullinated peptide (CCP) 2 antibodies (Immunoscan RA Mark 2; Euro-Diagnostica, Arnhem, the Netherlands). Anti-CCP2 positivity had a cut-off level of 25 arbitrary units, according to manufacturer's instructions. Patients also filled in a Health Assessment Questionnaire (HAQ)¹³ and radiographs of hands and feet were taken and scored by one experienced reader (the intraclass-observer correlation coefficients was 0.91), using the Sharp van der Heijde method.¹⁴

Cohort of non-RA patients

As well as the RA patients, 5634 participants with available DNA from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) were studied. In short, PROSPER is a randomized double-blind placebo-controlled trial that assessed whether pravastatin treatment in elderly men and women diminished the risk of major vascular events.¹⁵ Participants were screened and enrolled in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden) between December 1997 and May 1999. Written informed consent was obtained from all participants. The study was approved by the appropriate local institutional review boards of all centers. The primary endpoint in the study was a combination of death from coronary heart disease (CHD), non-fatal myocardial infarction (MI), and fatal or non-fatal stroke. After three years of follow up, CVD and transient ischemic attacks (TIAs) were less prevalent in the group treated with pravastatin.¹⁶

SNP genotyping

rs10818488 was genotyped in the RA cohort and rs2416808, which is in complete linkage disequilibrium with rs10818488 ($r^2 > 0.99$), was genotyped in the non-RA cohort. Genotypings were performed using the MassArray matrix-assisted laser desorption ionisation time-of-flight mass spectrometry, according to the protocols recommended by the manufacturer (Sequenom, San Diego, CA, USA). Each 384-well plate contained at least 4 positive (CEPH DNA) and 4 negative controls, to check for assay performance and contaminations, respectively. Spectro- Caller software (Sequenom, San Diego, CA, USA)

supplied by the manufacturer was used to automatically identify the genotypes. Clusters were checked and all doubtful calls were manually evaluated. Ten percent of the genotypes were performed in duplicate and the error rate was below 1%. Allele frequencies and Hardy-Weinberg equilibrium consistency were determined with Haploview.¹⁷ Both SNPs were in agreement with Hardy-Weinberg equilibrium. Both rs10818488 and rs2416808 are in complete linkage-disequilibrium with rs3761847 genotyped by Panoulas and colleagues ($r^2 > 0.99$ data from Hapmap, and Kurreeman and colleagues).^{5,6,10}

Notification of death

In the EAC, patients were followed longitudinally from the moment of their inclusion until 1 April, 2008, or death. All RA patients were tracked nationally using the civic registries (Gemeentelijke Basis Administratie) to ascertain life or death status. Causes of death for RA patients were obtained from Statistics Netherlands¹⁸ and coded according to the International Classification of Diseases 10th revision of the World Health Organization.¹⁹ In the non-RA cohort, patients were followed for 3.2 years and the causes of death in this period were obtained from post-mortem reports and/or certification of death. All endpoints were adjudicated by a study endpoint committee.

Analysis of data

Data are expressed as mean ($\pm$ standard deviation (SD)) with a 95% CI for continuous variables and as proportions for categorical variables. Differences in baseline patient characteristics between the single nucleotide protocol (SNP) genotypes were compared using a oneway analysis of variance test or Kruskal Wallis test for continuous variables and the chi-squared test for nominal variables. Associations between genotype and mortality were tested with univariate cox regression analyses and log rank tests.

In a study in RA patients (unpublished) we observed that age, CRP level and Sharp-van der Heijde score were independently associated with mortality. In order to investigate whether *TRAF1/C5* is associated with mortality after adjusting for gender, HAQ-score and other previously found risk factors, a multivariate cox regression analysis was performed. Subjects from the cohort of non-RA patients who withdrew consent or died during the study were censored at the date of death or at the last date of follow up. Cox regression analyses in the cohort of non-RA patients were adjusted for gender, age, pravastatin or placebo use, and country.

Panoulas and colleagues observed a HR of 3.96. The RA cohort has a power of 99.6% to identify such an association with C5/TRAF1 based on the observed genotype frequencies and an alpha of 0.05. In the non-RA cohort this power was 100%. Assuming that the finding by Panoulas and colleagues was affected by the winners curse and the true HR would be lower, for example a HR of 1.5, then the power of the RA cohort and non-RA cohort to observe an association was 28% and 97.5%, respectively.

All statistical analyses were performed using Statistical Package for Social Sciences version 16.0 (SPSS, Chicago, IL, USA). In all tests, P values below 0.05 were considered to be significant.

RESULTS

Baseline characteristics

The 615 RA patients had mean ($\pm$ SD) age of 56.4 ± 15.6 years and 68.5% were female. The mean CRP concentration was 29.5 ± 33.1 mg/L, 57% were RF positive, 43.4% were anti-CCP2 positive, the mean HAQ score was 1.07 ± 0.72 and the median Sharp-van der Heijde score at baseline was 6 (range 2 to 12). The genotype frequencies for rs10818488 were: 29% GG (n = 180), 53% AG (n = 324) and 18% AA (n = 111). No differences in baseline characteristics between genotypes were observed (Table 1). The mean follow up was 7.6 ± 3.6 years (range 4.7 to 10.5 years).

In the cohort of non-RA patients 51.6% were female and the mean age was 75.3 ± 3.4 years. For baseline characteristics see Table 2. The slight difference in history of stroke was considered to be a spurious finding due to multiple comparisons. The genotype frequencies for rs2416808 were: 30.9% AA (n = 1743), 48.4% AG (n = 2725) and 19.9% GG (n = 1123). The mean follow up in these patients was 3.2 ± 0.6 years.

Mortality in RA cohort

Seventy-seven RA patients died during follow up; 46 (11%) women and 31 (16%) men. Twenty-five percent of these patients carried the GG genotype, 57% the AG genotype and 18% the AA genotype. The survival probability of rs10818488 genotypes and all-cause mortality is presented in Figure 1a. No significant difference in all-cause mortality was found across the genotypes (HR = 1.06, 95% CI = 0.76 to 1.46, P = 0.752). The major cause of death in RA patients was attributed to CVD (37.7%). This was most frequently caused by acute MI and the second most frequent cause of CVD-related mortality was heart failure. Besides CVD, two other major causes of death in RA patients were cancer (28.6%; n = 22), most frequently of the bronchus and lungs, and infection (9.1%; n = 7).

The 29 patients who died due to CVD had the following genotypes for rs10818488: 31% GG homozygotes, 52% AG heterozygotes and 17% AA homozygotes. Survival probability of CVD-related mortality is presented in Figure 1b. Also, here no significant difference was found between the three genotypes (HR = 0.91, 95% CI = 0.53-1.54, P = 0.713; Table 3).

Table 1. Baseline characteristics of the RA patients per genotype of rs10818488

	GG n = 180 (29%)	AG n = 324 (53%)	AA n = 111 (18%)
Age (years)	56.2 ± 15.2	56.3 ± 15.5	57.3 ± 16.5
Females, n (%)	132 (73.3)	218 (67.3)	71 (64.0)
Past or current smoker, n (%)	83 (51.2)	139 (48.1)	53 (54.1)
Swollen joint count	9.0 ± 6.6	9.4 ± 7.3	8.0 ± 6.0
BMI (kg/m ²)	25.5 ± 3.7	25.7 ± 3.8	25.7 ± 4.0
RF positive, n (%)	101 (57.1)	181 (57.3)	70 (63.6)
Anti-CCP positive, n (%)	75 (56.4)	146 (57.5)	46 (51.7)
CRP (mg/L)	28.1 ± 29.0	31.6 ± 36.1	25.8 ± 30.1
HAQ (0-3)	1.05 ± 0.70	1.10 ± 0.72	1.03 ± 0.77
Total Sharp- van der Heijde score, median (IQR 25-75)	6 (2-13)	6 (2-12)	5 (1.5-11)

Except if stated otherwise values are mean (standard deviation).

#Data not available for all cases (smoking status n = 66, swollen joint count n = 111, BMI n = 156, rheumatoid factor in n = 12, anti CCP n = 139, CRP n = 46, HAQ n = 113, Total Sharp- van der Heijde score n = 27).

BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; IQR, interquartile range; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 2. Baseline characteristics of the non-RA patients per genotype of rs2416808

	AA n = 1783 (32%)	AG n = 2725 (48%)	GG n = 1123 (20%)
Age (years)	75.24 (3.35)	75.39 (3.31)	75.35 (3.45)
Females, n (%)	898 (50)	1427 (52)	582 (52)
Current smoker, n (%)	459 (26)	738 (27)	311 (28)
BMI (kg/m ²)	26.85 (4.13)	26.85 (4.19)	26.76 (4.28)
Systolic blood pressure (mmHg)	154.36 (21.18)	154.78 (22.23)	154.89 (21.59)
Diastolic blood pressure (mmHg)	83.65 (11.34)	83.97 (11.45)	83.50 (11.67)
CRP (mg/L)	5.67 (8.65)	5.97 (11.58)	6.13 (13.32)
Total cholesterol (mmol/L)	5.68 (0.90)	5.66 (0.90)	5.74 (0.92)
History of diabetes, n (%)	203 (11)	281 (10)	113 (10)
History of hypertension, n (%)	1093 (61)	1721 (63)	678 (60)
History of myocardial infarction, n (%)	239 (13)	375 (14)	146 (13)
History of stroke or TIA, n (%)	174 (10)	321 (12)	137 (12)*
History of vascular disease, n (%)	770 (43)	1220 (45)	502 (45)
History of angina, n (%)	484 (27)	740 (27)	290 (26)
History of claudication, n (%)	124 (7)	180 (7)	75 (7)

Except if stated otherwise values are mean (standard deviation).

* History of TIA: P value 0.027.

BMI, body mass index; CRP, C-reactive protein; RA, rheumatoid arthritis; TIA, transient ischemic attack.

Multivariate cox regression analyses were performed to assess whether the *TRAF1/C5* susceptible genotype was associated with mortality after adjustments for other known risk factors for mortality. Also after adjustments, no significant association between rs10818488 genotype and all-cause (HR = 0.91, 95% CI = 0.61 to 1.37), cardiovascular (HR = 0.97, 95% CI = 0.54 to 1.76), cancer (HR = 0.66, 95% CI = 0.28 to 1.56) or infectious-related mortality (HR = 0.54, 95% CI = 0.09 to 3.13) was observed.

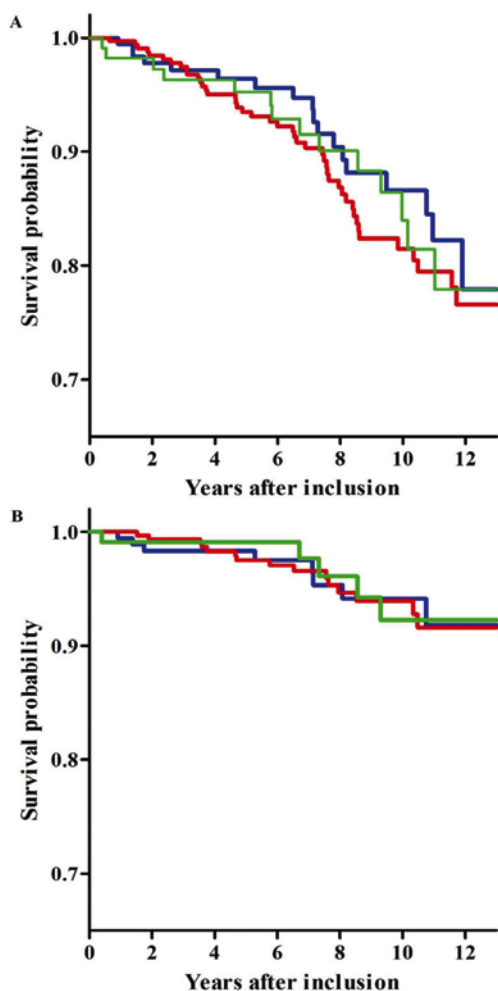


Figure 1. Survival curves for all-cause and cardiovascular mortality in RA patients per genotype of rs10818488.

Legend figure 1. The log rank tests showed P values for all-cause mortality and cardiovascular mortality of 0.69 and 0.93, respectively. (a) All-cause mortality. (b) Cardiovascular mortality. Blue line: GG n = 180. Red line: AG n = 324. Green line: AA n = 111.

Mortality in non-RA cohort

In the non-RA cohort, 586 participants died, 32% were AA homozygote, 48% AG heterozygote and 20% GG homozygote for rs2416808. Also, no significant association was found between the *TRAF1/C5* variants and allcause mortality (HR = 0.99, 95% CI = 0.89 to 1.11), CVD-related (HR = 0.95, 95% CI = 0.80 to 1.12) and cancer-related mortality (HR = 1.00, 95% CI = 0.82 to 1.21; Table 3). Analyzing only the placebo-treated group did not change the results (data not shown). Similarly, also in the non-RA cohort after adjustments, no significant association was found between rs2416808 and allcause (HR = 0.99, 95% CI = 0.88 to 1.11), cardiovascular (HR = 0.94, 95% CI = 0.80 to 1.11) or cancer-related mortalities (HR = 1.00, 95% CI = 0.82 to 1.22) in a multivariate cox regression analysis.

Table 3. Hazard ratios for genotypes rs10818488 and rs2416808 in the RA-cohort and Non-RA cohort in univariate cox regression analysis

Hazard ratios RA cohort				
Mortality	Trend		AA vs GG	
	HR(95% CI)	P value	HR (95% CI)	P value
All-cause	1.06 (0.76-1.46)	0.752	1.08 (0.54-2.15)	0.830
CVD	0.91 (0.53-1.54)	0.713	0.81 (0.27-2.43)	0.712
Cancer	0.90 (0.49-1.67)	0.741	0.73 (0.18-2.92)	0.657
Infectious	1.19 (0.41-3.51)	0.748	1.42 (0.09-22.7)	0.803
Hazards ratios non-RA cohort				
Mortality	Trend		GG vs AA	
	HR (95% CI)	P value	HR (95% CI)	P value
All-cause	0.99 (0.89-1.11)	0.890	0.99 (0.79-1.25)	0.924
CVD	0.95 (0.80-1.12)	0.512	0.89 (0.64-1.25)	0.515
Cancer	1.00 (0.82-1.21)	0.980	1.02 (0.70-1.50)	0.919

CI, confidence interval; HR, hazard ratio; CVD, cardiovascular disease; RA, rheumatoid arthritis.

DISCUSSION

The present study was performed to investigate the relation between a well-replicated genetic RA susceptibility factor, *TRAF1/C5*, and the mortality risk in a cohort of RA patients. No evidence for an association of this risk factor with mortality was observed. Panoulas and colleagues recently observed an increased mortality risk for carriers of the *TRAF1/C5* susceptibility risk genotype in RA patients.¹⁰ Both polymorphisms analyzed in the present study, rs10818488 and rs2416808, are in complete linkage-disequilibrium with the rs3761847 SNP genotyped by Panoulas and colleagues ($r^2 > 0.99$ data from Hapmap, and Kurreeman and colleagues).^{5,6} However, we could not replicate their finding, despite having a larger cohort (615 vs 400 RA patients), a longer follow-up duration (mean 7.6 vs 2.6 years) and a higher number of events (77 vs 23 deaths). In

addition, Panoulas and colleagues reported an increased risk of death due to cancer and sepsis, but not CVD. It is possible that the cohort design from Panoulas and colleagues was less suitable to study association with CVD-related mortality, because patients were enrolled at an advanced disease stage. In this setting, a possible relation between *TRAF1/C5* and cardiovascular mortality may be missed, because patients dying of CVD earlier in the disease course are not part of their cohort. This hypothesis was corroborated by our results in the RA cohort, which showed that most of the CVD-related deaths were concentrated in the first 10 years of disease. However, also in our EAC, no association was found between *TRAF1/C5* locus and cardiovascular mortality in RA.

In order to further unravel the eventual association between *TRAF1/C5* locus and mortality, we hypothesized that this risk would not be restricted to RA. Therefore, we also genotyped *TRAF1/C5* in a large cohort of elderly people that were prospectively followed in PROSPER. This large cohort was well-powered to detect also small HR (e.g. 1.5). Nonetheless, *TRAF1/C5* did not confer an increased mortality risk. This strengthened our findings of an absent association between *TRAF1/C5* and risk of death.

In the end, one might argue that any cohort that enrolls older participants is inappropriate to study mortality, because the risk genotype may cause an early death. In this sense, prospective studies that follow the participants over a period of decades may be more suitable to answer this question. Nevertheless, the rs10818488 genotype frequencies in our JIA cohort (GG = 30%, AG = 53%, AA = 17%), which has a mean age of 6.4 years at inclusion, did not differ from the frequencies in the adult EAC cohort.⁸ Also the minor allele frequency in the non-RA cohort is similar to those in the general population.²⁰ In addition, both cohorts were in agreement with Hardy-Weinberg equilibrium. This indicates that there was no selection of the protective genotype in the RA or non-RA cohort. This makes an early death in the risk genotype carriers unlikely and further supports the lack of association of these *TRAF1/C5* variants with mortality.

In the RA-cohort, mortality due to infections were relatively infrequent, the number of deaths attributed to infections is insufficient to make definite conclusions on the association between *TRAF1/C5* and this specific cause of mortality.

The important causes of death observed in RA patients in the present study are similar to the main causes of death in the general Dutch population.¹⁸ The frequency of CVD-related mortality itself is reported to be higher in RA patients than in healthy individuals.¹ Results from the Nurses Health Study revealed that women with RA had a relative risk of 1.8 for fatal MI.²¹ Unfortunately, we were unable to test whether the frequency of cardiovascular death was also increased in our EAC RA cohort, because we do not have mortality information on an age- and gender-matched Dutch control population.

CONCLUSION

In conclusion, *TRAF1/C5* polymorphisms predisposing to RA susceptibility are not associated with all-cause mortality or cardiovascular- or cancer-related mortality in RA and in an elderly cohort of persons without RA.

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CHAPTER 11

Rheumatoid factor and anti-citrullinated protein antibody positivity, but not level, are associated with increased mortality in patients with rheumatoid arthritis: results from two large independent cohorts

Jennifer H Humphreys, Jessica A.B. van Nies, Jackie Chipping,
Tarnya Marshall, Annette H.M. van der Helm-van Mil,
Deborah P.M. Symmons, Suzanne M.M. Verstappen

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ABSTRACT

Introduction

This study aimed to investigate rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) status and levels as predictors of mortality in two large cohorts of patients with early inflammatory arthritis (EIA).

Methods

Data from the Norfolk Arthritis Register (NOAR) and Leiden Early Arthritis Clinic (EAC) cohorts were used. At baseline, patients had demographic data and smoking status recorded; RF, ACPA and inflammatory markers were measured in the local laboratories. Patients were flagged with national death registers until death or censor date. Antibody status was stratified as negative, low or high positive by RF and ACPA levels individually. In addition, patients were grouped as seronegative, RF positive, ACPA positive or double antibody (RF and ACPA) positive. Cox regression models explored associations between antibody status and mortality adjusting for age, sex, smoking status, inflammatory markers and year of enrolment.

Results

A total of 4962 patients were included, 64% were female. Median age at onset was 56 (NOAR) and 54 (EAC) years. In NOAR and EAC respectively, 35% and 42% of patients were ACPA/RF positive. When antibody status was stratified as negative, low or high positive, there were no consistent findings between the two cohorts. Double antibody positivity was associated with excess mortality in both cohorts compared to seronegative patients: NOAR and EAC respective adjusted HR (95% confidence interval) 1.35 (1.09 to 1.68) and 1.58 (1.16 to 2.15).

Conclusions

Patients with EIA who are seropositive for both RF and ACPA have increased mortality compared to those who are single positive or seronegative. Antibody level in seropositive patients was not consistently associated with excess mortality.

INTRODUCTION

In patients with inflammatory arthritis, the autoantibodies rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) have been associated with poor outcomes, such as increased disease activity, radiographic progression and disability.¹⁻⁵ However, the utility of antibody level in predicting the prognosis of inflammatory arthritis, in particular rheumatoid arthritis (RA), has not been clearly established. In a recent multicenter prospective study of patients with early inflammatory arthritis (EIA), the presence of RF and/or ACPA was a significant predictor of RA diagnosis within two years, but level did not appear to be important.⁶ In contrast, in a study of patients with EIA from Norway in 2010, Mjaavatten et al. found that increasing levels of RF and ACPA were associated with persistent joint inflammation.⁷ Other studies have failed to show consistently that either RF or ACPA antibody level is important in predicting poor outcome in patients with EIA and RA [8-10]. In addition, recent data from a subset of the Leiden Early Arthritis Clinic have shown that the avidity of ACPA may be prognostically more important than the level itself.¹¹

Nevertheless, antibody level is included in the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA,¹² which aim to identify those patients with EIA with poor prognosis sufficient to require intervention with disease modifying therapy. The presence of RF and ACPA are weighted as part of the total score according to their level; patients are said to be low positive if their level is greater than the upper limit of normal (ULN) but less than three times the ULN, and high positive if their level is at least three times the ULN. Thus, patients with high antibody levels are more likely to fulfil the criteria, and it would be interesting to investigate whether these cut-offs are appropriate in predicting other adverse outcomes, such as mortality.

The increased mortality in patients with RA has been long established.¹³ It is also well recognised that the presence of RF in sera of patients with inflammatory arthritis (whether or not they meet formal classification criteria for RA) is associated with an increased risk of premature death.¹⁴⁻¹⁶ In fact, this association has been demonstrated even in subjects without symptoms of arthritis.¹⁷ ACPA positivity has also been shown to predict premature mortality in the Norfolk Arthritis Register¹⁸; however this association has yet to be confirmed in other cohorts.

The aims of this study were to investigate the association between mortality and RF and/or ACPA positivity and level in patients with EIA. The term EIA includes all patients with RA early in the disease process, and studying these patients allows additional inclusion of those patients who may later go on to meet formal classification criteria

for RA. It has been recognised that significant variability in antibody testing can occur between laboratories.¹⁹ Thus, to strengthen the external validity of the study results, we investigated these questions in two large prospective cohorts of patients with EIA: the Norfolk Arthritis Register (NOAR) in the UK and the Leiden Early Arthritis Clinic (EAC) in the Netherlands.

METHODS

Patients and setting

Patients in Norfolk, UK, were recruited to NOAR between 1990 and 2009 from primary and secondary care if they were adults (≥ 16 years) and had ≥ 2 swollen joints for ≥ 4 weeks; NOAR has been described in detail elsewhere.²⁰ Leiden EAC has also been described previously²¹; briefly patients in the region of Leiden, the Netherlands, with synovitis confirmed by a rheumatologist were recruited to the Leiden EAC from 1993 onwards if their symptom duration was less than two years at presentation. In order to make the two cohorts as comparable as possible, patients in NOAR were only included in this study if they had symptom duration of less than two years at presentation.

Assessment and follow up

Patients in NOAR are assessed at baseline by a research nurse who administers a structured questionnaire, including demographic details as well as disease and smoking history (never, past, current), performs a 51 tender and swollen joint count and obtains a blood sample. Sera are stored frozen and tested for C-reactive protein (CRP) and RF (latex test, low positive cut-off 40 units/ml, high positive cut-off 120 units/ml); subsequently ACPA, as defined by anti-CCP2 antibodies, are tested for using the Axis- Shield, Dundee, UK Diastat Anti-CCP kit (low positive cutoff 5 units/ml, high positive cut-off 15 units/ml). The Leiden EAC initial assessment includes medical history, clinical examination and joint counts. Blood samples are taken and tested for erythrocyte sedimentation rate (ESR), RF (IgM-RF in-house ELISA, low positive cut-off 5 units/ml, high positive cut-off 15 unit/ml) and ACPA (AntiCCP-2, Euro-Diagnostica, Malmo, Sweden ImmunoscanRA Mark 2, low positive cut-off 25 units/ml, high positive cut-off 75 units/ml). All cut-offs used are those recommended by the relevant manufacturers. Patients in NOAR are flagged with the NHS Information Centre (NHS IC) from baseline. NHS IC provide copies of death certificates to NOAR with approximately six months lag in reporting. They also provide a date of 'embarkation' for patients who leave the UK. Mortality data on patients recruited to the EAC are tracked nationally using the civic registries (Gemeentelijke Basis Administratie) in the Netherlands. NOAR is approved by Norfolk and Norwich University Hospital Local Research Ethics Committee UK, and EAC was approved by the local medical ethics committee LUMC The Netherlands.

Statistical analysis

Antibody levels were divided into negative, low positive and high positive as defined by the 2010 classification criteria.¹² These cut-offs were selected to investigate the ability of this aspect of the criteria to predict mortality. NOAR patients were censored for analysis at date of death, date of embarkation or 30 June 2012, whichever came first. Leiden EAC patients were censored at date of death or 1 May 2012. Analyses were conducted separately in each cohort. Kaplan-Meier survival curves were used to compare survival univariately in patients grouped according to their antibody status. Cox proportional hazard models were used to investigate the association between antibody status, antibody level and subsequent mortality. A number of different models were developed. Firstly, patients were categorised according to antibody status as negative, low positive or high positive, and two models were then developed considering RF and ACPA status separately. A third model investigated whether the presence (above the ULN) of both antibodies, rather than antibody level, was important in predicting mortality by categorising patients as seronegative, RF single antibody positive, ACPA single antibody positive and double antibody positive (that is, both RF and ACPA positive). Univariate models were constructed initially, then age and sex adjusted; finally a multivariate model was developed adjusting for age, gender, baseline smoking status (categorized as current, ever or never smokers), inflammatory marker (ESR in EAC or CRP in NOAR) level, and year of enrolment to the cohort as a proxy for changing treatment strategies over time. All analyses were repeated in the population of patients fulfilling the 2010 ACR/EULAR criteria for RA. We aimed to focus on the predictive properties of the antibodies specifically and were deliberately parsimonious with our variable selection in the multivariate model. Thus, if a variable was not considered a confounder *a priori*, that is, would not have associations with both antibody status and mortality, it was not included. Similarly, variables that might be on the causal pathway between antibody status and mortality (such as disease activity over time) were also not included, as the relationship between antibody status and disease activity can only occur in one direction.

In the model in which the presence of both antibodies was compared to single antibody positivity and seronegativity, only patients who had been tested for both antibodies were included. In NOAR, 2,195 (72%) patients had data on both antibodies; data were more complete for the EAC, where 1,663 (87%) had both antibodies measured. In NOAR, therefore, baseline characteristics of patients with and without complete antibody data were assessed for differences. In addition, in order to ensure that the reported results were representative, multiple imputation using chained equations was performed to impute the antibody status of those patients with missing data. A subsequent sensitivity analysis was performed using the imputed dataset and these results were compared with those from the complete case analysis. Data from NOAR were analysed using the Stata 11 software package (Stata, College Station, TX, USA), data from EAC were analysed using SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA).

Table 1. Demographic and baseline disease characteristics

Demographic/characteristic	NOAR number = 3,053	Leiden EAC number = 1,909
Female <i>number (%)</i>	1970 (65)	1205 (63)
Age at symptom onset (years) <i>median (IQR)</i>	56 (44 to 68)	54 (42 to 67)
Symptom duration (weeks) <i>median (IQR)</i>	26 (14 to 47)	17 (8 to 33)
RF/ACPA positive <i>number (%)</i>	1079 (35)	810 (42)
RF positive	912 (34)	704 (37)
RF low positive	315 (12)	256 (13)
RF high positive	594 (22)	445 (23)
ACPA positive	598 (27)	591 (31)
ACPA low positive	91 (4)	66 (3.5)
ACPA high positive	507 (23)	532 (27.9)
Inflammatory marker (CRP, mg/L)	9 (2 to 20)	-
Inflammatory marker (ESR, mm/hr)	-	25 (11 to 44)
Smoking status		
Never	998 (33)	740 (45)
Previous	1189 (39)	445 (27)
Current	748 (26)	450 (28)
2010 ACR/EULAR RA criteria positive <i>number (%)</i>	1701 (63)	1073 (57)
1987 ACR RA criteria positive <i>number (%)</i>	1303 (43)	736 (39)

Categorical variables are presented as number (% non-missing data). % percentage missing values for NOAR and Leiden EAC, respectively, were as follows; RF/ACPA 10% and 0.5%, RF 11 % and 1%, ACPA 27% and 12%, CRP 18%, ESR 1%, smoking status 4% and 14%, 2010 RA 11% and 1%, 1987 RA 0.5% and 0%. ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; CRP, C-reactive protein; EAC, Early Arthritis Clinic; ESR, erythrocyte sedimentation rate; EULAR European League Against Rheumatism; IQR, inter-quartile range; NOAR, Norfolk Arthritis Register; RF, rheumatoid factor; RA, rheumatoid arthritis. The italicised words describe how each characteristic is being presented numerically rather than the name of the characteristic itself, and are therefore italicised for clarity to make that distinction.

RESULTS

A total of 4,962 patients with EIA were included in the study (3,053 from NOAR, 1,909 from Leiden EAC). The cohorts had similar age and gender distributions, 65% (1,970) female in NOAR, 63% (1,205) female in the EAC, respective median (interquartile range) age at symptom onset 56 (44 to 68) and age at inclusion 54 (42 to 67) years. In NOAR, 63% of patients fulfilled the 2010 ACR/EULAR classification criteria for RA, in the EAC

this proportion was 57% of patients. Baseline characteristics of patients from the two cohorts are shown in Table 1. The mean (standard deviation) follow up in each study was 11.8 (5.8) years in NOAR and 8.5 (5.2) years in EAC. There were 787 deaths during 36,109 person years follow up in NOAR, and 275 deaths during 16,187 person years follow up in the EAC; this resulted in crude death rates of 21.8 and 17.0 deaths per 1,000 person years in each cohort, respectively. The number of deaths in each of the antibody subgroups are shown in Table 2.

Table 2. Number of deaths in each antibody group

Antibody group	NOAR	Leiden EAC
RF/ACPA negative	401	28
RF/ACPA low positive	39	40
RF/ACPA high positive	264	106
RF negative	444	137
RF low positive	52	54
RF high positive	202	82
ACPA negative	394	154
ACPA low positive	21	17
ACPA high positive	156	86
Both antibodies negative	339	119
RF positive ^a	47	35
ACPA positive ^a	51	9
Both antibodies positive	128	93

^aWhere patients had both antibodies tested. ACPA, anti-citrullinated peptide antibodies; EAC, Early Arthritis Clinic; NOAR, Norfolk Arthritis Register; RF, rheumatoid factor.

Antibody levels

The first Cox proportional hazards models (univariate and adjusted) examined RF and ACPA levels separately (Table 3). There appeared to be a marked difference in RF high and low positivity in the NOAR cohort: low positive RF adjusted hazard ratio (HR) (95% confidence interval (CI)) 0.80 (0.59 to 1.08), high positive RF adjusted HR (95% CI) 1.49 (1.25 to 1.77). However, this was not replicated in the EAC cohort: low positive RF adjusted HR (95% CI) 1.62 (1.16 to 2.26), high positive RF adjusted HR (95% CI) 1.63 (1.19 to 2.24). Differences between the two cohorts were also seen with ACPA (Table 3). In the EAC, low positive ACPA status was associated with increased mortality, but high positive ACPA was not, respective adjusted HR (95% CI) 2.21 (1.31 to 3.72) and 1.25 (0.93 to 1.69). Conversely, in NOAR there was a trend towards increased mortality in the low positive ACPA group, and high positive ACPA status was significantly associated, adjusted HR (95% CI) 1.32 (1.08 to 1.61). Of note, there were only a small number of patients and,

therefore, deaths in the ACPA low positive group in either cohort: 21 deaths in NOAR and 17 in the EAC. Similar findings were observed in the population of patients fulfilling the 2010 ACR/EULAR criteria for RA, although not always reaching statistical significance, probably due to smaller group sizes. Data on the full multivariate models are available as part of Additional file 1. The Additional file 1 also includes a model comparing patients negative for both antibodies to those with low and high levels of either antibody and models dividing RF and ACPA levels into tertiles rather than using the predefined cut-offs of the 2010 criteria. These additional models demonstrated similar results to those reported here.

Number of antibodies

This Cox model stratified patients by the number of antibodies present (negative, RF positive, ACPA positive, and double antibody positive if both RF and ACPA were positive). The results were more consistent between the two cohorts (Table 4 and Figure 1) and between the total EIA population and the 2010 ACR/EULAR RA population. In both NOAR and the EAC there was a trend towards increased mortality in patients who had a single positive antibody compared to no positive antibodies, other than single ACPA positivity in the Leiden EAC, where the number of deaths was small. In both cohorts the presence of two positive antibodies was significantly associated with increased mortality, adjusted HRs (95% CI) NOAR: 1.35 (1.09 to 1.68), EAC: 1.57 (1.15 to 2.14). No differences were identified in the baseline characteristics of patients with missing data in NOAR for this model, and the sensitivity analysis using imputed data produced similar results to the complete case analysis [see Additional file 1].

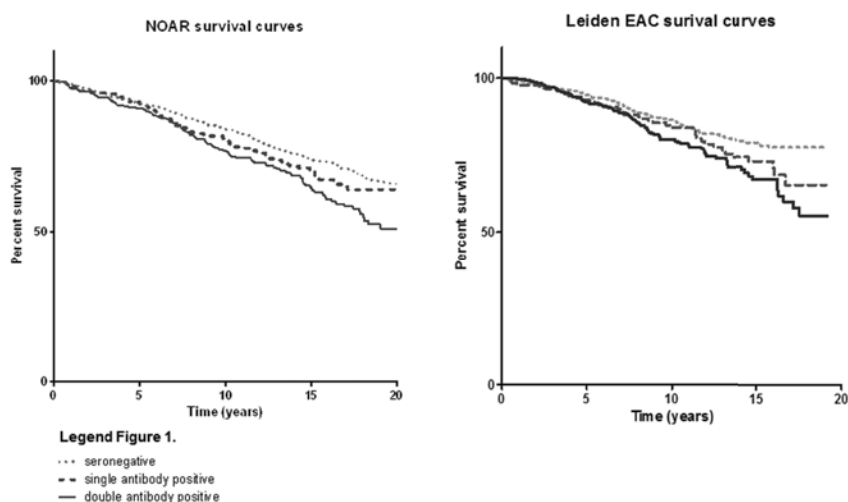


Figure 1. Unadjusted survival curves stratified by number of antibodies.

Table 3. Comparison of patients RF or ACPA negative to those with low and high RF or ACPA levels
NOAR

Model/predictor	NOAR				Leiden EAC			
	Total EIA		2010 ACR/EULAR		Total EIA		2010 ACR/EULAR	
	population		positive cohort		population		positive cohort	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
RF:								
<i>Unadjusted^a</i>								
RF low positive	0.90	0.68 to 1.20	0.90	0.66 to 1.24	2.13	1.55 to 2.91	1.75	1.21 to 2.54
RF high positive	1.67	1.41 to 1.97	1.43	1.18 to 1.74	1.75	1.33 to 2.31	1.39	0.99 to 1.93
<i>Age and sex</i>								
<i>adjusted^a</i>								
RF low positive	0.81	0.61 to 1.08	0.80	0.58 to 1.10	1.67	1.21 to 2.29	1.67	1.15 to 2.42
RF high positive	1.54	1.30 to 1.82	1.33	1.09 to 1.62	1.92	1.46 to 2.53	2.00	1.42 to 2.81
<i>Multivariate^{a,b}</i>								
RF low positive	0.80	0.59 to 1.08	0.85	0.61 to 1.18	1.62	1.16 to 2.26	1.57	1.07 to 2.32
RF high positive	1.49	1.25 to 1.77	1.40	1.14 to 1.71	1.63	1.19 to 2.24	1.68	1.16 to 2.44
ACPA:								
<i>Unadjusted^c</i>								
ACPA low positive	1.05	0.68 to 1.63	0.98	0.61 to 1.59	1.65	1.00 to 2.72	0.97	0.54 to 1.73
ACPA high positive	1.49	1.24 to 1.79	1.27	1.03 to 1.57	1.17	0.90 to 1.52	0.79	0.58 to 1.06
<i>Age and sex</i>								
<i>adjusted^c</i>								
ACPA low positive	1.16	0.75 to 1.81	1.19	0.73 to 1.93	2.52	1.52 to 4.18	1.99	1.10 to 3.61
ACPA high positive	1.41	1.17 to 1.69	1.29	1.04 to 1.59	1.45	1.11 to 1.90	1.37	1.00 to 1.89
<i>Multivariate^{c,b}</i>								
ACPA low positive	1.39	0.89 to 2.16	1.44	0.89 to 2.36	2.21	1.31 to 3.72	1.78	0.96 to 3.28
ACPA high positive	1.32	1.08 to 1.61	1.24	0.99 to 1.57	1.25	0.93 to 1.69	1.22	0.86 to 1.73

^aRF negative was used as a reference group; ^badjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort and inflammatory marker; ^cACPA negative was used as a reference group. Inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC. ACPA, anti-citrullinated protein antibodies; CI, confidence interval; HR, hazard ratio; RF, rheumatoid factor. The bold and italic text indicates subtitles, hence why there are no values in the table next to them. It is therefore essential that they look different to the predictor variables and the result values themselves.

Table 4. RF and ACPA positive versus single positive and both antibodies negative

Model/predictor	NOAR				Leiden EAC			
	Total EIA		2010 ACR/EULAR		Total EIA		2010 ACR/EULAR	
	population		positive cohort		population		positive cohort	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<i>Unadjusted</i>								
RF positive	1.11	0.83 to 1.49	1.10	0.79 to 1.53	1.88	1.29 to 2.74	1.53	0.99 to 2.36
ACPA positive	1.27	0.94 to 1.73	1.14	0.82 to 1.59	0.63	0.32 to 1.23	0.31	0.13 to 0.73
Both antibodies positive	1.51	1.23 to 1.85	1.29	1.02 to 1.64	1.59	1.21 to 2.09	1.12	0.80 to 1.57
<i>Age and sex adjusted</i>								
RF positive	1.05	0.78 to 1.41	1.10	0.79 to 1.54	1.45	0.99 to 2.13	1.54	0.99 to 2.37
ACPA positive	1.40	1.03 to 1.91	1.42	1.02 to 1.99	0.96	0.48 to 1.90	0.71	0.30 to 1.68
Both antibodies positive	1.38	1.12 to 1.69	1.25	0.99 to 1.59	1.82	1.38 to 2.40	1.83	1.29 to 2.60
<i>Multivariate^a</i>								
RF positive	1.11	0.82 to 1.51	1.22	0.87 to 1.72	1.48	0.99 to 2.21	1.47	0.94 to 2.30
ACPA positive	1.35	0.98 to 1.88	1.39	0.97 to 1.99	1.05	0.53 to 2.09	0.79	0.33 to 1.89
Both antibodies positive	1.35	1.09 to 1.68	1.31	1.01 to 1.69	1.57	1.15 to 2.14	1.59	1.08 to 2.32

^aAdjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort and inflammatory marker; both antibodies negative was used as reference group; inflammatory marker=C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC. ACPA, anti-citrullinated protein antibodies; CI, confidence interval; HR, hazard ratio; RF, rheumatoid factor. The bold and italic text indicates subtitles, hence why there are no values in the table next to them. It is therefore essential that they look different to the predictor variables and the result values themselves.

DISCUSSION

In two well established observational cohorts of EIA and its sub-population of patients with RA, we have shown that RF and ACPA positivity are predictors of excess mortality, and that the presence of both antibodies was a stronger predictor of mortality than single antibody positivity. However, in this first large study to investigate the association between antibody levels and mortality, the influence of increasing antibody level was not consistent between the two cohorts.

Our data have once again demonstrated the known relationship between RF positivity and early mortality,¹⁴ and confirmed that a similar association exists in patients who are ACPA positive. This has previously been described in NOAR¹⁸ but only reported

elsewhere by two other groups of investigators. The first study was in a subset of 299 patients in the Rochester epidemiology project,²² half of whom had RA. The second small study, by Sihvonen et al.²³ used logistic regression (which does not allow for censoring) rather than Cox models to analyse the data. It was, therefore, important to corroborate this association in another large EIA cohort, such as the Leiden EAC.

The results of our study are concordant with the findings of Ursum et al., who studied 545 patients with early arthritis in the Netherlands.¹⁰ They found no association after two years between antibody levels and early disease outcomes, including disease activity measured by DAS28, functional status measured by the Health Assessment Questionnaire (HAQ) and radiographic progression. Similarly, a number of other small studies have reinforced the association between ACPA positivity and other poor outcomes, such as increased disease activity and radiographic damage, but have failed to identify an association with increasing ACPA levels.^{8,24} By contrast, Syversen et al. conducted a study of 125 patients who met the 1987 ACR classification criteria for RA²⁵ in a subpopulation of the European Research on Incapacitating Disease and Social Support (EURODISS) project.²⁶ They found that 10 year radiographic progression was increased in patients with low-moderate ACPA levels ($>ULN$ and ≤ 8 times ULN), but this appeared to be further increased in patients with very high levels of ACPA (>8 times the ULN). However, they also demonstrated that the highest probability of radiographic progression occurred in patients who were positive for both RF and ACPA. A recent study in Italy examined progression from EIA to RA in 192 patients⁶. In accordance with our findings, they demonstrated the presence of both antibodies predicted RA, but antibody high or low positivity had no influence. In the Norwegian Very Early Arthritis Clinic (NOR-VEAC) study, Mjaavatten et al. showed additive value in testing for both antibodies in order to predict disease persistence.⁷ They also demonstrated an association between antibody level and persistent arthritis, however the number of patients per group was small (<30). In addition, their analysis employed last observation carried forward to account for patients who did not have complete follow up. It is possible, therefore, that their results were influenced by attrition bias; that is, patients whose arthritis resolved may not have attended further follow up, and at their last recorded visit, their arthritis appeared to be persistent even though it subsequently resolved. It is possible that the different characteristics and follow up of these cohorts account for the different findings; in addition the different cut-offs of the commercially available assays may not correspond. Nevertheless, this emphasises that the role of antibody levels in predicting outcomes for patients with inflammatory arthritis has not been robustly established.

There are limitations to our study. We decided not to perform a pooled analysis of data from both cohorts because the different inclusion criteria of the two cohorts could potentially produce misleading conclusions. We did not aim to develop a full predictive

model for mortality in RA, but focussed specifically on the association between antibody status and level, and mortality. Therefore, the number of confounders included in the multivariate model was small, and the final model does not account for all predictors of mortality in RA. As in all observational studies, there remains potential for residual confounding for which we have not adjusted. Further, in our analyses we did make the assumption that antibody status is fixed. This assumption seemed reasonable as the majority of studies have shown for both RF and, particularly, ACPA, that few patients convert from seropositive to negative over time,²⁷⁻²⁹ and when this does occur, risk of poor outcome may be maintained.³⁰

CONCLUSIONS

In conclusion, in this large study investigating the relationship between antibody levels and mortality in EIA, we have shown that patients with both RF and ACPA, rather than the higher levels of the antibodies, had increased rates of early death. We have also confirmed the association between ACPA positivity and excess mortality in a second large EIA cohort. Therefore, in patients presenting with early rheumatoid arthritis, the number of positive antibodies may be more important than the antibody levels in assessing the mortality risk in clinical practice.

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SUPPLEMENTARY DATA

Table S1: Univariate and multivariate Cox proportional hazard models comparing RF/ACPA high/low positive vs negative

	NOAR									
	Leiden EAC									
	Unadjusted		Age & sex adjusted		Multivariate*		Unadjusted		Age & sex adjusted	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
RF/ACPA negative	ref		ref		ref		ref		ref	
RF/ACPA low positive	0.85	0.61-1.18	0.81	0.59-1.10	0.80	0.57-1.13	2.38	1.67-3.39	1.89	1.13-2.70
RF/ACPA high positive	1.58	1.35-1.84	1.51	1.29-1.77	1.44	1.21-1.70	1.44	1.11-1.86	1.63	1.26-2.12
Female gender	-	-	0.70	0.60-0.81	0.77	0.65-0.91	-	-	0.73	0.57-0.92
Age at onset	-	-	1.10	1.09-1.11	1.11	1.10-1.12	-	-	1.10	1.09-1.11
Smoking Never	-	-	-	-	ref		-	-	-	-
Ever					0.98	0.81-1.18				
Current					1.68	1.34-2.10				
Inclusion year	-	-	-	-	0.96	0.94-0.98	-	-	-	-
Inflammatory marker	-	-	-	-	1.003	1.002-1.005	-	-	-	-

HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC
*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker
Additional file 1:

Table S2. Univariate and multivariate Cox proportional hazard models comparing RF and ACPA high/low positive vs negative

		NOAR					
		Unadjusted		Age & sex adjusted		Multivariate*	
		HR	95% CI	HR	95% CI	HR	95% CI
RF	RF negative	ref		ref		ref	
	RF low positive	0.90	0.68-1.20	0.81	0.62-1.06	0.80	0.59-1.07
	RF high positive	1.67	1.41-1.97	1.54	1.29-1.83	1.49	1.23-1.80
	Female gender	-	-	0.71	0.62-0.83	0.78	0.66-0.92
	Age at onset	-	-	1.10	1.09-1.11	1.11	1.10-1.12
	Smoking <i>Never</i>	-	-	-	-	ref	
	<i>Previous</i>					0.98	0.81-1.19
	<i>Current</i>					1.66	1.33-2.08
	Inclusion year	-	-	-	-	0.96	0.94-0.98
	Inflammatory marker	-	-	-	-	1,003	1.002-1.005
ACPA	ACPA negative	ref		ref		ref	
	ACPA low positive	1.05	0.69-1.60	1.16	0.80-1.68	1.38	0.98-1.97
	ACPA high positive	1.49	1.24-1.79	1.41	1.15-1.72	1.38	1.11-1.71
	Female gender	-	-	0.71	0.60-0.84	0.81	0.67-0.98
	Age at onset	-	-	1.10	1.09-1.11	1.11	1.10-1.12
	Smoking <i>Never</i>	-	-	-	-	ref	
	<i>Previous</i>					1.00	0.81-1.24
	<i>Current</i>					1.80	1.40-2.31
	Inclusion year	-	-	-	-	0.96	0.94-0.98
	Inflammatory marker	-	-	-	-	1,003	1.001-1.005

HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC

*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker

Leiden EAC					
Unadjusted		Age & sex adjusted		Multivariate*	
HR	95% CI	HR	95% CI	HR	95% CI
ref		ref		ref	
2.13	1.55-2.91	1.67	1.21-2.29	1.62	1.16-2.26
1.75	1.33-2.31	1.92	1.46-2.53	1.63	1.19-2.24
-	-	0.75	0.59-0.95	0.73	0.56-0.97
-	-	1.10	1.09-1.11	1.11	1.09-1.12
-	-	-	-	ref	
				0.99	0.70-1.40
				1.76	1.28-2.42
-	-	-	-	0.95	0.92-0.99
-	-	-	-	1,006	1.001-1.010
ref		ref		ref	
1.65	1.00-2.72	2.52	1.52-4.18	2.21	1.31-3.72
1.17	0.90-1.52	1.45	1.11-1.90	1.25	0.93-1.69
-	-	0.71	0.55-0.91	0.73	0.55-0.97
-	-	1.10	1.09-1.11	1.10	1.09-1.12
-	-	-	-	ref	
				1.04	0.73-1.48
				1.86	1.35-2.56
-	-	-	-	0.97	0.93-1.01
-	-	-	-	1,006	1.001-1.011

Table S3 Comparison of RF or ACPA levels in tertiles

	NOAR			Leiden EAC		
	Total EIA population			2010 ACR/EULAR positive cohort		
	RF: HR	95% CI		HR	95% CI	2010 ACR/EULAR positive cohort
Unadjusted †						
RF second tertile	0.92	0.69-1.23	0.73	1.37	0.96-1.94	1.03
RF third tertile	1.39	0.19-1.63	1.21	1.91	1.47-2.49	1.40
Age & sex adjusted†						
RF second tertile	0.83	0.62-1.10	0.85	1.49	1.05-2.12	1.46
RF third tertile	1.25	1.07-1.47	1.14	1.86	1.43-2.42	1.90
Multivariate†*						
RF second tertile	1.16	0.85-1.59	1.18	1.53	1.05-2.22	1.42
RF third tertile	1.29	1.09-1.52	1.25	1.66	1.23-2.23	1.68
ACPA:						
Unadjusted§						
ACPA second tertile	1.04	0.85-1.27	1.25	1.22	0.89-1.68	1.18
ACPA third tertile	1.29	1.06-1.57	1.31	1.26	0.91-1.73	0.82
Age & sex adjusted§						
ACPA second tertile	0.95	0.77-1.16	1.16	1.58	1.15-2.18	1.58
ACPA third tertile	1.18	0.97-1.44	1.26	1.77	1.28-2.46	1.59
Multivariate§*						
ACPA second tertile	1.00	0.81-1.25	1.24	1.21	0.84-1.74	1.22
ACPA third tertile	1.19	0.97-1.46	1.27	1.30	0.90-1.87	1.26

HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC

†RF first tertile was used as a reference group; §ACPA first tertile was used as a reference group

*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker

Table S4 Univariate and multivariate Cox proportional hazard models comparing RF&ACPA positive vs single positive & both antibodies negative

	NOAR						Leiden EAC					
	Unadjusted			Age & sex adjusted			Unadjusted			Age & sex adjusted		
	HR	95% CI	ref	HR	95% CI	ref	HR	95% CI	ref	HR	95% CI	ref
Both antibodies negative												
RF positive	1.11	0.83-1.49		1.05	0.78-1.41		1.11	0.82-1.51		1.45	0.99-2.13	
ACPA positive	1.27	0.94-1.73		1.40	1.03-1.91		1.35	0.98-1.88		0.96	0.48-1.90	
Both antibodies positive	1.51	1.23-1.84		1.38	1.11-1.72		1.35	1.09-1.68		1.82	1.38-2.40	
Female gender	-	-		0.72	0.61-0.85		0.81	0.67-0.98		0.72	0.57-0.93	
Age at onset	-	-		1.11	1.10-1.12		1.11	1.10-1.12		1.10	1.09-1.11	
Smoking Never	-	-		-	-		ref	-		-	-	
Ever							1.00	0.81-1.24				
Current							1.76	1.37-2.27				
Inclusion year	-	-		-	-		0.96	0.94-0.98		-	-	
Inflammatory marker	-	-		-	-		1.003	1.002-1.005		-	-	

HR, hazard ratio; CI, confidence interval, inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC

*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker

Table S5 Sensitivity analysis with imputed data

	NOAR		
	Multivariate*		
	HR	95% CI	FMI
Both antibodies negative	ref	-	-
RF positive	1.12	0.83-1.52	0.153
ACPA positive	1.31	0.95-1.83	0.198
Both antibodies positive	1.38	1.13-1.68	0.101
Female gender	0.76	0.65-0.90	0.002
Age at onset	1.11	1.10-1.12	0.005
Smoking	Never ref	-	-
<i>Ever</i>	0.97	0.80-1.18	0.001
<i>Current</i>	1.65	1.32-2.07	0.003
Inclusion year	0.96	0.94-0.98	0.002
Inflammatory marker	1,003	1.002-1.005	0.004

HR, hazard ratio; CI, confidence interval; FMI, fraction of missing information; inflammatory marker = C-reactive protein in NOAR

*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker

Abbreviations

ACPA: anti-citrullinated protein antibody; ACR: American College of Rheumatology; DAS28: Disease Activity Score based on 28 joint count; CRP: C-reactive protein; EAC: Leiden Early Arthritis Clinic; EIA: early inflammatory arthritis; ELISA: enzyme-linked immunosorbent assay; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; EURODISS: European Research on Incapacitating Disease and Social Support; HR: hazards ratio; NHS-IC: NHS Information Centre; IQR: interquartile range; NOAR: Norfolk Arthritis Register; RA: rheumatoid arthritis; RF: rheumatoid factor; ULN: upper limit of normal; 95% CI: 95% confidence interval.



CHAPTER 12

Improved treatment strategies reduce the increased mortality risk in early RA patients

Jessica A. B. van Nies, Zuzana de Jong,
Annette H. M. van der Helm-van Mil, Rachel Knevel,
Saskia Le Cessie and Tom W. J. Huizinga

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ABSTRACT

Objective

A higher mortality rate in patients with RA than in the general population has been reported in most series. Treatment strategies for RA have improved dramatically over the last decades, resulting in less inflammation and joint damage. We investigated whether this change in treatment corresponds to reversal of excess mortality by studying a large inception cohort of early RA patients exposed to different treatment strategies.

Methods

Six hundred and eighty-four RA patients included in the Leiden Early Arthritis Clinic between 1993 and 2008 were studied. Treatment was different for three inclusion periods. From 1993 to 1995 patients were treated with NSAIDs and only late in their disease with DMARDs. From 1996 to 1998 patients were promptly treated with HCQ or SSZ. From 1999 to 2008 patients were immediately treated with MTX monotherapy or in combination with other disease-modifying drugs. Life/death status was tracked nationally using the civic registries. Mortality rates were compared with the general Dutch population.

Results

In Periods 1 and 2, increased standardized mortality rates were found, 1.35 (95% CI 0.94, 1.93) and 1.23 (95% CI 0.91, 1.67), respectively, while a decreased standardized mortality rate was found for patients included in 1999–2006 [0.49 (95% CI 0.31, 0.77)]. Age of onset [hazard ratio (HR) 1.10 (95% CI 1.07, 1.13)], erosive disease [HR 2.03 (95% CI 1.22, 3.37)], high CRP level [HR 1.09 (95% CI 1.01, 1.18)], smoking [HR 2.39 (95% CI 1.31, 4.38)] and higher baseline HAQ score [HR 1.53 (95% CI 1.06, 2.20)] associated with mortality.

Conclusion

Current treatment strategies for early RA, such as that given in inclusion Period 3, might contribute to the reversal of excess mortality in RA.

INTRODUCTION

RA is a chronic inflammatory disease that is characterized by polyarthritis joint damage, disability and decreased work participation.¹ A recent review showed that mortality rates in RA are 1.5- to 1.6-fold higher than in the general population; this was based on 84 unique cohorts.² The attributed causes of death are similar to the general population with cardiovascular diseases being the primary cause of death.^{2,3} Patient or disease characteristics that are associated with a severe course of RA were found associated with higher risks of death.²

In the past 20 years, treatment strategies for RA have dramatically changed. Prompt start of DMARDs, combination therapy and tight control of disease activity are currently proved to be essential for beneficial disease outcome.⁴⁻⁶ Treatment strategies composed of these three components are more effective in achieving remission and preventing joint damage.⁷ Since the increased mortality risk is associated with other severity outcomes such as joint damage and since levels of joint destruction are reduced by the improved treatment strategies, we hypothesized that mortality rates benefit from these treatment strategies as well. This hypothesis is supported by observational studies on RA patients treated with MTX and anti-TNF, which showed improved survival.⁸⁻¹⁰ However, whether nowadays treatment strategies indeed reduce the increased mortality risk is thus far unknown.

Therefore, the present study aimed to investigate whether changes in treatment strategies are also reflected by changes in mortality rates. For this we took advantage of a unique longitudinal cohort of early RA patients that includes patients since 1993 and in which treatment strategies have changed dramatically over time. From 1993 till 1995 a wait-and-see policy applied and initial MTX was almost never used. From 1996 till 1998 treatment with HCQ or SSZ was initiated immediately but initial MTX was infrequently prescribed. From 1999 onwards, however, immediate treatment with MTX or combination therapy was initiated.

METHODS

Study design

The Leiden Early Arthritis Clinic (EAC) is a clinical inception cohort consisting of patients with recent-onset arthritis referred to the Department of Rheumatology of the Leiden University Medical Center (LUMC) from 1993 and onwards.¹¹ Patients were included when arthritis was observed by a rheumatologist. At the time of analysis, April 2008, the EAC consisted of 2079 patients with recent-onset arthritis (no longer than 2 years) of any origin. Written informed consent was obtained from all participants. The study

was approved by the appropriate local institutional review board (Ethische Commissie van het LUMC). For this study we selected the patients who fulfilled, within 1 year of follow-up, the ACR 1987 revised criteria for RA ($n = 684$).¹² In order to investigate whether treatment influenced the survival of RA patients, patients were divided into three separate inclusion periods in which different treatment strategies were applied. The first inclusion period concerns 1993–95. The 108 RA patients included in this period were treated initially with NSAIDs and subsequently with chloroquine or SSZ if they had persistent active disease. The decision to start with, the dosage and the choice of DMARD were left to the treating rheumatologist's discretion. In the second inclusion period, 1996–98, 174 RA patients were routinely treated with NSAIDs and promptly treated with either chloroquine or SSZ.¹³ In the third period (inclusion between 1999 and 2006), the majority of the 402 RA patients were promptly treated with MTX monotherapy and a minority with monotherapy of other DMARDs or initial combination therapy (Table 1). In all three inclusion periods, an equal number of patients received biological agents somewhere during the follow-up period. Moreover, in 2000, treatment adjustments based on DASs were introduced.

Table 1. Differences in treatment strategy for the three inclusion periods

	1993–95, n = 108	1996–98, n = 174	1999–2006, n = 402
Initial monotherapy, %			
HCQ	50	29.5	15.2
SSZ	40	61.0	14.5
MTX	5	9.5	70.3
Other	5		
Initial combination therapy, %			
MTX + SSZ	1.5	2.5	5
MTX + SSZ + HCQ	1.5	6	7
Initial combination therapy with oral prednisone	13.9	19.5	16.2
Delay in treatment initiation, median (interquartile range 25–75)			
Time between symptom onset and inclusion, months	5.1 (2.6–10.7)	4.2 (2.2–6.9)	4.2 (2.4–8.6)
Time between symptom onset and start of DMARD therapy, months	9.9 (6.3–18.5)	6.1 (3.0–10.8)	6.0* (2.8–10.0)
Time between inclusion in EAC and start of DMARD therapy, days	107 (48.5–227.5)	20 (14–56)	27* (9–60)

None of the patients was initially treated with anti-TNF. During the available follow-up the frequency of anti-TNF use was not different between the three groups (2.8, 4.6 and 4.2%, respectively). * $P < 0.0001$.

Patient assessments

At inclusion, a physical examination was performed and smoking history was taken. Patients filled in a HAQ, modified for use in Dutch patients.¹⁴ Radiographs of hands and feet were made and scored by experienced readers, using the Sharp–van der Heijde method.¹⁵ Blood samples were taken to determine ESR, CRP and IgM RF (ELISA) and CCP status (ELISA) (Immunoscan RA, MARK 2; Euro-Diagnostica, Arnhem, The Netherlands). Anti-CCP positivity had a cut-off level of 25 arbitrary units.

Notification of death

Patients were followed longitudinally from the moment of their inclusion in the EAC cohort until 1 April 2008 or until their death. All patients were tracked nationally using the civic registries (Gemeentelijke Basis Administratie, GBA) to ascertain life/death status. Mortality data of the general Dutch population were obtained from Statistics Netherlands.¹⁶

Analysis of data

Differences in characteristics at inclusion were compared with the t-test and one-way ANOVA for continuous variables and the chi-square test for nominal variables. Data are expressed as mean (S.D.) with a 95% CI, unless otherwise stated. The mortality of RA patients is compared with the general population using standardized mortality ratios (SMRs). SMR is the ratio between the observed number of deaths of RA patients and the expected number of deaths in the general Dutch population adjusted for age, sex and inclusion period. Analyses were done stratified by inclusion period and for each inclusion year compared with the general Dutch population. Survival curves were calculated using Kaplan–Meier survival curves. Expected survival curves of the Dutch population were calculated using the methods of Hakulinen.¹⁷ This method is based on the concept of an expected life table and takes differences in patient withdrawal of subgroups of patients with equal relative survival rates into account.

Associations between risk factors for RA severity and survival were studied using univariate and multivariate Cox proportional hazards and regression models. All studied variables were entered in the multivariate model because the P-value in the univariate model can be falsely high or low if there are confounding effects. A number of patients had missing values for some of the variables [BMI (n = 253), RF (n = 22), anti-CCP (n = 168), erosions (n = 197), ESR (n = 28), CRP (n = 59), smoking (n = 79), HAQ (n = 131)], which would have resulted in their exclusion from the multivariate model. For these patients we used multivariate imputation by chained equations to obtain five imputed data sets [18] and the results of the analyses of the five imputed data sets were pooled to obtain the correct S.E.s of the estimates.¹⁹ Cox regression analyses were done with and without the imputed data.

All statistical analyses were performed by using Statistical Package for Social Sciences version 14.0 (SPSS, Chicago, IL, USA), STATA 11 was used to calculate the SMRs and expected survival curves and R was used to perform the multiple imputations.²⁰ In all tests, $P < 0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics

In total, 684 RA patients were included between 1 January 1993 and April 2006. Baseline characteristics of all RA patients as well as for the patients in the three inclusion periods are presented in Table 2. The delay between the first onset of symptoms and assessment by the rheumatologist was not significantly different in all three time periods, indicating a comparable referral strategy by the general practitioner in all treatment periods. In contrast, the patients included in the second and third inclusion periods had less delay in initiation of DMARDs after assessment by the rheumatologist compared with patients included in the first period.

Table 2. Baseline characteristics for RA patients divided into three inclusion periods

	1993–95, n = 108	1996–98, n = 174	1999–2006, n = 402	Total
Age, years	56.9 (14.4)	55.5 (17.2)	57.1 (15.3)	56.7 (15.7)
BMI	25.5 (3.1)	25.2 (3.1)	26.0 (4.1)	25.8 (3.8)
RF positive, n (%)	65 (60.2)	92 (52.9)	228 (60.0)	385 (58.2)
Anti-CCP positive, n (%)	65 (60.2)	90 (55.2)	125 (53.4)	286 (55.4)
ESR, first hour, mm	51 (34)	40 (26)	37 (25)*	40 (27)
CRP, mg/l	30 (25)	33 (34)	29 (37)	30 (35)
Past or current smoker, n (%)	51 (53)	75 (47)	180 (52)	306 (51)
HAQ (0–3)	1.03 (0.67)	1.07 (0.74)	1.12 (0.74)	1.1 (0.73)

Unless otherwise stated values are mean (S.D.). Age: age at inclusion in EAC cohort
follow-up: duration between inclusion date in EAC cohort and endpoint 1 April 2008 or death
smoking status: never smoked vs ever smoked (smoking in past and current). Data not available for all cases [BMI (n = 253), RF (n = 22), ESR (n = 28), CRP (n = 59), smoking status (n = 79), HAQ (n = 131)]. Proportion of missing data of the variables was equally distributed in the three inclusion periods. * $P < 0.0001$.

SMRs

During follow-up 90 RA patients died, while 85 deaths were expected within the general population. Mean age at death was 75.8 (S.D. 9.6) years. No difference in mortality was observed between all included RA patients [SMR 0.95 (95% CI 0.78, 1.17)] and the

matched general Dutch population. Male RA patients had an SMR of 0.87 (95% CI 0.63, 1.21) and female RA patients an SMR of 1.02 (95% CI 0.78, 1.33). Subsequently the SMRs for the three inclusion periods were determined (Fig. 1A–C). An increased mortality rate was found in Period 1 as well as in Period 2 [SMR 1.35 (95% CI 0.95, 1.93) and SMR 1.23 (95% CI 0.91, 1.67), respectively]. In contrast, a decrease in mortality rate was found in patients included from 1999 until 2006 [SMR 0.49 (95% CI 0.31, 0.77)]. The SMRs in the three inclusion periods were statistically significantly different ($P = 0.0002$), and together these data reveal a nullification of the increased mortality risk. The log rank test of the three inclusion periods had a $P = 0.008$.

Risk factors associated with mortality

In the univariate analysis, all analysed factors were associated with increased risk of mortality in our RA population except for BMI, RF, anti-CCP and smoking status (Table 3). The multivariate analysis revealed that a higher age [hazard ratio (HR) 1.10 (95% CI 1.07, 1.13)], the presence of erosive disease [HR 2.03 (95% CI 1.22, 3.37)], a higher CRP level [HR 1.09 (95% CI 1.01, 1.18)], smoking status [HR 2.39 (95% CI 1.31, 4.38)] as well as a higher HAQ-score [HR 1.53 (95% CI 1.06, 2.20)] at baseline were all independently associated with increased mortality. In the multivariate analysis, the inclusion period remained independently associated with mortality risk [HR 0.84 (95% CI 0.77, 0.92)] over time. As a sensitivity analysis, the multivariate analysis was performed with and without imputed data, revealing no differences (data not shown).

Table 3. Univariate and multivariate analysis of HRs for mortality in all RA patients.

Variables	Univariate model		Multivariate model	
	Hazard Ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years	1.09 (1.07-1.11)	<0.0001	1.10 (1.07-1.13)	<0.0001
Gender (male)	1.54 (1.01-2.34)	0.045	0.85 (0.50-1.46)	0.554
BMI	1.00 (0.94-1.07)	0.906	0.96 (0.88-1.05)	0.363
RF (positive)	1.36 (0.89-2.10)	0.234	1.23 (0.65-2.35)	0.522
Anti-CCP (positive)	1.14 (0.75-1.76)	0.527	1.41 (0.75-2.68)	0.289
Erosive disease (positive)	3.41 (2.21-5.26)	<0.0001	2.03 (1.22-3.37)	0.006
ESR, mm1 st hr	1.011(1.006-1.016)	<0.0001	0.990 (0.980-1.001)	0.065
CRP, 10mg/L	1.09 (1.05-1.14)	0.0001	1.09 (1.01-1.18)	0.030
Smoking status	1.50 (0.93-2.41)	0.095	2.39 (1.31-4.38)	0.006
HAQ (0-3)	2.08 (1.57-2.76)	<0.0001	1.53 (1.06-2.20)	0.022
Inclusion year	0.91 (0.84-0.98)	0.015	0.84 (0.77-0.92)	<0.0001

Age: age at inclusion in EAC cohort. Gender: female versus male, erosive disease: ≥ 3 erosions scored on X-hands and feet (Sharp- van der Heijde score). smoking status: never smoked versus ever smoked (smoking in past and current).

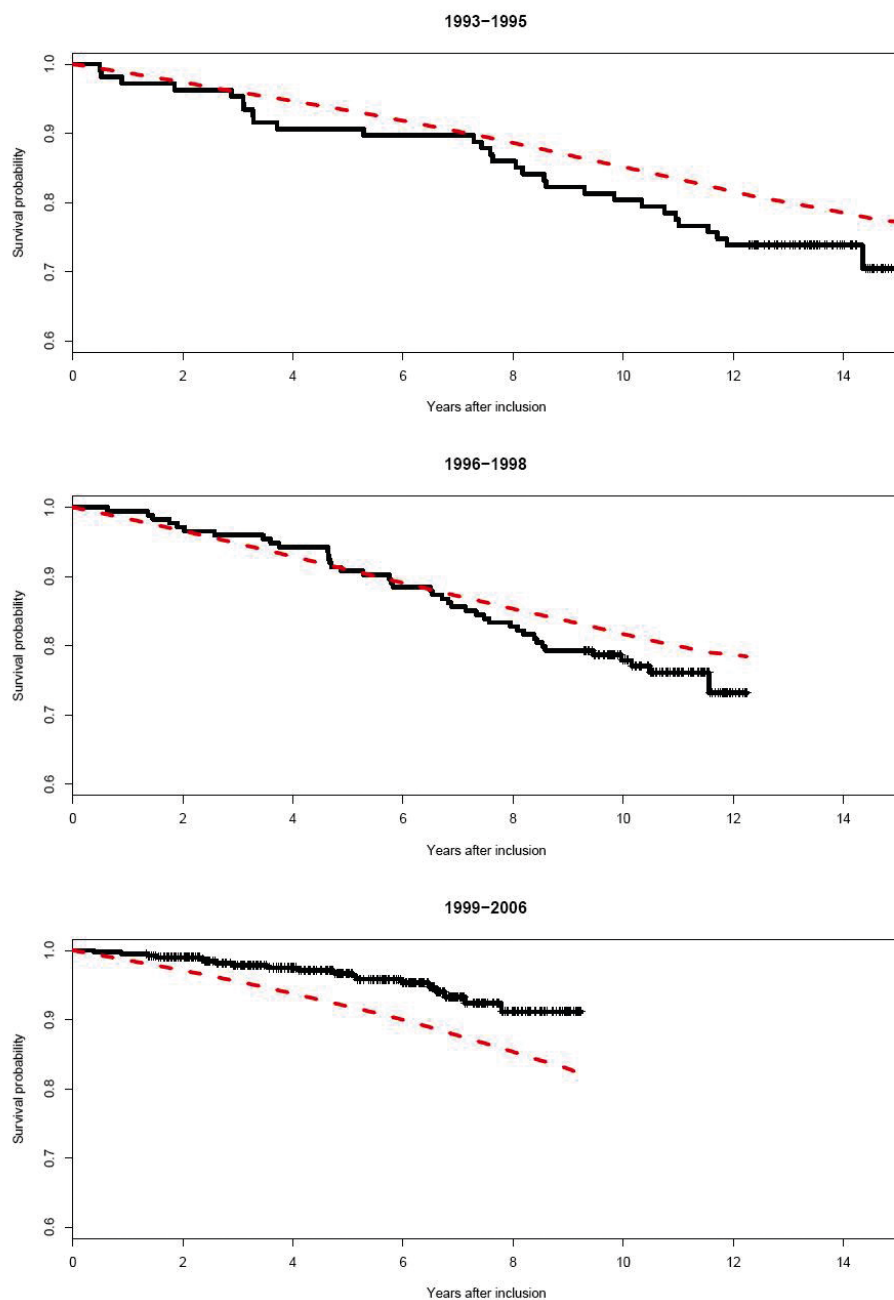


Figure 1. (A) Inclusion Period 1: 1993–95; SMR 1.35 (95% CI 0.95, 1.93); $P = 0.097$; **(B)** inclusion Period 2: 1996–98; SMR 1.23 (95% CI 0.91, 1.67); $P = 0.185$; **(C)** inclusion Period 3: 1999–2006; SMR 0.49 (95% CI 0.31, 0.77); $P = 0.001$.

The general Dutch population (---); the RA patients from the EAC cohort (—). x-axis, survival probability; y-axis, years.

DISCUSSION

The outcome of RA patients has improved over the last decade. This improvement is generally expressed by lower rates of joint destruction and higher remission rates. The findings of this study suggest that current treatment strategies might have positive impact on the survival of RA patients as well.

The relationship between therapies and mortality rates in patients with RA has been studied extensively; however, no consistent effects have been shown.² Importantly, to our knowledge no previous studies have investigated the relationship between different treatment strategies and mortality in an early arthritis cohort. In the present study, three treatment strategies were applied that differed importantly with regard to readiness to initiate DMARD therapy, choice of DMARDs and frequency of combination therapy (Table 1). The duration between first symptoms and first assessment by the rheumatologist was not different between the three periods, indicating that the observed findings were not thanks to early referral.

The present study not only observed reduction in the increased mortality risk in RA but also revealed a tendency towards a reduced mortality risk for patients included in the third period. At first glance, this reduced mortality rate is surprising. Apart from a higher ESR (observed in inclusion Period 1), no other differences in baseline characteristics between patients included in the three inclusion periods were found. This makes it unlikely that less severe patients were included in the third inclusion period. Another possible explanation is the presence of secular trends in mortality by specific adoption of healthier life styles by RA patients compared with the general population. As far as physical activities are concerned, even now RA patients spend less time on physical activities than the general population.²¹ It is, however, plausible that increased knowledge of modifiable risk factors for mortality resulted in better treatment of such risk factor comorbidities and thus contributed to the observed improved mortality rate. Another possible hypothesis is that patients with a serious, potentially fatal illness who also develop joint complaints will not be referred to the rheumatologist and as such contribute to the mortality rate of the general population but not of the arthritis population. At present, insufficient data are available to explore these potential explanations.

As mentioned before, this study observed a lack of increased mortality in the most recent cohort. Unfortunately, this last cohort is too small to allow a subanalysis in responders to therapy vs non-responders. So in theory it may be possible that there still is an increased mortality in the subgroup of patients who did not respond well. However, we are underpowered to make this analysis.

In line with the previous studies it was observed that a higher age at disease onset, erosive disease, a higher CRP level, smoking status and a higher HAQ-score at baseline are risk factors for mortality. Of these, erosive disease and HAQ-score are the two significant predictors of mortality (HR 2.03 and 1.53, respectively) in the univariate as well as the multivariate analysis. Smoking status was not associated with increased risk in the univariate model, though an association was found in the multivariate model. Our male patients tend to smoke more often than females and we hypothesize that this seemingly unexpected finding is due to the fact that we present HRs after adjustment for sex. Increased CRP level has previously been shown to associate with an increased risk of cardiovascular disease and cardiovascular mortality in particular. This suggests a link between ongoing inflammation and increased risk of cardiovascular events.^{22,23} Some variables like anti-CCP, RF and BMI are considered to be of predictive value for mortality. Although the presence of anti-CCP antibodies is associated with a more destructive disease course in RA patients, and increased BMI (irrespective of RA) is associated with mortality, we did not observe an association between anti-CCP or BMI and mortality in this study.^{24,25}

One might be reminded of another Dutch study that reported no increased mortality in RA patients.²⁶ This was probably based on their relatively short follow-up time, making it an observation too early. This was confirmed by their second research, where they observed that excess mortality emerged after 10 years.²⁷

However, a recent study from the states suggested that excess mortality is caused by accelerated ageing and that this phenomenon is responsible for the fact that RA patients at onset of disease are already effectively >2 years older than the general population,²⁸ so if this is true one would have expected to observe excess mortality in the last period as well.

In conclusion, clinical practice in rheumatology has shown impressive progress with regard to treatment of signs and symptoms of RA as well as slowing down the rate of joint damage and prevention of functional disability. These current treatment strategies are characterized by rapid institution of appropriate treatment schedules, tight control of disease activity and combination therapies.⁷ This study suggests an association between better care for patients with early RA and improved survival. As such it underlines the importance of early potent treatment strategies in comparison with wait-and-see policies.

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CHAPTER 13

Summary and Discussion

PART I: EARLY RECOGNITION OF ARTHRITIS

In the first part of this thesis we focused on the early recognition of arthritis patients. Previous research in the Leiden early arthritis clinic revealed that the median duration between onset of symptoms and the first visit to a rheumatologist in early arthritis patients was almost 14 weeks and in early RA patients about 18 weeks.¹ Keeping in mind that nowadays the challenge is to start therapy in RA patients as soon as possible, a change in diminishing this delay was preferable. The 'local' cause of this delay could mainly be attributed to delay on part of the general practitioner.

Therefore, a new initiative to tackle this problem was set up as described in **chapter 2**. As it can be difficult for GPs to recognize arthritis of the small hand and feet joints, it is understandable that GPs apply a wait-and-see approach.² In Leiden and Groningen a new initiative was launched to offer GPs help with this problem. GPs were encouraged to send patients in which they were unsure on the presence of arthritis to the early arthritis recognition clinics (EARCs). After 1 year, the results of these clinics were evaluated. We observed that in Leiden 42% (168/400) and in Groningen 49% (104/212) of the patients were diagnosed with arthritis. The major aim of these clinics was to reduce the so-called GP delay; this was successful in both EARCs and the observed median delays in the early arthritis patients were 2.0 (0.4–8.4) weeks in Leiden and 2.3 (0.6–9.1) in Groningen. More interestingly, the patients with undifferentiated arthritis (UA) or RA had a median GP-delay of approximately 2 weeks compared to 9 weeks of UA and RA patients that arrived at the outpatient clinic in the same timeframe via regular referrals. The aforementioned duration of GP-delay in the EARC and regular referrals was lower than the historical GP-delay on RA patients (median 11.8 weeks).¹

Even though the duration of the GP-delay was stable over time, between 1993-2006 the reduction in GP-delay is potentially not solely a consequence of the initiated EARCs. It has to be noted that before these EARCs were initiated, GPs in the surrounding area were educated on rheumatic diseases in general and they were introduced to the concept of the upcoming EARCs. Thereby, in 2009 renewed guidelines on arthritis was provided for Dutch general practitioners.³ Under these new guidelines, GPs are advised to refer patients of whom they suspect presence of RA within 4 weeks instead of after 6 weeks which was advised in the previous guidelines. Together, these factors may have played a role in raising the awareness and knowledge of (rheumatoid) arthritis and the need for prompt referral. For this reason, the presence of the EARC itself may not be the only cause of the substantial decrease in GP-delay in arthritis patients. Therefore, it would be interesting to get to know the motivations of GPs on their referral of patients via regular routes or via the EARC. If one obtains this information, new intervention methods may

be developed that specifically target referral tactics of GPs. It should be stressed that a long GP delay is mainly a problem in the Netherlands. For example, in the UK, studies revealed that patient delay was the most important contributor to delayed assessment by a rheumatologist.^{4,5} A recent study across ten centres in Europe revealed that the median delay caused by RA patients ranged from 2 till 8 weeks.⁽⁶⁾ Although this was relatively low in our cohort (median 2 weeks in early arthritis patients) it is fascinating to learn the motivations of patients to seek medical help. Motivations of arthralgia patients that visited the EARC are described in **chapter 3**. In all arthralgia patients the median symptom duration before they first visited a GP was 4 weeks. Patients that had arthritis sought medical help faster than arthralgia patients without arthritis (2.6 versus 5.9 weeks). In general, the motivations did not differ between arthritis and non-arthritis patients. Though, arthritis patients sought medical help because their symptoms occurred suddenly and because they were advised to do so by their friends and family. Besides comparing arthritis and non-arthritis patients we made comparisons between arthralgia patients that had a short patient delay (<4 weeks) and a prolonged patient delay (>4 weeks). This revealed that impairments either work-related or in physical functioning were major motivations to seek medical help promptly. One of the main questions was whether certain symptom characteristics, motivations or variables related to the ability to carry out work frequently occurred together. In other words, whether there was a clustering of variables in the same arthralgia patients. This was assessed by a data reduction method called a partial least square regression analysis (PLS). This indeed revealed two clusters. A group of patients was found that was characterised by a short patient delay, a sudden onset of symptoms, functional impairment and absenteeism. The other group of patients consisted of patients with a prolonged patient delay, a gradual onset of symptoms and no absenteeism. It has to be mentioned that these arthralgia patients are a selection of patients in which a GP was doubtful on the presence of arthritis so they do not represent all arthralgia patients that visit a GP. Besides that, musculoskeletal problems are very common in the general population, and a large survey (population-based with 3664 respondents) showed that just about half of these persons consulted their health professional.^{7,8} This is consistent with the findings of an Austrian initiative called the 'rheuma-bus', here as well they discovered that 40% of the persons with musculoskeletal problems never contacted a physician. Importantly, only 14% of all arthralgia patients that visited the EARC were aware that in case an arthritis is present it is relevant to act quickly (as in seeking medical help). Even knowing someone with RA was not necessarily a trigger for seeking medical advice or for recognition of symptoms.⁹ In combination with the previously observed findings and in combination with reports on the lack of knowledge on arthritis and RA in the UK and Canada,¹⁰⁻¹² this calls for a need to raise public awareness. However, in which way this can best be achieved remains open for debate. For instance, one might start to investigate if persons

are able to self-diagnose an arthritis, future research within the EARC could focus on the ability of patients to recognise a true arthritis by comparing the arthritis-manikins filled out by the patients as well as the physician on their concordance. Finally, the long-term effectiveness of the EARC has to be assessed.

PART II: A THERAPEUTIC WINDOW OF OPPORTUNITY IN RA

After early recognition by GPs and identification of RA by a rheumatologists the next concern is to start promptly with anti-rheumatic treatment. It has been established that delay in initiation of treatment after the diagnosis RA has been made has been associated with progression of joint damage.¹³ It has even been suggested that a certain window of opportunity for treatment exists in RA. It is thought that in this certain period the disease is not fully matured yet and that therapeutic intervention (DMARD-therapy) can alter the disease course in such a way that chronicity is prevented. In **chapter 4** we investigated whether such a period truly exists by performing a systematic literature research. Since many studies included symptom duration in their analysis we systematically reviewed all such studies to assess whether short symptom duration at treatment initiation was associated with less progression of disease. The quality of the studies was assessed by a predefined scoring system and best evidence synthesis was applied to determine the level of evidence per category. We observed that there was strong evidence for an association between short symptom duration and less radiographic damage and moderate evidence for an association between symptom duration and other outcomes in RA such as the achievement of certain disease states (remission under therapy defined as e.g. DAS-28<2.6 DAS-28<1.6, ACR remission et cetera). Another important outcome was DMARD-free sustained remission, which was defined as the sustained absence of synovitis after discontinuation of DMARD-therapy for at least one year. Via the qualitative approach we observed there was moderate evidence for an association between symptom duration and DMARD-free sustained remission. However, we had access to the raw data of these three cohorts and were able to perform a meta-analysis. This revealed that symptom duration was independently associated with DMARD-free sustained remission also when adjusted for age, gender and the more disease specific markers such as RF and ESR. One might argue that via this method we could not identify publication bias, since it is not possible to draw a funnel plot for a qualitative review. However, symptom duration was not the main subject of interest in these studies. Altogether, even taking patient heterogeneity into account, these data convinced us there might be a therapeutic window present and that indeed early treatment after diagnosis of RA is justified but, we were not able to point out when this window 'opens' of 'closes'.

In chapter 4, it was investigated whether an association existed between symptom duration and various outcomes in RA. As was observed in the meta-analysis an

association existed between shorter symptom duration and the chance of DMARD-free sustained remission. It has to be mentioned that this was achieved by comparing hazard ratios from cox-proportional hazard regression models. The applied model assumed a linear association between every week increase in symptom duration and the chance of DMARD-free sustained remission. This led us to the question regarding the shape of the association between symptom duration and DMARD-free sustained remission.

In **chapter 5** we explored the shape of the association of symptom duration with the persistence of RA. Until now it is unknown whether this relation is linear, referring to ‘the-earlier-the-better principle’ or whether a certain time-frame exists in which the disease is more susceptible to therapeutic interventions, referring to a ‘window of opportunity’. In a linear association it is presumed that the total inflammatory load (product of the severity and duration of inflammation) at the time of treatment onset is related to the disease outcome. On the other hand, in the literature a ‘window of opportunity’ in RA is often mentioned, it has been said to enclose the first twelve weeks after symptom onset. In this confined period the disease is presumably more susceptible to therapeutic interventions. This cut-off of 12 weeks seems to be based on expert opinion, though later on there are data available that support this window of 12 weeks, showing that patients with less than 12 weeks of symptom duration have a more beneficial outcome. However, it has not been shown that after a certain period of symptom duration the effect of treatment diminishes. We took advantage of two large early RA cohorts and the main outcome was DMARD-free sustained remission. We observed that over a 5-year period of follow-up the curves of the log-hazard ratios (chance on DMARD-free sustained remission) against symptom duration was non-linear. The log-hazard ratios were calculated by using cox-proportional hazards regression models with natural cubic splines. The advantage of this approach is that it does not assume linear associations. In addition, discrimination was measured by using time-dependent ROC-curves. The symptom duration with optimal discriminative ability was 14.9 weeks in the EAC and 19.1 weeks in ESPOIR. Since the course of disease in ACPA positive and ACPA negative patients differs, we hypothesized that processes that underlie the disease might be influenced differently. Although achieving DMARD-free sustained remission in ACPA positive patients is less frequent than in ACPA negative patients, we observed that the optimal discriminative ability in ACPA positive RA was 11.4 weeks and for ACPA-negative RA 15.0 weeks. The endpoint of DMARD-free sustained remission is not often achieved (5-11%) and relies on the opinion of the treating rheumatologist and willingness of the patient in question regarding the (dis)continuation of DMARD-therapy. Two additional endpoints namely a certain level of radiographic progression and sustained remission irrespective of treatment, though less fitting the hypothesis, were investigated. For these outcomes the shape of the log-hazard ratios curves wasn’t linear either. This suggests that there is a confined period present in RA patients in which it is more beneficial to start with

DMARD-therapy. Summarizing the data, the proposed 12-week window in the literature doesn't seem misplaced. Though based on current data one might say the window is confined to the first 5 or 6 months after symptom onset, taking the time until DMARD-treatment into account. Clearly, it is not possible to draw definitive conclusions on when this window 'opens' and 'closes'. For this project we relied on the patient's memory of when the 'symptoms' started and the willingness of both patients and rheumatologists to discontinue DMARD-therapy. With respect to the start of symptoms; although being assessed similarly there is no uniform definition of a 'symptom'. Despite the fact that criteria are proposed for standardised duration,¹⁴ the applicability remains to be seen since experiencing symptoms will always be an individual matter. With respect to the clinical practice the most important message is that indeed a 'therapeutic window of opportunity' exists in RA. Thus, it is better to start DMARD-treatment immediately in RA patients than waiting for example 6 months, even if the disease course appears to be mild. For basic translational research the existence of a window strongly suggests that there is a change in underlying processes. The questions remains open *which* processes change, *when* they originate and *how* these processes can be altered by specific targeted therapies. Currently, patients with arthralgia that are susceptible to develop RA are being followed longitudinally in the clinically suspected arthralgia cohort (CSA). This cohort can give insight in not only the phenotype of arthralgia patients that convert to RA but might also focus on changes in specific disease processes which in the long haul can be related to reversibility in RA patients.

PART III: DIAGNOSTIC AND PROGNOSTIC VALUE OF DISEASE SYMPTOMS, CHARACTERISTICS AND CLASSIFICATION CRITERIA IN ARTHRALGIA, EARLY ARTHRITIS AND RA PATIENTS

The presence of morning stiffness is easily assessed by taking a patient's history, and it is often mentioned to be one of the first symptoms of RA besides fatigue.¹⁵ Also, until recently it has been an item in the classification criteria for RA, though it was omitted from the 2010 ACR-EULAR criteria for RA.¹⁶ Data on the discriminative ability of morning stiffness between RA and various rheumatologic diseases, however, is scarce and information on the diagnostic ability in arthralgia patients and prognostic value in RA patients is absent. Therefore, in **chapter 6** we evaluated the diagnostic value of morning stiffness in arthralgia and early arthritis patients and the prognostic value in early RA patients. To this end, we used 1641 arthralgia patients from three cohorts. Two of these, the EARCs from Leiden and Groningen were described above.¹⁷ The third cohort was the Rotterdam Early Arthritis Cohort (REACH).¹⁸ Approximately 50% of the arthralgia patients that were referred to these cohorts were diagnosed with arthritis at their first visit with the rheumatologist. The analyses were performed cross-sectionally. We observed that

morning stiffness with a duration of ≥ 60 minutes in arthralgia patients was associated with the presence of arthritis (Leiden EARC OR1.49(95%CI1.001-2.20), Groningen EARC OR2.21 (1.33-3.69) and REACH OR1.55(0.97-2.47)). Overall, the sensitivities were low (21-38%) and the specificities ranged between 73-85%. Hereafter, we investigated the discriminative ability of morning stiffness among early arthritis patients in two cohorts, the Leiden EAC and the French ESPOIR cohort.^{19,20} First, the duration of morning stiffness was depicted against the diagnosis of the early arthritis patients after 1 year of follow-up. This demonstrated that the median duration in RA patients (classified according to the 2010 ACR/EULAR criteria) was 60 minutes and longer than that of other early arthritis patients (except SLE-patients, $n=22$). This was an interesting observation because only two studies in the literature describe that the discriminative ability of morning stiffness is poor, those studies had relatively small sample sizes (93 RA versus 46 non-inflammatory joint diseases and 31 RA versus 23 SLE and 34 osteoarthritis patients).^{21,22} The diagnostic ability of morning stiffness ≥ 60 minutes in early arthritis was significantly associated with the diagnosis of 2010-RA after 1 year, also independent of other predictors (SJC, ACPA, RF, symptom duration and ESR). Several factors may play a role in the omission of morning stiffness from the newly formed 2010 ACR/EULAR criteria. For instance, patients with a diagnosis other than RA or UA were excluded (which makes it more difficult to find a difference in patients that are quite alike). Secondly, the endpoint in the criteria was methotrexate use after 1 year. Furthermore, in 760 out of 3115 patients information on morning stiffness was missing and in the remaining patients, which did have information on morning stiffness, it was assessed differently in the various cohorts (present/absent, $</\geq 1$ hour, or categories on duration). We also looked at the optimal discriminative duration of morning stiffness in early arthritis patients for RA. Here we observed that in both cohorts the optimal discriminative duration was around 30 minutes of morning stiffness. Finally, we investigated whether certain duration of morning stiffness at baseline (≥ 30 , ≥ 60 and ≥ 90 minutes) had a prognostic value on long-term outcomes in RA, such as joint-destruction and DMARD-free sustained remission. We did not observe an association between these durations and a worse outcome. This was in contrast with a previous result from the QUEST-RA study where an association was observed between morning stiffness and a lower chance of remission. However it should be noted that the definitions of remission were different and that in patients from the Leiden EAC also a discontinuation of DMARD-therapy was achieved.²³ Though morning stiffness alone is not enough to use as a diagnostic, it should be used in clinical practice in the decision-making of the diagnostic process. Especially since it is easy to assemble.

In the past decades many genetic studies focused on susceptibility genes for RA. In **chapter 7** we studied whether *PTPN22*,²⁴ a strong susceptibility gene for RA, was also associated with joint destruction in RA patients. This gene was already tested in a different dataset and an association with joint destruction was found.²⁵ Though, no

adjustments were made for ACPA. Since replication is one of the keystones in science to prevent false positive findings current research was conducted in two ACPA-positive datasets. We observed that *PTPN22*, although it predisposes to ACPA positive RA, is not associated with increased radiological joint destruction.

To elaborate on radiological joint destruction in RA, in **chapter 8** we investigated the role of baseline erosions and its association with future joint damage in more detail. As established, joint erosions are a typical manifestation in RA and have been part of several classification criteria for RA for decades.^{26;27} On the other hand, one of the key goals in treatment of RA is to prevent joint damage. In this research it was further explored whether baseline erosions themselves were independently associated with future joint damage or whether this process was mediated via other mechanisms. To this end, RA patients were studied which had 7 years of follow-up; X-rays on hand and feet were scored via the Sharp-van der Heijde method. Several hypothesis were proposed and subsequently tested for mediation (by the mediation model proposed by Baron and Kenny).²⁸ In short the proposed 'variables' that were tested in mediation analyses were; symptom duration, auto-antibodies (RF and ACPA), systemic inflammation (ESR) and local clinical inflammation (SJC). These variables were chosen for the following reason. Symptom duration was chosen because we hypothesized that if patients presented later in time to a rheumatologists they would have a more advanced disease. Furthermore we hypothesized that since autoantibodies are associated with severe radiological joint damage they could also be associated with baseline erosions and finally that a more severe disease at presentation (reflected by systemic and local clinical inflammation) could be associated with baseline erosions. To summarize, baseline erosions were not located in the causal path of any of the above variables and thus had an independent effect on future joint damage. It is interesting to note that patients with baseline erosions at any point in time had 3.45 times more joint damage than patients without erosions at baseline. However, the exact mechanism for the development of baseline erosions was not explained yet. To this end, we investigated a subgroup of RA patients in which MRI data was present at baseline. These data led to the suggestion that subclinical inflammation (observed by MRI) is relevant for the development of baseline erosions but this study only provided an indication for causality and further research to the exact mechanism may be obtained from animal models in the near future.

The last years a collaborated initiative by the American College of Rheumatology and the European league against rheumatic diseases presented new classification criteria for RA (also referred to as the 2010 ACR-EULAR criteria for RA). One of the aims was to classify patients in an earlier phase of the disease. Many studies were conducted to evaluate the diagnostic testing properties of the 2010 criteria for RA. A recent meta-analysis on these studies showed that a sensitivity of 82% and a lower specificity of 61%, is used on

the intended population.²⁹ However, it was insufficiently clear whether the phenotype between the two criteria is different. Several studies observed that some disease characteristics of '2010 RA' were milder than in '1987 RA' patients. Yet, no studies were performed comparing long-term outcomes in RA patients. Therefore, in **chapter 9** we compared two long-term outcomes (radiological joint damage and disease persistence) in relation to the classification criteria of RA. At baseline, no large differences were observed, except that 1987 RA patients more often experienced morning stiffness than 2010 RA patients, which can be attributed to the fact that morning stiffness is a part of the 1987 criteria for RA. Less severe radiological joint damage and more frequent DMARD-free sustained remission was achieved in favour of the 2010 RA patients. Sub-analyses demonstrated that patients that were positive for both criteria sets had the worst prospects. In addition, analyses were repeated by adding the erosion-criterion for RA (≥ 3 erosive joints) in addition to the 2010-criteria point system and this didn't influenced the results. In conclusion, current study demonstrated that patient classified according to the 2010 criteria for RA have a milder disease course than patients classified according to the 1987 criteria for RA.

PART IV: MORTALITY IN RA

In **chapter 10** we set out to replicate whether a genetic variation in TRAF1/C5 was associated with mortality in RA. In the original investigation by Panoulas et al. an association was found between the susceptible genotype GG (of rs3761847) with increased mortality from sepsis or cancer, though not by cardiovascular death.³⁰ Cardiovascular death is the most common cause of death in the general population as well as in RA patients. The idea was that this might have been missed because patients were enrolled at an advanced disease stage. Therefore, we studied 615 RA patients that were prospectively followed in the Leiden EAC and were genotyped for rs10818488. In our cohort the main cause of death was cardiovascular disease (37.7%) followed by cancer (28.6%) and infections (9.1%). Contrary to Panoulas et al, we did not find an association between the susceptibility allele and overall mortality, nor with cardiovascular mortality, cancer-related mortality or mortality due to infections. In addition, analyses were repeated in a large (n=5634) non-RA cohort of elderly persons and here no associations were observed between rs2416808 ($R^2 > 0.99$ with rs10818488) and mortality or cardiovascular, cancer or infection related death either. This strengthened our observation of a lacking association between TRAF1/C5 and mortality.

Autoantibodies in RA (RF and ACPA) have been associated with poor outcomes, like radiological joint damage and disease persistence.^{31,32} In the 2010 criteria for RA a distinction has been made in assigning points, taking into account the titre of RF and ACPA. Assuming that a higher titre will lead to a poor outcome and therefore those

patients require therapeutic intervention. Though, no consistent findings are present with respect to altitude of the titre and subsequently a poor outcome. With respect to mortality in RA patients, presence of RF is well recognised to be associated with increased mortality risks. On the other hand, data on the presence of ACPA and mortality is still scarce. Therefore, in **chapter 11** we investigated, in 4962 early arthritis patients, whether there was an association between mortality and RF/ACPA positivity and their titre. Early arthritis patients from the Norfolk Arthritis Register (NOAR) and Leiden EAC were studied.^{19;33} Antibody status was stratified into negative, low or high positive (as proposed by the 2010 ACR/EULAR criteria for RA) and subsequently into negative and positive. When antibody status was stratified as such, no consistent findings between the cohorts were observed. More interestingly, when counting the number of antibodies in a patients (zero, one antibody and two antibodies) we observed that the presence of two antibodies (thus double positive) was associated with increased mortality adjusted HRs (95% CI) NOAR: 1.35 (1.09 to 1.68), EAC: 1.57 (1.15 to 2.14) compared to patients who had either one antibody or none antibodies.

Throughout this thesis various themes are presented, mainly focussing on early detection of those persons which are at risk for developing RA or those who have RA and are at risk of having a poor outcome. This all leads in one direction, namely to start treatment as early as possible! In the last decades treatment options as well as their approach in RA patients have changed dramatically. Nowadays, DMARD-therapy is started with such promptness that joint damage is prevented, low disease activity scores are achieved and even drug free remission is a real goal. Observing these beneficial outcomes in RA patients one final questions remains: do these improved treatment strategies also benefit the survival of RA patients? In **chapter 12** we investigated, in the Leiden EAC, the survival of 684 RA patients that were exposed to different treatment strategies compared to the general Dutch population. The applied treatment strategies were as follows; From 1993 to 1995 patients were treated with NSAIDs and only late in the course of their disease with DMARDs. From 1996 to 1998 patients were promptly treated with either HCQ or SSZ. From 1999 to 2008 patients were immediately treated with MTX monotherapy or a combination with other disease-modifying drugs. In the first 2 periods increased standardized mortality rates (SMRs) were observed 1.35 (95% CI 0.94, 1.93) and 1.23 (95% CI 0.91, 1.67), this means that patients that were diagnosed with RA between 1993 and 1998 had a higher mortality risk than their matched peers from the general Dutch population. Interestingly, RA patients included in the latest period had a decreased mortality ratio 0.49 (95% CI 0.31-0.77). To actually find a reduced SMR is surprising, but several explanation can be given for this. It might be explained by the presence of secular trends in mortality by specific adaptation of healthier lifestyles by RA patients versus the general population. On the other hand we know that RA patients even now spend less time on physical activities than the general population. Thus, most

likely there is increased awareness of risk factors for comorbidities which may result in better treatment and therefore lower mortality risks. Another plausible explanation is that patients with a potential fatal illness who also develop joint symptoms are not referred to the rheumatologists and therefore not included in our cohort and as such will contribute to the mortality rate of the general population instead of the RA-patients. It should be noted that mortality data are difficult to interpret. It is not possible to compare SMRs between countries, this is due to the differences in survival between general populations. Furthermore, one should also take into account the design of the cohort and the duration of follow-up. Since the analyses always take place over a certain time period that ran its course, it is important to keep in mind that the findings are outdated. This means that as a clinician you would like to know the mortality risk over e.g. 20 years period of a newly diagnosed RA patient in 2015 (so at this moment), you will need to wait another 20 years before you can answer this question. Nonetheless, current study suggests an association between better treatment of RA patients and improved survival.

CONCLUSIONS AND FUTURE PERSPECTIVES

To summarize, the current thesis presents a range of subjects starting with the success of the early recognition clinics in two University hospitals in the Netherlands (Leiden and Groningen). By this initiative the GP delay was diminished incredibly, which resulted in presentation of arthritis patients at the rheumatologists at an earlier stage. Important questions that are not addressed in the current thesis and deserve more attention are the: did the (rheumatoid) arthritis patients truly benefit from this early recognition in terms of prompt initiation of treatment and improved overall quality of life and are the EARCs cost-effective? With respect to these questions it remains difficult to find adequate parameters to study this. Possibly a combination by objective measures (joint damage either by MRI or X-rays) and patient reported outcomes (VAS-morning stiffness, -fatigue, work-participation) can be used to this end. Despite that it is good that because of the EARCs the GP-delay diminished, a next challenge is to understand the motives and doubts of GPs to refer or not to refer patients to a rheumatologist. When this has been ascertained, targeted interventions specifically for GPs can be developed.

In this thesis we strongly support the notion that there is a therapeutic window of opportunity in RA. Current observations are of course based on assumptions regarding the actual onset of the disease as reported by the patients themselves (so when they, for example, experience swelling or pain in their joints). It is, in that sense, extremely difficult to catch the 'true' moment of disease onset. Since we do not yet have a golden standard by specific cellular-, cytokine-, bone- alterations that are pathognomonic for RA and especially *this* is one of the objectives in research in the earliest phases of RA. An attempt to better understand the development of RA in a phase in which patients have

symptoms but not yet arthritis commenced with the establishment of the clinically suspect arthralgia (CSA) cohort. This cohort is still ongoing and more follow-up will show which symptoms and characteristics are important in the development of RA. If in the future a biological explanation for the 'start' of RA is found, the next step is to discover to 'off-switch' since this might give possibilities for targeted therapeutic intervention. On the other hand, it can also be assumed that mechanism that facilitate treatment-response are different from mechanisms that promote disease persistence or disease extinguishment. In this thesis we only studied the window of opportunity in RA patients that received therapeutic intervention (DMARDS/glucocorticoids). However, there remained a small portion of RA patients that achieved spontaneous remission without intervention. Another interesting question, and for a subject prone to future research, is to better understand the biological mechanism and alterations in these RA patients. With respect to mortality data, I do think there are many stones that have been left unturned in this area. For example, the results from the joined research with the NOAR that revealed having 2 antibodies predisposes for early mortality. It would be interesting to extend this research to include the latest discovery of anti-carbamylated proteins to the number of antibodies, as well as to study different causes of death in addition to overall mortality.

In conclusion, the current thesis showed that lots of progress was made in the attempt to recognize rheumatoid arthritis earlier, that a therapeutic window of opportunity exists and that with prompt initiation of adequate DMARD-treatment RA should no longer be tagged as a chronic condition but that drug-free remission and improved survival are both achievable goals.

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CHAPTER 14

Nederlandse samenvatting

Dankwoord

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NEDERLANDSE SAMENVATTING

Reumatoïde artritis

Reumatoïde artritis (RA) is een systemische auto-immuunziekte die zich voornamelijk kenmerkt door symmetrische synovitis (ontsteking) van de kleine hand- en voetgewrichten. Bij RA kan elk gewricht met synoviale bekleding aangedaan zijn. Deze ontsteking van het synovium aan de binnenzijde van de gewrichten uit zich aan de buitenzijde van het lichaam door een typische zwelling van gewrichten (artritis).

Naast synovitis, kunnen zich na langdurige ontstekingsactiviteit ook extra-articulaire manifestaties voordoen zoals diverse longaandoeningen, oogziekten, huidafwijkingen zoals reumanoduli (knobbels op bijvoorbeeld de ellebogen) en hart- en vaatziekten (HVZ). HVZ komen tegenwoordig in beperktere mate voor vanwege de betere kennis en behandeling van mogelijke risicofactoren. De prevalentie van RA in de Europese en Noord-Amerikaanse landen is ongeveer 0,5-1,0 procent met een incidentie van 20-50 nieuwe gevallen per 100.000 personen per jaar. Vrouwen krijgen twee tot drie keer vaker te maken met RA dan mannen. Hoewel RA bij volwassenen op iedere leeftijd kan voorkomen, zijn de meeste patiënten van middelbare leeftijd bij het begin van de ziekte. RA-patiënten kunnen naast gezwollen gewrichten ook last hebben van pijnlijke gewrichten, of ochtendstijfheid ervaren in en rondom de gewrichten; daarnaast kunnen ze bewegingsbeperkingen hebben en last hebben van vermoeidheid.

De exacte pathogenese van RA is nog niet bekend. Genetische en omgevingsfactoren (bijvoorbeeld roken) spelen beide een rol bij het ontstaan en het verloop van RA. In de jaren zeventig en tachtig van de twintigste eeuw, werden de belangrijkste genetische risicofactoren (*HLA-DRB1* allelen) voor de ontwikkeling van RA geïdentificeerd. Later zijn via kandidaat-gen-benaderingen en genoom-brede associatiestudies (genome-wide associations studies, hierna: GWAS), meer single nucleotide polymorphisms (SNPs) in de Kaukasische RA-patiënten geïdentificeerd die de gevoeligheid op het ontwikkelen van RA vergroten. In dit proefschrift komen twee van deze SNPs, te weten *PTPN22* en *TRAF1-C5* aan bod.

Als RA onbehandeld blijft, kan dit leiden tot aanzienlijke gewrichtsdestructie, die zelfs kan resulteren in invaliditeit van de patiënten. Echter, het ziekteverloop bij patiënten kan individueel verschillend zijn, variërend van mild en niet-destructief tot snel en destructief.

Auto-antilichamen

In RA zijn verschillende antilichamen zijn gevonden; de bekendste zijn de reumafactor en de anti-citrullinated peptide antilichamen (ACPA). Reumafactor is het meest 'klassieke' autoantilichaam in RA. Reumafactor wordt niet alleen gevonden bij RA-patiënten, maar

ook bij patiënten met andere auto-immuunziekten, infectieziekten en zelfs bij gezonde individuen. Niet alle patiënten die positief zijn bevonden voor reumafactor zullen RA ontwikkelen. Bij vroege RA-patiënten is de prevalentie van reumafactor ongeveer 60 procent. ACPA, daarentegen, is meer specifiek voor RA en de gedachte is dat het een belangrijke rol speelt in de pathogenese van de ziekte. De prevalentie van ACPA in vroege RA-patiënten is ongeveer 50%. Er is een overlap in de aanwezigheid van antistoffen bij RA-patiënten. Dit betekent dat de meeste patiënten die positief zijn getest op de aanwezigheid van ACPA ook positief zijn voor de aanwezigheid van reumafactor. Daar komt nog bij dat reumafactor en ACPA al aanwezig kunnen zijn nog voordat de diagnose RA is gesteld en nog voordat patiënten klachten ervaren. Dit is bekend geworden uit bloeddonor-onderzoek.

Classificatie van RA

In 1859 gebruikte Alfred Garrod de term “reumatoïde artritis” voor het eerst. Een arts stelt de diagnose RA op basis van een combinatie van bepaalde eigenschappen (zoals de aanwezigheid van auto-antilichamen) en symptomen (bijvoorbeeld ochtendstijfheid, symmetrische gewrichtszwelling, pijnlijkheid van gewrichten) die een patiënt heeft. Omdat het een klinische diagnose is kan dit leiden tot een heterogene groep patiënten. Bij onderzoek is het doel om de bevindingen te kunnen toepassen op groepsniveau. Om dat te bereiken, is een homogene groep patiënten nodig. Daarom zijn er door de jaren heen diverse classificatiecriteria opgesteld. In dit proefschrift zullen patiënten worden geclassificeerd volgens de ACR 1987 of 2010 ACR-EULAR criteria voor RA.

Behandeling en behandelstrategieën

De afgelopen vijftig jaar zijn de behandelkeuzen en de behandelstrategieën voor RA drastisch veranderd. In 1970 was het gebruikelijk om te beginnen met niet-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs zoals diclofenac). Opvallend was dat pas met een ziekte-modificerende anti-reumatische-geneesmiddel (disease modifying anti-reumatische drug (DMARD)- therapie werd gestart nadat er zichtbare radiografische schade aan gewrichten was aangetoond. Verschillende conventionele DMARDs waren beschikbaar, zoals anti-malariamiddelen (hydroxychloroquine), sulfasalazine, orale goudverbindingen, intramusculair goud, azathioprine en methotrexaat. Wanneer NSAID's hadden gefaald, werd gestart met een DMARD-therapie en bij voorkeur één die het minst giftig was. Destijds werd een zogeheten piramide-model toegepast; dit betekent dat wanneer de ziekteactiviteit onvoldoende werd onderdrukt een andere DMARD werd toegevoegd aan de behandeling. Aan het eind van de twintigste eeuw is deze vorm van behandelingsstrategie veranderd. Een DMARD-therapie werd namelijk veel eerder in het ziekteverloop gestart en ook werd vaker gestart met een zogeheten combinatietherapie. Verschillende klinische onderzoeken hebben laten zien dat gebruik van een combinatietherapie met corticosteroiden (zoals prednison) in een vroeg stadium van RA, heeft geleid tot minder gewrichtsschade. Naast de conventionele DMARDs is

een ander type DMARD op de markt gebracht, namelijk de 'biologicals'. Deze biologicals zijn geneesmiddelen die genetisch zijn gemanipuleerd, door gebruik te maken van menselijke genen in niet-humane celculturen om op die manier een biologische stof te produceren. Patiënten die biologicals gebruiken zijn vatbaarder voor infecties (bijvoorbeeld tuberculose). Daarnaast gaat het gebruik van biologicals gepaard met hoge kosten. Daarom wordt behandeling met biologicals beperkt tot RA-patiënten bij wie de behandeling van twee of meer conventionele DMARDS niet heeft aangeslagen.

Vroege herkenning en 'the window of opportunity'

Uit onderzoek is gebleken dat een vroege start van een agressieve behandeling bij RA-patiënten minder gewrichtsschade over de lange termijn oplevert. Het doel is daarom zo snel mogelijk te beginnen met de behandeling van RA-patiënten. Om een vroege start van DMARD-therapie mogelijk te maken is het noodzakelijk dat patiënten snel nadat hun klachten zijn begonnen door een reumatoloog worden gezien.

Hoe snel een reumatoloog patiënten ziet verschilt van land tot land. Dat heeft onder meer te maken met de beschikbaarheid van een reumatologisch centrum (bijvoorbeeld dicht in de buurt van de patiënten of op grote afstand) en met de manier waarop de gezondheidszorg is georganiseerd. In Nederland is de gezondheidszorg op zodanige wijze georganiseerd dat huisartsen controle hebben over de toegang tot medische specialisten zoals reumatologen (zij vervullen een poortwachtersfunctie).

Daarnaast moet de patiënt de drang hebben om medische hulp te zoeken vanwege zijn ontstane klachten. In het Nederlandse gezondheidszorgsysteem, zal een huisarts wel de combinatie van klachten en lichamelijk onderzoek als een potentieel reumatologische aandoening moeten herkennen en zo snel mogelijk moeten verwijzen naar een reumatoloog. In 2011 bezochten in Nederland in totaal, 295 per 1.000 mannelijke personen en 325 per 1.000 vrouwelijke personen hun huisarts vanwege klachten aan het bewegingsapparaat. Van deze bezoekers bleken 5 per 1.000 mannelijke personen en 6 per 1.000 vrouwelijke personen onder de diagnose 'reumatoïde artritis' te zijn geregistreerd. Hierbij dient wel opgemerkt te worden dat deze getallen zijn gebaseerd op zowel nieuwe patiënten als op reeds met RA gediagnosticeerde patiënten.

Naast het feit dat bij RA een vroege behandeling moet worden gestart, is zelfs de suggestie gedaan dat de behandeling in het zogenaamde therapeutische "window of opportunity" moet worden gestart. Hoewel dit concept nog niet volledig is uitgewerkt, is de gedachte dat dit een periode vertegenwoordigt in een zeer vroege fase van de ziekte waarbij therapeutische modificatie succesvoller is, wat waarschijnlijk te maken heeft met nog niet volledige volgroeide ziekteprocessen. Het idee is dat deze periode de eerste twaalf weken na het ontstaan van de klachten omvat.

In een recent onderzoek in Nederland is geconstateerd dat de totale vertraging tussen het ontstaan van de klachten en het bezoek aan de reumatoloog bij RA-patiënten 18,4 weken was (mediaan) en dat de huisarts-vertraging de grootste bijdrage had aan dit geheel (twee-derde deel). Bovendien bleek dat slechts 31% van de RA-patiënten werd gezien binnen de periode van twaalf weken na het begin van de symptomen.

Ernst van de ziekte: gewrichtsschade en persisterende ziekte

Er zijn verschillende manieren om de ernst van RA bestuderen. De vraag rijst wat wordt bedoeld met de term “ernst”, omdat artsen en patiënten deze term waarschijnlijk verschillend zullen interpreteren. Voor een patiënt kan het belangrijk zijn dat zijn of haar dagelijkse activiteiten niet zijn aangetast, dat hij/zij minder pijn, vermoeidheid en stijfheid heeft en dat hij/zij liever minder medicijnen gebruikt. Dat laatste kan ook andersom zijn. Sommige patiënten zijn juist bang om hun medicijngebruik af te bouwen omdat ze vrezen voor een terugval.

Reumatologen geven deels de voorkeur aan ‘objectieve’ parameters om de ernst van de ziekte te meten, bijvoorbeeld door het volgen van inflammatoire markers zoals de bezinking en het CRP, en de aanwezigheid van erosieve gewrichten op röntgenfoto's. Reumatologen zullen ook rekening houden met het aantal gezwollen en pijnlijke gewrichten dat ze vinden bij het lichamelijk onderzoek. Tegenwoordig worden ook nieuwe technieken toegepast om de ernst van de ziekte te bepalen -hetzij in de klinische praktijk of voor onderzoeksdoeleinden - zoals echografie en magnetische resonantie imaging (MRI) van handen en voeten.

Het hoofddoel van de behandeling bij RA is te streven naar ziekteremissie: dit is niet alleen een haalbaar doel in klinische studies en trials, maar ook in de klinische praktijk. Door de jaren heen is remissie als uitkomstmaat uitgebreid bestudeerd. Er bestaat heterogeniteit in de definitie van remissie, zo hoort bijvoorbeeld een bepaalde mate van ziekteactiviteit bij een bepaalde score (DAS-28 <2.6 of DAS-28 > 1.6) die wordt bereikt. Het ultieme doel is de DMARD-vrije remissie. De DMARD-vrije en aanhoudende remissie is in het onderhavige proefschrift gedefinieerd als de aanhoudende afwezigheid van artritis na het staken van een DMARD-therapie, waaronder biologicals en corticosteroïden voor de gehele follow-up en gedurende ten minste één jaar. Deze vorm van remissie valt te beschouwen als het tegenovergestelde van een persisterende ziekte en komt het meest in de buurt als surrogaat voor ‘genezing’ van RA.

Mortaliteit in RA

Sterfte is de meest onwenselijke uitkomst van een ziekte en voor RA is dit in de afgelopen jaren uitgebreid onderzocht. Hoewel dit resultaat onomkeerbaar is, kunnen voorspellers van mortaliteit aanwijzingen geven voor therapeutische interventies omdat die ook vaak andere uitkomsten op lange termijn voorspellen.

In eerdere onderzoeken is RA in verband gebracht met een verhoogd sterftecijfer in vergelijking met de algemene populatie (1,2-1,3 in inceptie-cohorten en 1,6-1,7 in niet-inceptie-cohorten). Verder is waargenomen dat de incidentie mortaliteit (IMR) in RA in de tijd afnam, met een geschatte gepoolde IMR van 4,7 / 100 persoons-jaren voor studies vóór 1970 tot 2,0 / 100 persoonsjaren voor studies gestart na 1985. Dit resulteerde in een relatieve daling van 2,6% per jaar tussen 1955 en 1995. Deze observaties zijn gebaseerd op de vroege RA-cohorten die zijn gestart tussen 1955-1995, dus voordat vroege en agressieve behandelingen werden geïntroduceerd.

De belangrijkste doodsoorzaken bij RA zijn HVZ, kanker en infecties; de percentages daarvan zijn vergelijkbaar met die van de algemene populatie. Hoewel de verhouding van cardiovasculaire sterfte niet hoger is dan die bij de algemene populatie, overlijden RA-patiënten wel op jongere leeftijd. RA is geassocieerd met HVZ, en het risico op HVZ is ongeveer twee tot drie maal hoger dan bij de algemene populatie. Vooral versnelde atherosclerose (aderverkalking) wordt waargenomen bij RA-patiënten, en die kan voorafgaan aan grote cardiovasculaire gebeurtenissen. Deze versnelde atherosclerose valt echter niet alleen te verklaren door de traditionele HVZ-risicofactoren die vaker voorkomen bij RA-patiënten, zoals hypertensie, hyperlipidemie, diabetes en roken, maar wordt waarschijnlijk ook veroorzaakt door een aanhoudende ontsteking.

Het doel van het onderhavige proefschrift:

De vier hoofddoelen van dit proefschrift zijn:

1. Het verbeteren van vroegtijdige herkenning van artritis.
2. Het onderzoeken van de aanwezigheid van een 'therapeutic window of opportunity' in RA.
3. Het onderzoeken van diagnostische en prognostische markers in artralgie, artritis en vroege RA-patiënten.
4. Het identificeren van voorspellers voor sterfte en het vergelijken van overleving van RA-patiënten met de algemene Nederlandse bevolking.

Het proefschrift is opgedeeld in vier delen.

De belangrijkste resultaten van het proefschrift

In **deel I** zijn de werkzaamheid van twee early arthritis recognition clinics (vroege artritis herkenning klinieken) geëvalueerd en de redenen voor artralgie-patiënten om medische hulp te zoeken. Zoals hiervoor beschreven is in Nederland de gemiddelde vertraging waarmee RA-patiënten worden gezien door een reumatoloog na het ontstaan van de symptomen 18,4 weken. In **hoofdstuk 1** staat dat twee-derde van deze vertraging valt

toe te schrijven aan de vertraging bij/door de huisarts. Dit bevestigt, in combinatie met eerdere gegevens over de 'wait-and-see approach', dat het voor huisartsen lastig kan zijn om artritis van de kleine gewrichten van de handen en voeten te herkennen. Om deze huisartsen-vertraging te verminderen is een nieuw inlooppreekuur gecreëerd in twee academische ziekenhuizen in Leiden en Groningen (Nederland): de *early arthritis recognition clinic* (EARC). In plaats van het toepassen van de wait-and-see aanpak, konden huisartsen wanneer ze onzeker waren over de aanwezigheid van artritis hun patiënten doorsturen naar de EARC. Dit inlooppreekuur werd twee keer per week gehouden; patiënten hoefden geen afspraak te maken. Nadat patiënten een kleine vragenlijst (over hun klachten en redenen om medisch hulp te zoeken) hadden ingevuld, werden zij gezien door een ervaren reumatoloog. Deze reumatoloog voerde vervolgens een volledig gewrichtsonderzoek uit. Wanneer tijdens het gewrichtsonderzoek artritis werd vastgesteld, kwam de patiënt binnen één week terug op de polikliniek voor een volledige anamnese en lichamelijk onderzoek inclusief extra laboratoriumonderzoek, röntgenfoto's van handen en voeten en de start van een passende behandeling.

In **hoofdstuk 2** zijn de eerstejaars resultaten van deze inlooppreekuren geëvalueerd. De huisartsen-vertraging was de belangrijkste uitkomst, gevolgd door de totale vertraging. In Leiden werd 42% (168/400) en in Groningen 49% (104/212) van de patiënten gediagnosticeerd met artritis. De doelstelling van deze klinieken was om de huisartsen-vertraging te verminderen. Dit was succesvol in beide EARC's en de waargenomen vertraging bij de vroege artritis-patiënten was 2,0 (0,4-8,4) weken in Leiden en 2,3 (0,6-9,1) weken in Groningen. Een interessante bevinding was dat patiënten met ongedifferentieerde artritis (UA) of RA via de EARC een mediane huisartsen-vertraging hadden van ongeveer twee weken in vergelijking met negen weken van UA en RA-patiënten die op de polikliniek reumatologie in dezelfde periode werden gezien en via normale verwijzing van de huisarts waren binnengekomen. Ook was de duur van de huisartsen-vertraging lager dan de historische huisartsen-vertraging bij RA-patiënten (mediaan 11,8 weken).

Hoofdstuk 3 bevat de bestudering van de beweegredenen van artralgie (gewrichtspijn)-patiënten om medische hulp te zoeken. De gemiddelde klachtenduur in alle artralgie-patiënten was vier weken voordat zij voor het eerst een huisarts bezochten. Het bleek dat patiënten die artritis hadden sneller de huisarts bezochten dan patiënten die geen artritis hadden (2,6 versus 5,9 weken). In het algemeen verschilden de redenen voor het zoeken van medische hulp niet tussen patiënten met en zonder artritis. Artritis-patiënten zochten vooral medische hulp omdat hun klachten plotseling waren ontstaan en omdat hun familie en vrienden dit adviseerden. Naast het vergelijken van artritis-patiënten met niet-artritis-patiënten is ook gekeken naar de vertraging bij de patiënten zelf; dus patiënten die kort (<4 weken) en lang (>4 weken) na het ontstaan van hun klachten naar de huisarts

zijn gegaan. Hieruit bleek dat zowel de werk-gerelateerde beperkingen als beperkingen met betrekking tot hun fysieke functioneren belangrijke redenen waren om snel naar de huisarts te gaan. Een belangrijke vraag in het onderzoek was of bepaalde klachten, bepaalde beweegredenen voor het bezoeken van de huisarts of bepaalde opvattingen over het functioneren op het werk vaker gezamenlijk voorkwamen. Met andere woorden of een clustering van deze variabelen vaak voorkwam bij eenzelfde soort artralgie-patiënt. Hiervoor is een data-reductie methode gebruikt: een partial least square regression analyse (PLS). Dit leverde twee groepen patiënten op. De eerste groep patiënten had als kenmerken een korte patiëntenvertraging (<4 weken na het ontstaan van klachten bij de huisarts), een plotseling ontstaan van de klachten, functionele beperkingen en ziekteverzuim. De tweede groep patiënten had als kenmerken een lange patiëntenvertraging, een geleidelijk ontstaan van de klachten, en geen werkverzuim. Het is belangrijk om te vermelden dat het hiervoor genoemde onderzoek is uitgevoerd bij patiënten met gewrichtspijn bij wie de huisarts twijfelde over de aanwezigheid van artritis. Het onderzoek omvat dus geen vertegenwoordiging van alle patiënten met gewrichtspijn die de huisarts bezoeken, maar betreft slechts een selectie.

In **deel II** van dit proefschrift is gekeken of een therapeutische ‘window of opportunity’ aanwezig was in RA. Eerdere studies hebben aangetoond dat een vroege start van de behandeling in RA leidt tot een gunstiger resultaat. Een ‘vroege start’ is door de jaren heen op verschillende manieren geïnterpreteerd; bijvoorbeeld binnen twee jaar na de diagnose RA tot starten met behandeling versus binnen een paar weken na de diagnose starten met behandeling. Daarom is de volgende onderzoeksvraag geformuleerd: Hebben RA-patiënten waarbij de behandeling is gestart snel nadat hun klachten zijn begonnen (korte klachtenduur) een gunstiger resultaat dan patiënten met een lange klachtenduur? Omdat in veel studies ‘klachtenduur’ als co-variabele is opgenomen in de analyse is in **hoofdstuk 4** een systematisch literatuuronderzoek uitgevoerd en zijn al deze studies systematisch beoordeeld om te onderzoeken of een korte klachtenduur bij aanvang van de behandeling in verband valt te brengen met minder progressie van de ziekte. De kwaliteit van een onderzoek is beoordeeld met behulp van een vooraf gedefinieerd scoresysteem en er is een ‘best evidence synthesis’ toegepast om de bewijskracht per categorie te bepalen. Sterk bewijs is gevonden voor een verband tussen een korte klachtenduur en minder radiografische schade, en matig bewijs voor een verband tussen klachtenduur en andere uitkomsten bij RA, zoals het verkrijgen van een bepaalde ziektestatus (remissie onder therapie is gedefinieerd door het behalen van bepaalde ziekteactiviteit scores; DAS-28 <2.6 DAS-28 <1,6, ACR remissie etcetera).

Een ander belangrijk resultaat was de DMARD-vrij aanhoudende remissie, die werd gedefinieerd als aanhoudende afwezigheid van artritis na het staken van een DMARD-therapie voor ten minste één jaar en gedurende de rest van de follow-up.

Via de kwalitatieve benadering is matig bewijs gevonden voor een verband tussen de klachtenduur en een DMARD-vrije aanhoudende remissie. Omdat er toegang bestond tot de ruwe data van deze drie cohorten was een meta-analyse uitvoerbaar. Hieruit bleek dat de kortere klachtenduur onafhankelijk van andere variabele verband hield met een grotere kans op een DMARD-vrije aanhoudende remissie ook na correcties voor leeftijd, geslacht en de meer specifieke ziektemarkers zoals de reumafactor en bezinking.

Deze resultaten leidden tot de volgende vraag: is deze associatie lineair volgens ‘the-earlier-the-better- principle?’ of ‘is er een bepaalde tijdsperiode waarin behandeling van de ziekte beter aanslaat onder verwijzing naar een ‘window of opportunity’’. Deze vraag is in **hoofdstuk 5** opgepakt door onderzoek te doen naar de vorm van het verband tussen de klachtenduur en een DMARD-vrije remissie (het tegenovergestelde van persisterende ziekte) in twee grote vroege RA-cohorten.

Wanneer enerzijds een lineair verband het uitgangspunt vormt, dan wordt aangenomen dat de totale inflammatoire belasting (product van de ernst en de duur van de ontsteking) op het moment van de start van de behandelingsamenhangt met de uitkomst van de ziekte. Anderzijds, wordt in de literatuur vaak een ‘window of opportunity’ in RA aangehaald dat zou bestaan uit de eerste 12 weken na het ontstaan van klachten. In deze periode zou de ziekte vermoedelijk gevoeliger zijn voor therapeutische interventies. Dit afkappunt van 12 weken lijkt te zijn gebaseerd op adviezen van experts. Deze adviezen zijn later wel ondersteund door onderzoeken waaruit bleek dat patiënten met minder dan 12 weken klachtenduur een gunstigere uitkomst hadden. Er is echter niet aangetoond dat na een bepaalde periode van symptoomduur het effect van de behandeling vermindert. Twee grote vroege RA cohorten zijn gebruikt en de belangrijkste uitkomst was: een DMARD-vrije aanhoudende remissie. Geobserveerd is dat, over een periode van 5 jaar follow-up, de curve van de log-hazard ratio (de kans op een DMARD-vrije aanhoudende remissie) afgezet tegen de klachtenduur, niet-lineair was. De log-hazard ratio's zijn berekend met behulp van cox-proportional hazards regression models met natural cubic splines. Het voordeel van deze benadering is dat het geen lineaire associaties veronderstelt. Bovendien is het discriminerend vermogen gemeten met time-dependent ROC-curves. De klachtenduur met het optimale onderscheidend vermogen was 14,9 weken in de EAC en 19,1 weken in ESPOIR. Het eindpunt van de DMARD-vrije aanhoudende remissie wordt niet vaak bereikt (5-11%) en is afhankelijk van het advies van de behandelend reumatoloog en de wil van patiënten om de DMARD-therapie te staken. Daarom zijn nog twee extra eindpunten, onderzocht: namelijk een zekere radiografische progressie én aanhoudende remissie ongeacht de voortzetting van de behandeling. Ook voor deze eindpunten was de vorm van het log-hazard ratio curves niet-lineair. Dit voert tot de conclusie, dat de hiervoor genoemde resultaten wel degelijk suggereren dat er een specifieke periode bestaat voor RA-patiënten waarin het voor hen voordelig is om te

starten met een DMARD-therapie. De voorgestelde 12-weekse periode in de literatuur lijkt dus niet misplaatst. Hoewel, op basis van de huidige gegevens zou kunnen worden gesteld dat deze periode de eerste vijf of zes maanden na het optreden van de eerste klachten bestrijkt.

In **deel III** van dit proefschrift is gekeken naar ziektekenmerken die een voorspellende of diagnostische waarde hebben in artralgie, vroege artritis en reumatoïde artritis patiënten.

In **hoofdstuk 6** is een bekend ziektekenmerk voor RA, namelijk ochtendstijfheid, die vaak wordt beoordeeld in de klinische praktijk, onderzocht op het diagnostisch vermogen in drie artralgie-cohorten en twee vroege-artritis cohorten en op het prognostisch vermogen in twee vroege RA-cohorten. Recent onderzoek naar ochtendstijfheid toonde verbanden aan met een verminderde functionele capaciteiten in de ochtend, de effecten op de kwaliteit van leven en verlies van werk. Daarnaast zou ochtendstijfheid een slechte discriminator zijn tussen RA en andere reumatologische aandoeningen. Deze waarnemingen zijn echter gebaseerd op studies met zeer lage patiëntenaantallen. Hiervoor zijn 1641 artralgie-patiënten uit drie cohorten gebruikt. Twee van deze cohorten, de EARCs uit Leiden en Groningen zijn hiervoor beschreven; het derde cohort was het Rotterdamse Early Arthritis Cohort (REACH). Ongeveer 50% van de artralgie-patiënten die werden verwezen naar deze cohorten, werden gediagnosticeerd met artritis bij hun eerste bezoek aan de reumatoloog. Geobserveerd is dat ochtendstijfheid met een duur van ≥ 60 minuten in artralgie-patiënten werd geassocieerd met de aanwezigheid van artritis (Leiden EARC OR1.49, Groningen EARC OR2.21 en REACH OR1.55). Hierna is het onderscheidend vermogen van ochtendstijfheid bij patiënten met vroege artritis in twee cohorten onderzocht, de Leiden EAC en het Franse ESPOIR cohort. De duur van ochtendstijfheid werd afgebeeld met de diagnose van de patiënten met vroege artritis na 1 jaar follow-up. Dit toonde aan dat de mediane duur 60 minuten was in RA-patiënten en langer dan de duur van alle andere reumatologische aandoeningen. Het diagnostisch vermogen van ochtendstijfheid ≥ 60 minuten in vroege artritis-patiënten liet een significant verband zien met de diagnose van de 2010-RA na één jaar, onafhankelijk van andere voorspellers voor RA (zoals gezwollen gewrichten, ACPA, reumafactor, klachtenduur en bezinking). Ook is gekeken naar de optimale discriminerende duur van ochtendstijfheid voor RA in vroege artritis-patiënten. Dat liet zien dat in beide cohort de optimale discriminerende duur van ochtendstijfheid ongeveer 30 minuten bedroeg. Ten slotte is onderzocht of een bepaalde duur van ochtendstijfheid bij aanvang (≥ 30 , ≥ 60 en ≥ 90 minuten) een voorspellende waarde zou hebben op de lange termijn resultaten in RA, zoals gewrichtsschade en een DMARD-vrije aanhoudende remissie. Hierbij is géén verband gevonden tussen ochtendstijfheid en een slechtere lange termijn uitkomst. Hoewel ochtendstijfheid alleen niet voldoende is om te gebruiken als een diagnosticum,

kan ochtendstijfheid in de klinische praktijk wel bruikbaar zijn in de besluitvorming van het diagnostisch proces.

In **hoofdstuk 7** is onderzocht of een SNP in het gebied van het protein tyrosine phosphatase non-receptor 22 (PTPN22) verband houdt met radiologische schade bij RA-patiënten in een selectie van ACPA-positieve RA-patiënten afkomstig van twee cohorten. Dit gebied codeert voor een negatieve regulatie van T-cel activatie en is een belangrijke risicofactor voor het ontwikkelen van RA in ACPA-positieve-patiënten. Dit gen werd al getest in een andere dataset en daar is een verband met gewrichtsschade gevonden. In dat desbetreffende onderzoek is geen correctie uitgevoerd voor ACPA. Omdat replicatie een van de hoekstenen in wetenschappelijk onderzoek vormt om zo de kans op vals-positieve bevindingen te verkleinen, is het onderzoek uitgevoerd in 2 ACPA-positieve datasets. Hierbij is géén verband gevonden tussen PTPN22 met radiologische gewrichtsschade in RA-patiënten.

In **hoofdstuk 8** is meer in detail de rol van baseline erosies (d.w.z. erosies die reeds aanwezig zijn op het moment dat de diagnose wordt gesteld) onderzocht en het verband met progressie van gewrichtsschade. Zoals bekend zijn gewrichtserosies een typische uiting in RA en maken ze al decennia lang deel uit van de verschillende classificatiecriteria voor RA. Eén van de belangrijkste doelen in de behandeling van RA is om gewrichtsbeschadiging te voorkomen. In dit onderzoek is verder onderzocht of de baseline erosies onafhankelijk in verband konden worden gebracht met toekomstige gewrichtsschade of dat zij in dit proces als mediator optraden via andere mechanismen. Hiervoor zijn RA-patiënten onderzocht die zeven jaar follow-up hadden en van wie röntgenfoto's van handen en voeten waren gescoord volgens de Sharp-Van der Heijde methode. Verschillende hypothesen zijn opgesteld en vervolgens getest voor mediatie. De volgende voorgestelde 'variabelen' die zijn getest in mediatie analyses: klachtenduur, auto-antilichamen (reumafactor en ACPA), systemische ontsteking (bezinking) en de lokale klinische ontsteking (aantal gezwollen gewrichten). Voor deze variabelen is gekozen omdat de gedachte was dat patiënten die zich later presenteerden bij een reumatoloog, mogelijk al een verder gevorderd stadium van de ziekte hadden (en dus daarom al baseline erosies hadden); aangezien auto-antilichamen verband houden met ernstige radiologische gewrichtsschade zouden deze ook in verband te brengen zijn met baseline erosies en tenslotte werd gedacht dat een ernstigere ziekte bij presentatie (gereflecteerd door systemische en lokale klinische ontsteking) ook verband zou kunnen houden met baseline erosies. Samenvattend, baseline erosies bevonden zich niet in het causale pad van een van de hiervoor staande variabelen en hadden dus een onafhankelijk effect op toekomstige gewrichtsschade. Verder is het belangrijk om op te merken dat patiënten met baseline erosies op elk tijdstip 3,45 keer meer gewrichtsschade hadden dan patiënten zonder baseline erosies. De precieze mechanismes voor de ontwikkeling van

baseline erosies zijn nog niet bekend. Om hierachter te komen is een kleine subgroep van RA patiënten, die ook MRI-data op baseline hadden, verder onderzocht. Deze data suggereerden dat subklinische ontstekingen (waargenomen met MRI) relevant zijn voor de ontwikkeling van baseline erosies. Hoewel dit onderzoek uitsluitend een indicatie geeft voor causaliteit is verder onderzoek nodig naar het exacte mechanisme van baseline erosies en dit valt mogelijk te doen met behulp van diermodellen.

De laatste criteria-set om RA mee te classificeren, de 2010 ACR-EULAR-criteria, wordt beschouwd als sensitief maar is minder specifiek voor RA. Bovendien is het doel van deze criteria-set om patiënten eerder in het ziekteverloop te identificeren, waardoor het mogelijk is om klinische trials uit te voeren met patiënten in een vroeger stadium, het liefst nog voordat ze structurele gewrichtsschade hebben ontwikkeld. Gebleken is dat het fenotype van '2010 RA-patiënten' milder is dan het fenotype van patiënten geclassificeerd volgens de 1987-criteria voor RA; de lange termijn uitkomsten voor deze twee criteria ontbraken echter. Daarom is in **hoofdstuk 9** gekeken naar de progressie van gewrichtsschade over zeven jaar follow-up en naar de DMARD-vrije remissie over tien jaar follow-up in RA-patiënten die zijn geclassificeerd volgens de 1987- en de 2010-criteria voor RA. Patiënten die geclassificeerd waren volgens de 2010-criteria als RA-patiënten ontwikkelden minder radiologische gewrichtsschade en behaalden vaker de DMARD-vrije remissie ten opzichte van patiënten die geclassificeerd waren volgens de 1987-criteria. Sub-analyses zijn verricht waarbij het nieuw ontwikkelde erosie-criterium voor RA is toegepast (≥ 3 erosieve gewrichten) naast het puntensysteem van de 2010-classificatie criteria. Hierbij werd een kleine groep patiënten op basis van het erosie-criterium alsnog als patiënten met 'RA' geclassificeerd. Dit was echter niet van invloed op de eerder geobserveerde resultaten. Dit leidt tot de conclusie dat de huidige studie heeft aangetoond dat patiënten die geclassificeerd zijn volgens de 2010-criteria voor RA een milder verloop hebben dan patiënten die volgens de 1987-criteria voor RA zijn geclassificeerd.

In **deel IV** van het proefschrift ligt de focus op de mortaliteit in RA-patiënten. Sterfte is de meest onwenselijke uitkomst van een ziekte en is door de jaren heen uitgebreid onderzocht. Hoewel dit resultaat onomkeerbaar is, kunnen risicofactoren/voorspellers voor sterfte wel aanwijzingen geven voor therapeutische interventies omdat deze zelfde voorspellers ook vaak verband houden met andere lange termijn uitkomsten (zoals gewrichtsschade). Uit eerdere onderzoeken is gebleken dat RA-patiënten een hoger sterftecijfer hadden, dus een kortere levensduur, dan de algemene populatie. Deze bevindingen waren afkomstig uit studies in een tijdperk waarin een afwachtend behandelingsbeleid werd gehanteerd; dus nog voordat de vroege en agressieve behandeling was geïntroduceerd. De belangrijkste doodoorzaken voor RA-patiënten zijn HVZ, kanker en infecties, en de percentages zijn vergelijkbaar met de algemene populatie.

In **hoofdstuk 10** is onderzocht of een genetische variatie in TRAF1 / C5 verband houdt met sterfte in RA-patiënten. In het oorspronkelijke onderzoek door Panoulas et al. werd een verband gevonden tussen de gevoelige genotype GG (van rs3761847) en een verhoogd sterfterisico door sepsis en kanker, maar is geen verband aangetoond met de cardiovasculaire dood. Het idee was dat dit verband niet werd gevonden omdat patiënten werden bestudeerd in een ver gevorderd stadium van hun ziekte (dat zou kunnen betekenen dat patiënten die in een eerdere ziektefase waren overleden aan hart en vaatziekten niet geïnccludeerd waren). Daarom zijn 615 patiënten met RA onderzocht die prospectief werden gevolgd in de Leidse EAC met genotypering voor rs10818488. In dit cohort waren de belangrijkste doodsoorzaken hart- en vaatziekten (37,7%), gevolgd door kanker (28,6%) en infecties (9,1%). In tegenstelling tot Panoulas et al, werd géén verband gevonden tussen het gevoeligheidsallel en sterfte in het algemeen, en evenmin met cardiovasculaire mortaliteit, kanker-gerelateerde sterfte of sterfte door infecties. Daarnaast zijn dezelfde analyses herhaald in een groot niet-RA cohort ($n = 5634$) van ouderen en ook daar zijn geen verbanden gevonden tussen rs2416808 ($R^2 > 0,99$ met rs10818488) met sterfte in het algemeen, noch met cardiovasculaire mortaliteit, noch met kanker-gerelateerde sterfte of sterfte door infecties.

In **hoofdstuk 11** is onderzocht of er een verband bestaat tussen sterfte en de aanwezigheid van reumafactor of ACPA alsook hun titer in vroege artritispatiënten. Uit eerder onderzoek is bekend dat auto-antilichamen (zoals reumafactor en ACPA) verband houden met een ongunstige uitkomst zoals radiologische schade en het voortbestaan van de ziekte. Wat betreft sterfte onder RA-patiënten, is enerzijds bekend dat de aanwezigheid van reumafactor verband houdt met verhoogd sterfterisico. Anderzijds zijn de gegevens over de aanwezigheid van ACPA en sterfte nog schaars. Vroege artritispatiënten uit de Norfolk Arthritis Register (NOAR) en de Leiden EAC zijn bestudeerd. De aanwezigheid van antilichamen werd gestratificeerd in een negatieve, een lage of hoge positieve titer (zoals voorgesteld door de 2010 ACR / EULAR-criteria voor RA) en vervolgens is gekeken naar de hoeveelheid aanwezige antilichamen. Wanneer de status van het antilichaam werd gestratificeerd op basis van de titer werden geen consistente bevindingen tussen de cohorten waargenomen. Wanneer echter het aantal antilichamen in een patiënt (nul, één antilichaam en twee antilichamen) werd geteld, leverde de aanwezigheid van twee antilichamen (dus dubbel positief) een relatie op met een verhoogde sterfterisico, dit in vergelijking met patiënten die ofwel één antilichaam of geen antilichamen hadden.

Zoals eerder beschreven, zijn in de laatste decennia de toegepaste behandelingsopties in RA-patiënten drastisch veranderd. Tegenwoordig wordt de DMARD-therapie gestart met een zodanige voortvarendheid dat gewrichtsschade wordt voorkomen, lage ziekteactiviteitscores worden behaald en zelfs medicatie-vrije remissie een streven is. Bij de observatie van deze gunstige uitkomsten in RA-patiënten resteert de vraag of met deze

verbeterde behandelingsstrategieën ook de overleving van RA-patiënten is toegenomen? In **hoofdstuk 12** is de overleving van 684 RA-patiënten (afkomstig uit de Leiden EAC) die volgens verschillende strategieën zijn behandeld, vergeleken met de algemene Nederlandse bevolking. De toegepaste behandelingsstrategieën waren als volgt:

- van 1993-1995 werden patiënten behandeld met NSAID's en pas later in de loop van hun ziekte met DMARDs;
- van 1996 tot 1998 werden patiënten direct behandeld met ofwel hydroxychloroquine of sulfasalazine;
- van 1999-2008 werden patiënten direct behandeld met methotrexaat monotherapie.

In de eerste twee perioden zijn de sterftcijfers van de RA-patiënten toegenomen. Dit betekent dat patiënten die werden gediagnosticeerd met RA tussen 1993 en 1998 een hoger sterfterisico hadden dan hun leeftijdsgenoten uit de algemene Nederlandse bevolking. Interessant is dat RA-patiënten die in de laatste periode (1999 -2008) werden gediagnosticeerd een lager sterfterisico hadden dan de algemene populatie. Deze laatste bevinding is verassend en hiervoor vallen verschillende verklaringen te geven. Een verklaring zou kunnen zijn de specifieke aanpassing van het volgen van een gezondere levensstijl door RA-patiënten in vergelijking met die van de algemene bevolking. Hoewel wel bekend is dat RA-patiënten nu minder tijd besteden aan lichamelijke inspanning dan de algemene bevolking. Verder zou het zo kunnen zijn dat er een toegenomen alertheid bestaat op risicofactoren die voor comorbiditeiten kunnen zorgen. Deze krijgen daarom een betere behandeling, wat leidt tot een lager sterfterisico. Een andere mogelijke verklaring is dat patiënten met een potentieel dodelijke ziekte die ook gewrichtssymptomen ontwikkelen niet worden verwezen naar de polikliniek reumatologie en dus niet in ons cohort worden geïncludeerd, waardoor zij bijdragen aan het sterftcijfer van de algemene bevolking in plaats van aan het sterftcijfer van de RA-patiënten. Omdat de analyses altijd gedurende een bepaalde periode hebben plaats gevonden waarin het onderzoek liep, is het belangrijk om in gedachten te houden dat de bevindingen zijn verouderd. Niettemin suggereert de huidige studie dat er een positief verband bestaat tussen een betere behandeling van RA-patiënten en toegenomen overleving.

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Dit proefschrift presenteert een scala van onderwerpen te beginnen met de inlooppreekuren voor vroeg-herkenning van artritis in twee academische ziekenhuizen in Nederland (Leiden en Groningen). Door dit initiatief is de huisartsenvertraging aanzienlijk verminderd, met als resultaat een snellere presentatie van artritis-patiënten bij de reumatoloog.

Vragen die dit proefschrift niet beantwoord maar die zeker aandacht verdienen zijn: Hebben de (reumatoïde) artritis-patiënten daadwerkelijk profijt van deze vroegtijdige herkenning in de vorm van een snellere behandelingsstart, een betere kwaliteit van leven? Zijn de EARC's kosten-effectief?

Het blijft een uitdaging om deze vragen te beantwoorden en lastig om adequate parameters hiervoor te vinden. Mogelijk kan een combinatie van objectieve uitkomsten (gewrichtsschade op röntgenfoto's of MRIs) en subjectieve uitkomsten (VAS-ochtendstijfheid, -moeheid, en arbeidsparticipatie) voor dit doel worden gebruikt. Een daarop volgende uitdaging is het, om nog beter de motieven en twijfels van de huisarts om patiënten te verwijzen of juist niet te verwijzen naar een reumatoloog in kaart te brengen.

Dit proefschrift onderschrijft het idee dat er een therapeutisch window of opportunity voor RA bestaat. Natuurlijk zijn deze waarnemingen gebaseerd op de veronderstelling dat de patiënt zelf de daadwerkelijke aanvang van de ziekte (het ervaren van pijn en zwelling in de gewrichten) waarneemt. Het is bijzonder moeilijk om het werkelijke moment waarop de ziekte begint vast te stellen. Er bestaat geen gouden standaard door specifiek cellulair-, cytokine- of bot-veranderingen die pathognomisch zijn voor RA. Dit is een van de doelstellingen in het onderzoek naar de vroegste fase van RA. Om beter inzicht te krijgen in de ontwikkeling van RA is een cohort opgericht waarin patiënten worden gevolgd in een fase waarin ze symptomen (klinisch verdachte gewrichtspijn) hebben maar nog géén artritis: het clinically suspect arthralgia (CSA) cohort. Dit cohort is nog gaande en follow-up zal uiteindelijk tonen welke verschijnselen en eigenschappen belangrijk zijn in de ontwikkeling van RA.

In dit proefschrift is alleen de window of opportunity in RA-patiënten die therapeutische interventie (DMARDs / glucocorticoïden) ontvingen, bestudeerd. Toch is er een klein deel van de RA-patiënten dat spontane remissie heeft bereikt zonder medicamenteuze interventie. Deze groep patiënten is niet bestudeerd, maar het zou zeer interessant zijn om de mechanismen die deze spontane remissie van artritis bewerkstelligen verder te ontrafelen. Met betrekking tot de sterftedata zou met het oog op de toekomst diepgaander gekeken kunnen worden naar de rol van antilichamen. De resultaten van het onderzoek in de Leiden EAC en het NOAR-cohort hebben onthuld dat patiënten met twee antilichamen een toegenomen sterfterisico hadden. Het zou interessant zijn om dat onderzoek uit te breiden en hierbij het recent gevonden anti-gecarbamyleerd- antilichaam toe te voegen en dan tevens te kijken naar mogelijke verbanden met de verschillende doodsoorzaken.

De conclusie is dat dit proefschrift aan toont dat veel vooruitgang is geboekt in het bevorderen van de vroege herkenning van reumatoïde artritis, dat een therapeutisch window of opportunity bestaat én dat RA niet langer moeten worden gezien als een chronische aandoening , maar dat medicatievrije remissie en een verbeterde overleving beide haalbare doelen zijn als een behandeling met adequate DMARD tijdig wordt gestart.

CURRICULUM VITAE

Jessica van Nies werd op 4 september 1986 geboren te Leidschendam. In 2004, na het behalen van haar gymnasiumdiploma aan het Erasmus college te Zoetermeer, startte zij met de studie Geneeskunde te Leiden. Tijdens haar studie deed zij in 2007 een onderzoeksproject naar het verschil tussen groot- en kleinschalig onderwijs voor het vak bewegingsapparaat onder begeleiding van dr. Z de Jong op de afdeling Reumatologie in het LUMC. Hiervoor ontving ze de prijs voor beste postervoorzucht op het Nederlandse Vereniging voor Medisch Onderwijs (NVMO)-congres 2008 in Egmond aan Zee. Hierna startte zij met haar wetenschapsstage tevens op de afdeling reumatologie onder supervisie van dr. Z. de Jong. Voor haar afstudeerscriptie "Early up-to-date treatment strategies prevent increased mortality in RA" ontving zij de Leidse Alumni Geneeskunde (LAG) scriptieprijs in 2009. Na het afronden van deze wetenschapsstage werd het doctoraal diploma behaald in 2008. Hierna heeft zij een jaar in Mazagón (Spanje) gewoond alwaar zij verder wetenschappelijk onderzoek heeft voortgezet onder supervisie van Prof. Dr. A.H.M. van der Helm-van Mil. In 2011, na het behalen van haar artsexamen, startte zij met haar promotieonderzoek onder begeleiding van Prof. Dr. A.H.M. van der Helm-van Mil en Prof. Dr. T.W.J. Huizinga. In oktober 2014 is zij begonnen aan haar opleiding tot reumatoloog (opleider prof. Dr. T.W.J. Huizinga), waarvan zij de eerste drie jaren interne geneeskunde in het Medisch Centrum Haaglanden in Den Haag volgt (opleiders Dr. A.H. Bootsma en Drs. M.J.M. de Vreede). Naar verwachting zal zij eind 2020 de opleiding tot reumatoloog hebben afgerond.

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*both authors contributed equally

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