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Studies on undifferentiated and early rheumatoid arthritis

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Studies on undifferentiated and early rheumatoid arthritis

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1

GENERAL INTRODUCTION

UNDIFFERENTIATED AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic auto-immune disease that most commonly affects the small joints of the hands and feet and may result in progressive joint destruction and physical disability (1,2). The disease activity and outcome can be positively influenced by an early start of adequate treatment with Disease Modifying AntiRheumatic Drugs (DMARDs) (3-5). For the purpose of conducting studies in RA, classification criteria were developed in the 1950s and revised in 1987 to include homogeneous patient groups. These classification criteria were developed for established RA and have been largely criticized for their lack of diagnostic value in RA, let alone early RA. Diagnosing early RA is not always easy since patients can have an insidious onset of symptoms, and may delay seeking a doctor's opinion on only one or two painful joints. It has now become clear that early referral of such patients is important because the inflammatory process can be smoldering before patients present with full blown typical complaints. Many patients already have joint damage at the time of diagnosis (3,4). Recently, new criteria have been developed with the purpose of identifying patients earlier and consequently starting treatment with DMARDs earlier (6,7). Table 1 shows the 1987 and 2010 criteria. Patients with an insidious onset type of RA may present with mono- or oligoarthritis which does not meet the classification criteria for RA. They have so-called undifferentiated arthritis (UA), which is a broader definition than 'early RA' since it includes all types of arthritis of one or more joints that do not meet the classification criteria for specific rheumatic disorders. Thus, UA appears to include several illnesses, as the disease course may vary from self-limiting arthritis to severe destructive RA. In various early arthritis cohorts, 6 to 55% of the patients with UA evolved into Rheumatoid arthritis (RA) within one year of follow-up (8).

Based on the 'window of opportunity' hypothesis, many now believe that early effective treatment, started in the phase when the classification criteria are not yet met, may not only provide symptom alleviation, but may prevent damage and redress the progressively autoreactive and pro-inflammatory process of rheumatoid arthritis towards remission, or at least the 'preclinical state' (5,9-11). It is however still unclear whether, when and how long this 'window' is 'open', or which treatment is (most) effective. If early effective treatment is available, failing to distinguish 'very early RA' from other forms of UA could result in undertreatment and an opportunity lost, but also in overtreatment with potentially dangerous side effects.

PREDICTION OF DISEASE OUTCOMES IN ARTHRITIS

To identify which UA patients are in fact RA patients in a very early phase of the disease, various prediction models, based on clinical and serological variables have been developed to predict disease outcome in UA (12,13). Although this prediction rule accurately estimates the risk of developing RA in more than 75% of patients with UA, it does not yet guide us in individual treatment decisions made in daily practice (12). Many of the predictive factors are also associated with a worse disease outcome in patients with classifiable RA (RA diagnosed according to the classification criteria).

Table 1. The 1987 ACR and the 2010 ACR/EULAR criteria. Adapted from Scott et al.

ACR 1987 criteria for RA	ACR/EULAR 2010 criteria for RA
1. Morning stiffness (at least 1 hour) 2. Arthritis of 3 or more joint areas 3. Arthritis of hand joints (at least 1 joint) 4. Symmetrical arthritis 5. Rheumatoid nodules 6. Serum rheumatoid factor 7. Radiographic changes (erosions or juxta-articular osteoporosis)	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) (3) • More than ten joints (at least one small joint) (5) 2. Serology (0-3) • Negative RF and negative ACPA (0) • Low positive RF or low positive ACPA (2) • High positive RF or high positive ACPA (3) 3. Acute phase reactants (0-1) • Normal CRP and normal ESR (0) • Abnormal CRP or abnormal ESR (1) 4. Duration of symptoms (0-1) • Less than 6 weeks (0) • 6 weeks or more (1)
Criteria 1-4 must be present for at least 6 weeks.	Points are shown in parentheses. Cut point for rheumatoid arthritis 6 points or more. Patients can also be classified as having rheumatoid arthritis if they have: (a) typical erosions; (b) long-standing disease previously satisfying the classification criteria.
For RA 4/7 criteria must be present.	

Evidence suggests that environmental, genetic as well as serologic factors influence the development and severity of RA (14). A wide variety of candidate genes has been investigated for their influence on susceptibility to and severity of RA. The most prominent genetic risk factors found so far are the Human Leucocyte Antigen (HLA) class II molecules. The relationship between RA and the HLA complex is thought to account for 30% to 50% of the genetic component of RA susceptibility (15-18). At the level of protein structure certain HLA-DRB1 alleles share an amino-acid sequence in the beta-sheet of the peptide-binding groove of the HLA molecule, the shared epitope. It is thought that the shared epitope containing HLA-molecules are important for the presentation of arthritogenic antigens. The shared epitopes QRRRA (DR1), QKRAA (DR4) and RRRRA (DR10) are not only associated with susceptibility to rheumatoid arthritis, but also with a more progressive disease course (19,20). Specific arthritogenic peptides that bind to the shared epitopes have not yet been identified.

Auto-antibodies are a prominent manifestation of auto-immunity in RA. To date there are two antibodies commonly tested in RA, Rheumatoid factor (RF) and anti citrullinated protein antibodies (ACPA). A promising new candidate is anti-CarP. These antibodies against carbamylated proteins have recently been shown to be present in RA, are also present in around 20% of ACPA-negative RA patients and are associated with more severe joint damage in this group (21). Rheumatoid factor was

the traditional antibody in RA for many years. RF positivity has a sensitivity for RA of 60-70% and a specificity of 80-90%. The more recently discovered anti citrullinated protein antibodies (ACPA) have a comparable sensitivity, but higher specificity of 95% (22). ACPA can be found in serum of patients years before the appearance of clinical symptoms of arthritis (23). In ACPA positive undifferentiated arthritis 93% of patients were found to progress to RA within three years, demonstrating the strong predictive effect of ACPA positivity with regard to disease outcome of UA. The fact that ACPA can also induce and aggravate arthritis in mice, also suggests an important role of ACPA in the pathogenesis of RA (24,25).

Half of patients with UA and one third of patients with RA do not have ACPA, but may present with similar symptoms and severity as patients who do. Genetic and environmental risk factors for ACPA positive and ACPA negative disease differ. For example the association between HLA-DRB1 SE alleles and RA was only observed for ACPA positive disease (17,26,27). So far, only HLA-DR3 is found to predispose for ACPA negative disease (28,29). Although more risk factors for ACPA positive disease are known, the comparable heritability in ACPA positive (68%) and ACPA negative (66%) RA indicate that more risk factors in ACPA negative disease remain to be identified. With regard to environmental risk factors, smoking was established as a relevant risk factor for ACPA positive disease, especially in subjects carrying one or two copies of the HLA-DRB1 SE (30,31).

Apart from genetic and environmental differences, histopathological features are different as well. In ACPA positive disease the synovial tissue contains more lymphocytes, whereas fibrosis and increased thickness of the synovial lining layer is more prominent in ACPA negative disease (32).

OLD AND NEW TREATMENT STRATEGIES

Nowadays treatment of RA is started earlier and is adjusted earlier than in the past decades. Until the 1990's, RA patients were treated according to the 'pyramid' strategy (33). When RA was diagnosed, patients in this delayed treatment strategy started with symptomatic treatment with non-steroid anti-inflammatory drugs (NSAIDs). Disease Modifying AntiRheumatic Drug (DMARD) treatment was only started in patients resistant to this symptomatic treatment. With this strategy, long term outcomes of patients with RA were poor, with severe joint destruction, disability and increased mortality (2,34). This led to a change towards the so-called 'sawtooth' treatment strategy. This encompasses earlier, continuous and serial use of DMARDs, substituting one DMARD for another or combining DMARDs when the response to the previous DMARD(s) starts to decline (35). As a result of prescribing DMARDs earlier in the disease process, lower disease activity and less progression of radiographic damage were observed. However, in most patients with established RA, the benefits of DMARD treatment were still insufficient in the long term (36-38). Better results were obtained when 'tight control' was introduced, followed by 'targeted treatment', i.e. a strategy where disease activity was measured and treatment was adjusted aiming at

low disease activity. This was made possible by the development of measuring tools such as the Disease Activity Score (DAS) (39-43). Newer therapies, designed to block pro-inflammatory cytokines such as Tumor Necrosis Factor, that plays a key role in sustaining the inflammatory processes of rheumatoid arthritis, further improved the outcome for both patients with longstanding and more recent RA (44-47). Finally, several studies demonstrated that initial combination therapy with (a) DMARD(s) and either prednisone or a TNF-blocker is superior in establishing early clinical improvement including remission, and in preventing joint damage progression, compared to initial DMARD monotherapy (46,48-50). However, most national laws and guidelines require that newly diagnosed RA patients start treatment with synthetic DMARDs, keeping the more expensive TNF-blockers (and other biologic DMARDs) as back-up treatment for patients who do not sufficiently respond to these drugs.

As 'gold standard' synthetic DMARD, methotrexate is recommended as the cornerstone of antirheumatic treatment. Widely introduced since the 1980s for the treatment of RA, it is a folate antagonist which is generally well tolerated, although mucosal and gastro-intestinal side-effects may occur (51,52). Apart from having a favorable efficacy/toxicity ratio, methotrexate was proven capable of suppressing radiographic joint damage.

With the lessons learned in the treatment of RA, starting anti-rheumatic therapy already in the UA phase might result in even more sustained benefits and potentially even a chance for cure during the 'window of opportunity' (10,53). In 1999 and 2004 two trials in UA/early RA were published that supported this hypothesis. An unblinded study in which a single dose of corticosteroids (either intramuscular or intra-articular) was administered to patients with early inflammatory arthritis reported that a disease duration of less than 12 weeks was the strongest predictor of disease remission at 6 months (54). In a small case-control study a few years later Nell et al. found significantly better clinical and radiological outcomes at 3 years in the 'very early' treatment group (diagnosis RA within 3 months of symptom onset) compared to the 'early' treatment group with longer symptom duration (55). In the former group UA patients, i.e. arthritis patients not fulfilling the 1987 criteria for RA, were admitted as well. A DAS28 remission state was achieved in 50% of the very early arthritis group, compared to 15% in the early treatment group.

TOOLS TO SCORE CLINICAL RESPONSE AND RADIOGRAPHIC DAMAGE / PROGRESSION

During the 1990s physicians and researchers recognized that in order to compare or combine results of various clinical trials a uniform set of disease measures was needed, representing the whole spectrum of the disease. These 'core set' variables have been formulated by the Outcome Measures in Rheumatoid Arthritis Clinical Trials Committee (OMERACT) and ACR/EULAR collaborations and include disease activity, functional ability and joint damage assessment (56,57).

Disease Activity

Disease activity can be assessed with measures reflecting clinical symptoms, such as joint tenderness and joint swelling (in one of various sets of joint count scores), laboratory measures reflecting systemic inflammation, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and patients' self-reported pain, global health, morning stiffness, disease activity and fatigue, for instance on a 100 mm visual analogue scale (VAS). These measures were combined into various indices of disease activity, of which the Disease Activity Score (DAS) is generally accepted and most frequently used in the Netherlands. The DAS is a formula that consists of the Ritchie articular index (tender joint count in 53 joints), a 44 swollen joint count, ESR and patient global health assessment (39). Treatment effect can be measured in either absolute values or as relative changes. Both ACR and EULAR have formulated response criteria (58,59). The DAS, and its spin-off the DAS28 involving evaluation of less (28 in stead of 44/53) joints, were designed and validated in RA patients, but it is possible that they are also useful in UA patients.

Functional ability

An important and relevant outcome measure in RA is physical function. The instrument most frequently used to measure functional ability in RA is the Health Assessment Questionnaire (HAQ). The HAQ is a self-administered questionnaire that evaluates the level of difficulty the patient experiences with daily activities and the degree of assistance required with these activities (60,61). The HAQ grades functional disability on a continuous scale of 0 (best) to 3 (worst). A difference in HAQ score of 0.22 is regarded as clinically significant (62). It has been shown that the HAQ correlates well with disease activity and is a strong predictor for future disability and mortality (63).

Radiographic Progression

Serial X-rays of the hands and feet are used to follow the course of the disease by an objective measure and to assess the long-term effects of treatment. One of the most widely used methods is the Van der Heijde modified Sharp score (SHS), which focuses on joint space narrowing and erosions in the hands, wrists and feet (64). Assessment of joint erosions is performed in 44 joints, compared to 42 joints for narrowing. The percentage of patients suffering progression above the level of measurement error can be calculated using the smallest detectable change (SDC) and individual data can be visualized in probability plots (65). In case of very little radiographic progression, inter-observer and intra-observer intraclass correlation coefficients are not suitable for measuring reliability and consensus scores can be reached for radiographs with interreader differences equal to or higher than the median difference in progression score.

Since radiographic damage and disease activity independently contribute to impaired physical function, it is important to aim treatment at minimal disease activity and damage progression (66). Whether these relationships hold true in UA is not known.

REMISSION IN RA

Since the optimal outcome of early treatment in UA and possibly RA is remission, in recent years there has been increasing debate on how remission should be defined. In daily practice, and particularly in patients with advanced RA, it is felt that the old ACR remission criteria were too strict. In particular 'no fatigue' and 'no joint pain' prove difficult to achieve even if rheumatologists are convinced that there is no more inflammatory activity (67). Composite disease activity scores such as the Simple Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI) and the DAS use their own cut offs that are consistent with clinical remission (68,69). For the DAS, a score < 1.6 has been shown to represent clinical remission and has been used as remission cut-off (70). These definitions however still allow for residual or subclinical inflammation and so it can be argued that remission should be defined more strictly. Recently, a committee of members of the American College of Rheumatology, the European League Against Rheumatism, and the Outcome Measures in Rheumatology Initiative has proposed two new definitions of remission (71). The first is the Boolean-based definition, where tender joint count, swollen joint count, CRP (mg/dl) and patient global assessment are all ≤ 1 . The other one is the SDAI where a score ≤ 3.3 defines remission. It is likely that the newly proposed and more stringent outcome measures will be applied increasingly in the near future, however, it is unclear whether more stringent criteria really constitute less disease activity, associated with better outcomes of functional ability and radiological damage progression (72). The ultimate goal in RA treatment is complete absence of disease activity which is sustained after discontinuation of therapy, denoting or at least closely resembling resolution of the disease. Previously found mainly in patients with longstanding RA which had 'run its course', more recently this state of drug-free remission has been achieved in a subset of patients much earlier in the disease course (73,74). Although this is a development that is encouraging, this subset is relatively small and includes many ACPA negative patients, who may be intrinsically prone to go into remission. Also, it is uncertain whether we are able to achieve early drug free remission with early intensive tightly controlled treatment (74). It is possible that in the phase of classifiable RA, the disease is already too advanced to induce prolonged drug free remission in these patients, at least with conventional therapies. In the phase of undifferentiated arthritis, this may be different.

REMISSION IN UA

Compared to RA, UA has a more variable natural disease course, including higher remission percentages (8,74). It has been suggested that patients with a shorter symptom duration have a higher likelihood of going into spontaneous remission. This would support the 'window of opportunity' theory. It is unclear whether early and temporary antirheumatic therapy can induce remission and achieve more drug free remission in UA patients. So far, only a few randomized clinical trials have been performed in UA

patients, but none of the trials had remission as their primary endpoint. Most are short term, and use static treatment, rather than dynamic treatment adjustments aiming at remission. If more dynamic treatment would be tried, it is necessary to assess if the DAS can be used to steer treatment also in a population of UA patients. The current thesis explores the necessity and possibilities of early treatment in patients with UA and very early RA.

OUTLINE OF THIS THESIS

Chapter 2 describes the history, present and future aims of the Leiden Early Arthritis Clinic (EAC), which was set up to detect and treat inflammatory disorders early in the disease state, especially Rheumatoid Arthritis (RA). In this EAC, several early arthritis trials have been conducted, leading to a better understanding of RA and improved treatment strategies.

Patients who present with undifferentiated arthritis in relatively few joints are likely to visit a rheumatologist relatively late and thus start antirheumatic treatment relatively late, compared to patients who experience rapid onset of arthritis in many joints and present with classifiable RA. Whether this is acceptable or potentially harmful depends on whether the subsequent disease course in 'insidious onset' patients is milder than in 'acute onset' patients. **Chapter 3** explores whether a difference in symptom onset predicts a difference in disease outcomes.

One of the examples of improved treatment strategies is the study performed by Lard et al, that compared the 'pyramid' strategy to early initiation of DMARDs. Less radiographic damage was seen in the latter group. Whether this beneficial effect could be sustained after 4 years, was described in **chapter 4**. The association between RA and genetic factors has long been observed in many different populations, but the functional role of HLA molecules in the pathogenesis of RA remained unclear. In **chapter 5**, the relationship between these genetic factors (RA associated HLA class II gene polymorphisms) and anti-CCP antibody production was investigated, as well as the relationship with disease severity in terms of radiographic damage.

In rheumatoid arthritis evidence for justification of early aggressive treatment is accumulating, aiming at the 'window of opportunity'. So far, treatment of undifferentiated arthritis with DMARDs had not been performed. Published in 2007, the PROMPT study was the first randomized controlled trial in which patients with undifferentiated arthritis were treated with a DMARD (methotrexate). The results of this study are presented in **chapter 6**. The next **chapter (7)** investigates in more detail the effect of MTX versus placebo on disease activity, joint damage and functional disability in UA using longitudinal data analysis. In addition, this chapter examines a theoretical background for early intensive treatment of UA, by investigating the longitudinal relationships between DAS, HAQ en SHS. The five year outcome of the PROMPT study is described in **chapter 8**. In this study the long term effect of initial treatment with methotrexate was investigated with regard to diagnosis and radiographic progression. In **chapter 9** the findings in this thesis are summarized and discussed.

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THE LEIDEN EARLY ARTHRITIS CLINIC

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ABSTRACT

In 1993 a special Early Arthritis Clinic (EAC) was established at the Department of Rheumatology of the Leiden University Medical Center in order to detect and treat inflammatory disorders early in the disease state, especially early rheumatoid arthritis. Patients with confirmed arthritis of recent onset (less than 2 years) were included by rheumatologists and trained research nurses. Parameters of first and follow-up visits (3, 6, 9 months and yearly) that were entered in the EAC-database include the medical history, physical-diagnostic examination, laboratory tests, questionnaires, radiographic joint scores and diagnosis. This database enables us to conduct research on arthritis, with an emphasis on rheumatoid arthritis, in many ways. Physicians and basic scientists have studied cellular immunology and genetic, environmental and clinical risk factors in order to determine the pathophysiologic mechanisms of inflammatory arthritis. The present article is a review on reports published from the EAC. Over the past ten years, these reports have been highly relevant for both daily clinical practice and research. Present and planned future studies, as described in this article, reconfirm the importance of an EAC framework to ensure that research continues on this disease in the Leiden EAC area.

A UNIQUE POPULATION-BASED INCEPTION COHORT

The Leiden Early Arthritis Clinic (EAC) was started in 1993 in order to detect and treat inflammatory disorders early in the disease state, especially early rheumatoid arthritis (RA) (1,2). In order to obtain early referrals by general practitioners (GPs), a campaign was started among GPs to refer patients with suspected arthritis as soon as possible to the rheumatology department of the Leiden University Medical Center. Our rheumatology outpatient clinic is the only center for rheumatic disease patients in a semi-rural area with more than 300,000 inhabitants. Patients can be seen at the Early Arthritis Clinic within 2 weeks. They are invited to be included in the EAC if the suspected arthritis is confirmed by a rheumatologist and the symptoms of arthritis do not exceed 2 years. Second opinions are excluded. All parameters, ranging from a medical history, physical-diagnostic examination (general physical examination and painful and swollen joint counts), laboratory tests and questionnaires to radiographic joint scores are obtained by rheumatologists and trained research nurses. These data are entered into the EAC-database by encoded numbers. Based on the test results, a diagnosis is recorded at the second visit, 2 weeks later, and is revised during the follow-up visits after 3 months, 6 months (in cases of probable or definite RA) and yearly.

A detailed follow-up schedule is shown in Table 1. The EAC follow-up procedure was terminated if arthritis had not been observed by a rheumatologist for 1 year without the use of disease-modifying antirheumatic drugs (DMARDs) or in cases of post-traumatic arthritis, pseudo-gout or gout. The tenth anniversary of the EAC was marked this year, and during this period over 1600 patients have been enrolled in the inception cohort and over 2000 variables have been measured in each patient.

Table 1. Follow-up schedule of the Leiden Early Arthritis Clinic

EAC visit number	1 inclusion	2 2 wks	3 3 months	4 (6 mnths)	5 1 year	6 2 years	7 3 years etc.
Check in-/exclusion-criteria	•						
Informed consent	•						
Visit rheumatologist	•	•	•		•	•	•
Visit research nurse	•		•		•	•	•
Joint assessment	•		•		•	•	•
Laboratory assessment (including PBMCs*)	•		•		•	•	•
HLA-typing	•						
Radiologic assessment	•			•	•	•	•
HAQ + AIMS questionnaires	•				•	•	•
Assessment of ending EAC follow-up						•	•

*PBMCs: Peripheral Blood Mononuclear Cells

Table 2 presents some of the baseline characteristics of 1000 patients included in this cohort, who had completed one year of follow-up. The age at diagnosis, duration of symptoms and delay in referral by the GP are reported for each diagnosis at 1 year.

From the diagnosis at first visit to the diagnosis at 1 year, the number of 'RA' and 'arthritis of unknown cause' diagnoses increased, while the number of 'probable RA' diagnoses decreased. This finding appears to be consistent with the course of probable RA. As expected, patients diagnosed with reactive arthritis, juvenile chronic arthritis, spondylarthropathy, sarcoid arthritis and lyme arthritis are quite young of age at the time of diagnosis. The duration of symptoms, recorded in days, is relatively long in those forms of arthritis with a remitting and relapsing character (i.e. RA, probable RA, palindromic RA, psoriatic arthritis, spondylarthropathy, SLE and osteoarthritis-/arthritis). Another explanation for this phenomenon is that some of these diseases are difficult for the GP to recognize, as indicated by a relatively long delay in referral.

In many disease states, deleterious characteristics are acquired during the course of disease. Examples can be found in oncology, where tumour cells spread from the

Table 2. Some baseline characteristics of 1000 EAC patients. Values are the median (25th-75th percentile)

Diagnosis	Age (years)	Duration of symptoms at 1 st visit (days)	Delay in referral (days)	1 st visit (number)	1 year (number)
Rheumatoid Arthritis	57 (47, 68)	148 (77, 280)	78 (38, 148)	95	284
Probable RA	51 (35, 62)	131 (66, 266)	64 (20, 160)	254	53
Palindromic RA	50 (37, 60)	141 (96, 237)	223 (220, 225)	13	6
Septic Arthritis	53 (33, 63)	10 (4, 15)	6 (4, 14)	35	10
Reactive Arthritis	35 (30, 39)	13 (7, 28)	11 (6, 22)	72	45
Crystal Induced Arthritis	54 (47, 70)	11 (5, 76)	3 (1, 16)	105	86
Psoriatic Arthritis	42 (34, 51)	189 (47, 373)	50 (22, 141)	63	52
Juvenile Chronic Arthritis	14 (13, 14)	70 (47, 92)	unknown	4	2
Spondylarthropathy	32 (23, 42)	204 (73, 360)	103 (50, 170)	22	18
Sarcoid Arthritis	31 (28, 37)	21 (12, 29)	16 (8, 23)	56	44
Lyme Arthritis	29 (24, 44)	26 (8, 129)	9 (2, 111)	3	8
Paraneoplastic Arthritis	52 (43, 66)	49 (21, 85)	28 (3, 60)	10	12
Systemic Lupus Erythematosus	32 (28, 48)	95 (19, 221)	122 (95, 149)	1	11
MCTD/Vasculitis	63 (46, 77)	69 (12, 152)	50 (11, 131)	12	11
Osteoarthritis/arthritis	59 (51, 70)	109 (44, 364)	63 (24, 288)	36	59
Post-traumatic Arthritis	48 (34, 55)	29 (10, 94)	7 (6, 93)	10	12
Arthritis of unknown cause	45 (35, 56)	73 (18, 161)	19 (1, 68)	36	149
Other causes	44 (33, 58)	66 (29, 151)	25 (6, 87)	39	141

original tumour to the regional lymphnodes and eventually disseminate to metastatic disease. The curative effect of a surgical or chemotherapeutical intervention depends heavily on the stage in which the disease is first treated. In RA, it is unknown if and when such deleterious characteristics are acquired during the course of the disease, although sequential events that take place in patients who develop RA have been suggested (3). These presumed steps in the pathogenesis of RA are presented in Figure 1. Our research has been focused on two major categories: risk factors (genetic, environmental and clinical) and cellular immunology (autoantibodies, T cells, synoviocytes, cartilage degrading products and cytokines). The interactions between these two categories and the course of inflammatory arthritis are presented in this figure.

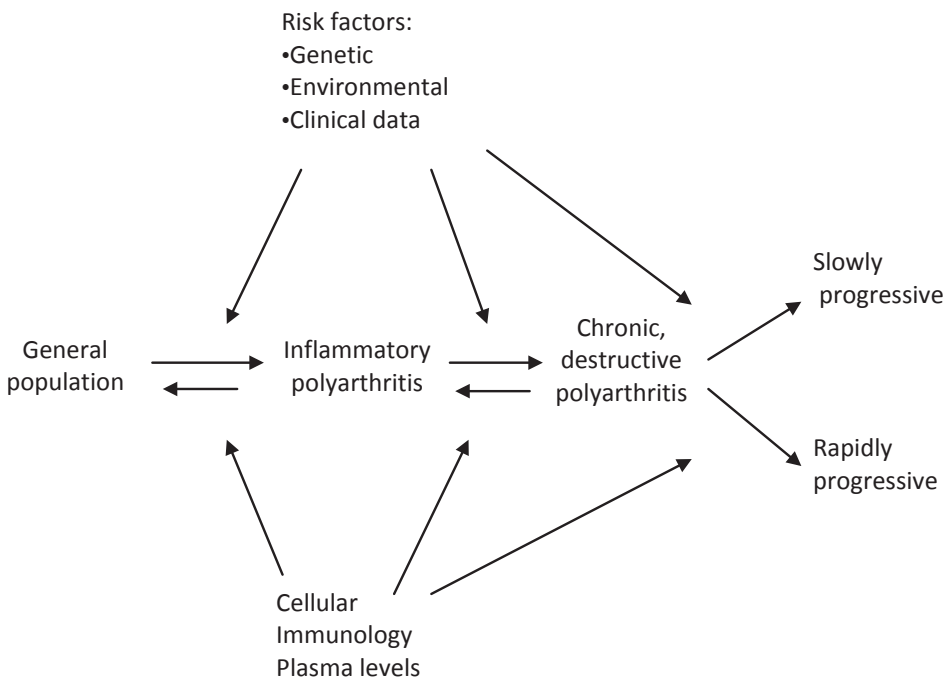


Figure 1. Working model for mechanisms involved in inflammatory arthritis.

GENETIC RISK FACTORS

Since the association between RA and HLA-DR4 was first described (4), genetic studies have implicated a role for specific HLA class II-dependent immune reactions in the pathogenesis of RA. The presence of HLA-DR Shared Epitope (SE) bearing alleles has been related to the severity of RA, with radiographic damage and rheumatoid factor positivity as measures of disease severity (5,6). Genetic research in a group of female Dutch RA patients confirmed this association between the Shared Epitope and

RA severity, reflected in the increased radiographic joint damage of this group (7), although this conclusion was challenged by several other groups (8,9).

Genetic research has been conducted to explain susceptibility to RA (8,10). A large population-based report on incident cases of RA demonstrated a limited contribution of HLA-DR-alleles, including the SE, to this susceptibility (11). Since not all (susceptibility and severity) questions could be solved with the Shared Epitope hypothesis, a new hypothesis was proposed in which different HLA class II alleles are associated with disease severity. In this so-called RA protection (RAP) model, certain DQ alleles (DQ3 and DQ5) predispose to RA, whereas certain DR alleles can modulate the effect of DQ by either enhancing or dominantly protecting against the DQ-associated predisposition. These protecting DR alleles share a common amino-acid motif 'DERAA' in the HV3 region of the protein (12-14). Applying this model to our EAC-population, we confirmed the strong predisposition of DQ alleles to RA in DQ3 and DQ5 positive individuals. Moreover, if this DQ positivity was accompanied by the presence of DRB1 alleles bearing the 'DERAA' motif, a dominant protective effect was observed (15,16). In the EAC population, the RAP model was significantly better able to predict remission rates and erosion scores in early RA patients than the SE model (17).

In the search for other genetic determinants than HLA-DR4, several genes have gained interest, for example the IL-1 and IL-10 gene cluster. IL-1 is secreted by activated macrophages and plays an important role in the progression of joint inflammation. Elevated serum levels of IL-1 in RA could be explained by a functional polymorphism in the IL-1 cluster gene. Genotyping for IL-1 α , IL-1 β and IL-1Ra single nucleotide polymorphisms (SNPs) in a group of 312 EAC patients revealed that the IL-1RN+2017 polymorphism is associated with susceptibility to RA. However, no significant associations could be demonstrated between IL-1 genotypes and disease severity (18).

With regard to the immunoregulatory cytokine IL-10, different roles have been reported for the different IL-10 gene variants. A protective effect against RA has been described for both high and reduced levels of IL-10. Since IL-10 production is largely under genetic control (19,20), the contribution of IL-10 gene variants to the pathophysiology of RA was studied by comparing the allelic frequencies of -2849G/A IL-10 promoter polymorphism of RA patients with other rheumatic disease patients from our EAC cohort. The results suggest that there is no association between the IL-10 genotype and RA incidence. A positive correlation was demonstrated for IL-10 gene polymorphism and disease severity, with high autoantibody production preceding the development of joint damage (21). However, a direct role of autoantibodies in the pathogenesis of RA still remains to be established.

Currently, we are focusing on the role of genes located at 1q32 (i.e. IL-10 and its homologues) on the susceptibility and course of RA. Together with the group of Corn  lis (GenHotel, Paris, France), the distribution of gene variants in well-defined patients with extremes of phenotypes is being studied by means of whole genome scans.

ENVIRONMENTAL RISK FACTORS

In 1999, a double-blind pilot study was performed to determine the effect of adjuvant blood transfusion on disease activity in RA. This study was a follow-up from our genetic studies and showed that a DRB1-matched blood transfusion improved symptoms in several RA patients according to the ACR 20 response criteria (22). However, the effect of this treatment was moderate and short-term. Given the known risks of blood transfusions and the growing number of therapeutic alternatives for RA, no further studies have been conducted to examine this transfusion effect.

Together with the Department of Obstetrics, Gynaecology and Reproductive Medicine, we examined whether fecundity (time of unprotected intercourse until first pregnancy) and miscarriage are associated with the severity of joint destruction in RA. The results indicate that miscarriage prior to disease onset and not fecundity is associated with the progression of joint damage (23).

In various Early Arthritis Registries, an association between cigarette smoking and RA has been reported (24). Possible links between smoking and the development of RA have been demonstrated, especially in seropositive RA (25,26). Currently, we are investigating the effect of smoking on the onset and course of RA in the Dutch EAC population.

CLINICAL RISK FACTORS

Clinical risk factors have been the subject of various investigations and range from referral by GPs to routine laboratory tests and treatment modalities. As mentioned earlier, GPs are encouraged to refer patients with suspected arthritis to our Early Arthritis Clinic. When referral delays were analyzed, however, female patients had a significantly longer delay in referral than male patients for various possible reasons (27).

The most commonly accepted clinical risk factors for severe erosive disease are rheumatoid factor and early radiographic damage (28), which have also been described for our EAC cohort (29). Over the last decade, early DMARD treatment has been advocated to improve both short and long term disease outcome. With regard to short term outcome it was observed that patients treated with DMARDs in an early phase of the disease (within 2 weeks after the first visit to the rheumatologist) had substantially less radiographic damage after two years compared to patients initially treated with analgesics (30). Radiographic evaluation of the same patients after four years however, showed no difference in the progression rate between the early and the delayed treatment group after the first year (31).

A problem frequently encountered in daily clinical practice is the outcome of undifferentiated arthritis. In order to predict arthritis outcome, a clinical prediction model was developed based on 22 potentially diagnostic determinants obtained at first visit (32). The final model of 7 variables (symptom duration, morning stiffness, arthritis of 3 or more joint areas, bilateral compression pain in the metatarsophalangeal

joints, rheumatoid factor positivity, anti-cyclic citrullinated peptide antibody positivity and the presence of erosions) was based on the first 500 patients who were included in the Early Arthritis Clinic. Whether this model can be validated in another set of EAC patients, is currently being analyzed.

Beside (early) RA, other forms of arthritis have also been studied from the EAC population, for example sarcoid arthritis (33). By clustering the data of 55 EAC patients with sarcoid arthritis and comparing these to the data of 524 patients with other arthritides, it was possible to describe the exceptionally high diagnostic value of the presenting clinical features, especially symmetrical ankle arthritis. When test positivity is defined as the presence of at least three of four criteria (symmetrical ankle arthritis, symptoms less than two months, age below 40 years and erythema nodosum), a high positive predictive value of 75% (PPV) and even higher negative predictive value of 99.7% provide a useful algorithm for the assessment of sarcoid arthritis in daily practice (34).

CELLULAR IMMUNOLOGY

Current knowledge of the nature of inflammatory attack in joints, derived mainly from experimental animal models, has led to improvement of anti-inflammatory treatment of RA by using cytokine inhibitors, like anti TNF-alpha and anti IL-1. However, such treatments can have serious side effects, since they may affect the patient's ability to resist infections and malignancies. Cellular immunology studies are directed to more specific immuno-modulatory mechanisms as a target for new therapies. Several cell types are thought to be important in the pathophysiologic mechanism leading to joint destruction in RA. In the research performed on EAC-material we focus on three cell types - B cells, T cells and synoviocytes.

B cells produce cytokines and autoantibodies. Rheumatoid factor (RF) was one of the first autoantibodies to be associated with RA and its severity. Lately, antibodies directed against Cyclic Citrullinated Peptides (CCP) have been reported to have a higher specificity for RA than RF (35,36). In 936 EAC patients with recent onset undifferentiated arthritis, we observed that the presence of anti-CCP antibodies has a positive predictive value (PPV) of RA of 93% with a sensitivity of 50%, which is higher than the PPV of 75% and sensitivity of 41% when using RF (37). The presence of anti-CCP antibodies in early arthritis could be useful as a predictive marker for disease progression to RA.

T cells are thought to play an important role in RA, depending on the nature of the secreted cytokines (pro- or anti-inflammatory) and on their interaction with other cells of the immune system. This way, T cells are able to increase and downregulate inflammation. In animal models, the induction or recruitment of so-called regulatory CD4+ T cells (Treg) has been proposed to actively downregulate inflammation. In humans, the presence of Treg cells has been shown, but their antigen-specificity, type of responses, molecular interactions and role in autoimmune disease such as RA are not known. T cell research in our EAC cohort focuses on these subjects.

Other cells involved in joint inflammation are synoviocytes, in which two cell types can be distinguished: fibroblastlike synoviocytes and macrophages. Both types play a pivotal role in the destruction of cartilage in RA by producing cytokines, thereby promoting inflammation, and by producing cartilage degrading matrix metalloproteinases (MMPs). Preliminary data suggest that fibroblast-like synoviocytes from RA patients can invade healthy cartilage in a more aggressive manner than synoviocytes from healthy donors. The mechanism responsible for this phenomenon is currently being investigated in our department. Several MMPs have been suggested to correlate with disease activity and joint damage progression (38,39). In an EAC cohort, we investigated whether serum levels of MMPs have a predictive value with regard to joint destruction. In this cohort, MMPs -3, -8 and -9 are associated with disease activity, while serum proMMP-3 levels are also predictive of radiographic joint damage progression in early RA (first two years of the disease), indicating a possible role for proMMP-3 as a predictor for progressive erosive disease (40).

A product of both T cells and synoviocytes is IL-16, which has been reported as a pro-inflammatory cytokine, as well as an anti-inflammatory cytokine in RA. In the EAC cohort, increased levels of IL-16 in recent-onset RA patients were observed, compared to IL-16 levels in patients with undifferentiated arthritis and healthy controls. Also, IL-16 levels of patients that presented with undifferentiated arthritis but developed RA over time, were increased compared to those of healthy controls and persistent undifferentiated arthritis patients. The positive correlation between high IL-16 levels and radiographic joint destruction during a two-year follow-up suggests a broad function of IL-16 in predicting both progression to RA and radiographic damage (41).

CLINICAL INTERVENTION STUDIES

Presently, early arthritis trials are embedded in the EAC follow-up structure in order to ensure long term follow-up of these patients. The 'BeSt' trial, a multi-center randomised trial, has been designed to determine the clinical and radiological outcome of four different treatment strategies: sequential monotherapy, step-up therapy, combination therapy including high-dose cortico-steroids and initial treatment with anti TNF-alpha blocking agents. The uniqueness of this trial is demonstrated by the fact that it is the first trial to compare so many different treatment strategies with a long term follow-up (5 years). Since little is known on the outcome and treatment of undifferentiated arthritis, a double blind, placebo-controlled trial is currently being conducted to determine the effect of methotrexate-treatment on early undifferentiated oligo-arthritis. This 'PROMPT' trial will not only provide the best treatment strategy for probable RA, but will also indicate important predictors for disease progression to RA, by means of the discussed research strategies.

WORK DISABILITY

Rheumatic diseases are a major cause of work disability and place a huge financial burden on the individual as well as on society. In addition, the noneconomic impact of work disability on the individual and his or her family is substantial. As a considerable amount of rheumatic disease associated work disability occurs in the first years of the disease (42-44), more and more attention is being paid to the question how the development of work disability in these early stages can be prevented. Although permanent work disability is usually preceded by sick leave, little data on the occurrence of prior working problems and sick leave are available. To gain more insight into the challenges encountered in the working situation resulting in sick leave or not, and into the complex process of vocational guidance, a prospective, observational study linked to the EAC was started.

CONCLUSION

This brief review has given an impression on the past, present and future work performed on the Leiden Early Arthritis Clinic (EAC). The EAC enables us to conduct research on arthritis in many ways. Physicians and basic scientists have studied cellular immunology and genetic, environmental and clinical risk factors in order to determine pathophysiologic mechanisms of inflammatory arthritis. Over the past ten years, reports on the EAC have been highly relevant for both daily clinical practice and research. The present and future studies, as described in this article, reconfirm the importance of an EAC framework to ensure continuous research of the Leiden EAC area.

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3

COMPARISON OF LONG TERM OUTCOME OF PATIENTS WITH RHEUMATOID ARTHRITIS PRESENTING WITH UNDIFFERENTIATED ARTHRITIS OR WITH RHEUMATOID ARTHRITIS: AN OBSERVATIONAL COHORT STUDY

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ABSTRACT

Background

The outcome of undifferentiated arthritis (UA) ranges from remission to rheumatoid arthritis (RA) fulfilling the American College of Rheumatology (ACR) classification criteria.

Objective

To report the outcome of UA after 1 year of follow up and compare the disease course of patients who presented with UA, but evolved into RA within 1 year (UA-RA group), with that of patients who presented with RA fulfilling the ACR criteria (RA-RA group).

Methods

The diagnosis of 330 patients who presented with UA was recorded at 1 year. The UA-RA and RA-RA groups were then followed up for 3 more years. Outcome measurements were radiographic progression, disease activity, and functional capacity.

Results

From 330 patients who were diagnosed UA, 91 had evolved into RA at 1 year; 62 patients had presented with RA. No significant differences were detected between the UA-RA and RA-RA groups in median Sharp/van der Heijde score at baseline, radiographic progression rates, disease activity, and functional capacity. However, significantly more disease modifying antirheumatic drugs were prescribed in the RA-RA group.

Conclusion

The disease outcome of patients who present with UA that evolves into RA within 1 year is the same as that of patients who present with RA as measured by radiographic progression, disease activity, and functional capacity.

INTRODUCTION

In various studies of patients with recent onset arthritis, 6–55% of the patients who presented with undifferentiated arthritis (UA) progressed into rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) classification criteria or according to the rheumatologist (1). Multivariate analysis of characteristics of these patients showed that the presence of antibodies to cyclic citrullinated peptide (anti-CCP), polyarthritis, symmetric arthritis, and erosions on radiographs predict the development of RA. Among these characteristics, anti-CCP has the highest specificity and positive predictive value for RA (2). Thus, either by clinical or by serological data, clinicians will be confronted with patients with UA who are likely to develop RA. The natural course of patients who present with UA and subsequently develop RA is unknown compared with patients who present with RA. In patients with RA many studies have demonstrated the benefit of the early initiation of disease modifying antirheumatic drugs (DMARDs), resulting in less disease activity and reduction of radiographic joint damage (3-5). Patients included in these studies fulfilled the 1987 ACR classification criteria for RA (6). However, the ACR classification criteria were not developed for the purpose of early diagnosis as is illustrated by the fact that a minority of patients with inflammatory polyarthritis fulfilled the ACR criteria at the first visit (7).

Although patients with RA benefit from early aggressive treatment (8), it is unknown whether patients with UA whose disease will evolve into RA will also benefit from such a treatment strategy. Hypothetically, if at presentation the duration of complaints is similar, patients who present with UA might have a disease course that evolves more slowly than that of patients who present with RA (figure 1). In the worst situation, the 'window of opportunity' for early treatment to induce long term disease modification

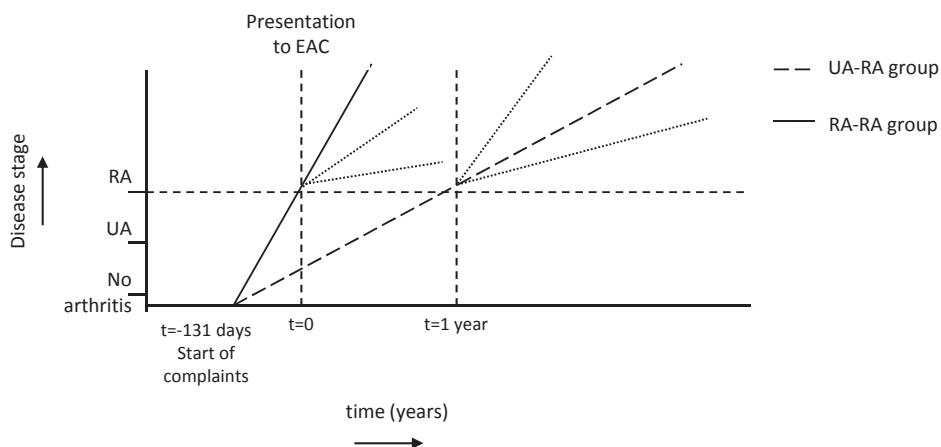


Figure 1. Hypothetical disease course of UA and RA.

in the patients who presented with UA has been passed once the diagnosis RA is made, and long term outcome will be comparable or worse than patients who were diagnosed with RA at presentation and treated immediately.

Here, we describe the 1 year diagnosis and outcome of patients who presented with UA, and compare the disease course of the patients with UA who had developed RA within 1 year after presentation (UA-RA group) with that of patients who presented with RA (RA-RA group). Radiographic progression was the major outcome measure; disease activity and functional capacity were minor outcome measures.

PATIENTS AND METHODS

Patients

The Leiden Early Arthritis Clinic (EAC) was started in 1993. General practitioners were asked to refer patients with suspected arthritis as soon as possible. Patients were included in the EAC cohort if a rheumatologist confirmed the suspected arthritis and the symptoms of arthritis did not exceed 2 years; for details of this cohort see Van der Horst-Bruinsma et al. (9). Patient history, general physical examination, a painful and swollen joint count, laboratory tests, questionnaires, and radiographic joint scores were

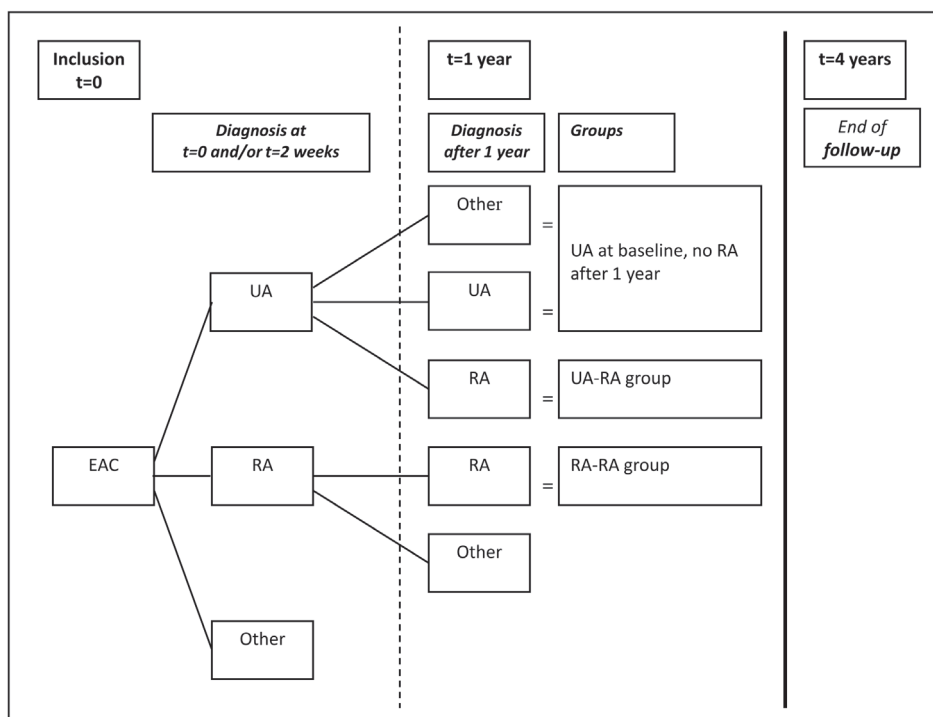


Figure 2. Flow diagram for definition of the groups.

performed at inclusion and at the follow up visits. Based on the test results, a diagnosis was recorded at the second visit, 2 weeks later, but could be revised during follow up.

Study design

From the EAC database (figure 2) patients diagnosed with UA at the second visit were selected and their subsequent diagnosis was recorded at 1 year. UA comprised arthritis of unknown cause and 'probable RA' according to the 1958 ACR criteria (10). The group of patients diagnosed with UA who evolved into RA fulfilling the 1987 ACR criteria within 1 year (UA-RA group) was followed up for 4 years. Because these patients had the opportunity to be treated with DMARDs as soon as the diagnosis was made, the long term outcome was compared with that of a group of patients in whom RA was diagnosed at the first and/or second visit and who still had RA after 1 year, and who were treated with DMARDs as soon as RA was diagnosed (RA RA group).

Outcome measurements

Major outcome measurements were radiographic joint damage and calculated radiographic progression rate. Radiographs of hands and feet were taken at inclusion

Table 1. Diagnosis after 1 year of follow-up of patients who presented with UA and the numbers of patients who had ended EAC follow up at 1 year, and their main reason for doing so

Diagnosis at 1 year	Patients No (%)	Patients who ended follow-up (n)	Main reason for end of follow-up No (%)
Arthritis of unknown cause	134 (40.6)	76	Remission 57 (75%)
Rheumatoid Arthritis	91 (27.6)	9	Death 3 (33%) Remission 3 (33%) Refusal 1 (11%) Other/unknown 2 (22%)
Probable RA	39 (11.8)	9	Remission 7 (78%)
Osteo-Arthrosis/Arthritis	11 (3.3)	10	End of treatment 7 (70%)
Psoriatic Arthritis	8 (2.4)	2	Remission 2 (100%)
Reactive Arthritis	6 (1.8)	6	Remission 6 (100%)
Crystal Induced Arthritis	4 (1.2)	3	EAC protocol 3 (100%)
Lyme Arthritis	4 (1.2)	2	Remission 2 (100%)
Paraneoplastic Arthritis	3 (0.9)	2	Remission 1 (50%) Life-threatening illness 1 (50%)
Systemic Lupus Erythematosus	2 (0.6)	0	
Palindromic RA	1 (0.3)	1	Move house 1 (100%)
Spondylarthropathy	1 (0.3)	1	EAC protocol 1 (100%)
Unknown cause	6 (1.8)	6	Remission 4 (67%)
Other causes	20 (6.1)	10	Remission 4 (40%)

in the EAC and yearly thereafter. Radiographic scoring according to the Sharp/van der Heijde method (11) was performed in random order by an experienced rheumatologist who was unaware of the clinical data and the study questions. The intraclass correlation coefficient for the assessor's scoring was 0.95, as measured in 62 patients.

Minor outcome measurements were disease activity, functional capacity, erythrocyte sedimentation rate (ESR) in the 1st hour, and C reactive protein (CRP) concentration. Disease activity was calculated by a modified version of the disease activity score (DAS) (8):

$$(0.54 \times (\sqrt{\text{Ritchie score}}) + 0.065 \times (\text{swollen joint score}) + 0.33 \times \ln \text{ESR} + 0.224).$$

Functional capacity was measured by the Health Assessment Questionnaire (HAQ) (12).

Statistical analysis

Differences between patient characteristics were tested with the Mann-Whitney U test or the χ^2 test. For each patient separately, simple linear regression was used to fit the course of the radiographic progression in time. Progression rates were calculated for varying time intervals, assuming that radiographic damage progresses at a constant rate (13,14). The slopes of these regression lines estimate the average increase in Sharp/van der Heijde score per year. Differences between slopes of the groups of interest were tested with the Mann-Whitney U test.

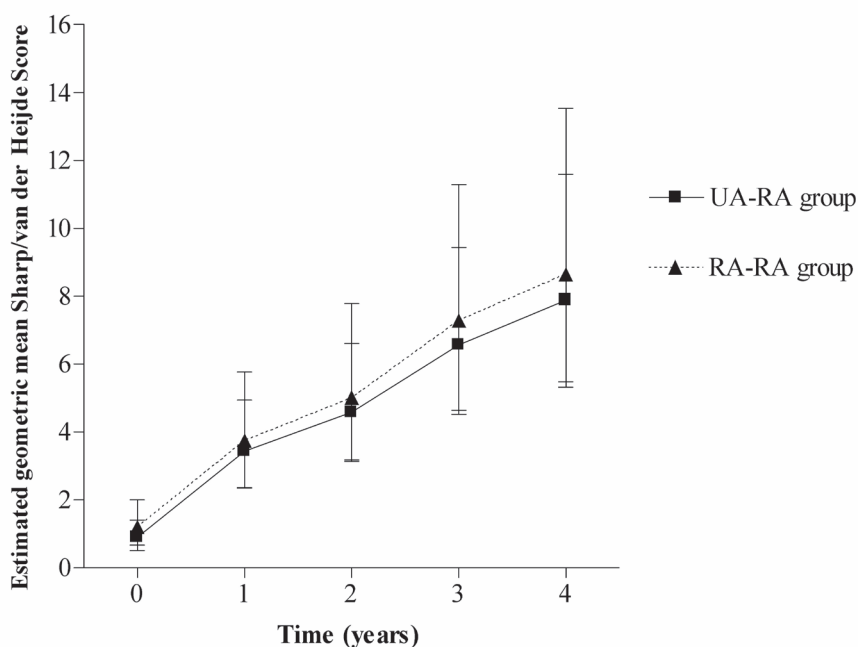


Figure 3. Estimated geometric mean Sharp/van der Heijde Score (95% confidence interval) of the UA-RA and RA-RA groups from baseline to 4 years.

To construct the radiographic progression as depicted in figure 3, the geometric mean of the Sharp/van der Heijde scores was estimated using a linear mixed model, in which account was taken of missing measurements (15). Differences in disease activity and functional capacity were compared with a linear mixed model. All tests were two tailed and p values ≤ 0.05 were considered significant.

RESULTS

Outcome of UA after 1 year

Between 1993 and 1999, 1064 patients were included in the EAC. At presentation, 330 patients were diagnosed with UA. Table 1 shows the diagnosis after 1 year of follow up of patients who had presented with UA and the numbers of patients who had ended follow up and their reasons for doing so. Ninety one patients had developed RA according to the 1987 ACR criteria (UA-RA group).

Table 2. Patient characteristics at baseline of the RA-RA group, the UA-RA group, and patients with UA who did not develop RA within 1 year

Patient characteristics	RA-RA group (n=62)	p-Value*	UA-RA group (n=91)	UA at presentation, no RA at 1 year (n=238)
Age (years)	53 (42-72)	0.683	55 (44-65)	46 (35-58)
Female patients	43 (69)	0.492	58 (64)	119 (50)
Duration of symptoms at first visit (days)	130 (61-278)	0.611	131 (73-230)	81 (20-164)
Duration of morning stiffness (min)	90 (45-150)	0.035	60 (18-120)	15 (0-60)
Number of swollen joints	7 (5-8)	<0.001	4 (2-6)	2 (1-3)
Modified DAS score	3.5 (3.1-4.0)	0.012	3.2 (2.7-3.7)	2.3 (1.9-2.8)
Rheumatoid factor positive	44 (71)	0.001	38 (42)	28 (12)
Anti-CCP antibodies	35/59 (59)	0.397	43/83 (52)	16 (8.2)
ESR (mm/1 st hour)	38 (20-56)	0.695	31 (19-53)	18 (9-37)
CRP (mg/l)	24 (9-41)	0.414	17 (8-46)	10 (4-26)
HAQ score	1.0 (0.6-1.4)	0.184	0.8 (0.4-1.2)	0.6 (0.1-1.0)
Erosive disease at baseline (hands and feet radiographs)	18/60 (30)	1.000	26/88 (30)	20 (13)
Sharp/van der Heijde score	1 (0-4)	0.281	0 (0-3)	0 (0-0)

*p Value of RA-RA group versus UA-RA group.
Results are shown as number (%) or median (interquartile range).

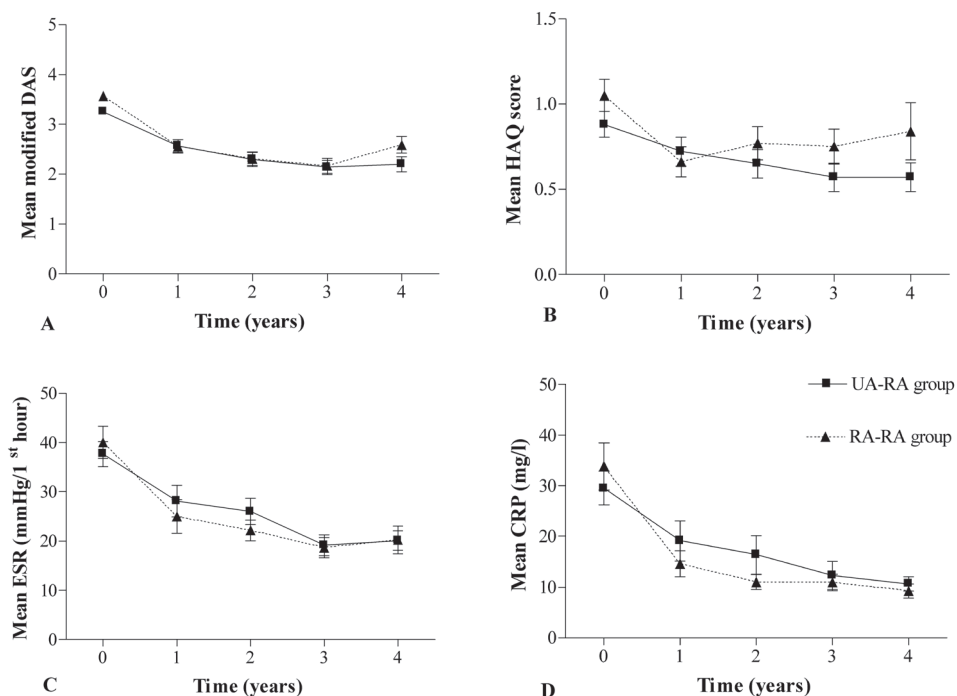


Figure 4. Secondary outcome values of the UA-RA and RA-RA groups from baseline to 4 years. (A) Modified Disease Activity Score; (B) Health Assessment Questionnaire score; (C) Erythrocyte Sedimentation Rate in mm/1st h; (D) C-reactive protein concentration. Mean values (SEM).

Patient characteristics at baseline

Table 2 shows the baseline characteristics of the UA-RA group, the RA-RA group, and the group of patients with UA who did not develop RA within 1 year. The UA-RA group differed from the RA-RA group in duration of morning stiffness, number of swollen joints, modified DAS, and percentage of patients who were rheumatoid factor (RF) positive. These differences reflect the ACR criteria for RA.

The patients with UA who did not develop RA within 1 year were significantly different at baseline from both the UA-RA group and the RA-RA group in all characteristics.

Radiographic joint damage

No significant differences were detected between the UA-RA and RA-RA groups for median Sharp/van der Heijde score (table 3, figure 3). At 4 years 75% of all patients in both the UA-RA group (77%) and the RA-RA group (73%) had erosive disease compared with 30% at baseline.

Table 3. Sharp/van der Heijde scores and radiographic progression rates (increase in score per year) in the UA-RA and RA-RA groups

	UA-RA group (n=91)		RA-RA group (n=62)	
	n	Median (IQR)	n	Median (IQR)
<i>Sharp/van der Heijde score</i>				
Baseline	88	0 (0-3)	60	1 (0-4)
1 year	79	4 (0-13)	56	5 (0-18)
2 years	71	8 (0-17)	48	5 (1-27)
3 years	66	10 (2-20)	45	11 (2-26)
4 years	53	9 (2-30)	41	15 (4-27)
<i>Radiographic progression rate</i>				
Slope 0-1 year*		2 (0-8)		2 (0-10)
Slope 0-2 years*		3 (0-8)		1 (0-8)
Slope 0-4 years*		2 (0-7)		2 (0-4)
Slope 1-4 years*		2 (0-8)		1 (-1-3)
Slope 2-4 years*		2 (-1-8)		2 (0-5)

* $p > 0.05$ in the UA-RA group versus the RA-RA group.

n is the number of patients with available data.

Disease activity and functional capacity

Figures 4A-D show the mean DAS, HAQ, ESR, and CRP of the two groups. During follow up no significant differences were seen.

DMARDs

Table 4 shows the use of DMARDs. At all time points significantly fewer DMARDs were prescribed in the UA-RA group than in the RA-RA group. Frequently prescribed DMARDs were hydroxychloroquine, sulphasalazine, and methotrexate or a combination of these. Prednisolone was also prescribed as single drug or combination therapy. Gold, azathioprine, and ciclosporin were prescribed in a minority of patients, and biological agents were not prescribed at all.

In the UA-RA group, 16/91 patients never received DMARDs during the follow up period of 4 years. Of these 16 patients, 11 were RF negative and in 10 patients erosive disease was seen during follow up.

Dropouts

Follow up of 3-4 years was available for 124 patients. Twenty nine patients were lost to follow up (dropouts). In the UA-RA group five patients were in remission, two refused follow up, five had died, one discontinued because of a concomitant illness,

Table 4. Number (%) of patients receiving prescribed DMARDs at 3 months, 1, 2, 3 and 4 years in the UA-RA and RA-RA groups

Time points	UA-RA group (n=91)	RA-RA group (n=62)	p-Value
3 Months	42 (46)	62 (100)	<0.001
1 Year	62 (68)	58 (94)	<0.001
2 Years	63 (69)	56 (90)	<0.001
3 Years	60 (66)	49 (79)	0.04
4 Years	52 (57)	48 (77)	0.003

Table 5. Baseline characteristics of dropouts (before or at 3 years of follow-up) versus completers

Patient characteristics	UA-RA group			RA-RA group		
	Dropouts (n=19)	Completers (n=72)	p Value	Dropouts (n=10)	Completers (n=52)	p Value
Age (years)	64 (46-75)	55 (44-63)	0.099	57 (36-85)	53 (46-69)	0.745
Female patients	57	65	0.598	60	71	0.479
Duration of symptoms at first visit (days)	102 (61-209)	144 (78-250)	0.381	159 (63-275)	126 (59-290)	0.851
Duration of morning stiffness (min)	60 (30-180)	60 (15-120)	0.341	75 (41-135)	90 (45-180)	0.875
Number of swollen joints	5 (3-8)	4 (2-5)	0.087	7 (4-8)	7 (5-8)	0.658
Modified DAS score	3.3 (2.8-4.2)	3.1 (2.6-3.6)	0.218	3.5 (2.9-4.7)	3.5 (3.1-4.0)	0.626
RF- positive	26	47	0.127	60	73	0.457
Anti-CCP antibodies	42	55	0.435	50	61	0.725
ESR (mm/1 st hour)	37 (25-65)	30 (18-50)	0.091	46 (25-61)	35 (19-57)	0.410
CRP (mg/l)	57 (13-74)	11 (7-32)	0.002	19 (9-44)	27 (9-42)	0.984
HAQ score	1.0 (0.12-1.37)	0.75 (0.5-1.12)	0.852	1.31 (0.65-1.75)	1.0 (0.5-1.37)	0.382
Erosive disease (hands and feet radiographs)	33	29	0.695	44	28	0.309

Results are shown as number or median (interquartile range).

and in six patients the cause was unclear. In the RA-RA group four patients were in remission, two refused follow up, one had died, one discontinued because of a concomitant illness, and in two patients the cause remained unclear. Table 5 compares the baseline characteristics of the dropouts with those of patients with 4 year follow up (completers). Only CRP in the UA-RA group was significantly higher in the dropout group than for the completers.

DISCUSSION

Here, the hypothesis was tested whether patients with UA who developed RA within 1 year have a different disease course than those who presented to the Leiden EAC with RA fulfilling the ACR criteria (6). Of the 330 patients who initially presented with UA, 91 (28%) had developed RA within 1 year. Although the patients with UA might hypothetically have evolved more slowly towards RA, joint damage, disease activity, and functional capacity were the same in both groups over a follow up period of 4 years.

UA is a commonly encountered problem in daily practice. In one third of patients with recent onset arthritis it is not possible to come to a definite diagnosis at presentation. Overall, 63% of the patients at the Leiden EAC had a self limiting disease course and 28% progressed from UA to RA. Other studies show that 6-55% of patients with UA will eventually evolve into RA (1). These percentages are dependent on the different inclusion criteria, recruitment procedures, and disease criteria. For example, low percentages are found in RF negative patients with monarthritis (16), and higher percentages are found in inception cohorts where patients with polyarthritis are diagnosed with RA, regardless of fulfilment of the ACR criteria (17).

Despite the fact that many studies have tried to describe the natural history of UA, the long term outcome of the subgroup of patients with UA who develop RA has never been described. As can be expected, the UA-RA and RA-RA groups differed at presentation in duration of morning stiffness, number of swollen joints, modified DAS, and percentage of RF positive patients, because these variables are directly or indirectly part of the 1987 ACR classification criteria for RA. The presence of anti-CCP was equal in both groups and is similar to previous studies (18). The group of patients with UA who did not develop RA within 1 year differed significantly in all patient characteristics at baseline from the other two groups. This is a very heterogeneous group considering the diagnosis after 1 year, but all these patients were diagnosed with UA at baseline.

Median symptom duration is about the same in both groups. However, given the large variation in symptom duration some misclassification of patients might have occurred. Theoretically, patients with UA who presented with short symptom duration might have belonged to the RA-RA group, and patients with RA with very long symptom duration might have had the chance of being included in the UA-RA group. However, analysis of subgroups with different intervals of symptom duration did not show an effect on joint damage.

In the dropout analysis, only CRP in the UA-RA group was significantly higher in the dropout group than for the completers. These data argue against the possibility that the UA-RA group equals the RA-RA group because the dropouts in the UA-RA group were the patients who presented with a milder disease, and only the patients with more aggressive disease completed the follow up.

At all time points, the UA-RA group received fewer DMARDs than the RA-RA group. In this observational study, this might reflect a historical development in DMARD prescription. It also might be a confounding by indication, as clinicians are inclined to prescribe DMARDs to patients who they expect to have a more destructive disease course. Then, patients in the RA-RA group might have a more aggressive disease course that is modified by DMARDs. However, the power to detect an effect of the presence or absence of DMARD use on radiographic progression was too low given the small number of patients with RA who did not use DMARDs (n=16). In the UA-RA group, 16/91 patients did not receive DMARDs during the 4 year follow up. Although 11 of these patients were RF negative, 10 had erosive disease. However, with a median radiographic progression of one point a year, this subgroup had less progressive disease than the group treated with DMARDs. A randomised clinical trial with DMARDs in patients with UA would be the most appropriate study design to overcome this issue.

The overall outcome of UA poses challenging treatment goals. Patients with UA who will go into remission will need treatment aimed at reducing symptoms, whereas patients prone to progress to RA will need treatment to improve their long term outcome as well. Furthermore, there is a need for new criteria to identify patients with UA that will evolve into RA, as the current ACR criteria for RA are not suitable for this purpose. This study implies that the long term outcome of patients who present with UA which evolves into RA is the same as that of patients who present with RA. New serological tests combined with clinical judgment will help to determine which patients with UA are most likely to develop RA. Randomised clinical trials in such patients with UA are currently under way to test whether this group of patients may benefit from very early DMARD treatment.

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4

RADIOLOGICAL OUTCOME AFTER FOUR YEARS OF EARLY VERSUS DELAYED TREATMENT STRATEGY IN PATIENTS WITH RECENT ONSET RHEUMATOID ARTHRITIS

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ABSTRACT

Objective

To determine the effect of different treatment strategies (early versus delayed) on the radiological progression of joint damage during 4 years. Additionally, to determine the effect of treatment strategy on the association of HLA class II alleles and joint damage.

Methods

Progression of radiographic damage and association of radiographic damage and genetic predisposition were compared in two cohorts, one treated according to the delayed treatment strategy (initial treatment with analgesics), the other treated according to the early treatment strategy (treatment with disease modifying antirheumatic drugs (DMARDs) chloroquine or sulfasalazine). Radiographic damage was measured by the modified Sharp-van der Heijde method. Genetic predisposition was determined by high resolution HLA-DR and DQ typing.

Results

A completers-only analysis of 153 patients (originally 206 patients) in a non-randomised design showed less radiographic progression from 0 to 4 years in the early treatment group (median Sharp progression rate 1.3 points/year, $n=75$) than in the delayed treatment group (2.5 points/year, $n=78$) ($p=0.03$). The progression from 1 to 4 years did not differ significantly between the groups. At 4 years, joint destruction in both groups was positively correlated with the presence of the shared epitope.

Conclusions

The beneficial effect of early DMARD treatment on the radiological progression of joint damage is still present at 4 years. However, the rate of joint destruction from 1 to 4 years did not differ between the delayed and early treatment group. Neither the radiographic nor the immunogenetic data suggest that longlasting disease modification has been induced by early treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a variable course and outcome, which may result in progressive joint destruction and physical disability (1–3). To reduce joint inflammation, joint destruction and, thereby, disability, disease modifying antirheumatic drugs (DMARDs) are prescribed. However, in most patients with established RA, the benefits of DMARD treatment are insufficient (4–6). A so-called ‘window of opportunity’ theory was proposed, in which institution of DMARDs at an early stage of the disease would have a dual effect. A short term effect would reduce clinical disease activity and a long term effect would modify the disease to a milder course. This theory is analogous with other disease states, where detrimental characteristics are acquired during the course of the disease. Examples can be found in oncology, where tumour cells spread from the original tumour to the regional lymph nodes and eventually disseminate to metastatic disease. The curative effect of a surgical or chemotherapeutic intervention depends heavily on the stage at which the disease was first treated. In RA, it is unknown if and when such detrimental characteristics are acquired during the course of the disease, although sequential events that take place in patients who develop RA have been suggested (7). The proposal of this ‘window of opportunity’ was indirectly supported by a number of trials and analyses that have studied early institution of DMARDs in patients with early disease (8–11). These studies demonstrated that early treatment with DMARDs effectively controls disease and/or reduces radiological progression in RA with median disease duration of <2 years with or without baseline joint damage. However, whether the observed beneficial effects of early treatment are temporary or long lasting remains to be determined. A study that examined this issue is the 5 year follow up of a placebo controlled study in which early treatment with auranofin was compared with a delayed treatment strategy. The results of this trial demonstrated improvement in the early treatment group for clinical variables, functional outcome measures, and radiographic progression, supporting the existence of a therapeutic ‘window’ within the first two years of the disease. However, the reported number of 75 patients (35 patients in the delayed versus 40 in the early treatment strategy) was relatively small (12). In a 6 year prospective cohort study, comparable favourable results were suggested with early treatment, mainly with sodium aurothiomalate during the first year, based upon the comparison of early treatment with historical controls (13).

Apart from radiographic outcome studies, immunogenetic studies have been performed to explore mechanisms of disease modification. In established RA, progression of joint damage is associated with HLA class II alleles (14–17). Recently, we demonstrated that early and aggressive treatment of very early RA (median disease duration 4 months) abolishes the association of HLA class II alleles with progression of joint damage, during the first 2 years of the disease (18). This effect was demonstrated for both the comparison of early versus delayed treatment and for the comparison of combination therapy including prednisolone, methotrexate, and sulfasalazine versus sulfasalazine monotherapy (19). Thus, it could be proposed that, next to the rate

of joint destruction, the association of HLA class II alleles with progression of joint damage can be used to assess whether disease modification has occurred by early treatment (18).

In the current study we investigated the effects after 4 years of early versus delayed DMARD treatment on the radiological outcome of RA. We presumed that longlasting disease modification had only occurred if the rate of radiographic progression was less in the early treatment group than in the delayed treatment group in the years after the period of different treatment. In addition, the association of HLA class II genes with progression of joint damage was determined in both groups to investigate whether early treatment modifies the disease mechanism.

PATIENTS AND METHODS

Patients

In 1993 a special early arthritis clinic (EAC) was started at the Department of Rheumatology of the Leiden University Medical Centre, The Netherlands, the only centre for rheumatic disease patients in an area with 300 000 inhabitants. General practitioners in this area were instructed to refer patients when arthritis was suspected. Patients could be seen at the EAC within 2 weeks. At the second visit, 2 weeks later, the diagnosis 'definite rheumatoid arthritis' was made according to the 1987 American College of Rheumatology (ACR) criteria (20), and the diagnosis 'probable rheumatoid arthritis' was made according to the 1958 ACR criteria, without the requirement of the 6 week observation period. Follow up visits were planned after 3 months, 6 months, and every year. The data of first and follow up visits were entered in the EAC database and consisted of history taking, physical diagnostic measurements, laboratory and radiographic parameters. For this study, we used the data of 4 years of follow up.

Study design

This was an observational study, in which two different treatment strategies were followed, during two subsequent time periods in a non-randomised design.

The delayed treatment group (n=109) group visited the EAC for the first time between January 1993 and December 1995, during which patients with RA were treated consistently according to the delayed or 'pyramid' strategy, in which DMARDs are restricted to patients who are resistant to symptomatic treatment (non-steroidal anti-inflammatory drugs (NSAIDs)). After about 5 months (median 152 days), patients who still had active disease received the disease modifying drug chloroquine or Salazopyrin (sulfasalazine), prescribed in therapeutic dosage, which at that time were the preferred drugs for early RA in the Netherlands. Patients were considered to have active disease if they fulfilled at least three of the following criteria: morning stiffness longer than 30 minutes, more than five swollen joints, Ritchie score greater than 15, or erythrocyte sedimentation rate greater than 28 mm/1st h. If disease control was insufficient according to the clinical judgment of the rheumatologist, or in cases of

intolerance, the rheumatologist was free to choose another DMARD. Patients with mild disease were not treated with disease modifying drugs.

The early treatment group (n=97) visited the clinic between January 1996 and December 1998, after the decision had been made to treat all patients with probable or definite RA as soon as possible with a DMARD in addition to NSAIDs 2 weeks after referral. Only those patients who were diagnosed with probable or definite RA within 2 weeks of their first visit were included in the study. DMARDs were prescribed according to the same protocol as described above, except that patients with mild disease were also treated with disease modifying drugs.

During the 4 year follow up, both patient groups were treated with DMARDs according to the judgment of the rheumatologist, varying from no drugs to combination therapy with or without prednisolone.

For this study we compared the treatment strategies (early v delayed) in relation to (progression of) radiographic joint damage, HLA class II association, and rheumatoid factor (RF) association.

Outcome measurements

Radiological progression

Radiographs of the hands and feet were obtained at study entry, at 6 months, and at 1, 2, 3, and 4 years. Radiographic damage was scored according to the modified Sharp/van der Heijde method (21) in two sessions by one experienced rheumatologist. During the first session radiographs of 0, 6 months, 1 and 2 years were randomly scored. The intraclass correlation coefficient for the assessor's scoring was 0.91, as measured in 52 patients. Radiographs of the third and fourth year were scored during the second session, with an intraclass correlation coefficient for the assessor's scoring of 0.98, as measured in 42 patients. The rheumatologist was unaware of the clinical data and the study questions.

Laboratory examinations

The presence of IgM RF was determined at study entry and was measured by enzyme linked immunosorbent assay (22). IgM RF titres ≥ 5 units were considered positive. The association between HLA class II alleles and joint damage was determined by looking at the presence of the shared epitope (SE) in relation to joint damage. According to the SE model, certain common amino acid sequences (so called shared epitopes) influence the interaction with the T cell receptor in RA associated HLA-DRB1 alleles (23). DNA isolation, DRB1 typing and subtyping, and DQB1 typing were performed as described previously (24,25).

The SE+ DRB1 alleles are *0101, *0102, *0401, *0404, *0405, *0408, and *1001.

Completers-only analysis

To avoid bias in the results by patients who were lost to follow up, we performed a completers-only analysis. In this analysis we included only those patients for whom a 3 to 4 year follow up (radiographs) was available.

Statistical analysis

For each patient separately simple linear regression was used to fit the course of the radiological progression. In both groups, the median slope was calculated. Progression rates were calculated, assuming that radiological damage progresses at a constant rate (26,27). Differences between the patient characteristics and slopes of the (sub)groups of interest were tested with the Mann-Whitney U test and Wilcoxon signed ranks test. All tests were two tailed and p values ≤ 0.05 were considered significant.

To construct figure 1, the geometric mean of the Sharp scores was calculated. Because the median Sharp scores of the two groups were very skewed as a result of missing measurements at different times, they were log transformed after adding 0.5 to the Sharp score. The average log Sharp scores with 95% confidence interval were estimated using a linear mixed model, with time, treatment group, and the interaction as fixed effects and the patient number as random effect. In this way account was taken of repeated Sharp measurements on one patient and missing measurements. The log means with confidence interval were then transformed back to the original scale, yielding estimates of the geometric mean of the Sharp score.

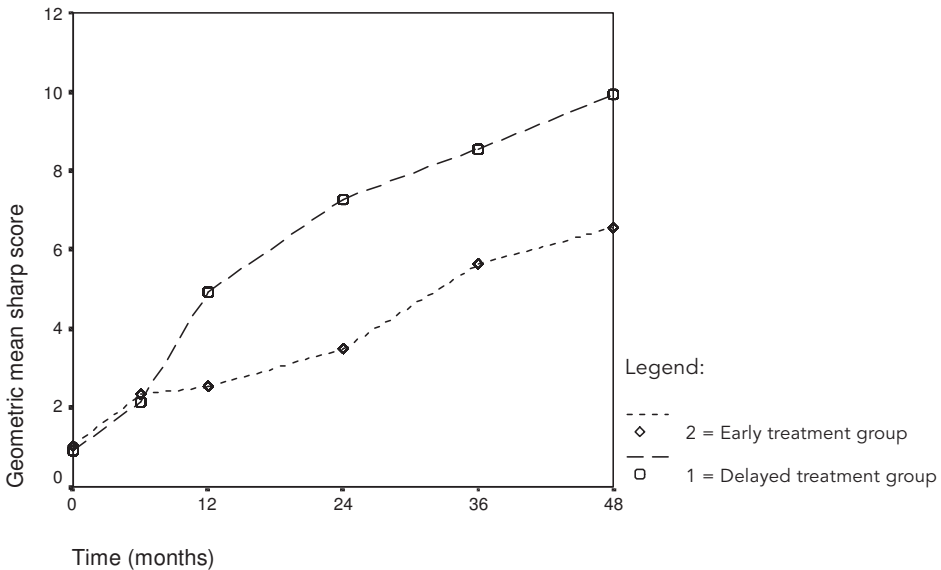


Figure 1. Geometric mean Sharp Score (see Patients & Methods; Statistical analysis) of Early versus Delayed treatment strategy from study entry to 4 years
95% CI for t=0 in group 1 (0.49, 1.49), group 2 (0.58, 1.70); for t=6 in group 1 (1.32, 3.35), in group 2 (1.45, 3.61); for t=12 in group 1 (3.32, 7.24), in group 2 (1.62, 3.81); for t=24 in group 1 (4.95, 10.63), in group 2 (2.28, 5.22); for t=36 in group 1 (5.88, 12.34), in group 2 (3.79, 8.26); for t=48 in group 1 (6.77, 14.43), in group 2 (4.40, 9.68).

RESULTS

Patient characteristics

Between 1993 and 1995 109 consecutive patients with RA (definite and probable) were included in the delayed treatment group. Subsequently, 97 consecutive patients were included in the early treatment group from 1996 to 1998.

Follow up of 3 to 4 years was available for 153 patients. Follow up of 53 patients (25%) was lost. Reasons for incomplete follow up of these 53 patients were diverse: 43 patients were definitely lost to follow up and of the remaining 10, radiographs were lost or not taken at the right time. In the delayed treatment group nine patients had died, six were in remission, four refused follow up, two had moved to different cities, five were lost because of unknown cause, and two because of concomitant illnesses. In the early treatment group two patients had died, three were in remission, three refused follow up, one had moved to another city, four were lost because of unknown cause, and two because of concomitant illnesses. Patients who were lost to follow up differed from the completers-only group in age (median age in the lost group was 64 years compared with 55 in the completer group; $p=0.02$) and presence of RF (percentage RF+ patients was 36% in the lost group compared with 63% in the completer group; $p=0.0001$).

Patients in the completers-only group (total $n=153$) had similar age, sex, duration of symptoms, presence of RF, and disease activity at diagnosis as the original group, as shown in table 1 and in the article by Lard et al (9). The median lag time for the institution of DMARD treatment after diagnosis was considerably longer in the delayed treatment group (about 5 months) than in the early treatment group (2 weeks), reflecting the different treatment strategies. The erythrocyte sedimentation rate (ESR) was significantly lower in the early treatment group at all times, but measured as a percentage the ESR decreased equally in both groups. At all times, the percentage of the groups who received DMARD treatment and the cumulative number of DMARDs used was higher in the early treatment group.

Outcome

Table 2 shows that at 1 year of follow up, a significant difference was found between the median radiological progression of 5.0 points Sharp score per year in the delayed treatment group and the 1.0 point per year in the early treatment group ($p=0.005$). At 2 years, this difference in progression rate was still substantial with 4.1 points per year in the delayed treatment group versus 1.0 point per year in the early treatment group ($p=0.001$).

When the progression rate was determined from study entry to 4 years, the difference between the two treatment strategies was still in favour of the early treatment group with 2.5 points per year in the delayed treatment group versus 1.3 points per year in the early treatment group, although less pronounced than during the first 2 years ($p=0.032$).

Table 1. Characteristics of the delayed treatment group and the early treatment group

	Delayed Group (n = 78)	Early Group (n = 75)	
Characteristic	Number (%) or Median (Interquartile Range)		p-Value
Age (year)	57 (44-65)	52 (42-68)	
Female sex	57 (73%)	51 (68%)	
Duration of symptoms at first visit (days)	171 (93-305)	128 (62-246)	
Definite rheumatoid arthritis	52 (67%)	51 (68%)	
Probable rheumatoid arthritis	26 (33%)	24 (32%)	
Rheumatoid factor-positive	48 (62%)	44 (59%)	
Active disease*	33 (42%)	34 (45%)	
Time to start disease-modifying drug treatment from first visit (days)	152 (55-293)	15 (14-21)	***
ESR (mm/1st hour) at baseline	36 (100%)	29 (100%)	***
6 months**	36 (100%)	20 (67%)	
1 year	32 (89%)	13 (45%)	
2 year	27 (75%)	18 (62%)	
3 year	24 (67%)	17 (59%)	
4 year	24 (67%)	17 (59%)	
DMARD-use (patients)			
2 weeks	0 (0%)	75 (100%)	***
1 year	42 (54%)	72 (96%)	***
2 year	41 (53%)	70 (93%)	***
3 year	48 (62%)	67 (89%)	***
4 year	49 (63%)	65 (87%)	***
Cumulative number of DMARDs per person in 4 years	1 (0-3)	2 (1-3)	***
Sharp score at baseline	0 (0-2)	0 (0-3)	

*defined as at least three of the following criteria: morning stiffness longer than 30 minutes, more than five swollen joints, Ritchie score greater than 15, or erythrocyte sedimentation rate greater than 28 mm/h

**percentage in relation to baseline ESR

***P < 0.05 in the delayed treatment group versus those in the early treatment group

Because we presumed that longlasting disease modification had only occurred if the rate of radiographic progression was less in the early treatment group than in the delayed treatment group in the years after the period of different treatment, the progression rates from 1 to 4 years and from 2 to 4 years were also calculated. During both intervals, the progression scores were not significantly different ($p=0.52$ and 0.82 , respectively).

Table 2. Median slopes reflecting radiologic progression per year (interquartile range) among patients with recent onset RA treated according to different strategies (Leiden EAC study)

Slope at year(s)	Delayed treatment Group (n=78)	Early treatment Group (n=75)	p-Value
Slope 0-1 year	5.0 (0, 15.0)	1.0 (0, 5.0)	0.005
Slope 0-2 years	4.1 (0.5, 12.6)	1.0 (0, 5.3)	0.001
Slope 0-4 years	2.5 (0.5, 7.7)	1.3 (0, 4.4)	0.032
Slope 1-4 years	0.9 (0, 7.0)	0.7 (0, 4.2)	0.52
Slope 2-4 years	1.0 (0, 6.5)	1.0 (0, 5.3)	0.82

Slope 0-1 year: based upon radiographs of study entry, 6 months and 1 year

Slope 0-2 years: based upon radiographs of study entry, 6 months, 1 and 2 years

Slope 0-4 years: based upon radiographs of study entry, 6 months, 1, 2, 3 and 4 years

Slope 1-4 years: based upon radiographs of 1, 2, 3 and 4 years

Slope 2-4 years: based upon radiographs of 2, 3 and 4 years

Figure 1 shows the differences in the progression of Sharp/van der Heijde scores between the two treatment groups over an observation period of 4 years. This figure shows a higher rate of radiographic progression during the first and second year than during the third and fourth year. During the last 2–3 years, radiological joint damage progressed at an equal rate in both groups.

Subgroup analysis

Comparable results were found in the subgroup of patients who fulfilled the ACR classification criteria at the first visit as in the total group (table 3). For those patients who fulfilled the criteria of probable RA, a beneficial effect of early treatment was seen at 2 years, but not at 4 years. For the intervals 0–4, 1–4, and 2–4 years, similar progression scores of approximately one point Sharp score per year were seen in both the delayed and the early treatment subgroup of patients with probable RA. Among patients with a Sharp score of 0 at diagnosis, no significant difference in the progression of radiological damage between the delayed and early treatment groups was seen. Among those with a Sharp score >0 at diagnosis, substantially less progression was observed in the early treatment group at all time points (1 year; $p=0.008$ (data not shown), 2 years; $p=0.001$, and 4 years $p=0.009$). For these Sharp subgroups, no differences between the intervals of 1 to 4 years and 2 to 4 years were seen.

Table 4 shows the significant differences in the progression of joint damage at both times in the delayed treatment group in patients who were SE+ or RF+ compared with patients who were SE– or RF–. In the early treatment group the association between radiographic progression and SE+ patients was also seen at 4 years ($p=0.041$), in contrast with the findings at 2 years (24,28). The difference in Sharp score between RF+ and RF– patients was significant at both 2 and 4 years.

Table 3. Modified Sharp progression rate (points per year) after 2 years, 4 years and from 1-4 years in the delayed and early treatment groups, stratified by diagnosis of definite versus probable RA and by Sharp score at baseline (Leiden EAC study)

Subgroup	No of patients	Delayed treatment Group			No of patients	Early treatment Group		
		Change 0-2 years	Change 0-4 years	Change 1-4 years		Change 0-2 years	Change 0-4 years	Change 1-4 years
<i>Diagnosis at baseline</i>								
Definite RA	52	6.1 [¶] (1.7,16.8)	3.1 [¶] (0.8,7.2)	1.0 (0,8.4)	51	1.6 (0,10.8)	1.8 (0.2,4.4)	0.6 (0,3.4)
Probable RA	25	1.9 [¶] (0,2.4)	0.8 (0.5,4.8)	0.7 (0,3.6)	24	0.0 (0,2.4)	0.6 (0,4.9)	0.8 (0,7.3)
<i>Sharp score at baseline</i>								
0	37	1.6 (0,6.5)	1.0 (0,6.8)	0.8 (0,6.1)	31	1.0 (0,4.7)	1.8 (0.4,5.6)	2.0 (0,6.0)
>0	36	7.2 [¶] (3.0,15.0)	3.0 [¶] (1.4,6)	0.8 (0,3.4)	39	1.0 (0,7.7)	1.1 (0,3.4)	0.5 (0,3.1)

Values are the median (25th - 75th percentile).

[¶] P < 0.05 in the delayed treatment group versus those in the early treatment group

Table 4. Influence of HLA class II antigens and rheumatoid factor on the joint damage progression score per year among patients with recent onset RA treated according to different strategies (Leiden EAC study)

		Delayed treatment Group				Early treatment Group	
	No of patients	Change 0-2 years	Change 0-4 years	No of patients	Change 0-2 years	Change 0-4 years	
<i>Shared epitope</i>							
Positive	52	7.0 [¶] (2.2,17.0)	3.1 [¶] (0.8,7.7)	45	1.0 [≡] (0,7.4)	2.2 [⊖] (0.3,5.6)	
Negative	24	0.5 (0,5.8)	0.8 (0,3.4)	26	0.9 (0,3.0)	0.5 (0,1.9)	
<i>Rheumatoid factor</i>							
Positive	48	6.7 [¶] (2.5,18.2)	3.4 [¶] (1.4,9.4)	44	2.0 [¶] (0,13.2)	2.5 [¶] (0.8,5.8)	
Negative	30	1.7 (0,7.6)	0.7 (0,2.8)	30	0.5 (0,2.0)	0.3 (0,1.3)	

Values are the median (25th - 75th percentile).

[¶] P < 0.05 versus those in the same treatment group who were negative for the feature;

[≡] P not significant versus those in the same treatment group who were negative for the feature;

[⊖] P = 0.041 versus those in the same treatment group who were negative for the feature.

DISCUSSION

In this study we tested whether early treatment with DMARDs would prevent acquirement of detrimental disease characteristics as measured by the rate of joint destruction. Except for the first year, the rate of joint destruction was found to be equal in both the delayed and the early treatment group. This higher rate of joint destruction in the delayed treatment group during the first year accounts for the beneficial effect of early DMARD treatment at 4 years in this radiographic analysis. However, once more than 50% of both groups received DMARD treatment, differences in the rate of joint destruction were no longer seen between the two groups. In this specific study, no support for the 'window of opportunity' hypothesis was seen. Thus, the fact that early treatment is associated with less inflammation and cumulative damage, does not imply a 'window of opportunity' for the long term effect.

Subgroup analysis of the group with probable RA and the radiographically undamaged group showed no long term favourable effects of early treatment. The observation that the association of HLA class II alleles and the rate of joint destruction is abolished by early treatment, was not seen after 4 years. This also indicates that longlasting modification of disease mechanisms was not achieved. The loss of association between HLA class II alleles and radiographic joint damage at 2 years was reported in both this cohort and the combination therapy group of the COBRA study, which compared initial intensive combination treatment, including high dose corticosteroids, with sulfasalazine monotherapy (18). To explain this finding it was suggested that early and aggressive treatment prevented the involvement of autoreactive T cells in the immune response. Because our 4 year data do not confirm a longlasting effect of early treatment, this theory is either incorrect or the effect of the currently investigated early treatment is not long lasting. Nowadays, RA is treated more aggressively than in the period during which this study was performed. So far, it is unknown whether the results of this study apply to present day treatment.

It needs to be discussed whether specific characteristics of our study may lead to limited generalisability. The present study is an observational cohort study, in which the rheumatologists were, apart from the delayed versus early treatment strategy, free to choose DMARDs. This led to a similar type of DMARD treatment in both cohorts, although not all patients were treated. The advantage of this approach is that the data reflect common practice, but the disadvantage is that subgroup analysis is no longer possible owing to confounding by indication. However, this line of reasoning does not inhibit subgroup analysis of prognostic factors not requested by the rheumatologist, such as genetic risk factors. As a result, the subgroup analysis of SE is valid, but the subgroup analyses of patients who fulfilled the ACR criteria for definite or probable RA as well as the Sharp subgroups may be affected by this phenomenon. Other disadvantages of this study are the 25% loss to follow up and the artefacts that may arise from secular changes, such as differences in preferential treatment in different time periods. This is reflected in the slightly higher percentage of DMARD treated patients in the early treatment group. However, this artefact would have skewed

the results towards a better radiological outcome in the early treatment group at all time points, thereby supporting the hypothesis that early treatment with DMARDs would have a longlasting effect on the joint damaging properties of RA. However, no difference in the rate of joint damage from 1 to 4 years was observed.

The baseline characteristics of the patients in this study are roughly comparable with those of other cohort studies in early rheumatoid disease, which have supported the short term 'window of opportunity' hypothesis (8,10,11). However, these trials have follow up duration of maximum 2 years, whereas the results of our study indicate that longer follow up is necessary. As mentioned earlier, long term follow up (>2 years) of early treatment strategies in order to confirm or reject this 'window of opportunity' hypothesis is scarce. The studies that have been carried out to answer this question, both reported the opposite result. Our findings are in accordance with a 3 year prospective study that compared DMARD treatment in very early RA (symptoms <4 months; n=27)) with that in early RA (symptoms 4–24 months; n=122) (29). The parallel progression rates in that study were addressed to a more aggressive form of RA in the very early treatment group, as pointed out by a significant difference in the duration of symptoms between the two groups (3.1 months in the very early group versus 9.2 months in the early group). However, in our present study, no indication for differences in disease severity was observed.

The question that arises from our results is whether the 'window of opportunity' hypothesis is incorrect or whether the timing and type of early treatment, as in the current study, are not enough to prevent acquirement of detrimental disease characteristics as measured by the rate of joint destruction.

Several studies show that combination therapy of several DMARDs or the combination with corticosteroids is more effective in suppressing disease activity and radiological progression, at least during the first 2 years (19,30,31). The recently published results of the 5 year follow up of the COBRA study show that the beneficial effect of combination therapy is sustained with regard to suppression of radiological progression, even after 5 years (32). The modified Sharp/van der Heijde progression rate was 5.6 points a year in the 74 patients originally randomised to the combination therapy group, compared with 8.6 in the 74 patients randomised to the Salazopyrin (sulfasalazine) group. The higher progression rates in this trial can be explained by the inclusion criteria of the COBRA study, which allowed only patients with more severe RA to be included. The progression rate of 5.6 points a year in a combination therapy treated group is very high, given the median progression of a couple of points a year in a general group of patients treated with DMARDs in a recent review on radiological progression in a large number of trials (33). The progression of joint destruction in a large number of DMARD treated patients in our cohort is comparable to the progression in DMARD treated patients as reviewed in this article.

In conclusion, the current data confirm that the beneficial effect of early DMARD treatment in reducing joint damage is still present at 4 years. However, after 1 year,

when more than 50% in both patient groups received DMARD treatment, no differences in the rate of joint damage could be observed. Thus, no prevention of detrimental characteristics during a 'window of opportunity' was seen from early DMARD treatment after 4 years.

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5

ASSOCIATION BETWEEN HLA CLASS II GENES AND AUTOANTIBODIES TO CYCLIC CITRULLINATED PEPTIDES (CCPs) INFLUENCES THE SEVERITY OF RHEUMATOID ARTHRITIS

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ABSTRACT

Objective

The functional role of HLA class II molecules in the pathogenesis of rheumatoid arthritis (RA) is unclear. HLA class II molecules are involved in the interaction between T and B lymphocytes required for long-lived B cell responses and generation of high-affinity IgG antibodies. We undertook this study to investigate the relationship between HLA class II gene polymorphisms and RA-specific IgG antibodies against cyclic citrullinated peptides (anti-CCP antibodies).

Methods

High-resolution HLA-DR and DQ typing and anti-CCP-2 antibody testing were performed on 268 RA patients from the Early Arthritis Clinic cohort at the Department of Rheumatology of the Leiden University Medical Center. The presence of anti-CCP antibodies was analyzed in carriers of the different DR and DQ alleles. Disease progression was measured over a period of 4 years by scoring radiographs of the hands and feet using the Sharp/van der Heijde method.

Results

Carriership of the individual alleles HLA-DRB1*0401, DRB1*1001, DQB1*0302, and DQB1*0501 was associated with the presence of anti-CCP antibodies. Carriers of DQ-DR genotypes containing proposed RA susceptibility alleles were significantly more often anti-CCP antibody positive. Carriership of one or two HLA-DRB1 shared epitope (SE) alleles was significantly associated with production of anti-CCP antibodies (odds ratio [OR] 3.3, 95% confidence interval [95% CI] 1.8–6.0 and OR 13.3, 95% CI 4.6–40.4, respectively). An increased rate of joint destruction was observed in SE+, anti-CCP+ patients (mean Sharp score 7.6 points per year) compared with that in SE–, anti-CCP+ patients (2.4 points per year) ($P = 0.04$), SE+, anti-CCP– patients (1.6 points per year) ($P < 0.001$), and SE–, anti-CCP– patients (1.6 points per year) ($P < 0.001$).

Conclusion

HLA class II RA susceptibility alleles are associated with production of anti-CCP antibodies. Moreover, more severe disease progression is found in RA patients with both anti-CCP antibodies and SE alleles.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease with autoimmune features. Previous studies have indicated that the risk of RA in siblings of affected individuals is 2–17 times higher than in siblings of unaffected individuals, pointing to a contribution of genetic factors in the pathogenesis of RA (1). An association between RA and the HLA complex, also known as the major histocompatibility complex (MHC), has long been observed in many different populations, and this is thought to account for approximately one-third of the genetic component of RA susceptibility (2).

Various paradigms have been put forward to explain the observed association between HLA and RA. It has been proposed that a conserved motif in the third hypervariable region (HVR3) of certain HLA–DR class II alleles plays a role in the presentation of ‘arthritogenic’ antigens to T lymphocytes, the ‘shared epitope’ (SE) hypothesis (3). Not only does carriage of SE alleles increase the risk of RA, but in RA patients, these alleles are also associated with a more severe disease type (4,5). However, since there are differences in the strength of association between SE alleles and RA, and since no convincing demonstration of the mechanisms underlying the associations is currently available, other paradigms that refine or complement the SE hypothesis have been put forward (6,7).

A prominent feature of RA is the presence of various types of disease-specific and non-disease-specific autoantibodies (8). Best known are the rheumatoid factors (RFs), which are antibodies to the Fc portion of IgG molecules. Although they are not disease specific, detection of IgM-RF is routinely used in the diagnosis of RA (sensitivity 60–70%, specificity 80–90%).

Recently developed assays detecting IgG antibodies against cyclic citrullinated peptides (anti-CCP antibodies) have a higher specificity of 98% at a similar sensitivity of 68–80% (9). Interestingly, using stored samples obtained from patients with RA, anti-CCP antibodies have been detected up to 9 years before the onset of arthritis (10). This suggests that production of these antibodies may be one of the earliest events in the disease. Indeed, we have recently shown that the presence of anti-CCP antibodies accurately predicts progression to RA in patients with undifferentiated arthritis (11).

Similar to IgM-RF, anti-CCP antibodies are a marker of severe disease. It has been shown that anti-CCP antibody-positive RA patients develop significantly more severe radiographic damage than do RA patients who are anti-CCP antibody negative (12).

Anti-CCP antibodies are directed against antigens containing the nonstandard amino acid citrulline (13), for example, citrullinated fibrin (14), which is found in the rheumatoid joint (15,16). Although citrullination or deimination of arginine residues of proteins may result in the formation of epitopes that are targets of antibodies, help from T lymphocytes is likely required for long-term B cell responses and antibody isotype switching. Accordingly, in mice transgenic for the SE allele HLA–DRB1*0401, it was recently demonstrated that citrullination of peptides could lead to the activation of CD4+ T cells, most likely as a result of increased binding of these citrullinated peptides to MHC class II molecules (17).

In RA patients, anticitrulline antibody production has been reported to be associated with the presence of certain HLA alleles (18,19). Using the antifilaggrin antibody (AFA) test, which is less sensitive than current anti-citrullinated peptides antibody tests (18), Bas et al showed that RA patients with AFAs were more likely to be carriers of SE alleles DRB1*01 and *04 (19). That study, however, was restricted to the carrier status of these two SE alleles only.

Given these results and the notion that anti-CCP antibodies are highly specific for RA, a thorough analysis of HLA class II alleles involved in generating autoantibodies to citrullinated antigens is important to gain a better understanding of this particular immune response.

In this study, we set out to determine whether the presence of certain HLA class II DR and DQ alleles in RA patients is associated with production of anti-CCP antibodies. Moreover, we analyzed the extent to which HLA genes and anti-CCP antibodies are associated with RA disease progression as measured by the extent of joint destruction.

PATIENTS AND METHODS

Patients

In 1993, after approval of the Institutional Review Board, a special Early Arthritis Clinic (EAC) was started at the Department of Rheumatology of Leiden University Medical Center, the primary referral center for patients with rheumatic disease in an area with ~300,000 inhabitants in the western part of The Netherlands. General practitioners were encouraged to refer patients directly when arthritis was suspected. Patients referred to the EAC could be seen within 2 weeks and were included in the program when the physician's examination of the patient revealed arthritis and the symptoms had lasted <2 years. Second opinions were excluded (20).

A standard diagnostic evaluation was performed at the first visit. This consisted of a patient history, physical and laboratory examinations, and radiographs of the hands and feet (20). Baseline laboratory examination included an enzyme-linked immunosorbent assay (ELISA) for IgM-RF as previously described (21) and an anti-CCP-2 antibody ELISA (Immunoscan RA Mark 2; Euro-Diagnostica, Arnhem, The Netherlands) which was performed according to the manufacturer's instructions (sensitivity 74%, specificity 97–99%). Patients included in this study all had a definite diagnosis of RA according to the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 revised criteria (22) 1 year after inclusion in the study.

Radiographic progression

Radiographs of the hands and feet at baseline, at 6 months, and at years 1, 2, 3, and 4 were available for the first 126 of the 268 RA patients included in this cohort (23,24). Radiographic damage was scored using the modified Sharp/van der Heijde method (25) in two sessions by one experienced rheumatologist. During the first session,

radiographs taken at baseline, 6 months, 1 year, and 2 years were randomly scored. The intraclass correlation coefficient for the assessor's scoring (in 52 patients) was 0.91. Radiographs taken at the third and fourth years were scored during the second session, with an intraclass correlation coefficient for the assessor's scoring (in 42 patients) of 0.98. The rheumatologist was blinded to the clinical data and unaware of the study questions. With 11% of radiographs not taken, not taken within an acceptable time frame, or not available for scoring, 5 radiographs on average (range 2–6) were scored per patient. Two patients (1.6%) had only 2 radiographs scored; both patients had a Sharp score of zero on both radiographs.

HLA typing

HLA-DQB1 and DRB1 typing and subtyping were performed by polymerase chain reaction using specific primers and hybridization with sequence-specific oligonucleotides. DQA1 genotype was deduced from DRB1 typing based on the strong linkage disequilibrium of the genes in the Dutch population.

DRB1 alleles *0101, *0102, *0104, *0401, *0404, *0405, *0408, *0413, *0416, and *1001 are SE alleles (26). In the RA protection (RAP) hypothesis, DQB1*0301, *0302, *0303, *0401, or *0402 combined with DQA1*0301 or *0302 are defined as DQ3 molecules, and DQB1*0501 combined with DQA1*0101 or *0104 are defined as DQ5 molecules. DRB1 alleles bearing the DERAA motif in their HVR3 are *0103, *0402, *1102, *1103, *1301, and *1302 (27). DQ3/3 and DQ5/5 patients have two doses of DQ3 or DQ5, respectively, and DQ3/5 patients are DQ3/DQ5 heterozygous.

HLA typing performed on blood from 306 healthy, unrelated Dutch donors served as a control (28).

Power calculation and statistical analysis

Approximately 60% of Dutch RA patients are carriers of one or two SE alleles (23). Anti-CCP antibodies are found in ~55–60% of patients with early RA (11,29). In an unmatched cohort, at a power of 80% and a confidence level of 95%, 222 RA patients (133 SE carriers and 89 non-SE carriers) are required to detect that SE carriership confers a risk for production of anti-CCP antibodies (odds ratio [OR] 2.25).

Study power, ORs with 95% confidence intervals (95% CIs), and P values obtained with the chi-square test were calculated using the Epi Info Statcalc computer program (Centers for Disease Control and Prevention, Atlanta, GA). When cell values were <5, results from the 2-tailed Fisher's exact test were used.

In the analysis of rate of joint damage, to correct for radiographs missing or taken at an irregular interval, the course of radiographic progression for each patient was fitted using simple linear regression. For all groups, the mean slope was calculated. Progression rates were calculated with the assumption that radiographic damage progresses at a constant rate (30). Differences between groups of interest were tested with a 2-tailed Mann-Whitney U test. For all tests, P values less than or equal to 0.05 were considered significant.

RESULTS

HLA–DRB1 and DQB1 carriership and anti-CCP antibodies

Of the RA patients included in this study, 53% (142 of 268) had anti-CCP antibodies at baseline (Table 1). Univariate analysis of the presence of anti-CCP antibodies in conjunction with HLA–DRB1 carriership was performed (Table 2). Not taking alleles with <10 carriers into account, carriership of two HLA–DRB1 alleles, DRB1*0401 and *1001, was associated with the presence of anti-CCP antibodies with the 95% CI for DRB1*0401 not including 1 (Table 2). Seven DRB1*0401 carriers were homozygotes, with 6 of them having anti-CCP antibodies (not shown). HLA–DRB1*1001 homozygotes were not found in our cohort (not shown). Carriership of HLA–DRB1*0301 was inversely correlated with production of anti-CCP antibodies with the 95% CI not including 1. Anti-CCP antibodies were not detected in the 5 HLA–DRB1*0301 homozygotes.

Carriership of HLA–DQB1*0302 and DQB1*0501 was associated with the presence of anti-CCP antibodies (Table 3). All 5 HLA–DQB1*0302 homozygotes and all 6 DQB1*0501 homozygotes had anti-CCP antibodies (not shown). HLA–DQB1 alleles for which carriership was inversely correlated with anti-CCP antibodies (with 95% CIs not including 1) were DQB1*0201 and *0603, and no anti-CCP antibodies were detected in the 3 HLA–DQB1*0201 homozygotes (not shown).

Table 1. Baseline clinical features of the 268 patients with early rheumatoid arthritis in the study*

Age, mean (range) years	57 (17–93)
Female, %	66
Caucasian, %	100
IgM rheumatoid factor positive, %	54
Anti-CCP antibody positive, %	53
Erosions on radiographs of hands and feet, %	25
Duration of symptoms, median (range) weeks	11 (0–52)

* CCP = cyclic citrullinated peptide.

Anti-CCP antibodies and DQ–DR genotypes

HLA–DR and HLA–DQ alleles are in strong linkage disequilibrium. Therefore, to gain a detailed knowledge of the presence of anti-CCP antibodies in combination with HLA–DRB1 and HLA–DQB1 gene variants, we combined the data from the two loci into HLA DQ–DR genotypes. Due to the large number of possible combinations for these two genes, we focused on specific HLA–DRB1 and DQB1 alleles.

HLA–DRB1 SE alleles and specific HLA–DQB1 molecules called DQ3 and DQ5 have been proposed to confer susceptibility to RA (7,26), whereas HLA–DRB1 alleles encoding the motif DERAA, when present in combination with DQ3 or DQ5, have

Table 2. HLA-DRB1 allele carriership and anti-CCP antibody status in rheumatoid arthritis patients*

DRB1	No of carriers	Anti-CCP+	Anti-CCP–	OR (95% CI)†
*0101	60	36	24	1.4 (0.8–2.5)
*0102	11	5	6	0.8 (0.2–2.9)
*0301	68	24	44	0.4 (0.3–0.8)
*0400	3	3	0	–
*0401	84	56	28	2.0 (1.2–3.4)
*0402	1	0	1	–
*0403	4	2	2	0.9 (0.1–8.9)
*0404	28	19	9	2.0 (0.8–4.8)
*0405	3	3	0	–
*0406	1	1	0	–
*0407	3	1	2	0.4 (0.0–6.3)
*0408	9	6	3	1.8 (0.4–9.2)
*0701	47	22	25	0.8 (0.4–1.5)
*0800	6	3	3	0.9 (0.1–5.6)
*0901	11	7	4	1.6 (0.4–6.5)
*1001	12	12	0	–
*1101	25	14	11	1.1 (0.5–2.8)
*1104	4	2	2	0.9 (0.1–8.9)
*1102	3	1	2	0.4 (0.0–6.3)
*1200	7	4	3	1.2 (0.2–6.8)
*1301	21	7	14	0.4 (0.2–1.2)
*1302	19	6	13	0.4 (0.1–1.1)
*1303	4	1	3	0.3 (0.0–3.2)
*1401	12	5	7	0.6 (0.2–2.3)
*1500	69	32	37	0.7 (0.4–1.3)
*1600	2	1	1	0.9 (0.0–32.9)
Total	517‡	273	244	

* CCP = cyclic citrullinated peptide; OR = odds ratio; 95% CI = 95% confidence interval.

† ORs were calculated comparing against all other groups.

‡ Of the 268 patients, 19 were homozygous for HLA-DRB1. HLA-DRB1*0400, *0800, *1200, *1500, and *1600 represent DR 4, 8, 12, 15, and 16, respectively. DRB1 shared epitope alleles *0104, *0409, *0410, *0412, *0413, *0416, *1402, and *1406, which are rare in the Dutch population, were not found in our cohort.

been proposed to provide protection against severe RA (31). Therefore, to reduce the complexity of combinations of HLA-DRB1 and HLA-DQB1, patients were grouped based on the presence of proposed RA-predisposing SE, DQ3, and DQ5 alleles and on the presence of DERA-encoding alleles proposed to protect against RA (Table 4).

Table 3. HLA-DQB1 allele carriership and anti-CCP antibody status in rheumatoid arthritis patients*

DQB1	No of carriers	Anti-CCP+	Anti-CCP–	OR (95% CI)†
*0201	60	23	37	0.5 (0.3–0.9)
*0202	27	12	15	0.7 (0.3–1.5)
*0301	75	41	34	1.0 (0.6–1.7)
*0302	79	57	22	2.5 (1.4–4.4)
*0303	20	12	8	1.3 (0.5–3.5)
*0304	1	1	0	–
*0402	5	3	2	1.3 (0.2–10.0)
*0501	76	49	27	1.6 (1.0–2.8)
*0502	3	2	1	1.7 (0.1–46.8)
*0503	12	9	3	2.6 (0.6–12.1)
*0601	0	0	0	–
*0602	64	30	34	0.7 (0.4–1.2)
*0603	18	3	15	0.2 (0.0–0.6)
*0604	17	8	9	0.7 (0.3–2.1)
*0609	3	1	2	0.8 (0.0–5.9)
Total	460‡	251	209	

* See Table 2 for definitions.

† ORs were calculated comparing against all other groups.

‡ Data are based on results from 237 patients. Of these 237 patients, 14 were homozygous for HLA-DQB1.

Anti-CCP antibodies were found in 84% of patients (32 of 38) with two susceptibility alleles at both DQB1 and DRB1 (combinations 3/3–SE/SE, 3/5–SE/SE, and 5/5–SE/SE). Compared against individuals having no susceptibility alleles, carriership of genotypes 3/3–SE/SE and 3/5–SE/SE was significantly associated with the presence of anti-CCP antibodies (OR 23.4 [95% CI 4.4–165.8], $P < 0.001$ and OR 6.2 [95% CI 1.5–28.3], $P = 0.007$, respectively). Of the few patients having genotypes with two predisposing DQ alleles and one SE allele (3/3–SE/x and 3/5–SE/x), 71% (5 of 7) had anti-CCP antibodies, and these genotypes combined were significantly associated with the presence of anti-CCP antibodies (OR 6.7 [95% CI 1.0–57.8], $P = 0.02$).

Anti-CCP antibodies were detected in 62% of patients (63 of 102) with genotypes bearing one DQ and one SE allele (3/x–SE/x and 5/x–SE/x). Both genotypes were associated with anti-CCP antibodies (OR 4.3 [95% CI 1.9–10.1], $P < 0.001$ and OR 4.6 [95% CI 1.9–11.8], $P < 0.001$, respectively).

Proposed protective DRB1 alleles encoding DERA were infrequent. DERA allele carriership was not inversely correlated with anti-CCP antibodies when compared with individuals with no susceptibility alleles (not shown).

Table 4. HLA-DQ and HLA-DR rheumatoid arthritis susceptibility genotypes and association with the presence of anti-CCP autoantibodies*

DQ-DR genotype†	No of carriers	Anti-CCP+	Anti-CCP–	OR (95% CI)‡	p-Value
3/3–SE/SE	19	17	2	23.4 (4.4–165.8)	<0.001
3/3–SE/x	6	4	2	5.5 (0.8–48.7)	0.06
3/3–x/x	1	1	0	–	
3/5–SE/SE	13	9	4	6.2 (1.5–28.3)	0.007
3/5–SE/x	1	1	0	–	
5/5–SE/SE	6	6	0	–	
3/x–SE/x	59	36	23	4.3 (1.9–10.1)	<0.001
3/x–x/x	6	3	3	2.8 (0.4–19.7)	0.3
5/x–SE/x	43	27	16	4.6 (1.9–11.8)	<0.001
3/x–SE/DERAA	8	3	5	1.7 (0.3–9.4)	0.7
3/x–x/DERAA	3	1	2	1.4 (0.0–21.6)	1.0
5/x–x/DERAA	12	6	6	2.8 (0.7–11.6)	0.2
x/x–x/x	60	16	44		
Total	237	130	107		

* SE = shared epitope; DERAA = motif carried by DRB1 alleles in their third hypervariable region (see Table 2 for other definitions).

† DQ3 = DQB1*0301, *0302, *0303, *0401, or *0402 combined with DQA1*0301 or *0302; DQ5 = DQB1*0501 combined with DQA1 *0101 or *0104; SE = DRB1*0101, *0102, *0401, *0404, *0405, *0408, and 1001; DERAA = DRB1*0103, *0402, *1102, *1103, *1301, and *1302.

‡ ORs were calculated comparing against the no-DQ and no-DR (x/x–x/x) group.

However, anti-CCP antibodies were found in 43% of patients (10 of 23) with one DQ3 or DQ5 allele and one DERAA allele (3/x–x/DERAA, 3/x–SE/DERAA, and 5/x–x/DERAA) compared with 61% of patients (66 of 108) with one DQ3 or DQ5 allele but no DERAA allele (3/x–SE/x, 3/x–x/x, and 5/x–SE/x). Carriership of DERAA in combination with one DQ3 or DQ5 allele appeared to be inversely correlated with the presence of anti-CCP antibodies (OR 0.5, 95% CI 0.2–1.3), but this was not significant ($P = 0.1$).

Subsequently, we analyzed which of the two models (RAP or SE hypothesis) described the best association with the presence of anti-CCP antibodies. To do this, the two models were simplified. Both models essentially distinguish 3 categories: two susceptibility factors (two SE alleles or two times DQ3 or DQ5), one susceptibility factor (one SE allele or one dose of DQ3 or DQ5), or no susceptibility factor/dominant protective factors (no SE or DERAA/DQ5, DERAA/DQ3, and no DQ [DQ x/x]). Using these categories, a 2×3 table was constructed for both models. The results of the chi-square tests for both models were similar, although the chi-square value for the RAP model was slightly higher than that for the SE model ($\chi^2 = 39.6$, 2 degrees of freedom [2df], $P < 0.001$ and $\chi^2 = 32.5$, 2df, $P < 0.001$, respectively). This was no great

surprise, given that we found no protective effect of the DERAA motif and given that the proposed susceptibility alleles in both models are highly linked (Table 4).

Table 5. Association of HLA-DRB1 shared epitope (SE) alleles and anti-CCP autoantibodies in rheumatoid arthritis*

SE status†	No of carriers	Anti-CCP+	Anti-CCP–	OR (95% CI)‡	p-Value
SE/SE	40	34	6	13.3 (4.6–40.4)	<0.001
SE/x	141	82	59	3.3 (1.8–6.0)	<0.001
x/x	87	26	61		
All	268	142	126		

* See Table 2 for other definitions.

† SE alleles include DRB1*0101, *0102, *0401, *0404, *0405, *0408, and *1001.

‡ ORs were calculated comparing double-dose SE carriers (SE/SE) and single-dose SE carriers (SE/x) against carriers of no SE alleles (x/x).

Anti-CCP antibodies and SE alleles

Since both HLA-DRB1 alleles for which carriership was associated with anti-CCP positivity (HLA-DRB1*0401 and *1001) were SE alleles, we separately tested the association of SE carriership with the presence of anti-CCP antibodies. In our cohort, 15% of patients (40 of 268) had two SE alleles (SE/SE), 53% (141 of 268) had one SE allele (SE/x), and 32% (87 of 268) had no SE alleles (x/x) (Table 5). Anti-CCP antibodies were found in 85% of SE/SE patients (34 of 40), 58% of SE/x patients (82 of 141), and 30% of x/x patients (26 of 87). Compared with carriership in x/x patients, SE/SE and SE/x carriership was significantly associated with production of anti-CCP antibodies (OR 13.3 [95% CI 4.6–40.4], $P < 0.001$ and OR 3.3 [95% CI 1.8–6.0], $P < 0.001$, respectively).

To determine whether the association between SE and anti-CCP antibodies was entirely due to the DRB1*0401 and DRB1*1001 alleles, we retested the association after excluding these two alleles. SE carriership, however, was still associated with the presence of anti-CCP antibodies (OR 2.9 [95% CI 1.6–5.6], $P < 0.001$).

Given the strong association between SE alleles and anti-CCP antibodies in patients with RA, we compared the distribution of SE alleles in anti-CCP+ and anti-CCP– RA patients with the distribution of SE alleles in controls. SE alleles were more common in anti-CCP+ RA patients than in controls. SE/SE carriership was found in 24% of anti-CCP+ RA patients and in 6% of controls ($P < 0.001$). SE/x carriership was found in 58% of anti-CCP+ RA patients and in 36% of controls ($P < 0.001$). In contrast, SE carriership did not differ between controls and anti-CCP antibody–negative RA patients. SE/SE carriership was found in 5% of anti-CCP– RA patients and in 6% of controls ($P = 0.9$). SE/x carriership was found in 46% of anti-CCP– RA patients and in

36% of controls ($P = 0.07$). These data suggest that the association between the SE and RA is mainly due to the underlying association between the SE and the production of anti-CCP antibodies found in RA patients.

Investigators in several studies have reported on SE carriership and IgM-RF in RA (5,32). In our cohort, in line with previous reports, carriership of SE alleles was associated with the presence of IgM-RF (OR 1.7 [95% CI 1.0–2.3], $P = 0.04$). However, this association was due to the association of SE/SE carriership with IgM-RF (OR 2.8 [95% CI 1.2–6.4], $P < 0.001$), but not to the association of SE/x with IgM-RF (OR 1.5 [95% CI 0.9–2.7], $P = 0.1$).

Anti-CCP antibodies and HLA class II genes as disease progression markers

HLA class II SE alleles and production of anti-CCP antibodies are both markers of the presence of joint erosions (33). We analyzed the interaction between the two factors in predicting the extent of joint damage progression. Figure 1 shows the rate of joint damage per year as measured on radiographs of the hands and feet using the modified Sharp/van der Heijde method.

The highest rate of joint damage over 4 years in early RA was found in patients with both anti-CCP antibodies and SE alleles. The mean $\pm$ SD rate in this group was 7.6 ± 10.4 Sharp points per year (Figure 1). The mean $\pm$ SD rate of joint damage in

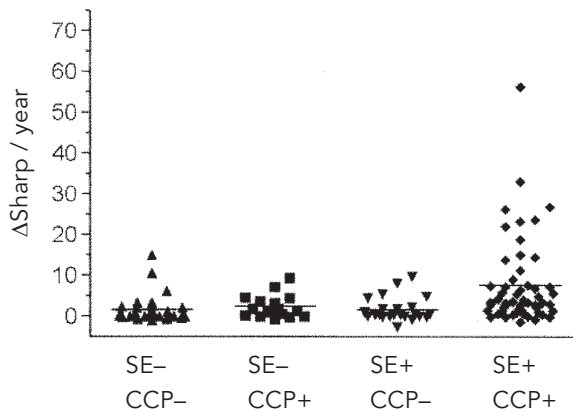


Figure 1. Rate of joint damage per year in patients with recent-onset rheumatoid arthritis over a period of 4 years. Patients were grouped by shared epitope (SE) status and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity. At baseline, no differences were seen in joint damage between groups. SE+, anti-CCP+ patients ($n = 54$) had a significantly higher rate of joint damage than did SE-, anti-CCP- patients ($n = 33$) ($P < 0.001$), SE-, anti-CCP+ patients ($n = 16$) ($P = 0.04$), and SE+, anti-CCP- patients ($n = 23$) ($P < 0.001$). Horizontal bars indicate the mean change in Sharp score per year for each group. The SE alleles are DRB1*0101, *0102, *0401, *0404, *0405, *0408, and *1001. Results could not be explained by differences in treatment or differences in the presence of IgM rheumatoid factor (see Results for details).

patients with early RA without anti-CCP antibodies and without SE alleles was 1.6 ± 3.9 Sharp points per year, which was significantly lower ($P < 0.001$) than that in anti-CCP+, SE+ RA patients. Patients with anti-CCP antibodies but without SE alleles had a rate of 2.4 ± 2.8 Sharp points per year, and patients without anti-CCP antibodies but with SE alleles had a rate of 1.6 ± 2.8 Sharp points per year ($P = 0.04$ and $P < 0.001$, respectively, versus anti-CCP+, SE+ patients).

Treatment strategy (23), mean age, and sex were approximately equally distributed among the 4 groups (data not shown). Each year an average of 75% of patients were treated with disease-modifying antirheumatic drugs (DMARDs). In the anti-CCP+, SE+ group, this value was 81%, which was not significantly different from the percentages in the other groups (data not shown). At the end of the study, the cumulative number of DMARDs used was higher in the anti-CCP+, SE+ group (mean 2.2, range 0–5) than in the anti-CCP–, SE– group (mean 1.5, range 0–5) ($P = 0.01$) or in the anti-CCP–, SE+ group (mean 1.3, range 0–4) ($P = 0.005$), but did not differ from the number used in the anti-CCP+, SE– group (mean 2.2, range 0–4) ($P = 0.9$).

However, IgM-RF was more common in groups with anti-CCP antibodies (86%) than in groups without anti-CCP antibodies (25%). Nonetheless, in a regression analysis model with joint damage progression as the dependent variable and IgM-RF and anti-CCP antibodies as predictors, there was a significant relationship between anti-CCP antibodies and joint damage progression (β 0.32, standard error of the regression coefficient 0.13, $P = 0.02$), but not between IgM-RF and joint damage progression (β 0.17, standard error of the regression coefficient 0.14, $P = 0.21$). Taken together, these data indicate that the increased rate of joint destruction observed in patients with anti-CCP antibodies and SE alleles cannot be explained by differences in treatment or differences in the presence of IgM-RF.

In contrast to what was initially assumed, the rate of joint destruction did not progress in a linear manner over the 4-year period of the study. A significantly higher mean $\pm$ SD rate of joint damage was observed in the first year than in years 2–4 (7.5 ± 12.6 Sharp points per year versus 4.3 ± 8.3 Sharp points per year; $P = 0.003$). In both time periods, however, the anti-CCP+, SE+ group had a significantly higher rate of joint damage compared with all the other groups (data not shown).

DISCUSSION

To investigate the immunogenetic background of the antibody response against citrullinated antigens, high-resolution DQB1 and DRB1 typing and anti-CCP antibody testing were performed on 268 Caucasian patients with early RA. Carrier analysis revealed that HLA-DRB1*0401, DRB1*1001, DQB1*0302, and DQB1*0501 were associated with the presence of anti-CCP antibodies. Moreover, associations were found between DQ-DR genotypes bearing proposed RA susceptibility alleles and the production of anti-CCP antibodies.

Carrier analysis such as that shown in Tables 2 and 3 appears to be fairly straightforward but has several disadvantages. Given the polymorphic nature of HLA genes, large numbers of patients are needed in order to assess the association for each allele. In this study, this is reflected in the wide CIs for the less frequent alleles. In addition, carrier analysis does not take into account the allele on the other chromosome. For highly polymorphic genes, this cannot be circumvented by homozygote analysis, since these are generally rare. Both issues can be illustrated by our findings for the DRB1*0901 allele. This allele, which is thought to be a neutral allele in RA susceptibility (34), seemed to be associated with anti-CCP antibodies. Eleven carriers of the allele were found in the cohort, and 7 had anti-CCP antibodies, giving an OR of almost 2; however, the CI included 1. More importantly, the possible association of this allele with anti-CCP antibodies is likely due to the fact that 5 of 10 anti-CCP antibody-positive DRB1*0901 carriers had an SE allele on the other chromosome, and these are significantly associated with anti-CCP antibodies.

Furthermore, when there is linkage disequilibrium between alleles of different loci, such as for HLA-DRB1 and DQB1, the contribution of individual alleles can be difficult to establish. For instance, HLA-DRB1*0401 and HLA-DQB1*0302, which were both associated with anti-CCP antibodies, are a part of the extended DQB1*0301;DQA1*0300;DRB1*0401 (DQ3-SE) haplotype. To provide insight into the relationship between HLA-DRB1 and DQB1 alleles, DQ-DR genotypes were analyzed. The analysis showed that anti-CCP antibodies were commonly found in patients with genotypes containing proposed susceptibility alleles from the RAP model (DQ3 and DQ5) and, consistent with previous reports (18,19), from the SE model. Patients with the protective DERA motif (according to the RAP hypothesis) were infrequent, as expected, and when this motif was present, it was not significantly inversely correlated with anti-CCP antibody production even after we attempted to correct for the presence of susceptibility alleles.

The presence of HLA susceptibility alleles and anti-CCP antibodies heralded a more severe disease type. Anti-CCP+, SE+ patients at baseline had a significantly higher rate of joint destruction than did all other patients. Although an increased rate of joint destruction was not found in every anti-CCP+, SE+ patient in our cohort, patients in this category constituted 92% (12 of 13) of those with joint damage progression above the 90th percentile (11.2 Sharp points per year). Surprisingly, the rate of joint destruction did not differ between anti-CCP+, SE- patients and anti-CCP-, SE+ patients ($P = 0.01$) or between anti-CCP-, SE+ patients and anti-CCP-, SE- patients ($P = 0.09$). This means that a higher rate of joint damage was only found when both anti-CCP antibodies and SE alleles were present.

A possible explanation might be the higher mean $\pm$ SD levels of anti-CCP antibodies in anti-CCP+, SE+ (SE/SE and SE/x) patients than in anti-CCP+ and SE- (x/x) patients ($1,033 \pm 1,028$ arbitrary units [AU] versus 666 ± 594 AU). However, although this difference was significant ($P = 0.03$), it is unclear what it means, given that both mean values are well above the cutoff level of anti-CCP antibody positivity (36 times and

22 times the cutoff level, respectively). Currently, we are investigating whether these differences in the rate of joint destruction are due to a different composition of IgG subclasses, since these subclasses have different properties, such as the ability to activate complement (35).

It has been shown in mouse models of arthritis that citrullination occurs in the synovium. In spite of citrullination of several proteins under inflammatory conditions, these mice do not develop antibodies to citrullinated proteins (16). Moreover, in RA patients both with and without anticitrulline antibodies, citrullinated proteins have been detected in the synovium (36). Although it is conceivable that only citrullination of specific sequences of proteins leads to an immune response, these data suggest that the presence of citrullinated proteins in synovium by itself is not sufficient for persistent production of anticitrulline antibodies, but that additional factors are required.

The peptidylarginine deiminases type 4 (PADI4) gene locus on chromosome 1, which encodes an enzyme capable of citrullinating proteins, has been reported to be a susceptibility locus for RA. A haplotype of the PADI4 locus associated with increased stability of PADI4 transcripts was found more often in RA patients, and this haplotype was associated with the presence of antibodies to citrullinated proteins. Based on these findings, the authors speculated that a genetically determined, increased ability to citrullinate proteins is a risk factor for RA (37).

Moreover, given that during the conversion of arginine to citrulline the charged imino side-chain group is changed into an uncharged carbonyl group, citrullination is likely to affect the ability of peptides to bind to HLA molecules. In DRB1*0401 transgenic mice, citrullination of peptides not only increased peptide-MHC affinity, but also led to activation of CD4+ T cells (17). Since activation of T cells is important in B cell responses, we propose that the observed association between HLA class II genes and anti-CCP antibodies is based on an increased ability of citrulline-containing peptides to bind to certain HLA class II molecules, and that this increased binding ability promotes an antibody response against citrulline-containing antigens (17).

In summary, anti-CCP antibodies are associated with HLA class II RA susceptibility alleles, and the presence of these two factors is indicative of a severe disease course.

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6

EFFICACY OF METHOTREXATE TREATMENT IN PATIENTS WITH PROBABLE RHEUMATOID ARTHRITIS. A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Objective

To determine whether patients with undifferentiated arthritis (UA; inflammatory, nontraumatic arthritis that cannot be diagnosed using current classification criteria) benefit from treatment with methotrexate (MTX).

Methods

The PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study was a double-blind, placebo-controlled, randomized, multicenter trial involving 110 patients with UA who fulfilled the American College of Rheumatology (ACR) 1958 criteria for probable RA. Treatment started with MTX (15 mg/week) or placebo tablets, and every 3 months the dosage was increased if the Disease Activity Score was >2.4 . After 12 months, the study medication was tapered and discontinued. Patients were followed up for 30 months. When a patient fulfilled the ACR criteria for RA (primary end point), the study medication was changed to MTX. Joint damage was scored on radiographs of the hands and feet.

Results

In 22 of the 55 patients (40%) in the MTX group, UA progressed to RA compared with 29 of 55 patients (53%) in the placebo group. However, in the MTX group, patients fulfilled the ACR criteria for RA at a later time point than in the placebo group ($P = 0.04$), and fewer patients showed radiographic progression over 18 months ($P = 0.046$).

Conclusion

This study provides evidence for the efficacy of MTX treatment in postponing the diagnosis of RA, as defined by the ACR 1987 criteria, and retarding radiographic joint damage in UA patients.

INTRODUCTION

For a number of autoimmune diseases, such as diabetes mellitus, it has been suggested that a critical period exists during which intervention may reverse the disease process (1). For rheumatoid arthritis (RA), such a window of opportunity may also exist, because laboratory abnormalities, such as antibodies against cyclic citrullinated peptide (anti-CCP), can occur years before disease onset (2). In previous studies of patients with undifferentiated arthritis (UA), defined as an inflammatory arthritis in which no definitive diagnosis can be made (3), it was observed that the presence of anti-CCP, with an odds ratio of 38, is an important predictor of the development of RA (4). Of all the patients who present with UA, depending on the study population, 6-55% develop RA within 1 year (5).

Current treatment of UA patients mainly consists of nonsteroidal antiinflammatory drugs (NSAIDs), and treatment with disease-modifying antirheumatic drugs (DMARDs) is not initiated until the disease has progressed to RA (3). Once patients fulfill the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for RA (6), early initiation of DMARD treatment results in less disease activity, reduction of radiographic joint damage, and maintenance of function, as compared with delayed treatment (7-9). Consequently, it is hypothesized that DMARD treatment that is started as early as possible in UA patients may alter disease progression and may prevent the development of RA.

Therefore, we designed a double-blind, placebo-controlled, randomized clinical trial to compare 2 treatment strategies. The immediate treatment strategy consisted of methotrexate (MTX) for a course of 1 year followed by tapering the amount of treatment if UA had not evolved into RA (as defined by fulfillment of the ACR classification criteria). The control group received conventional treatment with NSAIDs, and MTX therapy was initiated only if the patients fulfilled the ACR criteria for RA (the primary end point). The primary outcomes of the PRObable RA: Methotrexate versus Placebo Treatment (PROMPT) study were diagnosis at the end of the study and progression of radiographic joint damage.

PATIENTS AND METHODS

Study setting and design

The PROMPT study was a prospective double-blind, randomized, placebo-controlled, multicenter trial involving 110 patients. Randomization was performed by the pharmacist. The study was conducted between March 2001 and January 2006 in 4 hospitals in Leiden, The Hague, and Delft, The Netherlands. The study was approved by the medical ethics committee of the participating hospitals. Patients started with 6 tablets, each containing either 2.5 mg MTX or placebo. Every 3 months, the medication was increased by 2 tablets if the Disease Activity Score (DAS) was >2.4 (10), to a maximum of 12 tablets or 30 mg of MTX (Figure 1). The DAS was calculated using a tender joint count (Ritchie Articular Index; RAI), the erythrocyte sedimentation

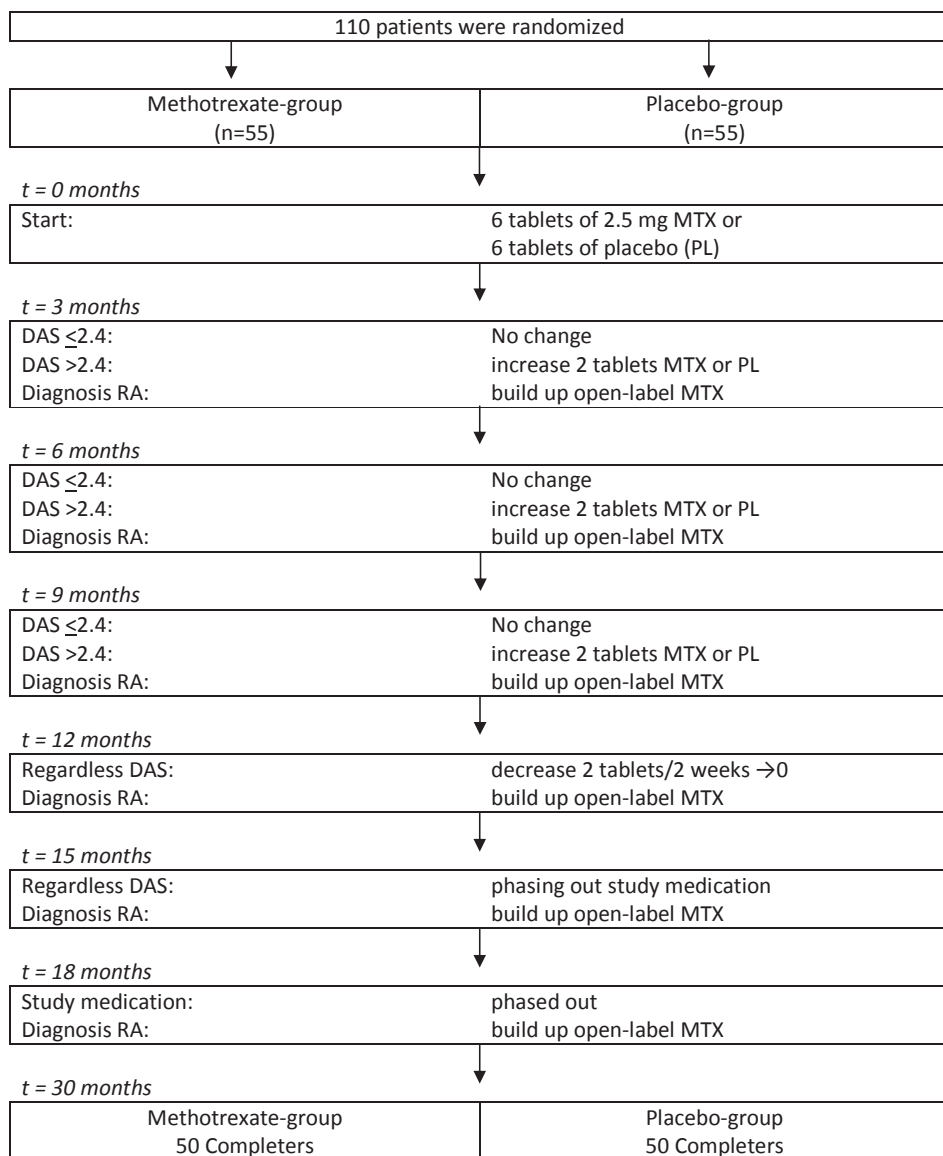


Figure 1. Overview of treatment strategy. Patients received open-label methotrexate (MTX) if rheumatoid arthritis (RA; n=49) or psoriatic arthritis with erosive disease (n=2) was diagnosed. PL = placebo; DAS = Disease Activity Score.

rate (ESR), and a visual analog scale (VAS) for general health (gh) status, according to the following formula:

$$\text{DAS} = 0.54 \times \sqrt{(\text{RAI})} + 0.065 \times (\text{swollen joint count}) + 0.33 \times \ln(\text{ESR}) + 0.0072 \times (\text{VAS gh})$$

Trained research nurses calculated the tender and swollen joint scores. To minimize the side effects of MTX, all patients, including those in the placebo group, received folic acid daily (1 mg) or weekly (5 mg). In both groups, patients were allowed to take NSAIDs, but no other immunosuppressive therapies, including steroids, were allowed. In cases of side effects that might be related to MTX, the treatment was adjusted.

If a patient reached the primary end point during followup, defined as fulfilling the ACR 1987 RA classification criteria, it was considered unethical to continue with study medication (possibly placebo), and the treatment was initially continued by building up open-label MTX to the same amount as in the study medication scheme. After 12 months, the study medication was decreased by 2 tablets every 4 weeks until it reached a level of 0 in the patients who did not reach the primary end point. At study inclusion and at 3, 6, 9, 12, and 18 months thereafter, a tender and swollen joint count, a Health Assessment Questionnaire, and a VAS for general health were obtained (11,12). Every 6 months, radiographs of hands and feet were obtained. At 30 months, the diagnosis was recorded.

Participants

Eligible patients attended the rheumatology outpatient clinic of the participating hospitals, had symptoms of arthritis that did not exceed 2 years in duration, were 18 years of age or older, and were diagnosed as having UA (i.e., did not fulfill classification criteria for any rheumatologic disorder). Given the lack of criteria for UA, patients had to fulfill the ACR 1958 criteria for probable RA (13). One patient with psoriasis was also included because the small joints of the hands and feet were involved. Exclusion criteria were RA (according to the ACR 1987 criteria), impaired kidney or liver function, alcoholism, bone marrow insufficiency, pregnancy or the desire to become pregnant within 21 months from inclusion in the study, and DMARD use in the past. All patients provided written informed consent.

Outcome

The diagnosis at the end of the study and the radiographic progression were prespecified primary outcomes. After 30 months, a diagnosis of RA, UA, remission, or other was recorded. Remission was defined as no clinical symptoms of arthritis according to the patient's rheumatologists and no DMARD use in the preceding year.

Radiographic damage was graded by 2 experienced readers (JvA and HvD) using the Sharp/van der Heijde scoring method (SHS), with the radiographs in chronological order and patient identity masked (14,15). The interobserver intraclass correlation coefficient (ICC) was 0.898. The intraobserver ICCs for both readers were 0.990 and 0.993, as measured in 20 patients. The smallest detectable change (SDC) was 3.02 (16). Prespecified secondary outcomes were changes in disease activity represented by the ESR and the DAS.

For a post hoc analysis of the outcomes according to anti-CCP status, the presence of anti-CCP was measured at the end of the study in baseline serum samples from all patients, before decoding the treatment arms.

Statistical analysis

Using historical data from the Leiden Early Arthritis Clinic (EAC), 40% of the patients with UA were expected to develop RA within 1 year (4). It was estimated that immediate treatment with MTX would result in <20% of the patients with UA developing RA. A sample size of 46 patients per treatment group was required in order to attain a power of 80% to detect a significant difference between groups with a P value of 0.05. To allow for dropouts, 110 patients were included in the study.

Demographic and baseline characteristics, changes in the DAS and ESR, and radiographic progression in the 2 treatment groups were compared using the chi-square test, Student's 2-tailed t-test, or the Mann-Whitney U test. Because MTX reduces radiographic joint damage in RA and the SHS method does not allow for healing, radiographic progression was tested 1-sided (15,17). Differences in the development of

Table 1. Demographic and clinical characteristics at baseline of members of the PROMPT study and of the UA patients in the Leiden EAC study*

	MTX group n=55	Placebo group n=55	EAC group n=330
Age, years	51 (42-60)	51 (42-56)	48 (36-61)
Female, no. (%)	35 (64)	38 (69)	177 (54)†
Duration of symptoms at first visit, days	312 (195-507)	263 (169-432)	92 (31-186) †
Duration of morning stiffness, minutes	30 (10-60)	30 (10-60)	30 (0-60)
No. of swollen joints	3 (2-5)	2 (2-4)	2 (1-4) †
3-variable DAS	2.7 (2.1-3.1)	2.4 (2.0-3.0)	2.5 (2.0-3.1)
4-variable DAS	2.7 (2.2-2.7)	2.5 (2.0-3.0)	
RF positive, no. (%)	20 (36)	19 (35)	66 (21) †
Anti-CCP positive, no. (%)	12 (22)	15 (27)	55 (20)
ESR, mm/hour	12 (5-24)	11 (5-25)	22 (10-40) †
CRP, mg/liter	5 (3-11)	5 (3-9)	11 (5-31) †
HAQ score	0.75 (0.38-1.13)	0.75 (0.25-1.13)	0.62 (0.25-1.12)
Patients with erosive disease, no. (%)	2 (4)	3 (6)	37 (16) †
Sharp/van der Heijde score	0.5 (0-2.5)	1 (0-3.0)	0 (0-1.0) †

* Except where indicated otherwise, values are the median (interquartile range). PROMPT = PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment; UA = undifferentiated arthritis; EAC = Early Arthritis Clinic; MTX = methotrexate; DAS = Disease Activity Score; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide antibody; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire.

†P ≤ 0.05 versus the PROMPT group.

RA during the study were determined using a Kaplan-Meier curve with a log rank test. The Cox proportional hazards model yielded the hazard ratios and 95% confidence intervals. P values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of the study patients

The demographic and clinical characteristics of the patients at baseline are shown in Table 1. To allow for assessment of the external validity of this trial, the baseline characteristics of the total group of patients in the PROMPT study were compared with a control group of UA patients who were included in the Leiden EAC study between 1993 and 1999 (3). In the PROMPT study group, the duration of symptoms was longer and the proportion of patients who were rheumatoid factor (RF)-positive was higher than in the EAC group. The ESR and C-reactive protein (CRP) levels were lower in the PROMPT group than in the EAC group.

Diagnosis at the end of the study

Figure 1 shows the randomization and treatment strategy. After 30 months, in 22 of 55 of the patients in the MTX group (40%) versus 29 of 55 in the placebo group (53%) UA had eventually progressed to RA. However, in the placebo group, all patients whose disease had progressed to RA fulfilled the ACR criteria within 1 year, versus only one-half of the RA patients in the MTX group ($P = 0.04$) (Figure 2A). The other half of the RA patients in the MTX group reached the diagnosis during or after tapering of the study medication. After 30 months, a similar number of patients achieved remission in both treatment groups: 15 in the MTX group and 13 in the placebo group (Table 2).

Table 2. Diagnosis at 30 months, by subgroup*

Group (n)	RA	UA	UA in remission	Other	Lost to follow up
Total					
MTX (55)	22	10	15	3 (2 osteoarthritis, 1 autoimmune hepatitis)	5
Placebo (55)	29	4	13	4 (3 osteoarthritis, 1 diabetic arthropathy)	5
Anti-CCP-positive					
MTX (12)	8	2	2	0	0
Placebo (15)	14	0	1	0	0
Anti-CCP-negative					
MTX (43)	14	8	13	3 (2 osteoarthritis, 1 autoimmune hepatitis)	5
Placebo (40)	15	4	12	4 (3 osteoarthritis, 1 diabetic arthropathy)	5

* RA = rheumatoid arthritis; UA = undifferentiated arthritis; MTX = methotrexate; anti-CCP = anti-cyclic citrullinated peptide antibody

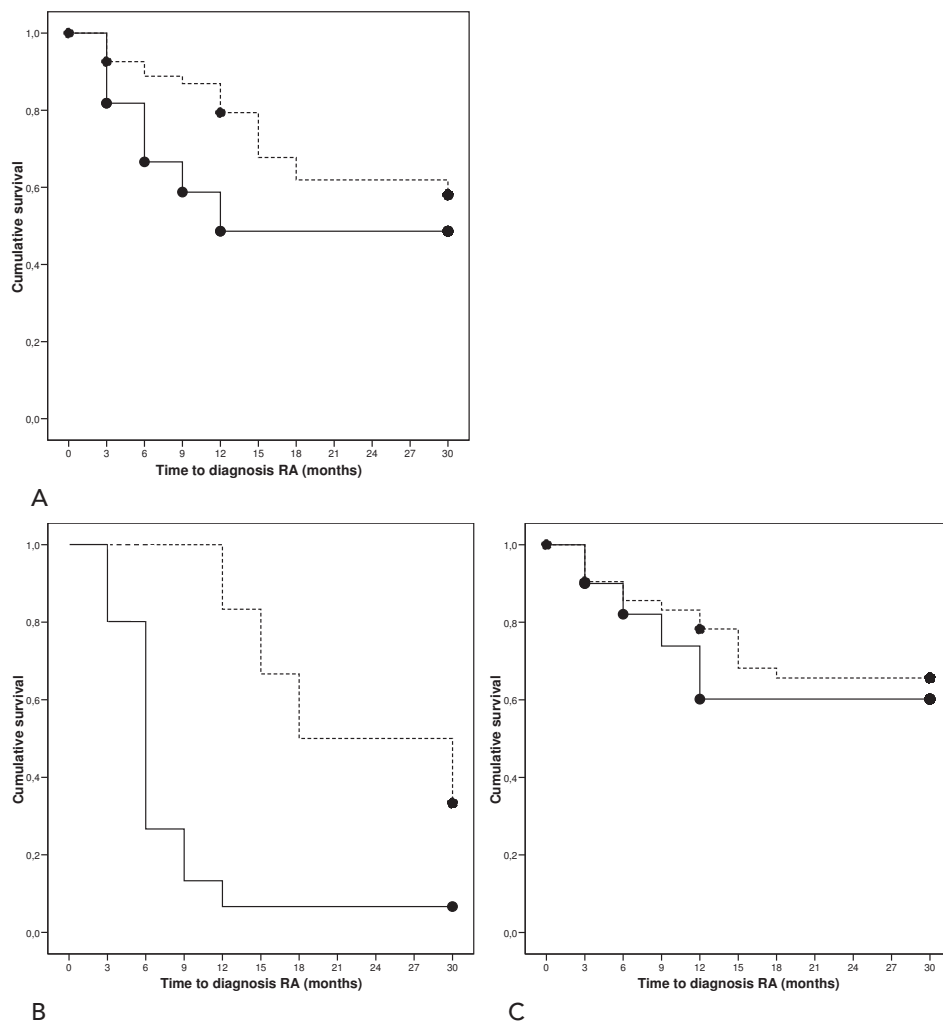


Figure 2. Kaplan-Meier survival analysis for the diagnosis of rheumatoid arthritis (RA). The methotrexate (MTX) group is indicated by the broken line, the placebo group is indicated by the solid line, and drop-outs are indicated by circles. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) indicate the risk of developing RA during the study in the placebo group versus the MTX group. A, Total group (n=110) (HR 1.7 [95% CI 0.99-3.01], $p=0.04$). B, Members of the subgroup positive for antibodies against cyclic citrullinated peptide (anti-CCP) (n=27) (HR 4.9 [95% CI 1.88-12.79], $p<0.001$). C, Members of the subgroup negative for anti-CCP (n=83) (HR 1.3 [95% CI 0.61-2.63], $p=0.51$).

Radiographic progression

The distribution of the radiographic progression over 18 months is shown in Figure 3A. In both groups, 51 patients had completed radiographic followup. After 18 months, the majority of patients had no radiographic progression at all: 73% in the placebo group and 88% in the MTX group. However, 6 patients in the MTX group versus 14 patients in the placebo group showed radiographic progression above the SDC ($P = 0.046$). Individual progression measured only in patients with erosions was significantly lower in the MTX group versus the placebo group ($P = 0.035$).

Subgroup analysis

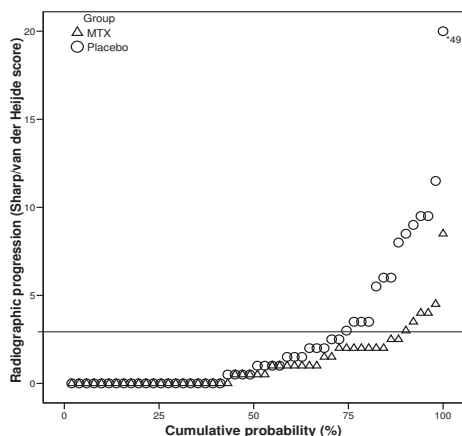
In the anti-CCP-positive subgroup treated with placebo, UA in 14 of the 15 patients (93%) progressed to RA and did so at an earlier time point than that in 8 of the 12 patients (67%) in the MTX group ($P < 0.001$) (Table 2 and Figure 2B). In contrast, in the anti-CCP-negative subgroup no differences in outcome at 30 months were seen (Figure 2C). Similar effects on radiographic progression were observed (Figures 3B and C). In the anti-CCP-negative group, no MTX effect could be detected, whereas in the anti-CCP-positive group, the progression was slowed down significantly ($P = 0.03$).

Subgroup analysis for the presence of RF showed considerable overlap with the presence of anti-CCP: 26 of 39 RF-positive patients (67%) were anti-CCP positive, whereas 60 of 61 RF-negative patients (98%) were anti-CCP negative. In the placebo group, UA in 13 of the 19 RF-positive patients (68%) progressed to RA and did so at an earlier time point than did 11 of the 20 RF-positive patients (55%) in the MTX group ($P = 0.036$). In contrast, in the RF-negative subgroup, no differences in outcome at 30 months were seen ($P = 0.403$). With regard to radiographic progression, RF-positive patients in the placebo group showed a trend for more radiographic progression than those in the MTX group (data not shown).

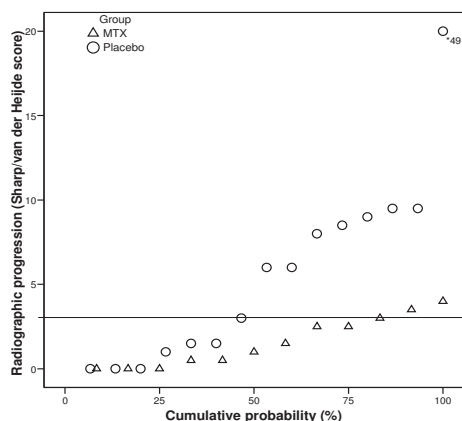
Subgroup analysis of the development of RA over time for autoantibody-positive (anti-CCP-positive or RF-positive) patients weakened the significance as compared with analysis of the anti-CCP-positive patients alone ($P = 0.024$). Of the 27 anti-CCP-positive patients, only 1 was RF negative. This patient received placebo and was diagnosed as having RA 6 months after study inclusion. The outcome of the 26 patients who were anti-CCP-positive and RF-positive is shown in Table 2.

Cross-sectional followup

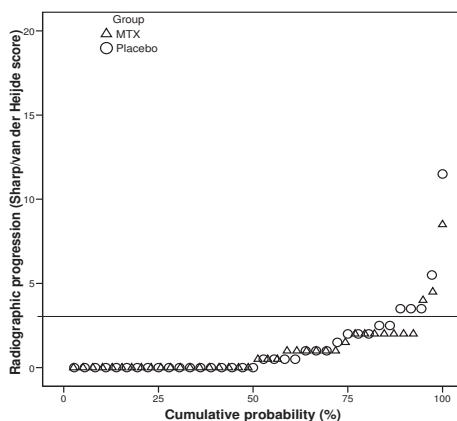
At the time of submission of this article, further followup data were not available for all patients due to different followup periods. However, we can report on 5 of 27 patients in the anti-CCP-positive subgroup (18%) who did not develop RA after 30 months (Table 2). The 3 patients who were in remission at 30 months (1 in the placebo group and 2 in the MTX group) were still in remission without DMARD treatment 4 years after study inclusion. However, the 2 patients with persistent UA (both from the MTX group) restarted MTX treatment after 30 months, 1 because of recurrent symptoms and, ultimately, arthritis shortly after withdrawal of study medication and 1 because of recurrent arthritis



A



B



C

Figure 3. Occurrence of radiographic progression. The presence or absence of radiographic progression (Sharp/van der Heijde score) at 18 months in 102 patients who completed radiographic followup was calculated. Each symbol represents 1 patient. Horizontal lines represent the smallest detectable difference (indicating radiographic progression). A, Total group (n = 102). B, Patients positive for antibodies against cyclic citrullinated peptide (anti-CCP) (n = 27). C, Patients negative for anti-CCP (n = 75). For methotrexate (MTX)-treated versus placebo-treated patients, $P = 0.15$ in the total group, $P = 0.03$ in the anti-CCP-positive patients, and $P = 0.46$ in anti-CCP-negative patients.

after a 6-month remission period. The patients continued to receive MTX at the time of submission of this article. As a result, although only 1 fulfilled the ACR criteria for RA, it can be argued that they both have RA, given the recurrent arthritis symptoms that require DMARDs. Taking these data into account, 10 of 12 anti-CCP-positive patients (83%) in the MTX group eventually developed RA and 2 of 12 patients (17%) achieved sustained remission, emphasizing that MTX postponed, but did not prevent, RA.

Disease activity

After 3 months, the mean decrease in DAS (from 2.7 to 2.3) and ESR (from 17 mm/hour to 13 mm/hour) values in the MTX group differed significantly from the mean change in DAS (from 2.5 to 2.5) and ESR (from 15 mm/hour to 16 mm/hour) in the placebo group ($P = 0.01$ and $P = 0.02$, respectively). However, subgroup analysis showed that in the anti-CCP-positive patients, the mean DAS decreased (from 2.8 to 1.9) in the MTX group and increased in the placebo group (from 2.6 to 3.1) ($P < 0.001$). However, in the anti-CCP-negative patients, the mean DAS decreased irrespective of treatment group (from 2.7 to 2.4 versus from 2.5 to 2.3 in the MTX and placebo groups, respectively; $P = 0.62$).

After 12 months, study medication was decreased regardless of the DAS. In the MTX group, 8 of 40 patients who still received study medication had a DAS >2.4 at 12 months and started phasing out the study medication; the UA in 2 of these 8 patients later progressed to RA. Of the 32 patients with a DAS ≤ 2.4 , the UA in 9 of them progressed to RA. Of the anti-CCP-positive patients in the MTX group, only 1 of the 10 who still received study medication at 12 months had a DAS >2.4 and later developed RA. Of the 9 patients with a DAS ≤ 2.4 , 5 developed RA, 2 had UA without fulfilling the ACR criteria for RA at 30 months, and 2 went into remission.

Toxicity

Adverse events were recorded during the first 18 months, the intervention period of the study. Of the patients who were taking study medication, 26 of 55 patients (47%) in the MTX group and 18 of 55 patients (33%) in the placebo group experienced ≥ 1 (serious) adverse event ($P = 0.173$). While taking the study medication, a total of 44 adverse events and 5 serious adverse events occurred in the MTX group versus a total of 25 adverse events and 4 serious adverse events in the placebo group (Table 3).

When patients fulfilled the ACR 1987 RA classification criteria during followup, they were switched to open-label MTX. If MTX produced undesirable adverse events or was ineffective, other DMARDs were prescribed. The 20 patients who developed RA in the former MTX group in the first 18 months were subsequently treated with MTX (19 patients), sulfasalazine (1 patient), hydroxychloroquine (3 patients), and/or leflunomide (1 patient). Adverse events (12 adverse events and 3 serious adverse events) were reported in 7 of 20 patients while they were treated with these DMARDs. In the former placebo group, the 29 patients who developed RA in the first 18 months were treated with MTX (29 patients), sulfasalazine (2 patients), hydroxychloroquine (5 patients), leflunomide (1 patient), infliximab (2 patients), etanercept (1 patient), and/or adalimumab (2 patients). Adverse events (39 adverse events and 3 serious adverse events) were reported in 18 of 29 patients while they were treated with these DMARDs.

Table 3. Adverse events and serious adverse events during the use of the study medication and during the use of DMARDs after RA diagnosis, by treatment group*

	During use of study medication		During use of DMARDs after RA diagnosis	
	MTX	Placebo	Former MTX	Former Placebo
All adverse events				
Gastrointestinal	11	6	1	12
Dermal / mucosal	9	7	2	5
Neurologic	3	5	5	4
Cardiologic	3	-	-	2
Pulmonary	3	1	3	1
Hematologic	1	1	-	-
Ophthalmologic	3	-	1	2
Elevated serum liver enzyme levels	6	1	-	4
Other				
Tiredness	1	1	-	2
Giant cell tumor	1	-	-	-
Rhinitis	1	-	-	-
Not feeling well	2	-	-	1
Fracture	-	1	-	-
Hair loss	-	1	-	3
Synovectomy	-	1	-	1
Arthroplastic surgery	-	-	-	1
Weight gain and oedema	-	-	-	1
Total	44	25	12	39
Serious adverse events				
Necessitating discontinuation of medication				
Gastrointestinal	1	1	NA	NA
Erythema annulare centrifugum	1	-	NA	NA
General unwellness	-	1	NA	NA
Dyspnea, insomnia, weight gain	-	1	NA	NA
Necessitating hospital admission				
Pancreatitis	1	-	-	-
Knee replacement surgery	1	-	-	-
Erosive arthritis	1	-	2	3
Meningitis	-	1	-	-
Venous thrombosis	-	-	1	-
Total	5	4	3	3

* Values are the number of events. DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; MTX = methotrexate; NA = not available.

DISCUSSION

This study indicates that MTX treatment of patients with UA can postpone progression to RA, as defined by fulfillment of the ACR 1987 criteria, and can retard radiographic joint damage. However, the results do not suggest that a 1-year course of MTX treatment can prevent the development of RA from UA. Although these findings must be confirmed in future trials, the PROMPT study provided the first evidence of the efficacy of MTX treatment in UA patients.

Data from the current study showed that initiation of MTX treatment in UA patients in the stage before they fulfilled the ACR criteria for RA resulted in postponement of the diagnosis of RA. During the first year, the incidence of RA was lower in the MTX group than in the placebo group, but after 12 months, the opposite was seen. Furthermore, the results suggest that MTX did not induce more remission, but prolonged the period of persistent UA. Interestingly, the benefit of this effect seemed to be the retardation of radiographic progression. The majority (62%) of the 29 RA patients in the placebo group had already fulfilled the ACR criteria and started taking open-label MTX within 6 months. Nevertheless, the results still show a more favorable outcome in the group that immediately received MTX after study inclusion.

This is the first double-blind, randomized, placebo-controlled trial that addresses early DMARD treatment in patients with UA before they fulfill the ACR criteria for established RA. Although these criteria are currently under debate for use in clinical practice, for research purposes they are regarded as the standard for objectively describing the RA phenotype and have been widely used as inclusion criteria for trials. Moreover, results from many randomized controlled trials have shown that in patients who fulfill the ACR criteria for RA, DMARDs improve the outcome (18,19). Thus, for ethical reasons, a placebo-controlled trial in UA patients could not be extended once the patients fulfilled the criteria. Therefore, the primary outcome of the study, the diagnosis of RA as defined by fulfillment of the ACR 1987 classification criteria, seems a reasonable end point.

Patients with UA included in this study are not completely representative of the average UA patient. This was illustrated by comparing the data from the patients in the PROMPT study with controls from the Leiden EAC. Longer symptom duration and lower ESR and CRP levels were seen in the patients in the PROMPT study. This indicates that the UA patients were no longer in the earliest and most active disease state by the time they were included in the current study. The best explanation for this observation seems to be that physicians at the 4 centers were reluctant to expose patients with UA to a 1-year course of MTX treatment, given the high spontaneous remission rate and the risk of unnecessary toxicity (3,20). Also, the use of the ACR 1958 criteria for RA as inclusion criteria could have resulted in a selection of UA patients. Despite the fact that UA patients already had longer disease duration, a 1-year course of MTX treatment was still able to provide beneficial effects on disease and joint damage progression.

The existence of a therapeutic window of opportunity in UA patients, defined as a period of time in which the disease process can be reversed, might not be demonstrated in this study. However, it is possible that with a different design and a different medication scheme, such a therapeutic window can be addressed. First,

the incidence of RA increased during tapering of the study medication in the MTX group. This raises the question of what would have happened if MTX had not been tapered. Second, MTX as monotherapy could not have been sufficient, since in the MTX group, half of the RA patients still developed RA while taking study medication, and 6 patients still showed progression of joint damage. Trials in RA patients have shown that treatment with combination therapy and/or biologic agents is more effective in preventing radiographic joint damage (18,19,21). Finally, dosages of study medication were altered according to the DAS because rheumatologists are generally satisfied and do not intensify therapy when the DAS is <2.4 in RA patients (22,23). It is possible that treatment in UA patients should aim at remission or a lower cutoff value of the DAS.

In this study, 53% of the patients in the placebo group developed RA and 24% achieved spontaneous remission, demonstrating that MTX treatment is overtreatment in a considerable proportion of UA patients. Because it is undesirable to start a potentially harmful drug in UA patients who will remit spontaneously, there is a need to identify those UA patients who will most likely develop RA and who will benefit the most from DMARD treatment. In previous studies and in a recently published prediction model that calculates the UA patients' risk of developing RA based on clinical variables, the presence of anti-CCP emerged as one of the strongest predictors of RA (2,4,24). Moreover, applying the model to our study, theoretically initiating treatment in patients with a prediction score ≥ 8 and withholding treatment in patients with a prediction score ≤ 6 , only 6% of the patients would have been inaccurately withheld from treatment, and no patients would have been inaccurately treated.

In the current study, subgroup analysis revealed that the beneficial outcomes were most pronounced in patients with anti-CCP. In striking contrast, in the anti-CCP-negative subgroup, the effect of MTX on the development of RA, the radiographic progression, and even on the signs and symptoms, was not demonstrable. The same observations were made for patients who were or were not RF-positive, although this could reflect the overlap with anti-CCP. Although the current groups are small, this post hoc analysis suggests that only anti-CCP-positive UA patients, who have the highest risk of developing RA, benefit from early MTX treatment. It also supports the growing evidence that anti-CCP-positive and anti-CCP-negative UA are different disease entities that should be approached differently.

We conclude that treatment with MTX benefits patients with UA by reducing signs and symptoms, by postponing the progression to RA as defined by the ACR 1987 criteria, and by retarding radiographic joint damage. Furthermore, with the guidance of a prediction model and the antibody status, it seems feasible to identify a subset of UA patients who are most in need and who will benefit the most from initiation of MTX therapy, thereby avoiding unnecessary toxic treatment. Although these findings have to be confirmed, and the optimal duration and intensity of treatment still have to be determined, the PROMPT study provides evidence for the efficacy of MTX treatment in UA patients.

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DISEASE ACTIVITY, JOINT DAMAGE AND FUNCTIONAL DISABILITY AND THE EFFECT OF METHOTREXATE TREATMENT IN PATIENTS WITH UNDIFFERENTIATED ARTHRITIS WITH OR WITHOUT ANTI-CITRULLINATED PROTEIN ANTIBODIES

A rationale for early treatment of
undifferentiated arthritis

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ABSTRACT

Objective

To investigate the relationships between disease activity, joint damage and functional disability, and the effect of methotrexate (MTX) therapy, in patients with undifferentiated arthritis (UA) with or without anti-citrullinated protein antibodies (ACPA).

Methods

In the PROMPT study, 110 UA patients were randomized to one year MTX or placebo therapy. The disease activity score (DAS), health assessment questionnaire (HAQ) and patient-reported symptoms on a VAS were measured 3-monthly. Joint damage was scored on 6-monthly radiographs using the Sharp-van der Heijde score (SHS). The longitudinal relationships between DAS-HAQ, DAS-SHS and SHS-HAQ, and the effect of MTX treatment on all outcomes were analyzed via generalized estimating equations (GEE) regression. Differential associations for ACPA-positive and ACPA-negative patients were explored via interaction terms.

Results

A change in DAS was related to a change in HAQ ($\beta=0.15$, 95%CI 0.08-0.21) and a change in SHS ($\beta=0.24$, 95%CI 0.03-0.44), for both ACPA-positive and ACPA-negative UA patients. The still low SHS was not associated with the HAQ. Compared with placebo, MTX treatment was associated with lower DAS ($\beta=-1.0$, 95%CI -1.4;-0.6), less symptoms, and lower SHS ($\beta=-5.1$, 95%CI -7.9;-2.3) in ACPA-positive, but not in ACPA-negative patients. HAQ decreased significantly only in ACPA-positive patients ($\beta=-0.03$, 95%CI -0.05;-0.01).

Conclusion

Similar to RA, in UA, disease activity is related to functional disability and joint damage, irrespective of ACPA, providing a rationale for early intensive treatment of UA. MTX therapy improves symptoms, function and damage progression only in ACPA-positive UA, indicating that effective therapy for ACPA-negative UA needs yet to be found.

INTRODUCTION

Traditionally, for rheumatoid arthritis (RA) a relationship between disease activity and joint damage has been established as well as an association of both of them with functional disability (1-5). This forms an important part of the rationale behind current RA treatment: aiming at minimal disease activity and inhibition of radiographic progression in order to maintain functional ability. As a result, early start of disease modifying anti-rheumatic drugs (DMARDs), combination therapies, biologicals, and tight control strategies, have significantly improved the outcome of RA (6-8).

It has been suggested to start treatment even earlier, in patients with undifferentiated arthritis (UA), aiming at a 'window of opportunity' for remission induction or even cure (9). This is in part based on the observation that in 40% of UA patients the disease progresses to RA within three years and joint damage and functional impairment can already be present (10-12). If relationships between inflammation, joint damage and function can be shown to exist in UA as in RA, this would give more insight into the entity of undifferentiated arthritis and provide an additional argument for early intensive treatment in UA.

In the PROMPT study, we recently showed that one year methotrexate (MTX) therapy in UA delayed, but not prevented, the diagnosis of RA and reduced radiographic progression compared with a delayed start of DMARD treatment, in anti-citrullinated protein antibody (ACPA)-positive but not in ACPA-negative patients (13). This observation fits with the growing evidence that ACPA-positive and ACPA-negative arthritis represent two different disease entities, which might need a different therapeutic approach (14-16). However, the use of fulfilling the 1987 ACR criteria for RA as primary outcome in the PROMPT study has been questioned (17). If the effect of MTX treatment on more validated outcome measures as disease activity, functional ability and patient-reported symptoms would also be different for ACPA-positive and ACPA-negative patients, this would strengthen our previous findings and have implications for future trials investigating treatment strategies for UA.

Therefore, in the current paper, we set out to investigate i) whether in UA a relationship exists between disease activity and functional disability, disease activity and radiographic damage, and between joint damage and disability, ii) whether MTX treatment in UA is beneficial with regard to disease activity, functional ability and patient-reported symptoms, and iii) whether the results for i) and ii) are different for ACPA-positive or ACPA-negative UA patients.

PATIENTS AND METHODS

Patient population

The study group comprised of 110 patients with UA (DMARD-naive, symptoms <2 years), randomized in the PROMPT study to one year MTX or placebo therapy (13). All patients fulfilled the 1958 ACR criteria for probable RA, and did not fulfill any other rheumatologic classification criteria (18). Treatment started with 15 mg MTX or

6 placebo tablets and every three months the dose was increased by 5 mg (2 tablets) to a maximum of 30 mg (12 tablets) in order to achieve a disease activity score (DAS) ≤ 2.4 (19). If during the trial a patient progressed to fulfilling the 1987 ACR criteria for RA, medication was switched to open-label MTX (17). Thus, the study was a delayed-design trial, and the real difference between MTX and placebo is underestimated. Further details on the study and results on the primary outcomes diagnosis and radiographic progression have been published elsewhere (13).

Outcomes

At study inclusion and at 3, 6, 9 and 12 months the DAS was scored, functional ability was measured via the health assessment questionnaire (HAQ) and patients reported symptoms of disease activity, pain, morning stiffness and fatigue on a 100 mm visual analog scale (VAS) (19,20). The DAS consisted of a 44 swollen joint count (SJC), the Ritchie articular index (RAI), the erythrocyte sedimentation rate (ESR) and a VAS for general health status. C-reactive protein (CRP) was also measured. Radiographs of hands and feet obtained at baseline, 6, 12 and 18 months were available in 102 patients (93%). Radiographic damage was scored according to the Sharp-van der Heijde score (SHS) in chronological order by two independent readers blinded for patient identity and treatment allocation (21). The interobserver correlation coefficient for the change scores was 0.90 and the intraobserver coefficients were both 0.99. Radiographic progression was defined as an increase in SHS >3 , according to the smallest detectable change (SDC) which was 3.02 in this study (22). The presence of IgM rheumatoid factor (RF) and ACPA was determined in baseline sera with commercial kits (Euro-Diagnostica, Arnhem, The Netherlands). ACPA levels >25 IU/ml and RF levels >5 IU/ml were considered positive.

Statistical analysis

Generalized estimating equations (GEE)

We explored the longitudinal relationships between disease activity, radiographic damage and functional disability across 12 months time using longitudinal regression analysis with generalized estimating equations (GEE) (23). The advantage of GEE above ordinary regression techniques is that it takes into account the whole pattern of repeated measurements over time, corrects for the fact that these are correlated within individual patients, and is robust against violation of normality. To correct for the within-patient correlation, we chose an 'unstructured working correlation matrix', which would impose the least restriction on the models and best fitted our data. The Identity link and the linear model were applied. SPSS version 16.0 software (SPSS, Chicago, IL) was used.

Relationships DAS-HAQ, DAS-SHS, SHS-HAQ

To investigate the relations between DAS-HAQ, DAS-SHS and SHS-HAQ, three GEE models were built following a multistep approach. For each model, in the first step the outcome variable (3-monthly HAQ scores or 6-monthly SHS) was modeled with

the covariate time (in months) to describe the course of the variable in time. In the second step the explanatory variable of interest (DAS or SHS) was added to the model. In the third step potential baseline predictors were introduced to investigate their contributory or confounding effect on the relationship of interest. Finally, we investigated whether the identified associations were different for ACPA-positive or ACPA-negative patients by introducing interaction terms.

Autoregressive GEE

Because we were particularly interested in the longitudinal relationships (meaning for example, in patients whose mean DAS increases/decreases, the HAQ simultaneously increases/decreases) rather than the cross-sectional relationships (patients with a high DAS have on average a high HAQ), we used first order autoregression, correcting each value of the outcome variable for the value one time point earlier, which can be interpreted as modeling change (24). For the relation DAS-HAQ for example, we related the consecutive 3-months mean interval DAS $(DAS_{t-1} + DAS_t)/2$ with the HAQ at the end of each time interval, corrected for the previous HAQ. This resulted in the following regression equation: $HAQ_t = \text{constant} + \beta_1 \text{time} + \beta_2 DAS_{\text{mean interval}} + \beta_3 HAQ_{t-1} + [\text{corr}] + \text{error}$, in which the β 's are the regression coefficients and [corr] the correction for the working correlation structure.

Effect of MTX treatment

The effect of MTX versus placebo treatment on the DAS, its separate components, the HAQ, patient-reported VAS scores and SHS during the one year treatment period, was investigated in two ways. Time-integrated means were calculated for the outcome variables as areas-under-the-curve divided by the total time. The time-integrated means were compared between MTX and placebo treatment via student t-test or Mann-Whitney test for the total group and stratified for ACPA status. Secondly, we used GEE analysis to be able to correct for the within-patient correlation and potential confounders. For each outcome the 3-monthly (for SHS 6-monthly) scores were modeled with time, adjusted for the baseline value. In a stepwise manner, the effect of treatment group, ACPA, potential modifying baseline variables and the interaction between ACPA and treatment was investigated. For example, the final regression equation for the outcome DAS was: $DAS_t = \text{constant} + \beta_1 \text{time} + \beta_2 DAS_{\text{baseline}} + \beta_3 \text{treatment} + \beta_4 ACPA + \beta_5 \text{treatment} * ACPA + \beta_6 \text{confounder} + [\text{corr}] + \text{error}$.

RESULTS

At baseline, all UA patients had active disease, but ACPA-positive patients had significantly higher ESR and CRP levels, were more often RF positive and already displayed more joint damage than ACPA-negative UA patients (table 1).

Relationships DAS-SHS-HAQ

A total number of 531 (419 mean interval) DAS scores, 526 HAQ scores and 423 (313 mean interval) SHS scores were available for the GEE analyses.

Table 1. Baseline characteristics of 110 UA patients included in the PROMPT study, stratified by ACPA status

Baseline characteristics	ACPA-positive (n=27)	ACPA-negative (n=83)	p-Value
Age, mean $\pm$ SD	50.8 (10.6)	51.6 (14.0)	0.788
% Females	17 (63%)	56 (68%)	0.667
Symptom duration, median (IQR) weeks	40 (29-67)	42 (25-68)	0.962
DAS, mean $\pm$ SD	2.72 (0.72)	2.59 (0.79)	0.442
RAI, median (IQR)	5.0 (2.0-9.0)	6.0 (3.0-10.0)	0.851
SJC, median (IQR)	2.0 (1.0-4.0)	3.0 (2.0-5.0)	0.042
CRP, median (IQR) mg/L	7 (4-16)	3 (2-9)	0.013
ESR, median (IQR) mm/hr	25 (7-32)	9 (4-21)	<0.001
HAQ, mean $\pm$ SD	0.77 (0.60)	0.79 (0.53)	0.884
VAS global health, mean $\pm$ SD mm	40 (24)	39 (23)	0.897
% RF positive	26 (96%)	13 (18%)	<0.001
SHS, median (IQR)	1.5 (0-4.0)	0 (0-2.0)	0.015
% Erosions $\geq$ 1	15 (56%)	11 (13%)	<0.001

ACPA = anti-citrullinated protein antibodies; SD = standard deviation; IQR = interquartile range; DAS = Disease Activity Score; RAI = Ritchie Articular Index; SJC = swollen joint count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; VAS = Visual Analogue Scale; RF = rheumatoid factor; SHS = Sharp/van der Heijde score.

DAS-HAQ

The GEE model for the relation DAS-HAQ showed that on average the HAQ decreased in time in the total patient group (table 2A, model 1). In addition, the mean interval DAS was significantly longitudinally related to the HAQ ($\beta=0.15$) (table 2A, model 2). This relationship was not modified by age, gender, ACPA status or treatment arm (table 2A, model 3). As the HAQ scores were corrected for the previous HAQ (first order autoregression), the results can be interpreted longitudinally: UA patients who have a change in mean interval DAS of 1 point, have a corresponding change in HAQ of 0.15 points, compared to the previous time interval. This relation was present in both ACPA-positive and ACPA-negative patients ($\beta=0.17$ and 0.14 , respectively) (table 2A, model 4), and the interaction term DAS*ACPA was not significant ($\beta=0.027$, 95%CI $-0.10;0.15$, $p=0.672$). Of the individual components of the DAS, the RAI and the SJC, but not the ESR were significantly longitudinally associated with the HAQ (data not shown).

DAS-SHS

The GEE model for the relation DAS-SHS showed that on average the SHS increased in time (table 2B, model 1). In addition, the mean interval DAS was significantly longitudinally related to the SHS ($\beta=0.24$), adjusted for the previous SHS (table 2B, model 2). This

Table 2. Building the GEE model for the longitudinal relationship between A. disease activity (DAS) and functional disability (HAQ) in UA patients, and B. between disease activity (DAS) and joint damage (SHS)

A	Model 1	Model 2	Model 3	Model 4
Time (months)	-0.01* (-0.02;-0.01)	0.004 (-0.01;0.01)	0.004 (-0.01;0.01)	0.004 (-0.01;0.01)
HAQ previous	-	0.93* (0.90;0.96)	0.93* (0.90;0.96)	0.93* (0.90;0.96)
DAS mean interval	-	0.15* (0.08;0.21)	0.15* (0.09;0.21)	-
In ACPA pos				0.17* (0.07;0.27)
In ACPA neg				0.14* (0.06;0.21)
B	Model 1	Model 2	Model 3	Model 4
Time (months)	0.10* (0.06;0.14)	-0.06* (-0.12;-0.01)	-0.05* (-0.10;0.004)	0.004 (-0.01;0.01)
SHS previous		1.34* (1.25;1.44)	1.32* (1.22;1.41)	0.93* (0.90;0.96)
DAS mean interval		0.24* (0.03;0.44)	0.28* (0.04;0.52)	-
In ACPA pos				0.61* (0.03;1.18)
In ACPA neg				0.17# (-0.004;0.34)

Values are the regression coefficients (95% confidence intervals) for the dependent variable functional disability as measured by the HAQ (A) or joint damage as measured by the SHS (B). Model 1 describes the course of the HAQ/SHS over time. Model 2 describes the longitudinal relationship between disease activity and functional disability/joint damage in time, with correction for the previous HAQ/SHS score (autoregression). In model 3 potential confounders were added to the model to investigate their influence on the relationship between disease activity and functional disability (gender, age, ACPA, treatment arm, all not significant) or joint damage (gender, baseline CRP*, ACPA, treatment arm*). In model 4 the interaction between DAS and ACPA was investigated to see whether the relation between disease activity and functional ability/damage was different for ACPA-positive or ACPA-negative patients. * $p < 0.05$, # $p = 0.056$. For abbreviations see table 1.

implies that a change in disease activity over time results in a corresponding change in radiographic damage. Although only 8 (11%) ACPA-negative patients compared to 12 (44%) ACPA-positive patients experienced damage progression above the SDC, the relation between DAS and SHS was found for both patient subsets. Although the magnitude of the relation appeared larger in ACPA-positive patients ($\beta = 0.61$) than in ACPA-negative patients ($\beta = 0.17$), the interaction term did not reach significance ($\beta = 0.44$, 95%CI-0.11;0.99, $p = 0.115$). Confirming our previous findings, MTX

treatment was a significant determinant of (less) joint damage over time ($\beta=-0.56$, 95%CI -1.0;-0.13, $p=0.012$), but it did not influence the relation between DAS and SHS (14). Trends for a longitudinal relation with joint damage were found for the RAI and the SJC, but not for the ESR (data not shown).

SHS-HAQ

The mean interval SHS was not longitudinally associated with the HAQ in the GEE analysis ($\beta=-0.02$, 95%CI -0.04;0.001), neither for ACPA-positive nor ACPA-negative UA patients separately (data not shown).

Effect of MTX on disease activity, patient-reported symptoms, function and damage

In figure 1 (A,B) the development of the mean DAS during 12 months of MTX or placebo treatment is depicted for the ACPA-positive and ACPA-negative patients. The ACPA-positive patients treated with MTX showed a large initial decrease in DAS compared to the patients treated with placebo. For ACPA-negative patients, the DAS decreased less and irrespective of the treatment group. However, 32/83 (39%) ACPA-negative patients achieved (spontaneous) remission during the study, and this might have influenced the results. After stratification, in the 41 (49%) of the ACPA-negative patients who continued to have UA or progressed to RA still no treatment

Table 3. Time-integrated means of disease activity parameters, functional disability and patient-reported symptoms over 12 months time, compared between MTX or placebo treatment stratified for ACPA status via Mann-Whitney or t-tests

Parameter (AUC)	ACPA-positive			ACPA-negative		
	MTX (n=12)	Placebo (n=15)	p-Value	MTX (n=43)	Placebo (n=40)	p-Value
DAS	2.0 (1.0)	2.7 (0.5)	0.044	2.4 (0.8)	2.3 (1.0)	0.889
Ritchie, median (IQR)	2 (1-6)	5 (4-8)	0.064	6 (3-9)	4 (2-11)	0.652
SJC, median (IQR)	1 (1-2)	2 (2-5)	0.048	2 (1-3)	2 (1-4)	0.531
ESR, median (IQR)	12 (8-22)	23 (10-27)	0.130	10 (5-16)	9 (4-19)	0.766
CRP, median (IQR)	3 (2-5)	12 (2-20)	0.121	5 (3-9)	4 (2-6)	0.201
HAQ, median (IQR)	0.4 (0.1-1.3)	0.6 (.01-1.0)	0.979	0.8 (0.2-1.1)	0.7 (0.3-1.2)	0.604
VAS disease activity	26 (18)	41 (17)	0.043	39 (16)	39 (18)	0.961
VAS pain	26 (19)	38 (16)	0.069	39 (15)	37 (18)	0.545
VAS morning stiffness	28 (18)	37 (20)	0.248	35 (19)	34 (22)	0.779
VAS general health	26 (20)	34 (20)	0.329	39 (17)	36 (16)	0.388
VAS fatigue	34 (26)	37 (26)	0.809	48 (24)	42 (23)	0.252
SHS, median (IQR)	0.5 (0.4-2.6)	3.0 (1.0-6.5)	0.050	0 (0-1.0)	0 (0-1.5)	0.867

Mean (standard deviations) are given except where indicated otherwise. AUC = area under the curve; MTX = methotrexate. For further abbreviations see table 1.

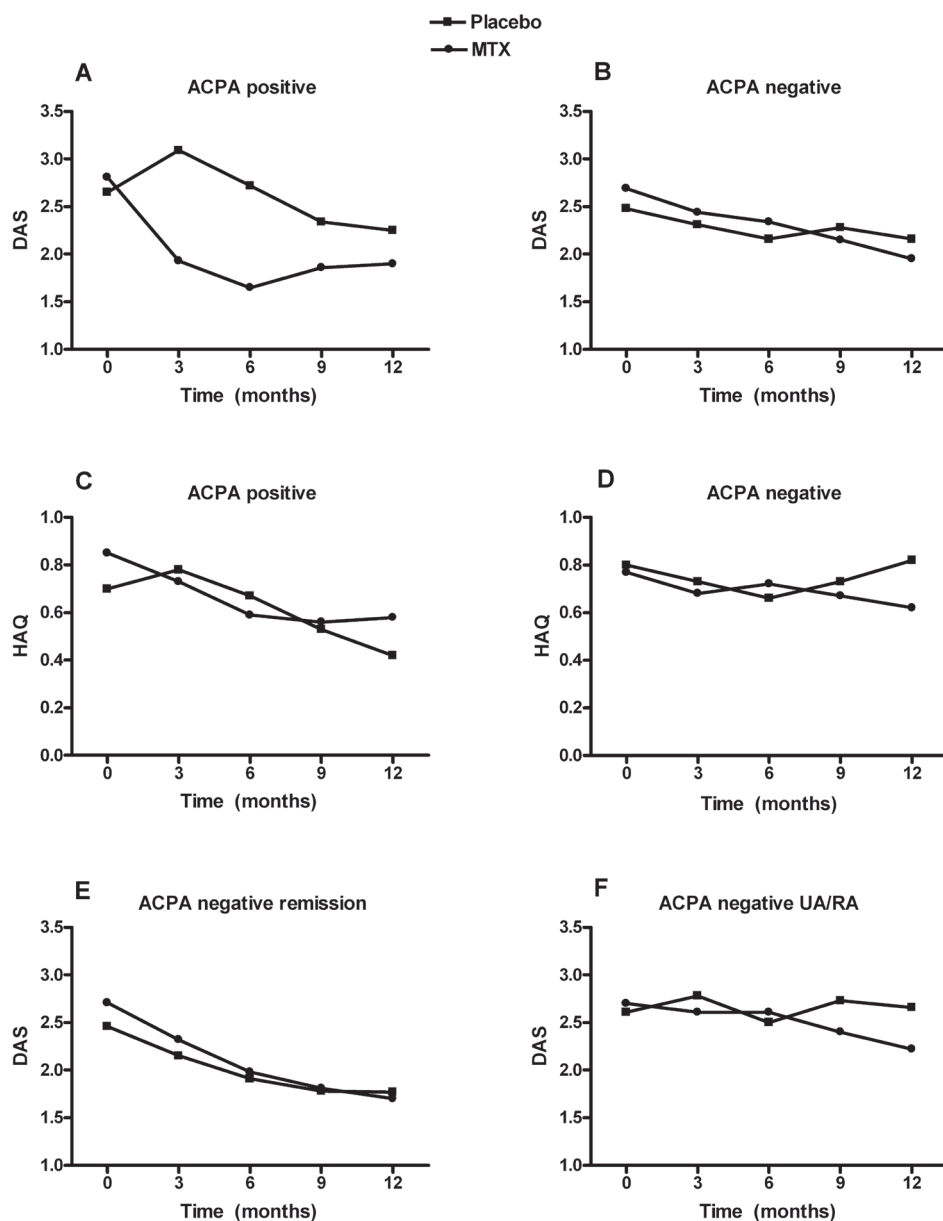


Figure 1. The development of the mean DAS (A,B) and HAQ (C,D) during 12 months of MTX or placebo treatment in the PROMPT study, stratified for ACPA-positive ($n=27$) and ACPA-negative ($n=83$) UA patients. E and F show the subanalysis of DAS in ACPA-negative patients who achieved remission or had persistent UA/RA. For abbreviations see table 1.

Table 4. The overall effect of MTX versus placebo treatment on DAS during 12 months and the differential effect in ACPA-positive and ACPA-negative UA patients, results from the GEE analysis

	Model 1	Model 2	Model 3	Model 4	Model 5
Time (months)	-0.05* (-0.06;-0.03)	-0.05* (-0.06;-0.03)	-0.05* (-0.06;-0.03)	-0.05* (-0.06;-0.03)	-0.05* (-0.07;-0.03)
Baseline DAS	0.85* (0.69;1.01)	0.88* (0.729;1.03)	0.85* (0.69;1.01)	0.71* (0.53;0.88)	0.71* (0.55;0.87)
ACPA pos	-	-	0.01 (-0.31;0.33)	0.002 (-0.26;0.27)	-
MTX therapy	-	-0.33* (-0.58;-0.09)	-	-0.27* (-0.49;-0.04)	-
In ACPA pos					-1.00* (-1.4;-0.6)
In ACPA neg					-0.04 (-0.3;0.2)

Values are the regression coefficients (95% confidence intervals) for the dependent variable disease activity as measured by the DAS. Model 1 describes the course of the DAS over time, corrected for the baseline DAS. Model 2 describes the effect of MTX treatment on DAS under the correction of time. Model 3 describes the effect of ACPA on DAS under correction of time. In model 4 known predictive factors (gender*, age*, baseline HAQ) were added to the model to investigate their influence on the effect of MTX therapy on DAS. In model 5 the interaction between MTX and ACPA was investigated to see whether the effect of MTX was different for ACPA-positive and ACPA-negative patients. *p<0.05. MTX= methotrexate; GEE = generalized estimating equations. For further abbreviations see table 1.

effect emerged and DAS scores remained elevated (figure 1E,F). This suggests that the ACPA-negative UA patients with the propensity to have persistent/progressive arthritis, seem to have less benefit from MTX therapy than ACPA-positive UA patients.

This was further investigated by comparing the 12 months time-integrated mean DAS, RAI, SJC, ESR, CRP, VAS scores, HAQ and SHS between the MTX and placebo group, separate for ACPA-positive and negative patients (table 3). For ACPA-negative patients the time-integrated means of all parameters were similar for both treatment groups. However, for ACPA-positive patients, the time-integrated means of DAS, SJC, VAS disease activity and SHS were significantly lower in the MTX group than in the placebo group and there were trends for lower RAI, ESR, CRP and VAS pain. This was confirmed in the subsequent GEE analysis. MTX treatment was significantly associated with a 0.27 point lower DAS over time (table 4, model 4), but the effect was different for ACPA-positive and ACPA-negative patients according to the interaction term treatment*ACPA (beta=-0.96, 95%CI -1.45;0.47, p<0.001). ACPA-positive patients treated with MTX had on average a 1.0 point lower DAS than patients treated with placebo, while for ACPA-negative patients there was virtually no treatment effect (table 4, model 5). Similar results were found for the effect of MTX treatment on the SJC, RAI, ESR, CRP, VAS scores for pain and disease activity and SHS in ACPA-positive

Table 5. The differential effects of MTX versus placebo treatment on disease activity parameters, patient-reported symptoms and functional disability during 12 months in ACPA-positive and negative UA patients

Effect of MTX on parameters	in ACPA-positives (n=27)			in ACPA-negatives (n=83)		
	Beta	95% CI	p-Value	Beta	95% CI	p-Value
DAS	-1.00	-1.4 ; -0.6	<0.001	-0.04	-0.3 ; 0.2	0.763
SJC	-1.88	-3.9 ; 0.1	0.065	-0.41	-1.2 ; 0.4	0.310
TJC	-4.15	-6.1 ; -2.2	<0.001	-0.68	-2.3 ; 1.0	0.421
ESR	-7.54	-11.5 ; -3.6	<0.001	-1.45	-4.1 ; 1.2	0.284
CRP	-4.97	-9.3 ; -0.6	0.025	0.58	-2.1 ; 3.3	0.670
VAS						
disease activity	-12.43	-22.5 ; -2.4	0.015	-2.17	-4.6 ; 9.0	0.532
pain	-10.82	-21.1 ; -0.5	0.039	3.15	-3.1 ; 9.4	0.322
morning stiffness	-8.80	-21.1 ; 3.5	0.160	2.59	-3.9 ; 9.1	0.435
general health	-6.34	-16.2 ; 3.5	0.207	2.44	-3.6 ; 8.5	0.430
fatigue	-3.08	-14.4 ; 8.2	0.593	2.36	-5.1 ; 9.8	0.533
HAQ	-0.05	-0.32 ; 0.21	0.702	-0.04	-0.16 ; 0.09	0.567
SHS	-5.11	-7.9 ; -2.3	<0.001	0.12	-0.7 ; 1.0	0.781

Each row represents a separate GEE analysis from which the effect of MTX therapy (beta) is reported. MTX = methotrexate; CI = confidence interval. For further abbreviations see table 1.

patients (table 5). In contrast, MTX did not significantly reduce the VAS for morning stiffness, general health or fatigue compared with placebo therapy.

For the outcome HAQ, there appeared to be no effect of MTX versus placebo therapy, neither in the total group, nor for ACPA-positive and negative patients separately (figure 1C,D; table 3 and 5). However, the interaction term ACPA*time revealed that the HAQ improved significantly over time in the ACPA-positive patients (beta=-0.03, 95%CI -0.05;-0.01, p=0.002), but not in the ACPA-negative patients (beta=-0.003, 95%CI -0.01;0.01, p=0.515). This might still reflect an effect of MTX treatment in ACPA-positive patients, since 14 out of 15 ACPA-positive patients in the placebo group switched to open-label MTX during the first 12 months of the study, as their UA progressed to RA.

DISCUSSION

We have demonstrated that in patients with undifferentiated arthritis (UA) disease activity is closely related to functional disability and radiographic joint damage, irrespective of the ACPA status, providing a rationale for early intensive treatment. In addition, we showed that MTX therapy improved disease activity, symptoms and function, but only in ACPA-positive UA patients, indicating that effective therapy for ACPA-negative UA needs yet to be found.

We showed that in UA, similar to in RA, changes in disease activity, measured by the 3-month mean interval DAS, were significantly related to changes in physical function, measured by the HAQ (1,2,5). Using autoregressive GEE, we found that the HAQ was predominantly determined by the previous HAQ, and further by changes in disease activity, with for every 1 point change in DAS a corresponding 0.15 point change in HAQ. This can be regarded as a clinically relevant effect, as the minimal important difference for the HAQ varies around 0.10 and 0.20 in clinical practice and clinical trials, respectively (25,26). Furthermore, the relation DAS-HAQ existed for both ACPA-positive and ACPA-negative UA patients in comparable strength. Not only the composite measure DAS, but also the separate parameters RAI and SJC were associated with the HAQ, which strengthens the results. These findings suggest that in UA, similar to in RA, keeping disease activity as low as possible will maintain functional ability.

Fluctuations in disease activity also precede changes in radiological progression in RA (24,27). Correspondingly, for UA, we found that for every 1 point increase in DAS radiographic damage increased with 0.3 SHS points. The effect was not large, probably reflecting the overall minimal joint damage (progression) in this population, but it was present in both ACPA-positive and ACPA-negative UA patients. Interestingly, the effect appeared more pronounced in ACPA-positive patients, similar to what has been reported for RF-positive RA patients (24). These results combined suggest that already in this early stage of arthritis it is important to rapidly lower disease activity to prevent damage progression. Furthermore, the resemblance to RA adds to the view that UA (ACPA-positive and negative) is likely to be an early stage of RA.

We were not able to find a relationship between joint damage and functional disability in UA. Due to the large proportion of patients without radiographic damage in our study population (80%), we might have lacked power to detect any association. On the other hand, our results fit with the observation that also in RA this relationship is more pronounced later in the disease course (1,5,28,29). As UA is an even earlier phase of arthritis, the amount of joint damage in UA might be too little to result in difficulties in daily physical functioning. Also, the HAQ might not be sensitive enough to pick up subtle changes in joint damage in UA, especially since the HAQ is strongly influenced by disease-specific factors such as pain, depression and comorbidity as well (30-32).

Previously we showed that early versus delayed MTX treatment in UA postponed, but not prevented, the progression to RA and reduced radiographic damage, but only in ACPA-positive patients (13). However, the use of the 1987 ACR criteria as primary outcome in that study has been questioned, since these were neither designed nor validated for that purpose. We now showed that MTX rapidly improved the DAS, SJC, RAI, ESR, CRP, and VAS scores for pain and disease activity, again only in ACPA-positive patients. Finding similar effects in multiple outcome measures, both physician- and patient-oriented, with two types of analyses (AUC and GEE), adds to the robustness of our results. Given the delayed-design of the PROMPT study, a considerable number of ACPA-positive patients switched from placebo to open-label MTX during the first

12 months. Therefore, the reported effects and differences between MTX and placebo are even underestimated and will probably be larger in reality.

We have shown that MTX therapy does not appear to have a positive effect in ACPA-negative UA, neither by postponing RA nor reducing signs and symptoms (13). One could argue that ACPA-negative patients, with lower disease activity at baseline, could improve less than ACPA-positive patients. This was indeed true regarding the ESR and CRP levels, but not for the DAS, RAI or VAS scores. As ACPA-negative UA is a heterogeneous patient population, including patients who will not progress to RA, or who will remit spontaneously, this might also have diluted any treatment effect. Therefore, we performed a subanalysis leaving out the ACPA-negative patients who achieved spontaneous remission, but for the remaining ACPA-negative UA patients who had persistent arthritis, still no treatment effect emerged. Not even a trend for improvement was observed. A type 2 error cannot be ruled out, but would not explain why significant effects were found in the smallest patient subset (n=27 ACPA-positives) and not in the largest population (n=83 ACPA-negatives). Therefore, in light of the growing evidence that ACPA-positive and ACPA-negative arthritis represent different disease entities, it is conceivable that ACPA-negative UA may need a different therapeutic approach than ACPA-positive UA (14-16,33).

In light of the recently published new 2010 ACR criteria for RA, this has even further implications, as these criteria aim to identify UA patients with a sufficient risk of persistence to be considered for DMARD therapy (34). However, when the disease entity RA is redefined by these new criteria, existing data on available therapies will have less relevance, as these come from trials in which a different patient population was included, namely patients fulfilling the 1987 ACR criteria for RA. Moreover, our observation that MTX appears ineffective in a subset of patients in an earlier phase of arthritis (58% of the PROMPT population fulfilled the new ACR criteria at baseline), indicates that it can not be assumed that existing therapeutic strategies in 'old criteria RA' will perform the same in patients fulfilling the new criteria for RA. Therefore, not only our findings, but also other strategies need to be (re)investigated and validated before clear treatment recommendations for UA can be given.

In summary, we have provided a rationale for starting early intensive treatment in UA since disease activity is closely related to functional disability and radiographic damage, irrespective of the ACPA status. MTX monotherapy improves symptoms, function and damage progression, but only in ACPA-positive patients, and it is not sufficient to prevent progression to RA. This implicates that for both ACPA-positive and negative UA better treatment strategies are needed.

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8

FIVE YEAR OUTCOMES OF PROBABLE RHEUMATOID ARTHRITIS TREATED WITH MTX OR PLACEBO DURING THE FIRST YEAR (THE PROMPT STUDY)

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ABSTRACT

Objective

To assess long-term disease outcome of undifferentiated arthritis (UA) after initial treatment with methotrexate (MTX) or placebo.

Methods

110 patients with UA were randomized to receive MTX (n=55) or placebo (n=55) for 1 year. After 5 years the outcomes for diagnosis (rheumatoid arthritis, 1987 criteria (RA (1987)), UA or UA in remission) and radiographic progression were compared between treatment arms and anti-citrullinated protein antibody (ACPA)-positive and -negative patients. Outcomes were recalculated for patients who, with hindsight, might have been classified at baseline as having RA according to the 2010 criteria (RA 2010)).

Results

25 patients in the MTX group and 29 in the placebo group progressed to RA (1987) (p=0.45). MTX delayed progression from UA to RA (1987) but only in ACPA-positive patients. Drug-free remission was achieved in 35 patients, 20 of whom were initially treated with MTX, and 32 were ACPA-negative. ACPA-positive patients had more radiographic progression, regardless of treatment. Forty-three patients (39%) could be reclassified as having had RA (2010) at baseline, 6/24 (25%) of whom achieved remission after placebo treatment.

Conclusions

After 5 years there is no lasting benefit of a 1 year initial course of MTX for patients with undifferentiated arthritis, compared with initial placebo. Progression to classifiable RA was not suppressed, drug-free remission not induced and the progression of radiological damage was similar in both groups. Reclassification at baseline with the 2010 criteria showed that 25% of patients with RA (2010) achieved spontaneous drug-free remission.

INTRODUCTION

Patients with inflammatory arthritis may present with undifferentiated arthritis (UA) not fulfilling any classification criteria (1). Although UA may be a self-limiting disease, a considerable proportion of patients with UA has an early manifestation of rheumatoid arthritis (RA). For patients with recent-onset RA, a timely start of treatment with disease-modifying antirheumatic drugs (DMARDs) has proved to be crucial for achieving better clinical and radiographic outcomes. Therefore starting antirheumatic treatment already in UA might result in even more sustained benefits and potentially a chance for cure (2,3).

In the PROMPT study, we showed that treatment with methotrexate (MTX) compared with placebo for 1 year did not prevent, but (in anti-citrullinated protein antibody (ACPA)-positive patients at least) delayed, the development of UA into RA (4). MTX reduced signs and symptoms at 12 months and radiographic progression at 18 months—again, particularly in ACPA-positive patients with UA. It remains to be determined whether this very early introduction of MTX has benefits in the long term.

In this study, the effect of early MTX treatment on clinical and radiological outcomes was assessed after 5 years. In addition, we identified predictors for disease progression to classifiable RA and for persistent remission in patients with UA. Finally, we re-evaluated current and previous study results using the 2010 classification criteria for RA to see whether MTX monotherapy in patients who fulfill the 2010 criteria and have relatively low disease activity is sufficient to achieve remission (5).

PATIENTS AND METHODS

Study setting and design

The PROMPT study is a prospective double-blind, randomized, placebo-controlled multicenter trial evaluating the effect of 1 year MTX versus placebo treatment (4). All 110 patients fulfilled the 1958 classification criteria for probable RA (6), were DMARD-naïve and had a symptom duration of <2 years.

Patients started treatment with MTX 15 mg/week (6 tablets of 2.5 mg) or the equivalent number of placebo tablets. No other DMARDs or steroids were allowed during the first year of treatment. Every 3 months, medication was increased by 5 mg MTX or two tablets placebo to a maximum of 30 mg or 12 tablets placebo a week as long as the Disease Activity Score (DAS) was >2.4. As soon as a patient fulfilled the 1987 ACR classification criteria for RA (7) (RA (1987)) during the first year, medication was switched to open-label MTX. After 12 months, the study drug was tapered and discontinued in the patients who had not developed RA (1987). IgM rheumatoid factor (RF) and ACPA were measured retrospectively in serum samples taken at baseline using commercial kits (Euro-Diagnostica, Arnhem, The Netherlands). ACPA levels >25 U/ml and RF levels >5 IU/ml were considered positive. Further details of the study and results of the primary outcomes have been published elsewhere (4).

To substantiate the PROMPT study results, the patients were reclassified at baseline according to the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR)/EULAR criteria for RA (5).

Outcomes

At 3, 6, 9, 12, 30 and 60 months the diagnosis was recorded as classifiable RA (1987) (7) or UA (UA not fulfilling the 1987 ACR criteria), drug-free remission (DFR) without progression to RA (1987) or other (lost to follow-up or other diagnosis). Remission was defined as a DAS $\leq$ 1.6 (8) or the absence of synovitis or self-reported absence of symptoms without use of DMARDs. Radiographs of the hands and feet were obtained at inclusion and at 6, 12, 18, 30 and 60 months. Radiographic progression was scored by two independent readers using the Sharp–van der Heijde scoring (SHS) method (9) with radiographs blinded for patient identity, treatment group and time order.

Statistical analysis

Baseline and disease characteristics were compared between the two treatment arms, between ACPA-positive and ACPA-negative patients and between patients with RA (1987) and patients in DFR using the χ^2 test, Student t test and the Mann–Whitney U test. To assess differences in time to reach one of the endpoints (RA (1987) or DFR), Kaplan–Meier curves with a log rank test were used.

In a large proportion of patients the readers independently scored no radiological damage progression (71% and 73%, respectively). Consequently, interobserver and intraobserver intraclass correlation coefficients were not suitable for measuring reliability (10). In 71% of patients both readers scored the same progression. A consensus score was reached for the radiographs with inter-reader differences $\geq$ 1, based on a median (IQR) difference in progression score between readers of 0 (0–2). The mean score of the readers was used for the analyses. We performed a completers' analysis, then repeated the analyses with imputed values according to last observation carried forward, for incomplete series.

Univariate logistic regression analysis was used to identify potential predictors for fulfilling the criteria of RA (1987) after 60 months and for DFR, including age, sex, symptom duration, baseline SHS, baseline erosion score, baseline DAS, baseline Health Assessment Questionnaire, ACPA status and RF status. The univariate predictors that reached statistical significance ($p\leq 0.1$) were entered stepwise in a multivariate model. Age and gender, as known predictors, were forced into the model. To avoid problems of colinearity, separate analyses were done with either ACPA or RF.

RESULTS

After 5 years, seven patients were lost to follow-up because they had either moved away or had died. Radiographs after 5 years were obtained for 67 patients.

Baseline and disease characteristics of the 110 patients with UA (55 receiving MTX, 55 placebo) are shown in table 1.

Table 1. Baseline and disease characteristics for both randomization groups

Characteristics	MTX (n=55)	Placebo (n=55)	p-Value
Age (years)	51 (42-60)	51 (42-56)	0.39
Female	35 (64)	38 (69)	0.55
Symptom duration (days)	312 (195-507)	263 (169-432)	0.29
Morning stiffness (minutes)	30 (10-60)	30 (10-60)	0.95
RF positive	20 (36)	19 (35)	0.96
ACPA positive	12 (22)	15 (27)	0.51
DAS	2.72 (0.78)	2.52 (0.76)	0.19
HAQ	0.79 (0.51)	0.79 (0.58)	0.90
Sharp-van der Heijde score	0 (0-2)	0 (0-2)	0.98
Fulfilled ACR-EULAR 2010 RA criteria	19 (35)	24 (44)	0.33

Data are presented as means $\pm$ SD, medians and IQR, or numbers and percentages (%) when appropriate.

ACR, American College of Rheumatology; ACPA: anti-citrullinated protein antibodies; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor.

Diagnosis at 60 months

1987 RA criteria

After 60 months 54/110 patients (49%) had disease progression and fulfilled the 1987 RA classification criteria. In the MTX group 25/55 patients (45%) progressed to RA (1987), in the placebo group 29/55 (53%) patients ($p=0.45$) (table 2). All the 29 patients in the placebo group who progressed to RA (1987) did so within 1 year, compared with 11/25 in the MTX group. Yet, possibly owing to small numbers, Kaplan–Meier analyses showed no significant difference in time to progression to RA between the treatment groups ($p=0.11$) (figure 1A). Of the patients who progressed to RA (1987), the 25 patients in the MTX group used a median of 1 (1–2) DMARDs in 5 years, compared with a median of 2 (1–3) DMARDs in the 29 patients of the placebo group. ACPA-positive patients progressed significantly faster to RA (1987) than ACPA-negative patients ($p<0.001$). Initial MTX treatment delayed progression to RA (1987) in the ACPA-positive group but not in the ACPA-negative group ($p<0.001$) (figure 1B,C).

Drug-free remission and persistent UA

In the MTX group 25/55 patients (45%) did not progress to RA (1987). At 5 years, of those 25 patients, 19 were in persistent DFR since 1 year, and one was in DFR after using hydroxychloroquine for 35 months. Five were still diagnosed as having active UA (table 2). In the placebo group 17/55 (31%) patients did not progress to RA (1987) and 15 were in DFR after 60 months, two still had arthritis (table 2). None of these 15 patients had used DMARDs since 1 year. Of the total group, 35/110 patients

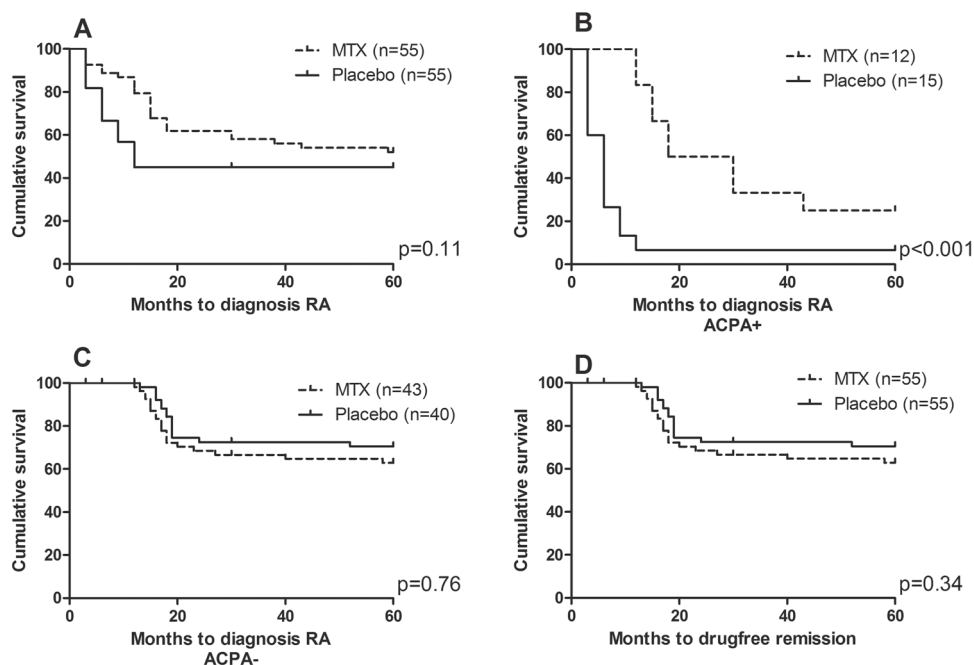


Figure 1. Kaplan-Meier survival analysis for (A) the time to diagnosis of rheumatoid arthritis (RA) in the total group; (B) in ACPA-positive patients; (C) in ACPA-negative patients; (D) the time to drug free remission in the total group. ACPA, anti-citrullinated protein antibodies; MTX, methotrexate.

Table 2. Diagnosis after 30 and 60 months follow up in patients initially treated for 1 year with MTX or placebo

Diagnosis	30 months		60 months	
	MTX	Placebo	MTX	Placebo
RA (1987 criteria)	22	29	25	29
UA (active arthritis)	10	4	5	2
Drug free remission	15	13	20	15
Other diagnosis	3*	4**	3*	4**
Lost to follow up	5	5	2	5
Total	55	55	55	55

Values indicate the number of patients.

* 2 osteoarthritis, 1 autoimmune hepatitis. ** 3 osteoarthritis and 1 diabetic arthropathy.

MTX, methotrexate; RA: rheumatoid arthritis, UA: undifferentiated arthritis.

(32%) were in DFR at 60 months. The survival analysis did not show a difference in time to achieve DFR between the MTX and the placebo group ($p=0.34$) (figure 1D). Most patients who achieved DFR were ACPA negative (32/35), and achieved DFR significantly earlier than the three ACPA-positive patients ($p=0.008$).

2010 RA criteria

Based on signs and symptoms, 43/110 patients with UA (39%) fulfilled the 2010 ACR/EULAR classification criteria for RA (RA (2010)) at baseline (table 1). Nineteen of these patients were randomized to the MTX group. Of these patients, 12/19 (63%) had disease progression to fulfilling the 1987 classification criteria, 5/19 (26%) achieved DFR. Of the 24 RA (2010) patients randomized to the placebo group, 17/24 (71%) progressed to RA (1987) and 6/24 (25%) achieved DFR.

Predictors of drug-free remission and fulfilling the criteria for RA

The univariate predictors for fulfilling the 1987 classification for RA after 60 months were, separately tested, ACPA positivity (OR=9.7, 95% CI 3.1 to 30.5) and RF positivity (OR=3.0, 95% CI 1.3 to 6.8). Multivariate analyses including ACPA or RF, age, gender, SHS and DAS at baseline, showed ACPA (OR=8.9 95% CI 2.7 to 29.1), SHS at baseline (OR=1.3, 95% CI 1.01 to 1.6) and RF (OR=2.9, 95% CI 1.2 to 7.1) as independent predictors for progression to RA (1987).

Absence of ACPA (OR=5.0, 95% CI 1.4 to 18.0) was identified as the only independent predictor for DFR (OR=5.1, 95% CI 1.4 to 18.5, in the multivariate analysis including ACPA, age and gender).

Radiographic damage

Completers

After 60 months, 67 patients had completed the radiographic follow-up. Patients who completed follow-up were more often ACPA positive (36% vs 7% in non-completers) and more had progressed to RA (1987) (66% vs 23% in non-completers). In 39/67 patients (58%) there was no radiological progression at all. Radiological damage progression was comparable in patients who had progressed to RA (1987) and those who were in DFR after 5 years ($p=0.08$). There was significantly more damage progression in the ACPA-positive than in the ACPA-negative patients (median (IQR) 1.8 (0–6) vs 0 (0–0.5); $p=0.001$).

Total group

Imputation of missing values by last observation carried forward was done in 107 patients (no imputation in three patients with only baseline scores). In 73/110 (66%) patients were estimated to have no progression. In the 34 patients who showed progression, median progression was 2 (1–7). The median (IQR) progression of patients initially treated with MTX was 0 (0–1) and in the placebo group 0 (0–1) ($p=0.78$). After 5 years, patients who progressed to RA (1987) had more progression than patients in DFR (respectively 0 (0–2) vs 0 (0–0); $p=0.02$). Again, ACPA-positive patients showed more radiological progression than ACPA-negative patients (1.5 (0–3)

points progression in SHS vs 0 (0–0), $p < 0.001$), regardless of initial treatment (figure 2). Two ACPA-positive patients who initially received placebo showed rapid radiological progression, defined as an increase in SHS of ≥ 5 points in year 1 (figure 2A) (11,12). None of the other patients showed rapid radiological progression.

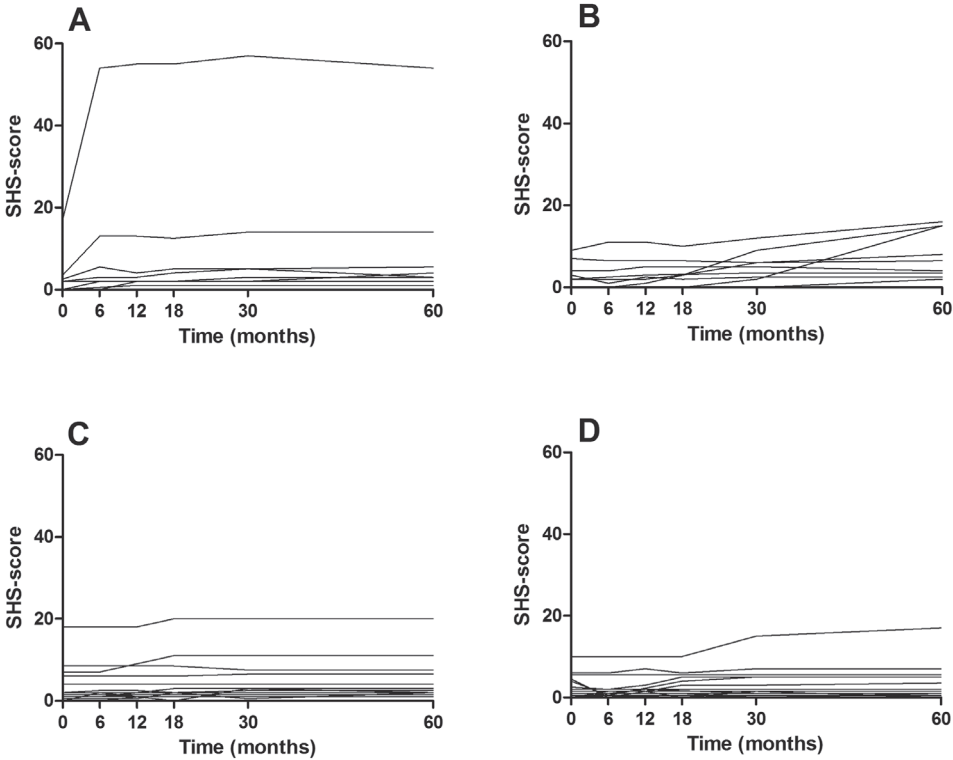


Figure 2. Sharp-van der Heijde Score at every time point for individual patients who were either (A) ACPA positive and treated with placebo (n=15); (B) ACPA positive and treated with MTX (n=12); (C) ACPA negative and treated with placebo (n=40); (D) ACPA negative and treated with MTX (n=43). ACPA, anti-citrullinated protein antibodies; MTX, methotrexate; SHS, Sharp-van der Heijde Score.

DISCUSSION

The PROMPT study, a randomized clinical trial in patients with UA, was set up to establish whether very early treatment with MTX could induce drug-free remission or prevent progression to RA (1987). Early study results showed that MTX can postpone progression from UA to RA and suppresses radiological damage progression, in particular in ACPA-positive patients (4). In this study we have found that after 5 years there is little lasting benefit of early MTX treatment. Overall, patients with UA treated

with MTX did not achieve more DFR, did not progress less often to RA (1987) and had comparable damage progression compared with patients with UA who initially were treated with placebo. Only in ACPA-positive patients did initial MTX postpone progression to RA (1987). These results indicate that early treatment with MTX is ineffective in altering the disease course of UA. This may be owing to inefficacy of the drug, duration of treatment, characteristics of the targeted illness, inadequate timing of treatment, or all of the above.

MTX may be seen as the cornerstone of antirheumatic treatment (13,14), yet MTX monotherapy as initial treatment in patients with RA is often inferior to initial combination treatment with corticosteroids or biological DMARDs (15–18). It may be that such initial combination treatment in our population would have been more successful in altering the disease course than MTX monotherapy. It is also possible that discontinuation of MTX after 1 year was too soon, but longer treatment cannot be seen as induction therapy, which was the target of the PROMPT study.

The finding that initial treatment with MTX delayed progression to 1987 classifiable RA only in ACPA-positive patients suggests that the effect of treatment may depend on the type of illness presenting as UA. We found that ACPA and RF are independent predictors for disease progression to RA (1987) after 60 months. Time to progress to RA (1987) was significantly shorter in ACPA-positive patients than in the ACPA-negative patients. Absence of ACPA was the only independent predictor of drug-free remission after 5 years. ACPA-positive patients showed more radiographic progression, despite the fact that having progressed to classifiable RA many started treatment with open-label MTX, after which damage progression was suppressed. Overall, we found no difference in radiographic progression between the MTX- or placebo-treated groups. These results suggest that ACPA-positive and ACPA-negative early arthritis are different disease entities, which may require different treatments. In addition, the persistence of remission in the majority of ACPA-negative patients (also those treated with placebo) suggests that these had a temporary disease, which could not be identified at presentation, by symptom duration or characteristics other than ACPA status.

It might be that we started initial treatment with MTX too late. We included and treated patients who were at the time considered to have UA, but who now would be classified as RA, based on the 2010 classification criteria for RA (5). In retrospect, 43 patients (39%) of the patients included as UA fulfilled the 2010 ACR/EULAR criteria at baseline, 23 of whom were ACPA positive. It is possible that for these patients the opportunity to achieve a change in the disease course by whatever treatment, might already have been lost. On the other hand, the new criteria may also misclassify some patients as having RA, and lead to overtreatment. Twenty-four of the 43 patients fulfilling the 2010 criteria were randomized to initial placebo treatment, and six of those 24 achieved clinical remission. This means that, had we started MTX in all patients who fulfilled the 2010 criteria, we would have overtreated these six patients (25%). We also started MTX treatment in 36 patients who in retrospect did not fulfill the

2010 classification criteria, which may also qualify as overtreatment. Of these patients, 13 did progress to RA (1987), which more effective treatment might have prevented.

In summary, in this randomized clinical trial comparing the outcomes after 5 years of initial MTX treatment and placebo in patients with UA, there is no lasting effect of MTX treatment given in the first year. A positive ACPA status and radiological damage at baseline are independent predictors for progression to RA and a negative ACPA status is a predictor for DFR. The observed rate of spontaneous remission, particularly in the ACPA-negative patients, demonstrates that initiation of MTX treatment in all patients who fulfill the 2010 ACR/EULAR criteria would constitute overtreatment in 25% of patients. On the other hand, mostly in ACPA-positive patients, initial MTX monotherapy is insufficient to prevent disease progression. Further research should focus on early and correct recognition of RA, as well as identifying a treatment that might truly alter the disease process.

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9

GENERAL DISCUSSION AND CONCLUSIONS

SUMMARY OF RESULTS

Over the past 3 decades the treatment and future perspectives of RA patients have changed dramatically. As a chronic systemic auto-immune disorder, RA does not only affect the joints but other organs as well (1). From a disabling disease due to chronic inflammation and destruction of bone and cartilage, it has become a much more manageable condition with the arrival of better medication and treatment strategies. Early Arthritis Cohorts have given us a better understanding of genetic, environmental and clinical risk factors of inflammatory arthritis and its pathophysiology, as described in **chapter 2**. In the Leiden Early Arthritis Clinic (EAC) patients with confirmed arthritis of recent onset were included in the Cohort and had regular follow-up. Data from this cohort have given us a better understanding of RA, e.g. by showing the relation between the Shared Epitope and RA severity with regard to radiographic damage. Genetic analyses from the EAC have led to confirmation of the 'DERAA' hypothesis, in which certain DR alleles were found to have a dominant protective effect in RA patients on disease and outcome. With regard to environmental risk factors the effect of smoking on RA has been studied and recently led to the understanding that smoking promotes non-specific citrullination rather than citrullination of specific antigens (2). As far as clinical risk factors are concerned, the relationship between rheumatoid factor and erosive disease was confirmed in this cohort. As observed in the Leiden EAC, RA can have different clinical presentations with possible implications for disease severity and persistence. Data from the EAC showed that in about one third of the patients no diagnosis could be made despite extensive differential diagnostic work-up (3). It was proposed at the end of the last century to classify these patients as Undifferentiated Arthritis (UA). RA may present as UA or as RA from the start. In the study as described in **chapter 3**, the disease course of patients with UA that evolved into RA within 1 year was compared to patients that presented with RA, fulfilling the 1987 classification criteria for RA. Radiographic joint damage, disease activity and functional capacity had a comparable disease course in both groups, measured over four years. So undifferentiated arthritis does not always follow a more benign disease course. A possible caveat of this retrospective observational study was the difference in patients treated with DMARDs, as fewer DMARDs were prescribed in the UA-RA group than in the RA-RA group. By comparing different historic treatment strategies in the EAC, we were able to confirm the beneficial effect of early treatment with DMARDs on disease outcome after two years (4). That this effect on radiographic damage was sustained after four years, is described in **chapter 4**. The major benefit of starting a DMARD early in the disease course was observed during the first year of treatment. After one year, when more than 50% in both treatment groups received DMARD therapy, no differences in the rate of joint damage could be observed. With a symptom duration varying from 18 to 24 weeks per group, no evidence of a 'window of opportunity' in the prevention of detrimental characteristics could be found. Given the observation that carriership of SE alleles is associated with more severe disease, as are Rheumatoid factor and ACPA, in **chapter 5** we investigated whether certain

HLA class II DR and DQ alleles in RA patients are associated with production of anti-CCP antibodies (5-7). Carriership analysis revealed that Shared Epitopes HLA-DRB1*0401, DRB1*1001, HLA-DQB1*0302 and DQB1*0501 were associated with the presence of anti-CCP antibodies. Moreover, associations were found between DQ-DR genotypes bearing proposed RA susceptibility alleles and the production of anti-CCP antibodies. Combining the immunogenetic with radiographic data showed a more severe disease course in those patients that were both anti-CCP and SE positive. The mean $\pm$ SD modified Sharp/van der Heijde (SHS) scores of patients with both anti-CCP antibodies and SE alleles was 7.6 ± 10.4 Sharp points per year, compared to 1.6 ± 3.9 Sharp points in the SE-/ACPA- group, 2.4 ± 2.8 in the SE-/ACPA+ group and 1.6 ± 2.9 in the SE+/ACPA- group. As it is hypothesized that effective treatment in the phase of UA can prevent deterioration to RA and possibly redress the inflammatory process to remission ('window of opportunity' hypothesis) we questioned whether methotrexate could be that effective treatment. To investigate this, the PROMPT study was designed (chapter 6). In this study, patients with undifferentiated arthritis were treated with either methotrexate (MTX) or placebo. In the MTX group, the progression to RA was postponed, signs and symptoms were reduced and radiographic damage was retarded. The effects were most pronounced for the ACPA positive subgroup. Follow-up in the PROMPT study was 12 months for DAS and HAQ and 18 months for diagnosis and radiographic damage. Chapter 7 focuses on the secondary outcome measures of the PROMPT study. The relationships between disease activity, joint damage and functional disability, and the effect of methotrexate (MTX) therapy were investigated. Similar to RA, in UA, disease activity is related to functional disability and joint damage, irrespective of ACPA, providing a rationale for early intensive treatment of UA. Since MTX therapy only improves symptoms, function and damage progression in ACPA-positive UA, an effective therapy for ACPA-negative UA still needs to be found. The long term outcome of the PROMPT study is described in chapter 8, with regard to (persistence of) diagnosis and radiographic progression. After 5 years we found no lasting effect of methotrexate on disease outcome. A positive ACPA-status and radiological damage at baseline are independent predictors for progression to RA and inversely a negative ACPA-status is a predictor for drug free remission. The observed rate of spontaneous remission, particularly in the ACPA negative patients, demonstrates that initiation of MTX in all patients that fulfill the 2010 ACR/EULAR criteria would be overtreatment in 25% of patients. On the other hand, mostly in ACPA positive patients, treatment with MTX monotherapy is insufficient to prevent disease progression or induce lasting remission.

UA AND (NEW CRITERIA FOR) RA

As described, one third to half of the patients with inflammatory arthritis do not meet criteria for any specific disease at first visit(s) and are therefore named Undifferentiated Arthritis (UA) (3,8). The characteristics of patients that present with early UA and early classifiable RA differ. UA patients are younger, less often female, have a different

antibody profile, less swollen joints and less erosive disease at baseline (**chapter 5**). Over time, a definite diagnosis can be made in an increasing number of UA patients due to accumulation of disease specific characteristics. This pattern was also observed in the PROMPT study, where the number of active UA patients decreased from 110 to 7 patients after 5 years (**chapter 8**). The other way around 54 out of 110 patients developed RA according to the 1987 criteria. The understanding of the processes responsible for progression from UA to RA is far from complete. As mentioned before, 6-55% of UA evolved into RA within one year of follow-up and 40-55% went into spontaneous remission (9,10). It remains unknown if and how very early UA (fewer than 12 weeks) may be an immunopathologically distinct phase compared with later disease. Studies that have focused on synovial tissue have not revealed substantial differences (11,12). In UA one of the strongest predictors for RA is the presence of ACPA. In mono/oligo arthritis, early UA patients with ACPA have an approximately 70% chance of being classified as RA by the 1987 ACR-criteria 1 year following the UA diagnosis. This was also shown in the PROMPT study (**chapter 8**), where almost all ACPA-positive UA patients eventually developed RA. As the inclusion criteria of the PROMPT study called for 'patients with at least one inflamed and one other painful joint *who are clinically suspect of having early RA*', the 'gut feeling' diagnostics of rheumatologists appears to be relatively accurate. Compared to a prediction rule based on common clinical risk factors alone, adding information on currently known genetic risk factors for RA did not improve the prediction of RA (13).

Given that the established RA-criteria were unsuitable to classify early RA, a joint committee of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) decided to develop new criteria for those patients in which a rheumatologist would start MTX therapy (14). The new set of classification criteria for RA captured also a proportion of the patients that were previously in the UA group (1987 UA). This may lead to a lower prevalence of UA, and also to a changed set of patient characteristics of the new (2010) UA group. In a recent cohort report, these two groups were compared and 45.9% of the 2010 UA patients achieved sustained remission compared to 34.2% of the 1987 UA group (15). Fewer patients in the 2010 UA group were prescribed DMARDs during the first year of follow up: 32.7% compared to 45.2% in the 1987 UA group. The effect of the different classification criteria is also illustrated by the results of PROMPT and the IMPROVED study. If the 2010 classification criteria were applied to the study population of the PROMPT study, 43 patients (39%) of these (1987) UA patients would have been classified as having RA at baseline. Of the 24 placebo treated patients in this group, 6 patients reached drug free remission, meaning that 25% would have been overtreated in case MTX had been started in all patients classified as (2010) RA (**chapter 8**). Also in the IMPROVED study, initiated before the new classification criteria were formulated, patients with (1987) UA were included, as well as patients with RA according to the 1987 criteria. Using the 2010 classification criteria, 115 1987 UA patients could be classified as RA, an increase of 19% in the RA patient group. In this study, where all patients were started on an initial

treatment with MTX and a tapered high dose of prednisone after 4 months remission percentages were similar in both RA and UA patients (63%) (16), and using the old or new classification criteria did not influence this outcome, probably due to the similarly short symptom duration in both groups. Looking at the patient characteristics, the change in diagnosis from UA to RA predominantly rests on numbers of (small) joints involved and on ACPA status. The 2010 UA population has fewer joints involved and is almost entirely ACPA negative.

EARLIER TREATMENT/WINDOW OF OPPORTUNITY

Since it is not yet known which events mark the onset of RA or at which point the disease might still be reversible, the current idea is the earlier treatment is started the higher the chance for a successful outcome. The hypothetical time frame during which this might be accomplished has been called the 'window of opportunity'. Data that support the presence of a window of opportunity are also obtained from cohorts and trials (17-20).

In 1999, an unblinded study of a single dose of corticosteroids in patients with mild early inflammatory arthritis (median 20 weeks) found the strongest predictor of disease remission at 6 months (defined as the absence of symptoms and signs in patients without anti-inflammatory treatment) to be a disease duration of less than 12 weeks at time of therapy (21). A few years later, Nell et al performed a small case-control study, in which clinical and radiological outcomes at 3 years were compared. Patients who started DMARD therapy within 3 months after disease onset had a significantly better outcome compared to the control group with a median disease duration of 12 months at the start of treatment (22). Remission was achieved in 50% of the first group and 15% in the latter group.

Early treatment starts with early referral. Using data of the Leiden Early Arthritis Cohort, Van der Linden et al showed that a rheumatologic assessment within 12 weeks of symptom onset was associated with significantly less damage to joints and a significantly higher chance to achieve drug free remission (20). These results may explain why in the PROMPT study (chapter 6) treatment of UA patients with methotrexate did not result in more drug free remission or even prevention of progression to classifiable RA, compared to treatment with placebo. Patients included in the PROMPT study had a median disease duration of more than 6 months; therefore it could well have been that the 'window of opportunity' was missed.

To improve early referral, the introduction of an Early Arthritis Recognition Clinic with a short clinical assessment by an experienced rheumatologist on whether or not arthritis is present, was established in 2 rheumatology centers in the Netherlands. Based on the first 612 patients, this approach helped to decrease the delay in diagnosis (either UA or RA) from (a median) 19.3 to 7.6 weeks. The proportion of patients that were assessed by a rheumatologist within 12 weeks after symptom onset was increased from 31-36% to 65% (23). Early Arthritis Recognition Clinics may be a useful tool to detect and consequently treat inflammatory arthritis earlier in the disease course.

OTHER THERAPIES

One could argue that based on the PROMPT results, methotrexate monotherapy is not potent enough to induce remission or cause a permanent change in the disease process. Shortly after the PROMPT study, three other Randomized Clinical Trials were carried out in very recent arthritis. In the SAVE study, 383 patients with undifferentiated early arthritis of less than 16 weeks (mean around 8 weeks) were given a single intramuscular injection of 120 mg methylprednisolone or placebo (24). With a follow-up of 52 weeks, no remission or delayed diagnosis of RA could be determined. The STIVEA trial had a comparable concept with a 3 week course of 80 mg intramuscular methylprednisolone in early inflammatory polyarthritis of 4-10 weeks duration (25). This treatment postponed the prescription of DMARDs in the glucocorticoid group at 6 months with a difference of 15% between the two groups. At 12 months 10% in the placebo group versus 20% in the glucocorticoid group had resolved disease. Unfortunately, follow up was no longer than one year. Even in the preclinical phase of arthralgia, Bos et al found no beneficial effect of intramuscular dexamethasone injections in the development of arthritis (26).

Two studies investigated the use of biologics in UA. Saleem et al. gave 4 infliximab infusions in UA patients with a disease duration of less than 12 months and a relapse of arthritis after a single parenteral corticosteroid injection. At 6 months no beneficial effect of treatment with infliximab was observed and by week 52 100% of the patients in the infliximab group and 71% in the placebo group had developed RA (27). The negative findings in this study can be explained by the small number of patients (17 in total) and the fact that most of them probably already had RA, considering the long disease duration, high percentage of rheumatoid factor and ACPA positive disease, as well as high swollen joint counts. In a very small study treatment with abatacept monotherapy showed a trend to prevent the development of RA, but there were no significant changes in clinical signs and symptoms. Looking at patient characteristics of this cohort, there is again the impression that this is an RA cohort. In this ADJUST trial, treatment with abatacept did impact radiographic and MR progression in favor of the abatacept group, but long-term results are lacking (28).

Currently the PRAIRI study is conducted in patients with 'preclinical RA' (arthralgia with subclinical signs of synovitis, positive rheumatoid factor and positive ACPA), in which a single infusion of rituximab is given. The aim is to decrease the development of arthritis with 75% in a 4 year period. Results of this study should give more information on the predictive value of arthralgia for development of arthritis, the existence of a window of opportunity, as well as the effect of B-cell depletion in the early phase of the inflammatory process. Although the PRAIRI study might give an answer on the best treatment for rheumatoid factor and ACPA positive arthralgia/arthritis, it remains to be determined how seronegative arthritis should be treated.

TREAT TO TARGET

In analogy of the BeSt study one could argue that it is not just the therapy (DMARD or biologic) itself, but treating to target which is important to achieve and maintain disease control (29). Possibly this approach may also ensure disease modification. Treatment strategy trials in UA patients may be the next step, using the DAS to steer treatment adjustments, as the DAS is a valid measure for use in UA as well (30-32).

One of the most promising trials that are currently performed is the already mentioned IMPROVED 'Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease' study, designed following results of the PROMPT and BeSt study. The first data from this study already showed that initial treatment with MTX and tapered high dose of prednisone after four months results in high remission rates of around 60% (16). One year results of this early remission group (not published yet) show that after tapering prednisone to zero, 68% of these patients still have persistent remission. Drug free remission one year after inclusion was achieved in 32% of this population. Patients who did not achieve early remission were treated according to 2 (randomized) treatment strategies, one with a combination of synthetic DMARDs (methotrexate, sulfasalazine, hydroxychloroquine) and low dose prednisone, the other starting with biologic DMARD adalimumab. At the end of the first year, remission in these patients was achieved in 25% and 40%, respectively. These results suggest the presence of a window of opportunity. Other explanations for the higher remission rates in the early remission group might be the inclusion of patients with a self limiting arthritis and a relatively low disease activity at baseline (33). The IMPROVED study intends to follow up all patients for 5 years, with continued treatment decisions aiming at (drug free) remission.

FUTURE PERSPECTIVES

The treatment of inflammatory arthritis has changed over the past decades: from the 'pyramid' to the 'sawtooth' strategy, from treatment with conventional synthetic DMARDs to biologics, from interview based symptom orientated care to disease activity orientated targeted therapy. Despite all these advances in treatment and subsequently outcome, an effective overall cure has not been found (yet?). Probably there is no ideal 'one-size-fits-all' treatment. It is important that inflammatory arthritis is recognized (very) early and subsequently referred to the rheumatologist, but even after the introduction of ready access 'Early Arthritis Recognition Clinics', 1 in 3 arthritis patients presents with a symptom duration of more than 12 weeks.

When the diagnosis UA or (early) RA is made, a tailor-made treatment should be given, depending on risk factors for persistence of arthritis/development of RA. In this risk-stratification ACPA status, and possibly presence of various isotypes of autoantibodies are very important (34). For some therapies, a beneficial treatment effect has been shown in ACPA positive UA and RA patients, but for the ACPA negative group there appears to be less benefit of current therapies.

Since earlier treatment has not yet prevented accumulation of detrimental disease characteristics, we should explore different targeted-treatment strategies and include the most effective (biologic) antirheumatic therapies, as is currently being done in the IMPROVED study. Within the near future, the best treatment (strategy) for ACPA positive disease will become clearer, but for ACPA negative disease this might not hold true. Despite the milder disease course in the latter group, it will be just as challenging to find the best treatment in ACPA negative arthritis. One of the problems is the heterogeneity in ACPA-negative disease and our current lack of understanding how to tackle this heterogeneity. So far, extensive attempts have failed to find subgroups. With regard to outcome the remission rates in ACPA-negative disease are higher so it will be challenging to identify the group that does not reach remission after e.g. one year. Subsequently the damage in this group is not as large as in ACPA-positive disease, so outcome measures in trials in ACPA negative disease may be better focused on disease activity such as DAS or on disability such as HAQ.

How should we treat UA in the meantime? In my opinion we can do no better than focus on early referral, early diagnosis and consequent treatment targeted at suppression of symptoms as well as of predicted damage. New trials with newer medications will help determine if cure can be achieved, or whether early optimal suppression of disease activity is the next best goal.

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NEDERLANDSE
SAMENVATTING

In de afgelopen 30 jaar zijn zowel de behandeling als de toekomstperspectieven van reumatoïde artritis (RA) patiënten dramatisch veranderd. Als chronische auto-immuunziekte, tast RA niet alleen de gewrichten aan, maar ook de inwendige organen. Van een invaliderende ziekte door chronische ontsteking en destructie van bot en kraakbeen is het met de komst van betere medicatie en behandelstrategieën een beter controleerbare aandoening geworden. 'Early arthritis'-cohorten hebben ons een beter begrip gegeven van de genetische, omgevings- en klinische risicofactoren van inflammatoire artritis en de pathofysiologie hiervan, zoals beschreven in **hoofdstuk 2**. In de Leiden Early Arthritis Clinic (EAC) worden patiënten met een recent ontstane artritis geïncubeerd en volgens een vast stramien vervolgd. Data uit dit cohort hebben ons een beter begrip van RA gegeven, bijvoorbeeld door het aantonen van de relatie tussen het Shared Epitope (SE) en de ernst van RA ten aanzien van radiologische schade. Genetische analyses in het EAC cohort hebben de 'DERAA' hypothese bevestigd, waarin bepaalde DR allelen een dominant beschermend effect hebben bij RA patiënten m.b.t de lange termijn uitkomst. Onderzoek naar omgevingsfactoren heeft geleid tot het begrip dat roken non-specifieke citrullinerings promoot en niet de citrullinerings van specifieke antigenen. Wat betreft de klinische risicofactoren kon de relatie tussen IgM reumafactor (RF) en het ontstaan van erosies in dit cohort worden bevestigd. Zoals reeds geobserveerd in de EAC kan RA verschillende presentaties hebben met mogelijke implicaties voor de ernst en het persisteren van de ziekte. Gegevens uit de EAC laten zien dat in ongeveer 1/3 van de gevallen er in eerste instantie geen diagnose kan worden gesteld, ondanks een uitgebreide differentiaal diagnose. Aan het eind van de vorige eeuw werd voorgesteld om deze patiënten te classificeren als Undifferentiated Arthritis (Ongedifferentieerde Artritis of UA). RA kan zich presenteren als UA of meteen als RA. In **hoofdstuk 3** wordt het ziektebeloop van patiënten met UA welke zich binnen een jaar tot RA ontwikkelde, vergeleken met patiënten die zich presenteerden met RA volgens de 1987 classificatiecriteria. Radiologische schade, ziekte activiteit en functioneren hadden een vergelijkbaar beloop in beide groepen, gemeten gedurende een periode van 4 jaar. UA heeft dus niet altijd een goedaardiger ziektebeloop. Een nadeel van deze retrospectieve observationele studie is het verschil in aantal patiënten dat met een Disease Modifying AntiRheumatic Drug (ziekte modificerend anti-rheumaticum ofwel DMARD) werd behandeld. In de UA-RA groep werden minder DMARDs voorgeschreven dan in de RA-RA groep. Door verschillende historische behandelstrategieën te vergelijken, kon het gunstige effect van vroege behandeling met DMARDs bevestigd worden na 2 jaar follow-up. Dat dit effect op radiologische schade behouden blijft na 4 jaar, wordt beschreven in **hoofdstuk 4**. Het grootste voordeel van snel starten met een DMARD werd geobserveerd in het eerste jaar van de behandeling. Toen na een jaar meer dan 50% in beide groepen behandeld werd met een DMARD, werden er geen verschillen meer gezien t.a.v. röntgenprogressie. Met een klachtenduur variërend van 18 tot 24 weken per groep, werd geen bewijs voor een 'window of opportunity' gevonden wat betreft het voorkomen van schadelijke kenmerken. Met de observatie

dat dragerschap van 'Shared Epitope (SE)' allelen geassocieerd is met een ernstiger ziektebeloop, zoals ook RF en ACPA (antistoffen tegen gecitrullineerde eiwitten, waaronder ook anti-CCP antistoffen), werd in **hoofdstuk 5** onderzocht of bepaalde HLA klasse II DR en DQ allelen bij RA patiënten geassocieerd zijn met de productie van ACPA. Dragerschap analyse toonde dat SE HLA-DRB1*0401, DRB1*1001, HLA-DQB1*0302 en DQB1*0501 geassocieerd zijn met de aanwezigheid van ACPA. Daarbij werden associaties gevonden tussen DQ-DR genotypes die bepaalde RA susceptibility genen dragen en de productie van ACPA. Patiënten met zowel ACPA als SE hadden een ernstiger ziektebeloop. Het gemiddelde van de gemodificeerde Sharp/van der Heijde (SHS) scores van patiënten met zowel ACPA als SE allelen was 7.6 (standaarddeviatie (SD) 10.4) Sharp punten per jaar, vergeleken met 1.6 (SD 3.9) Sharp punten in de groep zonder ACPA en SE allelen, 2.4 (SD 2.8) in de SE-/ACPA+ groep en 1.6 (SD 2.9) punten in de SE+/ACPA- groep. Gezien de bestaande hypothese dat effectieve behandeling in de fase van UA progressie naar RA kan voorkomen en het inflammatoire proces kan omkeren tot remissie (de 'window of opportunity' hypothese), ontstond de vraag of methotrexaat (MTX) deze effectieve behandeling kon zijn. Om dit te onderzoeken, is de PROMPT studie opgezet (**hoofdstuk 6**). In deze studie werden patiënten met ongedifferentieerde artritis behandeld met MTX of placebo. In de MTX groep werd progressie naar RA uitgesteld. De symptomen namen af en de radiologische schade werd vertraagd. Deze effecten waren het meest uitgesproken in de groep met ACPA. De DAS (Disease Activity Score of ziekte activiteitscore) en HAQ (Health Assessment Questionnaire of functionaliteitscore) werden 12 maanden vervolgd. De Radiologische schade werd 18 maanden vervolgd. **Hoofdstuk 7** spitst zich toe op de secundaire uitkomstmaten van de PROMPT studie. De relaties tussen ziekte activiteit, gewrichtsschade en functiebeperking enerzijds en het effect hierop van de behandeling met MTX anderzijds, werden onderzocht. De ziekte-activiteit bij UA is, net als bij RA, gerelateerd aan functiebeperking en gewrichtsschade, onafhankelijk van ACPA. Dit vormt een rationale voor vroege intensieve behandeling van UA. Behandeling met MTX verbetert echter alleen de symptomen, functie en radiografische schade bij anti-CCP positieve patiënten. De meest effectieve behandeling voor UA zonder ACPA moet nog gevonden worden. De lange termijn uitkomsten van de PROMPT studie worden beschreven in **hoofdstuk 8**, ten aanzien van (behoud van) diagnose en progressie van radiologische schade. Vijf jaar na de initiële behandeling kon geen blijvend effect van MTX op de ziekte uitkomst worden vastgesteld. ACPA en radiologische schade bij het begin van de studie zijn onafhankelijke predictoren voor progressie naar RA. Omgekeerd is het ontbreken van ACPA een predictor voor medicatie vrije remissie. Het geobserveerde percentage spontane remissie, vooral bij patiënten zonder ACPA, laat zien dat starten van MTX in alle patiënten die de 2010 ACR/EULAR criteria vervullen overbehandeling betekent in 25% van de gevallen. Aan de andere kant is, vooral bij anti-CCP positieve patiënten, MTX monotherapie onvoldoende om ziekteprogressie te voorkomen of langdurige remissie te induceren.

UA EN (NIEUWE CRITERIA VOOR) RA

Zoals beschreven voldoet een derde tot de helft van de patiënten met een inflammatoire artritis bij het eerste bezoek niet aan de criteria voor een specifieke ziekte. Deze patiënten worden geclassificeerd als UA. De karakteristieken van patiënten die zich presenteren met vroege UA en vroeg classificeerbare RA verschillen. UA patiënten zijn jonger, minder vaak vrouw, hebben een ander antistof profiel, minder gezwollen gewrichten en minder erosieve ziekte op baseline (**hoofdstuk 5**). In de loop van de tijd kan bij een toenemend aantal UA patiënten een definitieve diagnose gesteld worden door opeenhoping van ziekte-specifieke kenmerken. Dit patroon werd ook in de PROMPT studie geobserveerd, waarbij het aantal actieve UA patiënten afnam van 110 naar 7 patiënten na vijf jaar (**hoofdstuk 8**). Omgekeerd ontwikkelden 54 van de 110 patiënten RA volgens de 1987 criteria. Het begrip van de processen verantwoordelijk voor de progressie van UA naar RA is verre van compleet. Zoals eerder al genoemd, ontwikkelde 6-55% van de UA patiënten zich naar RA binnen een jaar en ging 40-55% spontaan in remissie. Het blijft onduidelijk in hoeverre UA (korter dan 12 weken) zich in een andere immunopathologische fase bevindt vergeleken met verder gevorderde ziekte. Studies op gebied van synoviaal weefsel hebben geen substantiële verschillen laten zien. Bij UA is een van de belangrijkste predictoren voor RA de aanwezigheid van ACPA. In mono/oligo-artritis hebben UA patiënten met ACPA ongeveer 70% kans om een jaar na de UA diagnose alsnog geclassificeerd te worden als RA volgens de 1987 criteria. Dit werd ook aangetoond in de PROMPT studie (**hoofdstuk 8**), waarin bijna alle patiënten met ACPA uiteindelijk RA ontwikkelden. Hiermee bleek het 'onderbuik gevoel' van de verwijzende reumatologen met de inclusie van patiënten met tenminste één gezwollen gewricht en tenminste één ander pijnlijk gewricht, 'klinisch verdacht voor vroege RA', redelijk accuraat. Vergeleken met een voorspel model gebaseerd op veel voorkomende klinische risicofactoren, verbetert het toevoegen van informatie over huidige genetische risicofactoren voor RA het voorspellen van RA niet.

Met het gegeven dat de 1987 RA criteria ongeschikt zijn voor het classificeren van vroege RA, heeft een commissie van ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) besloten nieuwe RA criteria te ontwikkelen voor die patiënten, waarbij de reumatoloog MTX wil starten. Deze nieuwe classificatiecriteria omvatten ook een deel van de patiënten die vroeger werden geclassificeerd als UA volgens de oude (1987) criteria. Dit kan leiden tot een lagere prevalentie van UA en een verandering in de patiënt karakteristieken van de nieuwe (2010) UA groep. In een recent onderzoek werden deze twee groepen vergeleken en bereikte 45.9% van de 2010 UA patiënten (aanhoudende) remissie, vergeleken met 34.2% van de 1987 UA patiënten. In de 2010 UA groep kregen minder patiënten DMARDs voorgeschreven gedurende het eerste vervolgjaar: 32.7% vergeleken met 45.2% in de 1987 UA groep. Het effect van de verschillende classificatiecriteria wordt ook geïllustreerd door de resultaten van de PROMPT en de IMPROVED studie. Als de 2010 classificatie criteria worden toegepast op de studiepopulatie van de PROMPT

studie, hebben 43 patiënten (39%) van de 1987 UA groep retrospectief RA bij het begin van de studie. Van de 24 patiënten die met placebo werden behandeld, hebben 6 patiënten medicatie vrije remissie bereikt, wat een overbehandeling van 25% betekent als MTX gestart was bij alle patiënten die voldeden aan de (2010) RA criteria. Ook in de IMPROVED studie, een studie opgezet vóór het formuleren van de nieuwe classificatiecriteria, zijn zowel (1987) UA als (1987) RA patiënten geïnccludeerd. Met de 2010 RA criteria worden 115 (1987) UA patiënten geclassificeerd als RA, een toename van 19% in de RA groep. In deze studie, waarin alle patiënten behandeld zijn met MTX en een getaperde hoge dosis prednison werd na 4 maanden een vergelijkbaar remissie-percentages van 63% gevonden in beide groepen. Er werd geen verschil gevonden tussen het gebruik van de oude of nieuwe criteria in het bereiken van remissie, waarschijnlijk door de vergelijkbare korte klachtenduur in beide groepen. Gelet op de patiënt karakteristieken berust het verschil in diagnose (UA of RA) vooral op het aantal ontstoken gewrichten en de aan-of afwezigheid van ACPA. De 2010 UA populatie heeft minder ontstoken gewrichten en is bijna volledig ACPA negatief.

VROEGE BEHANDELING/'WINDOW OF OPPORTUNITY'

Aangezien het niet bekend is welke gebeurtenissen het begin van RA markeren of tot welk punt de ziekte nog reversibel kan zijn, is de huidige gedachte dat vroege behandeling een grotere kans biedt op een succesvolle uitkomst. De hypothetische tijdspanne waarin een dergelijke succesvolle uitkomst bereikt kan worden, wordt 'The Window of opportunity' genoemd. Data die de aanwezigheid van een window of opportunity ondersteunen komen voort uit cohortonderzoeken en vergelijkende onderzoeken.

In 1999 werd in een ongeblindeerde studie een eenmalige injectie met corticosteroïden gegeven aan patiënten met een vroege (milde) inflammatoire artritis (mediane duur 20 weken). De belangrijkste voorspeller voor remissie (gedefinieerd als afwezigheid van klachten en symptomen bij patiënten zonder anti-inflammatoire behandeling) na 6 maanden was een ziekteduur van minder dan 12 weken ten tijde van het starten van de behandeling. In een case-control studie een paar jaar later, werden door Nell e.a. 3 jaars resultaten vergeleken t.a.v. klinische en radiologische uitkomsten. Patiënten waarbij een DMARD werd gestart binnen 3 maanden na begin van de ziekte hadden een significant betere uitkomst vergeleken met de controle groep met een mediane ziekteduur van 12 maanden bij het begin van de behandeling. Remissie werd bereikt in 50% van de eerste groep en 15% van de tweede groep.

Vroege behandeling begint met vroege verwijzing. Aan de hand van data uit het Leiden EAC cohort hebben Van der Linden e.a. laten zien dat een reumatologische beoordeling binnen 12 weken na ontstaan van klachten, geassocieerd is met een significant grotere kans op het bereiken van medicatie vrije remissie. Deze resultaten kunnen verklaren dat in de PROMPT studie (hoofdstuk 6) de behandeling van UA patiënten met MTX niet resulteerde in meer medicatie vrije remissie of het voorkomen van progressie naar classificeerbare RA in vergelijking met patiënten die met placebo

werden behandeld. Patiënten in de PROMPT studie hadden een mediane ziekteduur van meer dan 6 maanden. Hierdoor kan het 'window of opportunity' ook gemakkelijk gemist zijn.

Om vroege verwijzing te bevorderen zijn in 2 centra in Nederland 'Early Arthritis Recognition Clinics' (Vroege Artritis Opsporingsklinieken) opgericht, waarin tijdens een korte klinische beoordeling door een ervaren reumatoloog wordt vastgesteld of er sprake is van een artritis. Gebaseerd op data van de eerste 612 patiënten, helpt deze aanpak de vertraging in diagnose (UA of RA) te reduceren van (een mediane) 19.3 naar 7.6 weken. Het deel van de patiënten dat regulier beoordeeld werd door een reumatoloog binnen 12 weken na ontstaan van de klachten nam toe van 31-36% naar 65%. Met deze resultaten kunnen Early Arthritis Recognition Clinics een bruikbaar instrument zijn om inflammatoire artritis vroeger in het ziekte proces te detecteren en te behandelen.

ANDERE BEHANDELINGEN

Op grond van de PROMPT resultaten kan beargumenteerd worden dat MTX monotherapie niet krachtig genoeg is om remissie te induceren of permanente veranderingen in het ziekte proces teweeg te brengen. Kort na de PROMPT studie, zijn 3 andere gerandomiseerde klinische studies uitgevoerd bij vroege artritis patiënten. In de SAVE studie kregen 383 patiënten met een ongedifferentieerde vroege artritis met een klachtenduur van minder dan 16 weken (gemiddeld rond 8 weken) een eenmalige intramusculaire injectie met 120 mg methylprednisolon of placebo. Tijdens het vervolg van 52 weken werd geen verschil gevonden in remissie of uitstel van de diagnose RA. De STIVEA studie had een vergelijkbare studie-opzet met 3-wekelijks injecties van 80 mg methylprednisolon intramusculair bij patiënten met een vroege inflammatoire polyartritis (klachtenduur 4-10 weken). Deze behandeling vertraagde het voorschrijven van DMARDs in de glucocorticoïd groep bij 6 maanden met een verschil van 15% tussen de twee groepen. Bij 12 maanden bereikte 10% in de placebogroep en 20% in de glucocorticoïd groep remissie. Jammergenoeg zijn deze patiënten niet langer dan een jaar vervolgd. Ook in de preklinische fase van artralgie konden Bos e.a. geen gunstig effect aantonen van een intramusculaire dexamethason injectie op de ontwikkeling van artritis.

In twee studies werd het gebruik van biologics bij UA onderzocht. Saleem e.a. gaven 4 infliximab infusen aan UA patiënten met een ziekteduur van minder dan 12 maanden en een recidief artritis na een eenmalige parenterale corticosteroïd injectie. Na 6 maanden werd geen gunstig effect van behandeling met infliximab geobserveerd en na 52 weken had 100% van de patiënten in de infliximab groep en 71% in de placebo groep RA ontwikkeld. De negatieve uitkomsten van deze studie kunnen verklaard worden door het kleine aantal patiënten (17 in totaal) en het feit dat de meesten waarschijnlijk al RA hadden, gelet op de lange ziekteduur, het hoge percentage patiënten met RF en ACPA, evenals het hoge aantal gezwollen gewrichten. In een (zeer) kleine studie liet abatacept monotherapie een trend zien

richting het voorkomen van RA, maar er waren geen significante verbeteringen in klinische klachten en symptomen. De karakteristieken van dit cohort bekeken, bestaat er opnieuw de indruk dat dit feitelijk een RA cohort is. In de ADJUST studie heeft men laten zien dat behandeling met abatacept de radiografische en MRI progressie remt, maar lange termijn resultaten ontbreken.

Op dit moment wordt de PRAIRI studie uitgevoerd in patiënten met 'preklinische RA' (artralgie met subklinische tekenen van synovitis, positieve RF en positieve ACPA). In deze studie wordt een eenmalig infuus met rituximab gegeven. Het doel van deze behandeling is de ontwikkeling van artritis met 75% te verminderen gedurende een periode van 4 jaar. De resultaten van deze studie zullen ons naar verwachting meer informatie geven over de voorspellende waarde van RF/ACPA positieve artralgie in de ontwikkeling van artritis, het bestaan van een window of opportunity en het effect van B-cel depletie in de vroege fase van het inflammatoire proces. Ondanks dat de PRAIRI studie een antwoord kan geven op de beste behandeling voor RF en ACPA positieve artralgie/artritis, blijft het onduidelijk wat de beste behandeling is voor seronegatieve artritis.

DOELGERICHTE BEHANDELING ('TREAT TO TARGET')

Naar analogie van de BeSt studie kan beargumenteerd worden dat niet alleen de behandeling (DMARD of biologic) zelf, maar ook het nastreven van een behandeldoel (lage ziekteactiviteit) belangrijk is in het bereiken en handhaven van controle over de ziekte. Mogelijk kan deze benadering ook zorg dragen voor ziekte modificatie. Behandelstrategie studies bij UA patiënten kunnen de volgende stap zijn, met DAS gestuurde behandeling aangezien de DAS ook gevalideerd is in UA.

Eén van de meest veelbelovende studies die momenteel worden uitgevoerd is de reeds genoemde IMPROVED studie, ontworpen n.a.v. de resultaten van de PROMPT en de BeSt studie, waarin inductiebehandeling met MTX en prednison wordt gegeven aan RA en UA patiënten. De eerste data van deze studie hebben al laten zien dat initiële behandeling met MTX en een getaperde hoge dosis prednison na vier maanden resulteert in hoge remissie percentages van rond 60%. De resultaten na een jaar laten zien dat na het afbouwen en stoppen van prednison 68% van deze patiënten in de vroege remissie groep nog steeds in remissie zijn. Medicatievrije remissie werd bereikt in 32% van deze populatie een jaar na inclusie. Patiënten die niet snel in remissie kwamen, werden behandeld volgens 2 verschillende behandelstrategieën; een deel met een combinatie van synthetische DMARDs (methotrexaat, sulfasalazine, hydroxychloroquine) en een lage dosis prednison, het andere deel met het biologic adalimumab. Aan het eind van het eerste jaar werd in respectievelijk 25% en 40% van deze patiënten remissie bereikt. Deze resultaten suggereren het bestaan van een window of opportunity. Andere mogelijke verklaringen voor het hogere remissie percentage in de vroege remissie groep zijn inclusie van patiënten met een self-limiting artritis en een relatief lage ziekte activiteit bij het begin van de studie. De IMPROVED

studie zal patiënten gedurende 5 jaar vervolgen met DAS gestuurde behandeling gericht op (medicatie vrije) remissie.

TOEKOMSTPERSPECTIEVEN

De behandeling van inflammatoire artritis is veranderd in de afgelopen decennia: van de 'pyramide' tot de 'sawtooth' strategie, van behandeling met conventionele synthetische DMARDs tot biologics, van interview/symptoom georiënteerde zorg tot DAS gestuurde behandeling gericht op remissie. Ondanks alle vooruitgang in behandeling en uitkomsten, bestaat er nog steeds geen alzijdig genezende behandeling. Waarschijnlijk is er ook geen universele behandeling. Het is belangrijk dat een inflammatoire artritis (heel) vroeg wordt herkend en vervolgens wordt verwezen naar de reumatoloog. Maar zelfs na de introductie van inloop ' Early Arthritis Recognition Clinics', presenteert 1 op de 3 patiënten zich met een klachtenduur van meer dan 12 weken.

Wanneer de diagnose UA of (vroeg) RA is gesteld, dient een op maat gemaakte behandeling te worden gegeven, afhankelijk van de risicofactoren voor een persisterende artritis/ontwikkeling tot RA. In deze risico-stratificatie is de ACPA status en mogelijk de aanwezigheid van diverse isotypen van auto-antilichamen erg belangrijk. Voor sommige therapieën is een gunstig effect aangetoond in ACPA positieve UA en RA patiënten, maar voor de ACPA negatieve groep is dit effect minder uitgesproken.

Aangezien vroegere behandeling de opeenstapeling van schadelijke kenmerken nog niet voorkomt, zouden we verschillende behandelstrategieën moeten onderzoeken met hierin de meest effectieve vormen van (biologic) behandeling, zoals momenteel gedaan wordt in de IMPROVED studie. In de nabije toekomst zal de beste behandeling en/of strategie voor ACPA positieve ziekte duidelijk worden, maar voor ACPA negatieve ziekte hoeft dit niet te gelden. Ondanks het mildere ziektebeloop in deze laatste groep, zal het net zo uitdagend zijn om hiervoor de beste behandeling en/of strategie te vinden. Eén van de problemen is het heterogene karakter van ACPA negatieve ziekte en ons onbegrip hoe deze heterogeniteit aan te pakken. Tot op heden zijn uitgebreide pogingen om subgroepen te vinden mislukt. Aangezien de remissie percentages hoger zijn in ACPA negatieve ziekte, zal het een uitdaging zijn om de groep te onderscheiden die geen remissie bereikt in (bijvoorbeeld) een jaar. Ook is er minder radiologische schade in deze groep, zodat in ACPA negatieve ziekte beter gekozen kan worden voor ziekte-activiteit (DAS) of functionaliteit (HAQ) als uitkomstmaten.

Hoe moeten we UA in de tussentijd behandelen? Naar mijn mening kunnen we het momenteel niet beter doen dan ons richten op vroege verwijzing, vroege diagnose en vervolgens instellen van behandeling gericht op het onderdrukken van zowel de symptomen als radiologische schade. Nieuwe studies met nieuwe medicatie zullen bepalen of genezing kan worden bereikt of dat vroege optimale suppressie van ziekte activiteit het behandeldoel zal worden.



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CURRICULUM VITAE
DANKWOORD

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CURRICULUM VITAE

Jill werd geboren op 30 april 1974 te Oosterhout, Noord-Brabant. In 1992 behaalde zij het diploma aan het Sint-Oelbert Gymnasium te Oosterhout. Van 1992 tot 1994 studeerde zij Medische Biologie aan de Vrije Universiteit te Amsterdam, waar zij haar propedeuse haalde. In 1994 startte zij met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam. Haar wetenschapsstage liep zij in Québec, Frans Canada, waar onder leiding van dr. J. Kingma gekeken werd naar de genetische effecten van 'ischemic preconditioning' bij konijnen. In 1998 behaalde zij het doctoraal examen en ving zij aan met haar co-schappen. Eind 2000 werd het artsexamen behaald. Aansluitend was zij gedurende een jaar werkzaam als arts-assistent interne geneeskunde in het Rode Kruis Ziekenhuis te Beverwijk. Tijdens dit jaar werd de interesse in de reumatologie gewekt en werd zij door dr. P. Boom (cardioloog) voorgesteld aan prof. dr. T.W.J. Huizinga. Eind 2001 startte zij als arts-assistent op Sole Mio Ambulante Zorg, de reuma revalidatie afdeling van het LUMC. Medio 2002 ving zij aan met het in dit proefschrift beschreven promotieonderzoek onder leiding van prof. dr. T.W.J. Huizinga. Van januari 2004 tot mei 2006 volgde zij haar vooropleiding interne geneeskunde in het Rijnland Ziekenhuis te Leiderdorp (opleider dr. F.H.M. Cluitmans), waarna deze werd voortgezet in het Leids Universitair Medisch Centrum (opleider prof. dr. J.A. Romijn). Vanaf mei 2008 was zij werkzaam op de afdeling reumatologie van het Leids Universitair Medisch Centrum (opleider prof. dr. T.W.J. Huizinga). In november 2009 werd zij geregistreerd als internist. Van oktober 2010 tot januari 2011 werkte zij als AIOS reumatologie in het Haga ziekenhuis te Den Haag (opleider dr. H.K. Rondag). In februari 2011 werd zij geregistreerd als reumatoloog. Sinds maart 2011 is zij lid van de Maatschap Reumatologie Kennemerland en als reumatoloog werkzaam in het Spaarne Ziekenhuis te Hoofddorp.



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