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The course of clinically suspect arthralgia and early rheumatoid arthritis : clinical features, imaging and genetics

Steenbergen, H.W. van

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Author: Steenbergen, H.W. van

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General introduction

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RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is characterised by persistent inflammation and destruction of the small joints ¹. The disease can result in significant morbidity with pain, loss of function and work disability and consequently high socio-economic costs ²⁻⁴. It is the most common inflammatory arthritis with a worldwide prevalence of 0.5-1% and mostly affects middle-aged female (female:male ratio 3:1), but it can occur at every age ¹. Based on data of Dutch general practitioners (NIVEL), the prevalence in the Netherlands was in 2013 1.3% ⁵.

The etiology of RA is largely unknown, but RA is considered to have an autoimmune origin because of the presence of autoreactive antibodies. These autoantibodies include rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) ¹. Especially ACPA has a high specificity for RA (ACPA is only present in 1% of the general population ⁶) and can be detected in 50-60% of all early RA patients ⁷⁻⁹. Although several pathophysiological mechanisms have been proposed, it is still unclear how RA-related autoantibodies exert their effects ¹⁰. However, ACPA-positive and ACPA-negative RA are considered different disease entities with different underlying pathogeneses and disease courses ¹¹. Recently, novel autoantibody systems in RA have been identified, such as anti-carbamylated protein antibodies (anti-CarP).¹² These autoantibodies were present in both ACPA-positive and ACPA-negative patients, suggesting broad autoantibody production within RA and autoimmunity also in patients currently considered as seronegative.

In addition, more than 100 genetic risk factors for RA have been identified thus far ¹³. Although the heritability of RA is reported to be up to 50% in both ACPA-positive and ACPA-negative RA ¹⁴, they have a different genetic background and most genetic risk factors are identified within ACPA-positive RA ^{11,15}. The most important genetic risk factor for ACPA-positive RA is located in the HLA-DRB1 region. The predisposing alleles share a similar amino acid sequence at positions 70-74 in the peptide-binding groove of the HLA-DRB1 molecule (the shared epitope (SE)). The SE hypothesis postulates that the SE motif itself may be directly involved in the pathogenesis of RA by allowing the presentation of an arthritogenic peptide to T-cells ¹⁶. Recently, a further refinement of the association of HLA with RA was proposed by making use of advanced statistical analyses ¹⁷. Variations in HLA-DRB1 position 11 most strongly associated with development of both ACPA-positive ¹⁷ and ACPA-negative RA ¹⁸; within ACPA-positive RA this association was independent of the SE status ¹⁷.

Furthermore, environmental factors might play a role in RA development. Many potential environmental risk factors have been suggested ¹⁹, but smoking is the only widely replicated environmental risk factor, especially for ACPA-positive RA in patients carrying HLA-SE alleles ²⁰.

Therapeutic approaches for RA have changed considerably the last decades from

conservative step-up strategies to early and aggressive treat-to-target strategies with disease-modifying antirheumatic drugs (DMARDs) and biologics ²¹. The importance of early treatment was set by observations that delay of treatment initiation was associated with a worse disease outcome, such as more severe joint damage and a lower chance on achieving remission ^{8,22,23}. The concept of the 'window of opportunity' proposed that there is an early phase in the disease in which the disease can be modified more successfully, presumably because the underlying disease processes are not yet fully matured ²⁴. The exact duration of this period is unknown, though it has been suggested that this period consist of 12 weeks and is a confined period ²⁵. Because treatment initiation in this early phase result in more beneficial long-term outcomes, the field of RA is moving into identifying RA in very early disease stages.

THE PHENOTYPE OF RA

A typical clinical presentation of RA consists of joint pain and swelling, morning stiffness and a symmetric polyarthritis of the small hand and foot joints. In addition, systemic symptoms such as fatigue and weight loss can be present. However, the presentation of RA may be considerably heterogeneous. In clinical practice, the diagnosis is made based on the judgment and expertise of the rheumatologist as no diagnostic test or diagnostic criteria for RA exist.

Classification criteria for RA have been developed to identify homogeneous groups of patients for enrolment in clinical studies, particularly trials. The 1987 ACR criteria for RA were designed to differentiate patients with established RA from patients with other types of rheumatic diseases (Table 1) ²⁶. These criteria included the items radiographic changes and rheumatoid nodules which are characteristic for advanced disease and classify mainly patients with established RA. With the increasing insights that early treatment initiation in RA is beneficial, clinical trials were designed to treat patients in more early disease phases. For this purpose, the 1987 criteria were inappropriate because of its poor sensitivity to classify patients with early RA.

The 2010 ACR/EULAR criteria for RA were developed to identify RA patients in early disease and focused on features in early arthritis that associated with persistent and/or erosive disease (Table 1) ²⁷. Radiographic changes were not included as these were not characteristic for early disease. However, it was decided that when erosions typically for RA were present a patient was classified as RA in order to capture also patients with established but inactive disease who did not fulfil the criteria of early disease ^{27,28}. The new criteria indeed classified more patients in early disease but also resulted in more heterogeneity in patients classified as RA ²⁹. In line with this, the phenotype at RA presentation and during the course of RA is different when disease is classified according to the 1987 criteria or 2010 criteria ^{30,31}.

Table 1. Classification criteria for RA

| 1987 ACR criteria ²⁶ | 2010 ACR/EULAR criteria ²⁷ |
|------------------------------------|--|
| Morning stiffness | Joint involvement* 1 large joint (0) |
| Arthritis of 3 or more joint areas | 2-10 large joints (1) 1-3 small joints (2) |
| Arthritis of hand joints | 4-10 small joints (3) >10 joints (at least 1 small joint) (5) |
| Rheumatoid nodules | Serology Negative RF and negative ACPA (0) |
| Serum RF | Low-positive RF or low-positive ACPA (2) High-positive RF or high-positive ACPA (3) |
| Radiographic changes | Acute-phase reactants Normal CRP and normal ESR (0) Abnormal CRP or abnormal ESR (1) Duration of symptoms <6 weeks (0) ≥6 weeks (1) |

1987 ACR criteria: patients fulfilling ≥ 4 out of 7 criteria are classified as RA

2010 EULAR/ACR criteria: patients with a score of ≥ 6 out of 10 are classified as RA

*Refers to any swollen or tender joint on examination

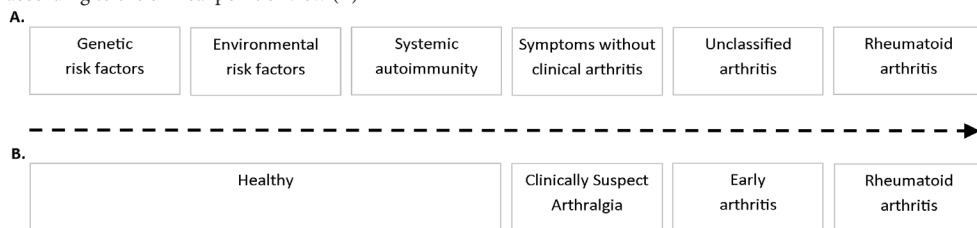
PRECLINICAL RA

RA has a period of preclinical disease. This became well-recognised because of observations that ACPA and RF could be detected several years before the presentation with RA ^{32,33}. This was studied in cohorts of blood donors from whom multiple blood samples of RA patients were available before their arthritis became clinically detectable. The frequency of autoantibody positivity as well as the level and the epitope spreading increased when approaching the moment of symptom onset ³²⁻³⁵, indicating maturation of the autoantibody response in the preclinical period. Using a similar study approach, markers of systemic inflammation and biomarkers of bone metabolism were found to be increased in the preclinical phase ³⁶⁻³⁸. These findings suggested that disease processes within RA can be active years to months before a patient presents with RA.

Recently, the EULAR study group for risk factors for RA formulated terminology to be used during the different preclinical and early phases of RA that could be used as framework for future research ³⁹. Six phases (phases A-F) of RA development were formulated: (A) genetic risk factors for RA, (B) environmental risk factors for RA, (C) systemic autoimmunity associated with RA, (D) symptoms without clinical arthritis, (E) unclassified arthritis and (F) RA (Figure 1) ³⁹. It was emphasised that the phases could be used in a combinatorial manner, indicating that a patient can be in two phases concurrently. In addition, patients do not have

to pass through all phases and the phases do not necessarily occur in the same order before RA develops. Importantly, the term 'pre-RA' should only be used retrospectively as it was considered inappropriate to label healthy persons with certain genetic or environmental risk factors as having pre-RA as the majority of them will never develop RA ³⁹. This latter, is in line with the clinical point of view of development of RA in which a patient is healthy until presenting with complaints (Figure 1).

Figure 1. The phases of RA development as defined by the EULAR study group for risk factors for RA (A) and according to the clinical point of view (B)



CLINICALLY SUSPECT ARTHRALGIA

One of the defined early phases in RA development was the phase of symptoms without clinical arthritis (Figure 1). Although it was widely recognised by the study group that many patients with RA have a period of symptoms that is likely to be related to the development of RA before they develop clinical arthritis, the symptoms that are specific for this early phase were not specified.

Identifying patients in the early symptomatic phase without arthritis is challenging as arthralgia is the main symptom of most patients presenting to rheumatologists and the majority will never develop RA. In addition, to allow studies on this early symptomatic phase it is needed that arthralgia patients with an increased prior chance on RA are identified. This can be done by adding the criterion of having RA-related autoantibodies to the arthralgia ^{40,41}. Another approach is to make distinctions based on the type of arthralgia. Patients with Clinically Suspect Arthralgia (CSA) have arthralgia that is because of the character of the symptoms considered by their rheumatologist as clinically suspect to progress to RA over time. This approach is based on the clinical expertise of the rheumatologist and proposes that clinical expertise is a valuable tool to select patients with an increased risk of RA. Selecting patients on clinical grounds before ordering additional tests is in line with clinical practice (Figure 1) and allows identifying both autoantibody-positive and autoantibody-negative RA in an early symptomatic phase.

Clinically Suspect Arthralgia cohort

The CSA cohort is an inception cohort that was set up in Leiden in April 2012 to study the early symptomatic RA phase without clinical arthritis. The inclusion criteria are the presence

of arthralgia of the small joints for less than one year which, because of the character of the symptoms, is considered by the rheumatologist as being suspect to progress to RA over time. No further criteria are made with regards to the type of symptoms and thus inclusion is essentially based on the expert opinion of the rheumatologist. Importantly, CSA is not present if clinical arthritis was observed at physical examination or another explanation for the arthralgia was more likely (such as osteoarthritis or fibromyalgia).

At baseline, questionnaires are completed, physical examination performed, blood obtained and X-rays and MRI made. Magnetic Resonance Imaging (MRI) of the MCP2-5, wrist and MTP1-5 joints of the most painful side, or the dominant side in case of equally severe symptoms at both sides, is performed within two weeks after clinical assessment. The joints are scanned with an 1.5 Tesla extremity MRI-scanner using contrast-enhancement and according to the RA MRI scoring system (RAMRIS) protocol ⁴².

Patients are prospectively followed with scheduled visits at 4, 12 and 24 months. If necessary (for instance when the patient noticed swollen joints) patients are seen in between the scheduled visits by their rheumatologist. Follow-up ends earlier when clinical arthritis has developed.

MRI in Clinically Suspect Arthralgia

Local subclinical inflammation might be present in the early symptomatic phase of RA without clinical arthritis ⁴³⁻⁴⁵. MRI is a very sensitive imaging modality and more sensitive than physical examination to measure local inflammation ^{42,46}. This makes MRI a suitable tool for evaluating the earliest inflammatory changes in the small joints of patients that might be in the early phase of RA. MRI depicts inflammation of the synovium of joints (synovitis) and tendons (tenosynovitis). In addition, it is the only imaging modality that can depict bone marrow edema (BME), which is also called osteitis in RA and is a strong predictor for progression of joint damage in RA ^{42,47}. The presence of a validated semi-quantitatively scoring methodology (the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring system (RAMRIS)) makes MRI very suitable for research as the extent and severity of MRI features can be compared objectively ^{42,48}.

SEVERITY OF RA COURSE

The course of RA is variable between patients; some patients have a disabling, persistent course with severe joint destruction while others have a more mild disease course. The biologic processes underlying these interindividual differences in joint destruction and disease persistence are incompletely understood thus far. In addition, differentiating patients who will develop a severe disease course from patients with a mild disease course is not yet accurate ^{49,50}, hampering individualised treatment.

To evaluate the disease course in RA several outcome measures are used. Disease activity is commonly assessed by the Disease Activity Score (DAS) which is a composite

measure of the swollen and tender joint count, the patient global assessment of the disease activity on a visual analog scale (VAS) and the level of acute phase reactants⁵¹. Functional disability is mostly measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) which consists of 20 questions in eight categories of functioning⁵². The traditional long-term outcome in RA is the severity of destruction of the small joints, one of the hallmarks of RA⁵³. Another important long-term outcome is arthritis persistence.

Joint damage as disease outcome

The severity of damage of the hand and feet joints, assessed on radiographs is the key outcome measure in RA. This outcome measure has several advantages. First, it is considered to reflect the cumulative burden of inflammation and thus represents the disease history⁵³. In addition, joint damage is strongly associated with other outcome measures, such as functional disability⁵⁵. And third, it is very suitable as outcome measure for research purposes because of the presence of validated scoring methods that allows evaluating the extent of joint damage on radiographs objectively⁵³.

The most commonly applied scoring method is the Sharp-van der Heijde scoring (SHS) method. This measure quantitatively evaluates the extent of erosions (range 0-280) and joint space narrowing (which reflects cartilage damage, range 0-168) in both hands and feet⁵⁶. Another scoring methodology is the Larsen score⁵⁷, which gives a combined score for erosions and joint space narrowing per joint. The SHS is more sensitive to detect changes over time though also more time-consuming than the Larsen score⁵³.

To study joint damage, it is preferred that the study population has serial radiographs over time instead of one radiograph at a single time point to capture the progression in joint damage over time adequately. In addition, when investigating specific risk factors for the severity of joint damage the studied patients are ideally untreated to evaluate the risk factor in relation to the natural course of joint damage. The latter may be the case for patients diagnosed and treated in eras when early tailored treatment and use of biologics were uncommon. However, large well-defined longitudinal cohorts including such patients are scarce. To overcome these limitations, results of several (small) cohorts can be combined in meta-analyses and adjustments can be made for the applied treatment strategy.

Risk factors for joint damage progression

Joint destruction is caused by a disbalance between bone degradation and formation. In RA, several inflammatory and immune cell types can be present in the synovial membrane. Two cell types can be considered of particular importance in destruction of bone and cartilage. Synovial fibroblasts are considered important for cartilage degradation. These cells, physiologically involved in the secretion of synovial fluid, can be present abundantly in the synovial membrane in RA and can behave aggressively with invasion of the underlying cartilage. Dysregulated osteoclast activation is mainly involved in bone degradation^{1,58}. Why these processes occur and how they are initiated is incompletely understood, but several risk

factors for joint damage have been identified.

The most important risk factor for severe joint damage progression is the presence of autoantibodies, mainly ACPA. Also inflammatory markers are associated with more severe joint damage progression. Autoantibodies and inflammatory markers together explain approximately 30% of variance in joint destruction after 5 years of disease ⁵⁹.

In addition, genetic factors play a major role in the severity of joint damage as the heritability of the severity of joint damage has been estimated to be 45-58% ⁶⁰. Several genetic risk factors for joint damage have been identified thus far and have been replicated in independent cohorts ⁶¹, which is needed in the field of genetics to prevent false-positive findings. Most findings were done using candidate gene studies ⁶²⁻⁷¹ that were dedicated to genes associated with RA development or genes involved in inflammation, immunity or bone homeostasis, though hypothesis-free genome-wide association studies (GWAS) have also been used ⁷². The *HLA-DRB1* SE was the first identified genetic risk factor for joint damage and similar as for the association of the SE with RA development, SE was not associated with joint damage progression as such but predisposed to ACPA-positive RA that is associated with more severe joint damage ⁶². In addition, genetic risk factors were identified in *CD40*, *C5orf30*, *IL15*, *IL2RA*, *IL4R*, *DKK1*, *GRZB*, *MMP9*, *OPG* and *SPAG16* ⁶³⁻⁷². However, a large part of the total genetic effect is considered to be still unexplained.

Arthritis persistence as disease outcome

Persistent arthritis is the other hallmark of RA and can be studied by evaluating its opposite: achieving DMARD-free sustained remission which is defined as the sustained absence of clinical arthritis at physical examination without the use of DMARDs (including corticosteroids). This outcome can be considered the most favourable outcome in RA as it approximates cure of RA ⁵⁴.

Only a few risk factors for arthritis persistence (absence of achieving DMARD-free sustained remission) have been reported and replicated. One of these factors is prolonged symptom duration at treatment start ^{23,54}, which points to the so-called 'window of opportunity' in RA. Another risk factor is the presence of autoantibodies ^{54,59}, but these explain only a proportion of the variance in arthritis persistence as the large majority of autoantibody negative patients have persistent disease and some patients with autoantibodies can achieve remission ⁷³. The *HLA-DRB1* SE is the only genetic risk factor that has been found associated with arthritis persistence thus far. To get more comprehension into the mechanisms promoting the chronic nature of RA further risk factors for arthritis persistence need to be identified.

AIMS AND OUTLINE OF THIS THESIS

In general this thesis has two main aims:

1. to investigate the early phase with Clinically Suspect Arthralgia
2. to identify genetic risk factors for disease severity in rheumatoid arthritis

The thesis contains three parts.

In **Part I**, the very early phases of RA without clinically detectable arthritis, mainly the phase of Clinically Suspect Arthralgia (CSA), is examined. In **Chapter 2**, it is systematically reviewed what is currently known on the preclinical phases of RA. This was done within the framework of the phases for the preclinical and early phases of RA formulated by the EULAR study group for risk factors for RA. In **Chapter 3**, the CSA approach and the CSA cohort are introduced. The characteristics of patients with CSA are described and the symptoms, signs and serological markers that are related to subclinical inflammation on MRI are studied. **Chapter 4** evaluates whether subclinical MRI-inflammation is, similar as in ACPA-positive arthralgia patients, also present in ACPA-negative arthralgia patients who are considered prone to progress to RA. For comparisons, also healthy controls and ACPA-negative RA patients are evaluated. **Chapter 5** is the first longitudinal study on patients with CSA and investigates progression from CSA to clinically detectable arthritis. Associations between clinical and serological factors and subclinical MRI-inflammation with the development of clinical arthritis are examined. In **Chapter 6**, the diagnostic accuracy of the clinical expertise for CSA is explored. **Chapter 7** describes the process in which a EULAR taskforce develops an expert-opinion based definition for CSA which may serve as the basis for observational studies and trials in this phase.

In **Part II**, genetic risk factors for a more severe course of RA, in particular joint damage progression, are investigated. These studies are mainly performed within the Leiden Early Arthritis Clinic (EAC) cohort⁵⁹. Since 1993 patients with arthritis of at least one joint and symptom duration less than two years have been included in this population-based inception cohort and prospectively followed during yearly visits. **Chapter 8** evaluates the contribution of the known genetic risk factors to the variance in the severity of joint damage progression and to the accuracy of predicting this severity. Chapter 9-11 describes candidate gene studies for the severity of joint damage. In **Chapter 9**, a variant in *FOXO3A* that was reported to associate with joint damage in RA is replicated. In **Chapter 10**, a variant in *SPP1* is studied that was reported to associate with the development of ACPA-negative RA. **Chapter 11** aims to clarify associations of variants in *IL6*, *IL10*, *C5-TRAF1* and *FCRL3* that have been reported to associate with joint damage but for which the results of different studies were contradictory. **Chapter 12** focuses on position 11 at HLA-DRB1 which was recently reported to have a strong association with RA development. In **Chapter 13**, genetic risk factors for joint damage are studied in relation to arthritis persistence, another long-term outcome. In **Chapter 14**, serum level osteoprotegerin is studied in relation to arthritis persistence.

In **Part III**, other outcomes are studied. In **Chapter 15**, it is investigated whether the occurrence of DMARD-free sustained remission is promoted by improved treatment strategies and the relevance of achieving this outcome from patient perspective. **Chapter 16** focuses on fatigue in RA; its eight year course and associations with inflammation and improved treatment strategies are studied.

Finally, **Chapter 17** provides a summary and discussion of the results that are described in this thesis.

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