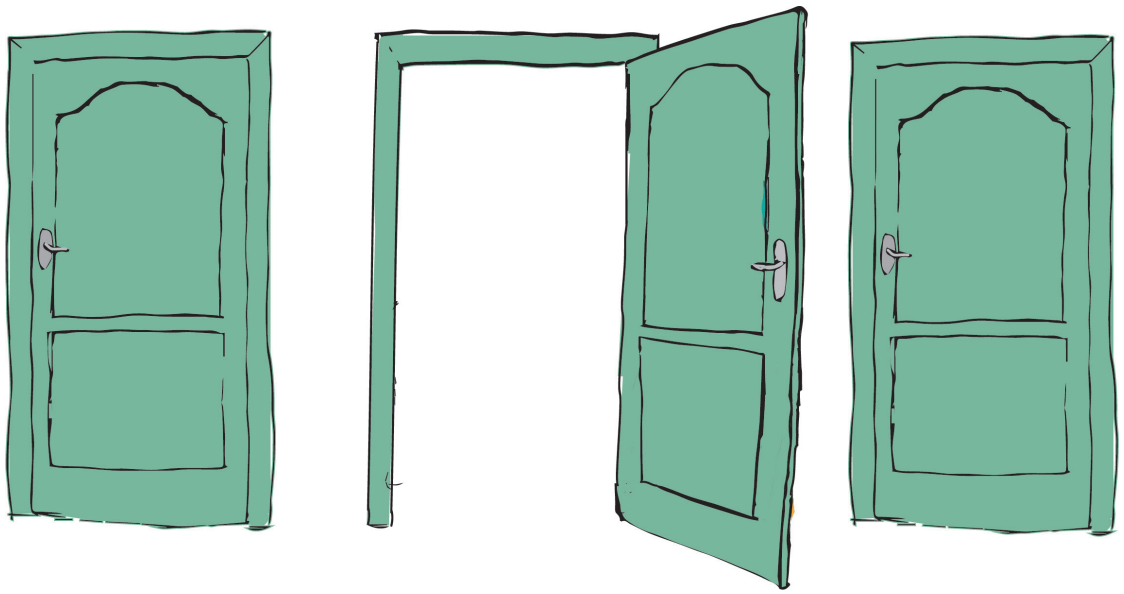
Differences and similarities of autoantibody-positive and autoantibody-negative rheumatoid arthritis during the disease course: on our way to personalized medicine

Matthijssen, X.M.E.

CHAPTER 1

Introduction



RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease. RA is predominantly characterized by inflammation of the small joints and often persists for a lifetime.[1] RA affects around 0.5% to 1% of the worldwide population, and every year, over 1 million patients are newly diagnosed with RA.[2] RA is more common in females than males (ratio 3:1), presents most often around the sixth decade of life and is more prevalent in western countries.[2]

Autoantibodies

Around 50% of RA patients have autoantibodies, such as anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF). These autoantibodies often co-occur and are rare in the general population.[3-5] RA-patients are often classified as either being autoantibody-positive (with autoantibodies) or autoantibody-negative (without autoantibodies), because these autoantibodies are influential during the whole disease course: they are already present before the first complaints,[6] generally persist throughout disease [7] and associate with a more severe disease course.[8]

Clinical presentation

Both autoantibody-positive and autoantibody-negative RA patients typically present similarly with symmetrical swelling, tenderness and morning stiffness of the hands and feet' small joints, accompanied by systemic complaints such as fatigue, malaise and weight loss.[8] However, the first clinical presentation of RA might be very heterogeneous. The diagnosis is often made based on the treating rheumatologist's judgment and expertise based on "pattern recognition".

Classification criteria

For research purposes in general and clinical trials in particular, classification criteria for RA were derived to identify a homogeneous group of RA patients. 1987 ACR criteria were designed to optimally discriminate between patients with RA and patients with other rheumatological diseases.[9] Since the 1987 ACR criteria include late RA manifestations such as rheumatoid nodules and radiographic changes, they have low sensitivity for early RA patients (Table 1).

To identify patients with very early disease, the 2010 ACR/EULAR criteria have been developed (Table 1).[10] These criteria were designed to identify patients with persistent and/or erosive disease in an early stage. Since autoantibodies are present in early disease and strongly associated with both persistent and erosive disease, the 2010 ACR/EULAR criteria heavily lean on the presence of autoantibodies. Consequently, the 2010 ACR/EULAR criteria are very sensitive for very early autoantibody-positive RA. In contrast, the fulfillment of these criteria requires > 10 affected joints in autoantibody-negative patients.[11] The disparity in number of joints needed for classification caused unintended differences between autoantibody-negative and autoantibody-positive patients identified by the 2010 criteria.

Table 1. Classification criteria for Rheumatoid Arthritis

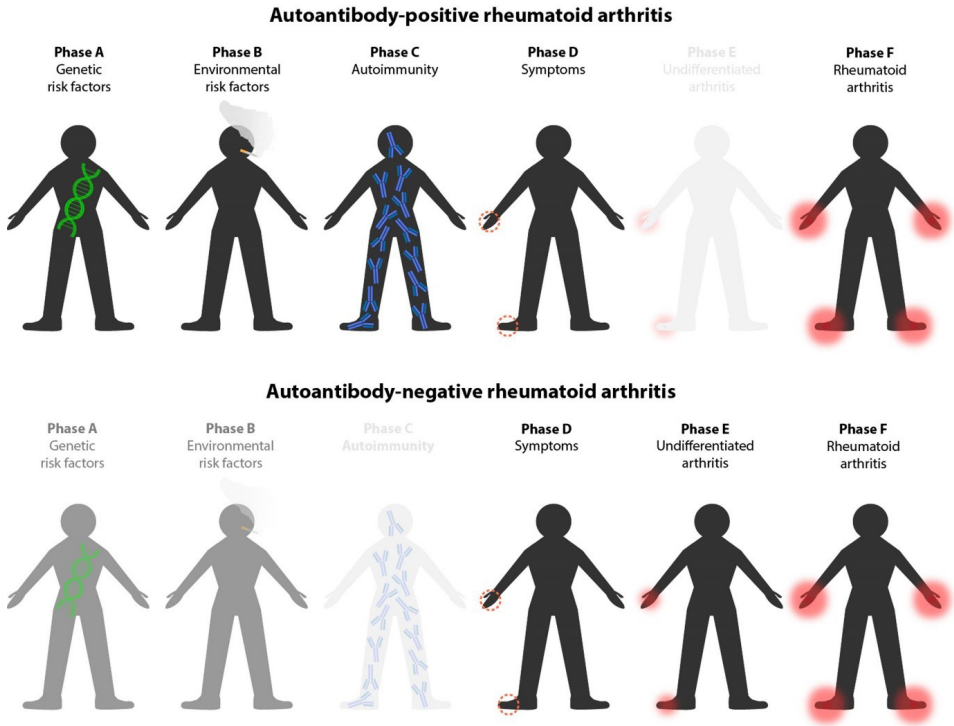
Revised ACR 1987 criteria	2010 ACR/EULAR criteria
Arthritis ≥3 joint areas (1)	Joint involvement
Arthritis of hand joints (1)	1 large joint (0)
Symmetric arthritis (1)	2–10 large joints (1)
Morning stiffness ≥ 1 hour (1)	1–3 small joints (2)
Rheumatoid nodules (1)	4–10 small joints (3)
Radiographic changes (erosions) (1)	>10 joints (5)
Presence of RF (1)	Serology
	ACPA and RF negative (0)
	Low-positive ACPA or RF (2)
	High-positive ACPA or RF (3)
	Acute-phase reactants
	Normal CRP and ESR (0)
	Abnormal CRP or ESR (1)
	Duration of symptoms
	<6 weeks (0)
	≥6 weeks (1)
4/7 criteria must be present to fulfil criteria	6/10 points must be present to fulfil criteria

Legend: ACR: American college of rheumatology; EULAR: European league against rheumatism; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate.

RA BEFORE DIAGNOSIS

The diagnosis with either autoantibody-positive or autoantibody-negative RA is often preceded by a preclinical phase with systemic alterations, arthralgia and (in case of autoantibody-positive RA) presence of autoantibodies.[6,12] The EULAR study group for risk factors for RA formulated terminology for future research.[13] The working group formulated six phases: (A) genetic risk factors for RA, (B) environmental risk factors, (C) systemic autoimmunity, (D) symptoms without clinical arthritis, (E) unclassified arthritis and (F) rheumatoid arthritis. However, not all phases are (equally) applicable to both autoantibody-positive and autoantibody-negative disease as displayed in Figure 1 and elaborated on below.

Figure 1. The phases of RA as defined by the EULAR study group for risk factors for RA in autoantibody-positive and autoantibody-negative RA



Legend: The shade of the phase represents the frequency of identification and/or presence of that phase to autoantibody-positive and autoantibody-negative rheumatoid arthritis, respectively. Black phases are often identified, grey phases are less often identified than in the other autoantibody group and light grey phases are (almost) never identified.

Phase (A): genetic risk factors

The overall heritability of RA is estimated to be ~40%. However, "genetic risk factors" are predominantly identified in autoantibody-positive RA and seem to play a more prominent role in this RA type. The best described genetic risk factor for RA, the HLA shared epitope, is associated with RA only in ACPA positive patients.[14,15] Moreover, autoantibody-positive RA has a higher heritability [16]. Genome Wide Association Studies (GWAS) have identified small frequent variations in the human genome, Single Nucleotide Polymorphisms (SNPs), that associate with RA risk. Similar to the HLA shared epitope, most SNPs only associate with the development of autoantibody-positive RA.[17] In contrast, extensive GWAS have failed to identify genetic risk factors for autoantibody-negative RA.[17] This difference between autoantibody-positive and autoantibody-negative RA might be explained by the heterogeneity of autoantibody-negative RA and misdiagnosis of autoantibody-negative RA patients. However, until now, no studies have supported the hypothesis that autoantibody-negative RA is more heterogeneous. Altogether, the genetic risk seems to be predominantly confined to autoantibody-positive RA.

Phase (B): environmental risk factors

Regarding phase B, "environmental risk factors", RA's most important risk factor is smoking.[18,19] Increasing evidence has stated that smoking is associated with mainly autoantibody-positive RA development.[19] Another environmental risk factor is microbiomic alterations, that also precede RA development. These microbiomic alterations are again mainly associated with the development of autoantibody-positive RA.[18] Here again, heterogeneity of the autoantibody-negative RA subtype might influence results and could have prohibited discovery of environmental risk factors. However, it seems that environmental risk plays a more prominent role in autoantibody-positive RA.

Phase (C): systemic autoimmunity

"systemic autoimmunity" is often defined as the presence of autoantibodies such as ACPA and RF. Autoantibody-negative patients might also have (undiscovered) autoantibodies. Many researchers have tried to close this so-called "serological gap" and discovered new autoantibodies such as AAPA and anti-Carp.[20] However, most patients with these autoantibodies already have ACPA and or RF, leaving the serological gap mostly unchanged.[21]

The absence of discovered autoantibodies might impose the idea that inflammation does not play a role in the pathogenesis of autoantibody-negative RA. However, this seems not to be the case as markers of systemic inflammation, such as erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP), are present and already increased compared to healthy controls before complaints both in autoantibody-negative and autoantibody-positive RA.[22,23]

Phase (D): symptoms without clinical arthritis

The fourth phase, symptoms without clinical arthritis, can be studied in risk groups of persons with a reasonable chance to develop RA. Two types of risk groups are often studied: autoantibody-positive persons with musculoskeletal complaints and clinically suspect arthralgia (CSA) patients. Since seropositivity generally persists, autoantibody-positive arthralgia patients usually convert to autoantibody-positive RA.

In contrast, clinically suspect arthralgia patients can be both autoantibody-positive and autoantibody-negative both at presentation and at the moment of arthritis development: At presentation, 14% of CSA patients are ACPA-positive whereas 45% of CSA patients who develop arthritis are ACPA-positive.[12,24] Because risk factors

for arthritis development might differ for autoantibody-positive and autoantibody-negative patients and the CSA cohort includes both autoantibody positive and autoantibody-negative patients, some identified risk factors might differ between strictly autoantibody-positive cohorts and the CSA cohort.

Phase (E): unclassified arthritis

The fifth phase, the phase of unclassified arthritis, is the phase in which arthritis is already present. Patients are suspect for RA but cannot be definitively diagnosed with RA yet. As mentioned before, the 2010 criteria were designed to classify patients as having RA in an earlier stage. However, the 2010-criteria also heavily load on the presence of autoantibodies. Therefore, patients with autoantibodies are classified as RA without many other factors present: they only need one small affected joint to be classified. In contrast, patients without autoantibodies need >10 affected joints to fulfill the 2010 criteria. Therefore, the remaining patients with unclassified arthritis are predominantly autoantibody negative and most autoantibody-positive patients apparently skip the phase of unclassified arthritis.

RA AT DIAGNOSIS AND DURING DISEASE

RA is a long-term, potentially invalidating disease. While RA predominantly affects the joints, it can also cause systemic symptoms such as fatigue, decreased functionality and extra-articular manifestations. On the societal scale, RA affects work productivity and participation. RA can cause excess mortality and RA treatment can cause increased healthcare costs. Therefore research on RA can focus on the joint level, the patient level and the societal level.

Joint-level

Clinical

Inflammation in RA at the joint level can lead to swelling of the joints, tenderness of the joint and movement impairment of the joint.[25] Because no objective measure of disease activity in RA exists, composite indices are used to measure disease activity in RA. These composite indices incorporate the number of swollen and the number of tender joints from a prespecified subset. Next to these joints scores, often a measure of patient evaluated global disease activity are incorporated.[26] Perhaps the most used example of a composite measure of disease activity is the disease activity score (DAS) and a simplification of the DAS that omits the joints in the feet (DAS28).[27,28] These composite measures also include objective systemic inflammatory markers (CRP, ESR). At baseline, the distribution of affected joints and DAS at baseline is similar for autoantibody-positive and autoantibody-negative RA patients.[8,29] Under randomized and protocolized treatment, DAS over time has been reported both to be lower and higher in autoantibody-positive and autoantibody-negative patients.[30,31]

Damage

Prolonged inflammation in joints can lead to permanent bone and cartilage damage in joints.[32,33] The Sharp - van der Heijde score is most often used to quantify bone and cartilage damage. This score incorporates erosions and joint space narrowing in the hands and the feet.[34] Damage can lead to disability.[35] Treating the DAS be below a certain threshold that we often call “remission” prevents long-term damage, for the most part, irrespective of medication used to keep remission.[36] Treating until remission is achieved is called the treat-to-target strategy. Drugs that are used to lower the DAS to in the end prevent damage are called disease modifying anti-rheumatic drugs (DMARDs). Autoantibody-positive patients have more damage progression over time.[8] Moreover, it has been hypothesized that the relationship between disease activity and joint damage is only present in autoantibody-positive RA.[32]

MRI + Ultrasound

While X-ray imaging can be used to detect damage in joints, X-ray images are not suitable to visualize inflammation. Ultrasound imaging and Magnetic Resonance Imaging (MRI) can be used to visualize both intraarticular inflammation such as synovitis as juxta-articular inflammation such as tenosynovitis.[37] MRI is more sensitive for the detection of these features.[37] Moreover, MRI has better reproducibility and MRI can visualize bone marrow edema that represents inflammation in the bone (osteitis).[38] MRI inflammation is predictive for arthritis development in both autoantibody-negative and autoantibody-positive arthralgia patients.[39] However, during progression to RA, the trajectories of MRI inflammation might differ between autoantibody-positive and autoantibody-negative RA. Therefore the optimal MRI predictors might differ between those subsets.[40] At arthritis diagnosis, the amount of synovitis and tenosynovitis is similar between autoantibody-positive and autoantibody-negative patients with UA or RA. In contrast, the amount of osteitis was higher in autoantibody-positive patients in this study.[41] However, comparisons of diagnosed RA patients are scarce and comparisons of the trajectories of MRI inflammation after arthritis between autoantibody-positive and autoantibody-negative RA patients were not performed yet.

Patient-level

Inflammation in the joint, damage of the joints and systemic inflammation can lead to disability and patient-reported disease-related complaints (PROMs) such as pain, fatigue and morning stiffness.[42,43] While inflammation contributes to these complaints, also other factors such as mental health and coping mechanisms contribute majorly to these complaints.[42]

Besides, RA is also related to a higher prevalence of stress and depression.[44] Stress and depression also predict higher disease activity over time.[44] Concludingly, inflammation, patient-reported complaints and mental health are factors that influence each other and strengthen each other. However, how and if this differs between autoantibody-positive and autoantibody-negative RA is insufficiently described. Depression is associated with subsequent development of autoantibody-negative RA but not autoantibody-positive RA.[45] Autoantibody-positive and autoantibody-negative RA patients have similar trajectories of functionality and PROMs over time.[46]

Societal impact

Epidemiology

Since RA often emerges in the sixth decade of life, the age distribution influences the incidence of RA. Since worldwide more persons reach the sixth decade, the incidence is rising.[2] Since autoantibody-negative RA patients tend to be older, it can be hypothesized that autoantibody-negative incidence will increase even more. However, until now, this remains to be elucidated.

The incidence of RA, the mortality of RA patients and the extent to which RA can be "cured" influence the prevalence of RA. RA patients experienced excess mortality compared to the general population. However, this excess mortality seems to have disappeared after the introduction of treat-to-target strategies.[36,47,48] Excess mortality in RA is predominantly caused by cardiovascular death. However, it is unknown whether this is true for both autoantibody-positive and autoantibody-negative RA.

Costs

The economic burden of RA depends on both the work productivity lost as well as the medication costs. The European medicine agency approved the first biological infliximab for RA treatment in the early 2000s.[49] Since biologicals are more expensive than other drugs, these contribute most to the medication costs of RA.[50] Altogether, ~80.000.000 euros are spent annually on the care of RA patients in the Netherlands. This number will probably rise by ~10.000.000 within the coming ten years.[51] Generally, autoantibody-positive RA more often requires biological treatment.[52] In contrast, work loss in RA is substantial and does not differ between autoantibody-positive and autoantibody-negative RA.[46]

CURE OF RA

While RA persists for a lifetime in most RA patients, some patients achieve sustained DMARD-free remission (SDFR). SDFR is the absence of any swollen joint after more than one year of DMARD cessation.[53] Therefore this is a clinical proxy for 'cure'. This outcome has become increasingly achievable since early methotrexate treatment is associated with normalization of functionality and low patient-reported symptoms.[54] The absence of autoantibodies and shared epitope alleles increased the chance of achieving DFR.[53]

AIMS

Concludingly, while autoantibody-positive and autoantibody-negative RA have similar clinical presentations, it has become increasingly clear that they also have many differences. Therefore it has been hypothesized that autoantibody-negative and autoantibody-positive RA are distinct diseases that require different diagnosis and treatment. However, this hypothesis has not been systematically studied.

Therefore this thesis aims to assess the differences and similarities between autoantibody-positive and autoantibody-negative RA from the start of complaints to the end of the disease.

The described research was performed with the ultimate goal to clarify whether autoantibody-negative and autoantibody-positive RA are distinct diseases that require different diagnoses and treatment.

COHORTS

CSA

To address these questions, we took advantage of two large observational cohorts based in the Leiden university medical center (LUMC): The CSA cohort and the early arthritis cohort (EAC). In the CSA-cohort patients are included that are at risk of RA development, according to their rheumatologist, that have not developed arthritis yet.[12] At baseline, rheumatologists and patients completed questionnaires, swollen and tender joint counts were performed and blood samples were taken for routine diagnostic laboratory screening. Besides, a unilateral 1.5 Tesla MRI of the MTP, MCP and wrist joints was performed. Patients were prospectively followed with scheduled visits at 4, 12 and 24 months; additional visits were scheduled in case of increasing symptoms.

EAC

Patients with recently developed arthritis were included in the Leiden EAC. This cohort

exists since 1993 and is extensively described elsewhere.[55] Also, in this cohort, patients received physical examinations, questionnaires and laboratory screening at baseline. In principle, patients are followed until discharge from the Rheumatology outpatient clinic. In 2010 MRI scans were added to the baseline visit, and until 2015 MRIs were repeated during the first two years.

The most prominent advantage of the Leiden EAC is that all rheumatologists in the Leiden area are affiliated to the LUMC and that inclusion in the Leiden EAC has been part of standard treatment for early arthritis patients since 1993. Moreover, inclusion criteria have not changed over time and all patients have been subjected to regular yearly follow-up visits by trained research nurses. This ensures a representative sample of arthritis patients with regularized measurements during follow-up.

OUTLINE

This thesis follows the disease course of a RA patient from start of complaints to the end of disease. Three phases are studied: The pre-arthritis phase from the beginning of complaints until arthritis development, the early arthritis phase from arthritis development until 2 years after and the long-term outcomes that were observed until 15 years after diagnosis.

Pre-arthritis

In **Chapter 2**, we studied the pre-arthritis phase and analyzed which combinations of MRI-features at presentation with CSA were predictive for RA-development to increase our comprehension of locations of RA-onset and improve the predictive accuracy of MRI in a cohort with both autoantibody-positive and autoantibody-negative patients.

Early arthritis

In **Chapter 3**, we studied early arthritis patients before treatment. We hypothesized that if MRI-detectable tenosynovitis is a true RA-feature, the sensitivity for RA is high at diagnosis, in both autoantibody-positive and autoantibody-negative RA, and lower in other diseases and investigated this in the EAC cohort. Again concerning early arthritis patients, in **Chapter 4** we determined trends in incidence of autoantibody-negative and autoantibody-positive RA around Leiden. We also examined how the age-distribution of the population affected this incidence and what this would implicate in the future. In **Chapter 5**, we studied the association of fatigue and MRI inflammation at diagnosis and during the first two years of disease course in a large consecutive cohort of >500 RA patients and stratified for autoantibody status. In **Chapter 6**, the time order of inflammation decrease after treatment was investigated in early UA and RA patients and compared between autoantibody-positive and autoantibody-negative patients

Long-term outcomes

In **Chapter 7,** we studied the changes in disease activity and three long term outcomes (functionality, mortality and SDFR) in autoantibody-negative and autoantibody-positive RA patients over the last 25 years. Because similar RA patients presented over these years and treatment changed, we could assess the influence of treatment on these long-term outcomes by using inclusion period as a proxy for treatment strategy. Finally, in **Chapter 8**, the impact of improved treatment on population corrected mortality was studied in both autoantibody-negative and autoantibody-positive RA.

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