Predictive factors for the development and disease course of rheumatoid arthritis

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General introduction

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an immune-mediated inflammatory systemic disease. RA affects 0.5-1% of the civilized population, three times more women than men and the prevalence rises with age.[1] RA has a clinical manifest of symmetric polyarthritis of especially the small hand and foot joints and can progress into a very immobilizing and disabling disease, without effective treatment and leads on socio-economic perspective to high costs and loss of work force.

RA is an auto-immune disease, with inflammation against own tissue in primarily the joints. Due to interaction between T cells, B cells, macrophages and fibroblast-like synoviocytes several pro-inflammatory cytokines are overproduced, like; tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6) and B cells start producing antibodies. These inflammatory cascades lead towards persistent synovial inflammation and destruction of cartilage and bone.[1] However, whether rheumatoid arthritis starts from inside the bone and spreads further into the tissue in the joint, or it starts with inflammation of the joint tissue which leads to bone involvement from outside, still remains unknown.[2]

RA is characterized by auto-antibodies like Rheumatoid Factor (RF) and anti-citrullinated peptide antigens (ACPA). ACPA and RF have a high specificity (80-90%) and a moderate sensitivity for the diagnosis of RA.[3] Approximately 55% of the RA patients are RF positive and 60% ACPA positive.[4-6] In addition, ACPA and RF positivity is also important for the disease course, because these are risk factors for a persistent and more destructive disease.[7] Furthermore, from previous studies we learned that these auto-antibodies are a median of 5 years present before the first symptoms of RA start and thus precede the clinical presentation phase of RA.[8] This might suggest that there is a pre-clinical stage present in RA.

From literature we learned that early recognition and treatment will result in a better outcome.[9,10] Some studies even suggest that treatment within this early 'window of opportunity' might alter the natural course of RA.[11]

UNCLASSIFIED ARTHRITIS

A patient with at least one swollen joint has arthritis. Together with other clinical symptoms, results from blood tests, imaging and other techniques the Rheumatologist will try to classify this patient. When all diagnoses, such as osteoarthritis, gout, reactive arthritis, spondyloarthropathy, systemic lupus erythematosis and of course rheumatoid arthritis are excluded, the patient can be classified as unclassified arthritis (UA).[12] Therefore UA is called a diagnosis per exclusion. 35% to 54% of the arthritis patients are classified as UA in the early arthritis cohorts.[5,13] However, the frequency is dependent on the duration of symp-

toms. Especially UA patients with a monoarthritis or oligoarthritis could not be classified as RA. Patients with unclassified arthritis can progress into rheumatoid arthritis (70% of the ACPA positive UA patients within 1 year) over time or can achieve remission or self-limiting disease.[14] The percentage of remission (40%-55%) in unclassified arthritis patients is larger than the percentage of remission in rheumatoid arthritis (10%-15%) and also the time to remission is shorter in unclassified arthritis patients.[14,15] This all suggests that the group of UA patients is a very heterogeneous group of patients and that remission is less common when the disease is more mature. However, UA can be pre-RA, but can also be a different disease and never progress to RA (Figure 1).

Figure 1. Disease phases of RA. Patients do not have to pass through all phases before RA eventually develops.

ARTHRALGIA

When taking a look even earlier in the course of the disease, even before the patient has arthritis, patients generally experience a period in which they have tender or painful joints, without the presence of a swollen joint. This is called arthralgia. Arthralgia can be accompanied by other symptoms. Some of these symptoms and characteristics about that patient with arthralgia can make the patient more suspect to finally progress into rheumatoid arthritis. The presence of ACPA and/or RF does increase the risk of arthritis development. A prediction model defined several additional risk factors for arthritis development in ACPA+ and/or RF arthralgia patients.[16] ACPA positive arthralgia patients have a 30% chance of RA development within 1 year.[17]

CLASSIFICATION CRITERIA AND PREDICTION MODELS FOR RA DEVELOPMENT

In 1987 a set of criteria has been developed to classify patients with arthritis as having rheumatoid arthritis.[18] These classification criteria were soon implanted as a diagnostic tool for Rheumatologists. However, the focus of diagnosing RA became more and more on early diagnosing and this criteria set is lacking in classifying early RA patients the 2010 classification criteria have been developed to classify more early RA patients.[19] Although,

officially these criteria are classification criteria to discriminate patients with and without RA in order to include in trials and to have a common definition in research communication and not to define patients who need early treatment, these criteria are more and more implanted in daily clinical practice (Figure 2).

These new criteria have resulted in classification of more early RA patients, but likewise a more heterogeneous group of RA patients with some over classification (patients with self-limiting disease).[4,6,20-22] These new criteria not only higher the prevalence of RA and

1987 criteria (4 out of 7)
1. Morning stiffness
2. Arthritis of 3 or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes
*and at least 6 weeks symptom duration

2010 criteria (score ≥6/10)	
1. Joint involvement (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (at least 1 small)	5
2. Serology (0-3)	
ACPA neg and RF neg	0
ACPA low-pos and RF low-pos	2
ACPA high-pos and RF high-pos	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)	
<6 weeks	0
≥6 weeks	1
*patients with RA typical erosions should be classified as having RA	
*synovitis not better explained by another disease	

Figure 2. 1987 and 2010 classification criteria for RA, in patients with arthritis.

lower the prevalence of UA patients, but will also change the characteristics and outcomes of both the RA and UA patients.

Another important development in classifying UA patients was the coming of prediction models for the individual UA patient. Two important prediction models to predict disease outcome in UA patients are the 'Van der Helm prediction model' and the 'Visser prediction model'. These prediction models can help the Rheumatologist to decide whether or not treating the UA patient.[23,24]

PREDICTING DISEASE OUTCOME OF RA

When a patient is classified as RA, the disease course is not yet known, due to a lot of variation in the disease course of RA patients. Some patients will rapidly progress in a very erosive and disabling disease, while others will develop (spontaneous) remission. It can be very useful to know the disease course of a patient, not only to inform the patient about his prognosis but also whether or not to start (more aggressive) treatment. This is very important to avoid undertreatment, because we know that early treatment will have a positive effect on the disease course. Nevertheless, overtreatment can be even that important, as a lot of the treatments have their (toxic) side effects.

Radiographic outcome

To measure the severity of the disease, an outcome measure has to be defined. Severe RA is not uniformly defined. Patients often refer to the degree of pain or fatigue and the ability to perform daily activities and work. Rheumatologists are more concerned with the level of inflammation (expressed by the number of inflamed joints), the level of acute phase reactants, and pooled severity indices such as disease activity scores. Scientists focus on outcome measures that can be assessed objectively, such as joint destruction and mortality. These perspectives are essentially similar, since levels of impaired functionality, inflammation, and structural damage are partly correlated.[25]

Furthermore, radiographic progression is highly variable between RA patients and correlates with the cumulative burden of inflammation over time, is highly linked with physical function and other outcomes such as work disability, and is inexpensive to measure using validated scoring methods; consequently, the rate of radiographic progression is a comprehensive endpoint in observational studies.

The most common and in RA research field widely accepted measure for radiographic joint destruction of hands and feet is the Sharp-van der Heijde score. This is a quantitative score that can be used by trained readers, and comprises an erosive and narrowing (reflection of cartilage damage) score of both hands and feet with a range of 0-448.[26]

Risk factors for a more severe disease outcome

An important risk factor for RA development is to have a relative with RA. This suggests that genetic background is of importance in RA and therefore the severity of the disease course could also have a genetic background. Twin studies have indicated that the radiographic progression rate is in part heritable.[27] Recent estimations on an Icelandic RA population yielded a heritability of 45-58%.[28] Over 40 genetic variants have been identified in RA susceptibility, by genome-wide association studies (GWAS), evaluating thousands of cases and controls. These susceptibility genes are prone to be of importance in RA severity, measured by radiographic progression. Another, approach of unravelling the genetic variants for radiographic progression, are more dedicated candidate gene studies focusing on pathways important in RA, such as genes involved in inflammation and bone cartilage pathways.

The presence or high levels of several serological markers are also predictors for radiographic progression in RA. Serological markers that are important for radiographic progression are auto-antibodies and other markers related to inflammation and bone and cartilage destruction, like RF, ACPA, anti-CarP , ESR, CRP, MMP3, CTX-I, CTX-II, COMP, TIMP1, PYD, RANKL/OPG and CXCL13.[29-52]

In addition, some studies investigated whether environmental risk factors, like smoking, could be of importance in risk predicting of radiographic progression in RA.[53-55]

MRI

MRI is becoming an important tool in RA research. MRI has important advantages over conventional radiographs as, in addition to structural damage, inflammation of the synovium of the joint, tendons and bone marrow edema (BME) can be visualized and quantified. MRI produces images by detecting signal from H+ ions. The detection of H+ ions by MRI means that tissues with high concentrations of water reflect a high signal on T2-weighted sequences. This can be used to detect free fluid and inflammation. In RA this means detection of synovitis, tenosynovitis, synovial effusion and bone marrow edema. When making sequences after infusion of gadolinium containing contrast a region can be specified as an active inflammation when there is enhanced vascularity, which could distinguish between synovitis and synovial effusion.

In order to evaluate MR images an international Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI in RA working group developed and validated a semi-quantitative scoring system; the RA MRI scoring system (RAMRIS). This scoring system was developed to assess RA inflammation and damage. The scoring system recommends having at least the following sequences: imaging in two planes with T1-weighted images before and after intravenous gadolinium contrast and a T2-weighted fat saturated sequence. This scoring system measures the following RA joint pathologies; synovitis, erosion and BME.[56-

[58] Haavardsholm et al described the additional scoring of tenosynovitis.[59] The sum score ranges in unilateral MCP2-5, wrist and MTP1-5 for synovitis 0-36, erosion 0-330, BME 0-99 and tenosynovitis 0-84.

Especially BME is of special interest in RA research. Normal bone marrow is a fatty-tissue inside the bone and is visualized as a bright signal on T1-weighted images and as a dark signal on T2-weighted images. When bone marrow edema is present the fatty tissue is replaced by more water-rich material and will be visualized as a dark signal on T1-weighted images and as a bright signal on T2-weighted images.[60] Previous studies have proven by histology of a pre-surgical defined region with bone marrow edema, that these regions reveal a lymphoplasmacytic inflammatory infiltrate within trabecular bone.[61-63] Several studies showed that BME has an additive value to known diagnostic criteria, to give a higher diagnostic accuracy.[64-66] Furthermore, BME is a very strong independent predictor of radiographic progression.[67-72]

In addition, because BME has a diagnostic value for predicting RA and has a prognostic value for predicting radiographic progression, MRI detected inflammation in RA is likely to become more important in the earlier phases of RA and also the pre-clinical phase without the presence of arthritis. Recent studies showed that MRI-detected subclinical inflammation is present in patients that are in clinical remission.[73-77]

AIMS AND OUTLINE THESIS

- Identifying predictive factors for RA development.
- Identifying predictive factors for more destructive outcome of RA.

EAC cohort

The major part of this thesis was investigated in the early arthritis clinic (EAC) in Leiden. This is an ongoing observational cohort that started in 1993. Patients presenting at the outpatient clinic at the Rheumatology department at the Leiden University Medical Centre, with at least one confirmed swollen joint and symptoms less than two years were included. At baseline, patients and Rheumatologist completed questionnaires, physical examinations were performed, radiographs were taken and blood was obtained to measure acute phase reactants, RF and ACPA. From 2010 on also MRI's were taken. After two weeks, when blood and radiographs results were known, a rheumatologist diagnosed the patients as having RA, UA or another diagnosis. Thereafter yearly visits with radiographs followed.[5]

Part I is focused on unclassified arthritis and the risk on development of rheumatoid arthritis. In 2010 new criteria were developed to classify also the early RA patient. Some studies thereafter showed what the new group of RA looked like in characteristics and

outcome. The most important findings were that the group of RA, according to the 2010 criteria, were more heterogeneous and less severe in presentation and outcome.[4,6,20] In **chapter two** we determined the characteristics and outcomes of unclassified arthritis, when applying the 2010 and 1987 criteria for RA. We compared these two groups on baseline characteristics and outcomes like; DMARD initiation in the first year, fulfilling the 1987 criteria for RA during the first year and achieving remission.

In **chapter three** we analyzed UA patients according to the 2010 criteria from our own Leiden EAC cohort and compared them to UA patients from two other cohorts. We investigated the risk of development of RA in this group of patients and we tried to explorer whether the Leiden prediction rule or ACPA positivity could help identify these UA patients that progress to RA.

Part II is focused on serologic and genetic factors in predicting the severity of joint destruction in rheumatoid arthritis. When a patient can be classified as RA, nothing is known about the prognosis yet. There is a lot of variability in the disease course of RA. Several risk factors for a more severe disease course are already known, such as ACPA and several genetic variants. In **chapter four** the thus far known risk factors (or biomarkers) for a severe disease course in RA, measured by radiographic progression, are summarized. In **chapter five** genetic variants in IL-15 and the association with severity of joint damage in RA was investigated in four cohorts. In **chapter six** we investigated whether genetic variants in the IL-4 and IL-4 receptor genes were associated with the severity of joint damage in RA, in 7 cohorts. Furthermore, in **chapter seven** we investigated genetic variants in granzyme-B and the association with severity of joint damage in RA, in four cohorts.

In **chapter eight** the collagen crosslink in cartilage and bone, pyridinoline, was analyzed in relation to the severity of joint destruction in RA. We investigated whether the levels of pyridinoline on baseline and during follow-up were associated to radiographic progression in RA patients.

Part III is focused on MRI in patients with arthralgia and early arthritis. Last decades, MRI is becoming a relevant tool in RA research. MRI can be used in different stages of the disease; arthralgia, early arthritis, early RA, RA and for different purposes; for better insight in disease pathogenesis in the pre-clinical or clinical stage, or for predicting diagnosis or prognosis. In **chapter nine** we evaluated MRI inflammation in hand and foot joints in ACPA positive arthralgia patients, by comparing these joints to joints of healthy controls and ACPA positive RA patients. This pilot study was to investigate MRI pathologies in an early phase of the disease; in arthralgic joints, without clinical arthritis. In **chapter ten** we determined the concordance between inflammation at physical examination and on MRI in early arthritis patients. These two chapters give a better insight on the pathogenesis in the early clinical and clinical phase. In **chapter eleven** the relevance of the MRI detected

subclinical inflammation was investigated. We calculated the relative risk of radiographic progression in joints with MRI detected subclinical inflammation compared to that in joints without MRI detected subclinical inflammation. In **chapter twelve** we analyzed the differentiating capacity of MRI for diagnosing RA in a group of early arthritis patients.

Part IV is focused on revisiting of the MRI scan protocol. The OMERACT group developed the semi-quantitative scoring method for scoring MRI in RA; the RAMRIS method. This method also describes the scanning protocol that is needed to have the necessary MRI sequences to score the images according to this protocol. The protocol recommends to make T1 images, primarily to score erosions, a T2 or STIR sequence to score BME and a T1 post-contrast sequence to score synovitis and tenosynovitis, for every joint. This resulted in a long scanning time which is costly and in which a patient needs to keep the hand or foot motionless or otherwise will lead to artefacts. To improve this, we tried to shorten the scanning protocol, with the same accuracy and validity of scoring. First, we compared in **chapter thirteen** scoring of BME on T2 and on T1 post-contrast sequences, which could result in removing the T2 sequences from the scanning protocol. And in **chapter fourteen** we compared scoring of synovitis on T1 post-contrast and on T2 sequences, which could result in removing the T1 post-contrast from the scanning protocol and no contrast infusion would be needed.

MRI is a very sensitive tool to measure inflammation and destruction and therefore could result in a reasonable percentage of false-positives, especially when normal daily activities could influence MRI measured pathologies in RA. In **chapter fifteen** we investigated whether wearing of high heels can influence MRI results.

Finally, in **chapter sixteen** the findings of this thesis are summarized and discussed.

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