The use of MRI in early inflammatory arthritis

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Introduction 1

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Rheumatoid arthritis

The term rheumatoid arthritis (RA) was first mentioned in the second half of the 19th century by Alfred Garrod. Before Garrod, terms like (chronic) rheumatism, gout and hybrid terms like rheumatic gout were used to describe a disease with inflammation of multiple joints resulting in distortion of the joints. Moreover, (pre)historic findings suggest that RA existed long before that.[1] Nowadays, RA is described as a chronic, systemic, inflammatory, immune-mediated disease, which is characterized by arthritis, more specifically symmetric polyarthritis affecting the small joints of the hands. Yet, the initial presentation and the course of RA vary broadly within patients. Most likely RA is a collection of different disease entities with a similar clinical manifestation.[2]

A prevalence of 0.5-1% and an annual incidence of 5-50 new cases per 100.00 person years have been described in Caucasians. RA is 3 times more frequent in women than it is in men and the incidence rises with age. Uncontrolled, the chronic joint inflammation leads to erosive joint destruction resulting in disabling joint deformities. Besides painful and swollen joints, systemic symptoms as morning stiffness and fatigue are frequently reported. In addition extra-articular manifestations of RA expressed in pulmonary and cardiovascular disease are described.[2] Furthermore, it has been shown that the disease processes ultimately leading to “classical” RA are already active before joint inflammation becomes clinically detectable.[3]

In the last decades considerable advances in the management of RA have been made. It has become apparent that early treatment with disease-modifying anti-rheumatic drugs (DMARDs) improves the disease outcome of RA-patients: patients develop less erosive joint damage and the number of patients that are able to achieve clinical remission increases. Some patients are even able to stop all medication and maintain in remission.[4] Tight treat-to-target therapy is recommended, aiming for clinical remission.[5]

Early initiation of therapy also requires the identification of RA-patients early in the disease process. This has led to changes to the diagnosis and classification of RA. These changes and their implications will be discussed in more detail hereafter.

Diagnosis and classification

There is no gold standard for the diagnosis RA, i.e. there is no test result that is pathognomonic for RA. In the clinical setting, the diagnosis is made by the rheumatologist by combining clinical, laboratory and imaging findings. In the research setting, classification criteria are used to select relatively homogeneous patient groups for the comparison of study results. The first classification criteria were proposed in 1956 and revised in 1958, these divided patients in classical, definite, probable and possible RA.[6] Although these criteria proved useful, new insights in RA and other forms of arthritis led to the development of new criteria. The 1987 ACR classification criteria for RA were developed to increase the specificity compared to the revised 1958 ACR criteria.[7] The 1987 criteria were derived to discriminate patients with established RA from those with other definite

rheumatologic diagnoses and they are well accepted for this purpose.

A drawback of the 1987 criteria is that although patients with established RA are well recognized, the identification of patients in earlier stages of disease is something left to be desired. With the recognition of the benefits of early therapeutic intervention, there was a growing need for clinical trials focusing on early RA. Thus, classification criteria which allowed the selection of patients in an earlier disease stage were needed: this led to the development of the 2010 ACR/EULAR classification criteria.[8] The 1987 and 2010 criteria are compared in Table 1. The most important changes were that findings in established disease e.g. rheumatoid nodules and radiographic erosions were no longer included and that acute phase reactants and anti-citrullinated peptide antibodies (ACPA) were added.

The 2010 classification criteria have indeed shown to be more sensitive than the 1987 criteria at the cost of a slight decrease in specificity.[9] The goal of classification in an earlier stage of disease seems to be realized by the 2010 criteria. It is important to take in mind that using new classification criteria has consequences for the composition of the studied patient groups. For example, in the 2010 criteria

Table 1 Comparison of 1987 and 2010 classification criteria for RA

1987 ACR criteria	2010 ACR/EULAR criteria	Points
● Morning stiffness >1 hour	● Joint involvement	
● Arthritis of ≥3 joint areas	◦ 1 large joint	0
● Arthritis of hand joints	◦ 2-10 large joints	1
● Symmetric arthritis	◦ 1-3 small joints	2
● Rheumatoid nodules	◦ 4-10 small joints	3
● Serum RF	◦ >10 small joints	5
● Radiographic changes	● Serologic tests	
	◦ Negative RF and ACPA	0
	◦ Weakly positive RF/ACPA	2
	◦ Strongly positive RF/ACPA	3
	● Acute phase reactants	
	◦ Normal CRP and ESR	0
	◦ Elevated CRP/ESR	1
	● Symptom duration	
	◦ <6 weeks	0
	◦ ≥6 weeks	1
At least 4 out of 7 criteria must be positive for classification of RA	At least 6 out of 10 points are needed for classification of RA	

RF, Rheumatoid Factor. ACPA, anti-citrullinated peptide antibodies. CRP, c-reactive protein. ESR, erythrocyte sedimentation rate. Target population of 2010 criteria: patients with at least 1 joint with clinical synovitis in which the synovitis is not better explained by another disease.

the presence of antibodies associated with RA (RF and ACPA) have a bigger role in the classification of RA than in the 1987 criteria. This increases the difference between RA with the presence of auto-antibodies (seropositive) and patients without these antibodies (seronegative). Whereas seropositive patients can be classified with arthritis of one small joint, seronegative patients need over 10 involved joints to be classified as RA.

There is also a group of patients presenting with inflammatory arthritis that cannot be classified as RA or another form of arthritis at initial presentation; these patients have undifferentiated or unclassified arthritis (UA). Although arthritis disappears spontaneously in the majority of these patients, some still go on to develop RA during follow-up. This makes UA patients interesting to study as ideally, the patients that go on to develop RA are identified as soon as possible.

Using either the 1987 or the 2010 classification criteria also results in a different population of patients with UA (hereafter 1987UA and 2010UA respectively). One of the important differences is the presence of ACPA in these patients. Studies in 1987UA had shown that ACPA is a strong predictor for RA development.[10] Because ACPA is included and heavily weighted in the 2010 criteria, 2010UA consists of predominantly seronegative patients. Predictors of RA development in 1987UA are less discriminating in 2010UA. Earlier studies have reported that up to 25% of the 2010UA patients will still develop RA during follow-up.[11] Part of the work presented in this thesis focused on the use of magnetic resonance imaging (MRI) to identify these patients.

Imaging in RA

Imaging of the joints is used for several purposes in RA: diagnosis, prognostication, disease monitoring, and as outcome measure in trials.[12] Although radiographs of the hands and feet are still the most frequently used imaging modality in the field of RA, MRI and ultrasound (US) are increasingly performed. Radiographs show structural damage of bones, including erosions and joint space narrowing. MRI and US however, allow visualization of inflammatory soft tissue changes shown as synovitis and tenosynovitis, in addition to more sensitive detection of small erosions.

With the recognition of the importance of early initiation of DMARD-treatment, and thus early identification of RA patients and the presence of little to no radiographic damage in early disease stages, MRI and US are imaging modalities of increasing interest. Furthermore, erosive joint destruction in RA has been massively reduced because of the improvements in the management of RA. In clinical trials nowadays, there is very little progression of radiographic joint damage in different treatment arms, hampering its use as outcome measure. Therefore, imaging modalities which are able to depict inflammatory lesions instead of the long-term consequences of inflammatory lesions are interesting for the comparison of treatment arms of clinical trials.

A unique feature of MRI is the capability to detect bone marrow changes described as bone marrow edema (BME) or osteitis. In established RA it has

been shown that bone marrow fat is replaced by an inflammatory cellular infiltrate in BME-lesions.[13–15] MR inflammatory changes as synovitis, tenosynovitis, but especially BME, has been shown to be a strong predictor for the development of erosions.[16–20]

Although the use of MRI and US is already recommended for these purposes by the imaging guidelines of EULAR, the level of evidence for these recommendations is low.[12] Further studies are needed to increase our knowledge on the use of MRI in inflammatory arthritis.

The outline of this thesis

This thesis is primarily aimed to further expand on the value of MRI in early (rheumatoid) arthritis. All studies in this thesis were performed in the population of the Leiden Early Arthritis Clinic (EAC). This observational cohort was started in 1993 with the increasing awareness of the importance of early initiation of DMARDS. The EAC contains consecutively included patients presenting at the rheumatology outpatient clinic of the Leiden University Medical Center with arthritis confirmed by physical examination and symptom duration less than 2 years. This is the only rheumatology outpatient clinic in an area of >400.000 inhabitants. Questionnaires, extensive clinical information and serum samples were obtained in these patients. The cohort does not have a treatment protocol and patients receive regular rheumatologic care. Patients are followed up till discharge of the outpatient clinic. Since 2010 MRI of the hand and foot joints was also performed in all consenting patients. MRI inflammation and erosive damage was assessed using the RA MRI Scoring system (RAMRIS).[21,22]

After the introduction of the RAMRIS scoring system, which consisted of a semi-quantitative scoring system for erosions, BME and synovitis in the wrist and MCP joints, an additional semi-quantitative score for tenosynovitis was introduced a couple of years later.[21,22] In Chapter 2 we have focused on MRI-detected tenosynovitis at the level of the MCP and wrist joints using this score. Although tenosynovitis is a common finding in RA, thus far the presence of MRI-detected tenosynovitis was only studied in relatively small numbers of patients and selected patient groups. We studied the prevalence of tenosynovitis in the patients of the EAC, assessed whether patients with RA presented with tenosynovitis more often than other arthritis patients, and assessed whether the presence of tenosynovitis is associated with a more severe course of RA. We did not only look at the presence of any tenosynovitis, but also analyzed the separate tendon groups.

The association with erosive progression of both MRI-detected synovitis and BME has been shown by several studies. However, previous studies focused on the total BME, synovitis and erosion scores. It had not been shown how specific BME and synovitis lesions change over time and how this relates to development of erosions. In Chapter 3 we tried to answer these questions. We studied the presence of MRI detected BME and synovitis per bone at three time points and assessed the relationship of the course of these lesions with erosive development in the same bone. Because synovitis and bone marrow edema are often simultaneously present, we also assessed whether the course of BME and

synovitis were independently associated with erosive progression.

In Chapter 4 and Chapter 5 we studied the diagnostic value of MRI for the early identification of RA-patients. Earlier recognition of RA-patients allows for earlier initiation of DMARD therapy and better disease outcome. The 2010 already focused on earlier identification, still about 25% of the patients presenting with undifferentiated arthritis develop RA. We assessed whether MRI is able to identify these patients at first presentation in the outpatient clinic and its additional value to other findings (e.g. those used in the 2010 criteria).
In Chapter 4 we replicated a study[23] which suggested that the diagnostic performance of the 2010 criteria for identifying those early arthritis patients that develop RA within a year would improve by also letting the criteria be fulfilled if the specific MRI findings were present in the wrist or MCP joints. It was suggested that especially the presence of BME would improve the diagnostic performance because of the increased sensitivity, despite a decrease in specificity.
In Chapter 5 we studied the diagnostic value of MRI of hand and feet to identify early RA in daily practice. Previous studies had some important limitations hampering clinical application. Most studies were performed before the introduction of the 2010-criteria in relatively small populations with selection criteria that resulted in a study population not resembling daily practice. Therefore Chapter 5 was performed in the large study population of the EAC using all consecutively included patients (n=589) . Previous studies showed that it is hard to distinguish different forms of arthritis with MRI.[24,25] Moreover, our group has shown that in symptom free controls also signs of inflammation are depicted on MRI, especially at higher age.[26] By including the MRI-data of the symptom-free controls we tried to reduce false-positive MRI findings. Several analyses were performed to assess the additional value of MRI to other clinical findings (e.g. clinically inflamed joints and elevated acute phase reactants).

In Chapter 6 we used the data in the EAC to replicate the results of a study[27] which used MRI-detected synovitis and BME in order to develop new composite scores to assess disease activity. The replicated hypothesis was that composite scores derived from MRI findings are a better reflection of the inflammatory disease burden than the current composite scores (DAS-28, SDAI and CDAI) which were derived from erosive progression on radiographs and clinical decision making.

In Chapter 7 we assessed the effect of age on MRI-inflammation in arthritis patients, since it was shown in symptom-free controls that MRI-inflammation increases with age.[26] The presence of an effect of age on MRI-inflammation could have consequences on the interpretation of MRI findings. Moreover, we assessed whether there is a general effect of age on MRI findings or whether the effect age is different (bigger or smaller) in arthritis patients than in symptom-free controls. We also assessed whether the presentation of inflammation was different for RA-patients presenting at different ages.

The last decades there has been an increasing focus on early identification of RA patients. Besides long term disease outcome, it is interesting to study whether earlier identification also leads to RA patients presenting with less severe disease. In Chapter 8 we evaluated whether RA-patients are now indeed earlier recognized over the 23 years of existence of the EAC and whether the presentation of

RA-patients at the rheumatologist changed over this time period.

In Chapter 9 the studies in this thesis are summarized followed by a general discussion.

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