Clinical and molecular classification of very early arthritis patients
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GENERAL INTRODUCTION
Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic immune-mediated inflammatory disease mainly affecting the joints, which afflicts approximately 1% of the population worldwide. Patients present with symptoms of pain, joint swelling, stiffness and limited range of motion. The inflamed synovium invades and destroys local articular structures, resulting in joint destruction, progressive deformity, and permanent disability.[1] Despite major developments in antirheumatic therapy, RA is still an important cause of long-term morbidity and early mortality with individual and socio-economical consequences.[2;3] Also co-morbidity, especially the risk of cardiovascular disease, is increased in RA.[4] Traditional cardiovascular risk factors in combination with the inflammatory status in RA patients contribute to the high prevalence of cardiovascular disease in RA.[5;6] Besides risk factor management aggressive treatment reducing inflammation is recommended.

Pathogenesis of RA

Although RA is thought of as an autoimmune disease, its etiology is not completely understood. It is known that genetic susceptibility [7-9] in combination with environmental factors create a condition in which tolerance can be broken and an autoimmune reaction can be initiated. So far, several genetic factors have been identified, such as HLA-DRB1 genes (DR0404 and DR0401), PTPN22, STAT4 and CTLA4 genes.[10] Cigarette smoking is known to be an important environmental risk factor especially in the context of anti-citrullinated peptide antibodies (ACPA) and in the presence of the HLA-DRB1 genes.[11] Both cells of the innate immune system, such as dendritic cells and macrophages, and cells of the adaptive immune system, such as B and T lymphocytes, are thought to play an important role. The autoimmune response may be initiated by antigen presentation, not-necessarily an RA-specific antigen, by antigen presenting cells to T cells in the context of co-stimulatory signals. Alternatively, mutations in either the B- or T cell receptor might lead to recognition of self-antigen, resulting in clonal activation and expansion of specific cells. Other theories suggest that either T- or B cell autoreactivity without interaction or co-stimulation between both cells may result in chronic inflammation,[12] even in the absence of an auto-antigen. Interaction and co-stimulation between B and T cells subsequently results in activation of the inflammatory cascade which evolves into massive systemic inflammation and recruitment of inflammatory cells in the synovial tissue leading to chronic synovial inflammation, production of inflammatory molecules and eventually joint destruction.[13]

In healthy people the synovium is a thin membrane that is attached to skeletal tissue at the bone-cartilage interface. Inflamed synovium in RA is characterized by intimal lining layer hyperplasia due to proliferation of the fibroblast-like synoviocytes which are in an altered activation state, and accumulation of intimal macrophages. In the synovial sublining, new vessels are formed that allow inflammatory cells such as B cell, T cells, macrophages, plasma cells, mast cells and dendritic cells to invade the tissue. In these cells various signal transduction cascades are active that influence gene expression and hereby regulate the inflammatory process. Studying the inflamed synovium might increase our insight into pathways active in initiation and perpetuation of RA.
The phase preceding clinically manifest arthritis: pre-arthritis phase

The phase during which there is a break of tolerance with a consequent autoimmune response, precedes the onset of clinically manifest arthritis. This phase is characterized by the presence of RA-specific autoantibodies, such as rheumatoid factor and ACPA.[14;15] Besides elevated serum levels of C-reactive protein (CRP), elevated chemokine levels can be detected in peripheral blood of individuals who later on will develop RA.[16] It has been hypothesized that before the onset of arthritis there is a phase characterized by subclinical synovial inflammation. This was shown in various animal models of RA, in which synovial tissue inflammatory changes were observed in the latency phase before the onset of arthritis [17] and by the presence of signs of chronic inflammation in the synovium of early RA patients when they first present with arthritis. The kinetics of these different stages are as yet not known, and it is also unclear where the immune response is initiated.

Early arthritis

As RA is known to be a potentially destructive inflammatory disease, and early treatment can improve disease outcome, it is important to diagnose RA early and start treatment accordingly. Until the recent development of the 2010 ACR/EULAR criteria for RA,[18;19] the 1987 ACR RA classification criteria of RA were applied to make the diagnosis of RA for research purposes.[20] However, not all patients with signs and symptoms of arthritis presenting in early arthritis clinics can be diagnosed with a definite diagnosis and are therefore classified as undifferentiated arthritis. Of these patients 50% will have benign self-limiting disease, whereas others will progress to persistent or even persistent, destructive arthritis.[21-23] For the latter group, a definitive diagnosis can usually be made over time, but therapeutic intervention might come (too) late. Moreover, with the emergence of the 2010 ACR/EULAR RA criteria the RA population is perhaps slightly more heterogeneous with a subgroup of RA patients having self-limiting disease.[24-26] This underlines the importance of the identification of patients with potentially persistent, destructive disease compared to self-limiting disease in an early stage of the disease. In order to make the optimal treatment decisions for the individual patient, novel predictive parameters are needed.

Treatment of RA

The last 2 decades treatment regimens for RA have drastically changed. Where in the past non-steroidal anti-inflammatory drugs were the initial treatment of choice and only in severe disease were followed by DMARDs, nowadays treatment principles are based on early initiation of DMARD treatment, aiming for a state of disease remission. If conventional DMARD treatment fails to induce remission, then biological treatments are considered, like TNF inhibition, B cell depletion, interleukin-6 receptor blockade, or abatacept treatment.[27;28] This therapeutic approach has significantly improved disease outcome.

RA a heterogeneous disease

RA is thought to be a clinical syndrome comprising various disease subsets, in which several different pathogenetic pathways are active that all lead to common signs and symptoms. First, there is variability in outcome: some patients will have self-limiting disease while others develop persistent disease with consequent joint damage and even extra-articular disease. Moreover,
different immunological features can be observed in peripheral blood and the synovium. For instance, serum rheumatoid factor and ACPA are present in about 50-80% of the RA patients, whereas others are autoantibody negative. Gene expression profiles in peripheral blood and synovial tissue also differ between various subgroups of RA in spite of a common clinical picture. In addition, some patients have diffuse lymphocyte infiltration in the synovium, while in others germinal center-like structures may be found.[17;30] The heterogeneity of RA is also illustrated by the variable response to different targeted treatments. Profiling these subsets based on molecular features may increase our understanding of the processes active in the different subgroups of RA patients.

**Imaging of the inflamed synovium**

Besides studying the histopathology of the inflamed synovium, specific radiological findings might allow stratification of early arthritis patients. Various imaging modalities have been applied to study RA-specific changes in the joint. Bone erosions are easily visualized by X-rays of the joints. [31;32] However, to study the synovium and the ligaments ultrasound or MRI need to be applied. [33;34] With greyscale ultrasound it is possible to visualize synovial hypertrophy, tenosynovitis and erosions. [34] Active synovitis, associated with development of radiographic damage, can be visualized by power Doppler. Synovial volume, bone edema, tenosynovitis and bone erosions can be studied by static MRI. Detection of synovial hypertrophy, bone marrow edema and erosions may support the clinical diagnosis of RA in early arthritis patients,[35] but sensitivity of these parameters varies between studies.[36] Dynamic contrast-enhanced (DCE) MRI is a relatively new technique evaluating uptake of the contrast agent over time in a specific tissue. Results can be quantified by evaluation of time-intensity curves (TIC), reflecting uptake and clearance of the contrast agent. Tissue characteristics such as vascularity, vessel permeability and interstitial space determine the shape of the TIC.[37] Conceivably, these imaging modalities may also be used to distinguish between different subsets of RA associated with distinct pathogenetic mechanisms.

**OUTLINE OF THIS THESIS**

**Chapter 2** introduces an international guideline for performing arthroscopic synovial tissue biopsies. This technique is applied in chapters 3, 5, 6, 7, 8.

It is known that the presence of circulating autoantibodies may precede the development of rheumatoid factor and/or ACPA positive RA by several years. It is however unclear where in the body this immune response is initiated. In **chapter 3** we analyzed synovium by DCE-MRI and immunohistochemical analysis of synovial tissue samples from individuals with an increased risk of developing RA to study if inflammatory synovial tissue changes are present in the preclinical phase of RA. These subjects have increased serum levels of IgM rheumatoid factor and/or ACPA.

Chronic inflammation is associated with an increased risk of cardiovascular disease in RA patients. Early RA already represents chronic inflammation. It is, however, not known if the increased risk of cardiovascular diseases is already present in the earliest phases of RA. In **chapter 4** we investigated atherogenesis in preclinical RA and early RA by evaluating intima media thickness (IMT).

Recently, novel criteria for the diagnosis RA have been developed by ACR and EULAR. The 2010 ACR/ EULAR criteria enable an earlier diagnosis of RA, but could also result in a more
heterogeneous RA population with possibly different inflammatory changes in the synovium. In chapter 5 we describe the synovial features of RA patients fulfilling the 2010 ACR/EULAR RA criteria compared to patients classified according to the 1987 RA criteria.

Early and aggressive treatment in RA has been shown to improve the disease course. We hypothesized that studying the synovium might allow the identification of new diagnostic and prognostic markers. In chapters 6, 7, and 8 we studied whether specific synovial tissue characteristics can be used as diagnostic or prognostic markers in early arthritis patients.

In chapters 9 and 10 we studied the inflamed synovium by DCE-MRI. This technique was shown to be of value in discriminating benign from malignant disease in various types of tumors. As the inflamed synovium shares several characteristics with malignancies we hypothesized that DCE-MRI might be of value in the stratification of patients in early arthritis.

REFERENCES


