

# **Chapter 1**

## **General introduction**

## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that may affect many tissues and organs, but is mainly characterized by chronic inflammation of the joints. The inflammation leads to joint destruction, joint deformity with loss of function and increased mortality.<sup>1,2</sup> RA is found in all ethnic groups. In the Northern European and North American population approximately 0.5 to 1% is affected, while in the Southern European population a lower prevalence of 0.3 to 0.7% is found.<sup>2</sup> The disease is more prevalent in women than in men, with a ratio of 2:1. In the Netherlands, in 2003, an incidence was reported of 0.7 per 1000 men and 1.4 per 1000 women.<sup>3</sup> The incidence of RA is highest between the ages of 40 to 60 years old.<sup>4</sup> RA is a complex, multi-factorial disease with contributions from (an interaction between) genetic, environmental and hormonal factors.

The present paradigm is that RA should be treated with medication as early as possible in order to reduce inflammation and retain or increase function. This has led to the introduction of specialist clinics for early assessment of patients with inflammatory arthritis, so-called 'early arthritis clinics' (EAC).<sup>5</sup> The first early RA cohort was established in Bath, UK, already in 1957.<sup>6</sup> Since the late 1980's, EAC have been set up in many countries.<sup>7-15</sup> In an EAC subjects with symptoms of inflammatory arthritis are assessed with the goal of identifying and treating patients as early as possible. Data from EAC have been used to find predictors and prognostic factors.<sup>16</sup> Outcome variables relate to disease severity, functional disability, erosive disease or mortality. The provision of EAC's allows earlier and more accurate diagnosis and the possibility to optimize treatment strategies.

Several risk factors for RA have been identified so far.<sup>2,13</sup> These include genetic susceptibility, smoking, socioeconomic factors, infectious agents, hormonal factors, dietary factors, age and gender. Genetic factors do not have the problem of relying on prospective data collected at a certain time point, unlike environmental factors which may change in time. This introduction will focus further on factors that were explored in the present thesis.

### Genetic factors

Genetic factors implicated in RA have been widely studied using both candidate genes and whole-genome screens.<sup>17</sup> The strongest genetic risk factor for RA remains the 'shared epitope' alleles at the human leukocyte antigen DRB1 locus within the major histocompatibility complex (MHC) region.<sup>18,19</sup> Outside the MHC region, the PTPN22 gene has been associated with RA. Making use of genome-wide association studies, new loci are identified, including IL6ST, SPRED2, RBPJ, CCR6, IRF5 and PXX.<sup>20</sup> The associated SNPs are located near genes of known immune function. Furthermore several other genes have been

the focus of recent research, such as genes encoding for pro- or anti-inflammatory cytokines, which have weaker associations. Single nucleotide polymorphisms (SNPs) in genes coding for cytokines like Tumour Necrosis Factor- $\alpha$  (TNF), Lymphotoxin- $\alpha$  (LTA), Interleukin-1 $\alpha$  (IL1A), Interleukin-1 $\beta$  (IL1B) and the natural IL-1 receptor antagonist (IL1RN) play a crucial role in the regulation of inflammation and seem to be important in the onset and progression of RA. Excessive production of pro-inflammatory cytokines can induce synovial inflammation and proliferation as well as degradation of articular cartilage and bone, which causes joint damage. It must be taken into account that there are substantial ethnic differences in RA genetic predisposition.<sup>21</sup> While the MHC contributes about 30% of the genetic burden of disease, so far only 5% is explained by validated and highly suggestive non-MHC RA risk alleles, indicating that additional non-MHC risk alleles remain to be discovered.<sup>17,22</sup>

### **Serological markers**

Rheumatoid factor (RF) is an antibody against the Fc portion of immunoglobulin G, which is itself an antibody. RF, mostly measured as IgM-RF, was the first widely used serological marker for the diagnosis of RA. It was found in 75% of RA patients; however later on it was also frequently observed in patients with other inflammatory diseases<sup>23</sup> as well as in healthy elderly persons.<sup>24</sup> RF is therefore not highly specific for RA.

Antibodies to citrullinated proteins/peptides (ACPA) have a high specificity for RA. ACPA comprise a group of antibodies against several citrullinated proteins, such as fibrin<sup>25</sup>, Epstein-Bar Virus Nuclear Antigen<sup>26</sup>, alpha-enolase<sup>27</sup> and vimentin<sup>28</sup>, which have been proposed as physiological targets for ACPA specificity. The detection of anti-citrullinated protein antibodies is a major development in the diagnosis and prognosis of rheumatoid arthritis. Antibodies against cyclic citrullinated peptides of the second generation (anti-CCP2) are most frequently used and have been studied intensively over the last years.

An important gene–environment interaction has been revealed in several studies; carrying specific HLA-DRB1 alleles encoding the SE and smoking establish a significant risk for ACPA in RA.<sup>29,30</sup> Therefore it was hypothesized for the aetiology of RA that smoking may trigger RA-specific immune reactions to citrullinated proteins.<sup>31,32</sup> Citrullinated proteins have been observed in the lining and sublining of the joint synovial membrane and also in extraarticular tissues in RA patients. However, citrullinated proteins are not specific for RA as they are also found in other rheumatic diseases with synovitis<sup>33</sup> and exist in 1-2% of the normal population.<sup>34</sup> It has been suggested that ACPA might have a path physiological role in RA<sup>35,36</sup>, whereas IgM-RF production more probably is a consequence of the rheumatoid inflammation. It is also suggested that RA might be subclassified into two subsets by ACPA-positivity.<sup>29,31</sup>

IgM-RF and anti-CCP positivity are both associated with disease onset, disease severity and poorer outcome.<sup>37-42</sup> Most studies only address RF and/or ACPA status as a possible risk factor. Concentration levels as a marker of production capacity might be informative but have been studied far less.

### **Additional features**

The disease course of RA may also be influenced by other characteristics that can be assessed at first presentation or early in the disease course. Apart from the aforementioned genetic and serological factors, the present thesis focuses on three additional topics, namely gender, hand function and osteoporosis. The incidence of RA is higher in women than in men and at onset women have a younger mean age.<sup>4,43</sup> Several studies have found differences between the genders in outcome measures such as disease activity, functionality or radiographic damage.<sup>44-50</sup> However, whether female sex is a marker of a more severe disease course is still under debate.<sup>5,51-53</sup>

Joint inflammation and joint deformity contribute to functional limitations in RA.<sup>54</sup> In the case of hand and wrist function, it is unknown to what extent hand and wrist symptoms and impairments and the resulting activity limitations are related to disease duration.

Osteoporosis is a major comorbidity of RA. Generalized osteoporosis increases with age in the general population.<sup>55</sup> In RA patients, both generalized and local bone loss are increased.<sup>56</sup> Therefore, the expected prevalence of vertebral deformities in elderly RA patients would be higher compared with the general population. It is unknown whether this effect is already present early in the disease course.

It is necessary to study both directly disease-related factors such as joint inflammation and indirect comorbid effects such as osteoporosis, in order to assess the full scope of the consequences of the disease. The resulting knowledge will facilitate the development of preventive measures in different stages of the disease.

### **Thesis Outline**

The aim of this thesis was to expand the knowledge of prognostic factors and outcome in early arthritis. Special interest was devoted to the distinct nature of RF and ACPA, the two RA-specific autoantibody systems. Furthermore, the prevalence of selected comorbidities or disease-specific consequences in patients with RA was assessed.

The prognostic factors and prevalence of comorbidities were studied in a cohort of early arthritis patients. Since September 1995 an EAC was initiated in the Jan van Breemen Institute in Amsterdam, a large outpatient clinic for rheumatology and rehabilitation. Not only RA patients enrolled in the EAC, but all early oligo- and polyarthritis patients. Patients were

included in the EAC if their age was 18 years or older and peripheral arthritis of two or more joints was present with symptom duration of less than three years. Patients who were previously treated with a disease-modifying anti-rheumatic drug and patients with spondylarthropathy, reactive arthritis, crystal-induced arthropathy, systemic lupus erythematosus, Sjögren's syndrome, or osteoarthritis were excluded.

Chapter **two** addresses selected genetic markers of immune response genes in relation to radiographic progression in patients with early undifferentiated arthritis. In Chapter **three** the frequency of SE and ACPA and levels of ACPA was assessed in patients with arthralgia and compared to patients with early and established RA in a cross-sectional study. In chapter **four** the relationship between serum levels of RF and ACPA over time on the one hand, and age and markers of inflammation on the other hand, was analyzed in a large group of patients attending one of the outpatient rheumatology clinics of the Jan van Breemen Institute. In chapter **five** it was studied whether baseline levels of ACPA or RF and changes in the year thereafter are associated with outcome in early arthritis patients, and whether levels of autoantibodies provide additional information over baseline autoantibody status. In Chapter **six** the possible additional value of a new ACPA test, anti-mutated citrullinated vimentin, in early arthritis is explored in comparison with already existing ACPA tests. Chapter **seven** addresses the difference between men and women with regard to the outcome of RA, taking medication into account. Chapters **eight to ten** are devoted to comorbidity and functional outcome. The prevalence of vertebral fractures in older patients with RA is addressed in chapter **eight**. The prevalence of hand impairments in patients with RA is addressed in chapter **nine**. Finally, in chapter **ten** risk factors of hand impairments after two years of disease are evaluated.

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