Best Practice & Research Clinical Rheumatology 29 (2015) 527–542

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/locate/berh

1

How does established rheumatoid arthritis develop, and are there possibilities for prevention?

Marian H. van Beers-Tas [a,*,1], Samina A. Turk [a,1,2], Dirkjan van Schaardenburg [b,3]

[a] Amsterdam Rheumatology and Immunology Center, Reade, Doctor Jan van Breemenstraat 2, 1056 AB Amsterdam, The Netherlands
[b] Amsterdam Rheumatology and Immunology Center, Reade and Academic Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Preclinical
Early and established rheumatoid arthritis
Undifferentiated arthritis
Prediction
Risk factors
Prevention

ABSTRACT

Established rheumatoid arthritis (RA) is a chronic state with more or less joint damage and inflammation, which persists after a phase of early arthritis. Autoimmunity is the main determinant of persistence. Although the autoimmune response is already fully developed in the phase of early arthritis, targeted treatment within the first months produces better results than delayed treatment. Prevention of established RA currently depends on the success of remission-targeted treatment of early disease. Early recognition is aided by the new criteria for RA. Further improvement may be possible by even earlier recognition and treatment in the at-risk phase. This requires the improvement of prediction models and strategies, and more intervention studies. Such interventions should also be directed at modifiable risk factors such as smoking and obesity. The incidence of RA has declined for decades in parallel with the decrease of smoking rates; however, a recent increase has occurred that is associated with obesity.

* Corresponding author. Department of Rheumatology, Jan van Breemen Research, Institute/Reade, PO Box 58271, 1040 HG Amsterdam, The Netherlands. Tel.: +31 205896222; fax: +31 20 6833498.
E-mail addresses: m.v.beers@reade.nl (M.H. van Beers-Tas), s.turk@reade.nl (S.A. Turk), d.v.schaardenburg@reade.nl (D. van Schaardenburg).
[1] M.H. van Beers-Tas and S.A. Turk contributed equally to this work.
[2] Tel.: +31 20 5896222; fax: +31 20 6833498.
[3] Tel.: +31 20 5896263; fax: +31 206834464.

http://dx.doi.org/10.1016/j.berh.2015.09.001
1521-6942/

Introduction

The concept of "established rheumatoid arthritis" (RA) appears to be clear for the clinician. The picture arises of a patient with a "longstanding disease" that has caused a certain amount of joint and comorbid damage, and it remains in a fixed state with more or less active disease. The counterpart is the concept of "early (rheumatoid) arthritis," a more fluid state of recent synovitis where everything is still possible, including spontaneous or induced complete remission. Although the contrasting states are clear, the transition between them is gradual and less well defined. It is reasonable to expect that causative factors for RA also influence the course of the disease, in this case the progression from early to established RA. For example, anti-citrullinated protein antibodies (ACPAs) are associated with both the risk of developing RA and the risk of a severe, unremitting course of RA.

In this chapter, we review risk factors for the development of early RA and for the transition to established RA. The concept of undifferentiated arthritis (UA) as a separate entity in a continuum from health to RA is undergoing changes due to new definitions. Finally, we focus on efforts to prevent RA from occurring (primary prevention) or from progressing from UA to RA (secondary prevention).

Apart from the uncertainty over the transitions between the different phases of RA, there is also considerable uncertainty over the question of whether RA is a modern or an ancient disease. The name RA first appears in the medical literature in 1876[1], and the first unequivocal description of RA dates from 1631 [2]. There is a scarcity of descriptions of the disease in Europe between 1700 and 1900 [3]. This, combined with the fact that the evidence of erosions compatible with RA has been found in ancient skeletons in North America, but not in Europe or the Middle East [4], has led to the suggestion that RA may be a communicable disease brought to the Old World after contact with the New World [1]. A good candidate factor for such an effect may be tobacco smoking, a habit imported from the New World that increased tremendously in the late 19th century followed by a decrease in the second half of the 20th century, roughly in parallel with changes in the incidence of RA.

Risk factors for RA development

The risk of developing RA is determined by genetic susceptibility combined with environmental factors [5,6]. Certain environmental factors operate already early in life, and they may help to lay the foundation for autoimmunity. In a large part of those later developing seropositive RA, there is a phase of autoimmunity and subclinical inflammation, during which another transient cause of inflammation such as an infection is thought to trigger the onset of clinically apparent disease [7].

In the following, we present a short overview of genetic and environmental risk factors for RA, with a focus on recent publications. Due to the preclinical phase that many later patients go through, biomarkers of autoimmunity and inflammation can also be used as risk factors or predictors of disease. Recently, several prediction models have been constructed using information from various cohorts of persons at risk of RA.

Genetic risk factors

Approximately 65% of RA risk has been shown to be heritable, and >100 risk loci are now known. Most of these confer a low risk, and together they explain approximately 16% of total susceptibility [8]. It has become clear that ACPA-negative and ACPA-positive disease have a genetically different background [5,9]. The major histocompatibility complex (MHC) class II, DR beta 1 (human leukocyte antigen (HLA)-DRB1) alleles play a central role in the genetic risk of "seropositive" (ACPA and/or rheumatoid factor (RF)-positive) RA, mainly in patients who are ACPA positive [5]. Multiple alleles from this complex are associated with RA, which all share a region of similarity termed the shared epitope (SE). Besides these, several non-HLA genes have been identified. Most of the evidence comes from genome-wide association studies (GWAS) [10]. Until now, most GWAS investigating RA have been performed in seropositive individuals with a European background [10]. Recently, a review was published of specific genetic risk in Asian populations [11]. Although most single-nucleotide polymorphisms (SNPs) have the same effect sizes for developing RA in European and Asian people, some differences are found, mainly for PADI4 and PTPN22, which are more strongly associated with RA in