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VIEWPOINT

Time sequence of autoimmune processes in the trajectory to rheumatoid arthritis development: what do we know?

Judith W Heutz ,[1] René E M Toes ,[2] Annette H M van der Helm-van Mil [1,2]

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[1]Department of Rheumatology, Erasmus Medical Center Rotterdam, Rotterdam, Netherlands
[2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

Correspondence to
Judith W Heutz;
j.heutz@erasmusmc.nl

ABSTRACT

The trajectory to RA development is a multi-step process that can take a decade. Understanding which processes occur at which moment during this trajectory is crucial when designing interventions to prevent disease development. Clinically, the period before RA onset can be divided into an asymptomatic and a symptomatic risk phase. Published visual representations of RA development often display the maturation of the autoimmune response occurring in the symptomatic risk phase or relatively short before RA development, but evidence underlying this notion is limited. To obtain more detailed insights into the time sequence of immune processes in the asymptomatic and symptomatic risk stages of RA development, we interpreted the current available literature against the level of evidence, as longitudinal studies with repeated measurements in patients are needed for a robust conclusion on temporal sequences. Regarding the development of ACPA-positive disease, maturation of the systemic autoimmune response seems to occur approximately 5-years before diagnosis, but the autoimmune response is stable during the symptomatic risk phase and progression to RA. Known genetic and environmental factors have a different effect in both risk phases. Less is known about the development of ACPA-negative RA, the symptomatic risk phase lasts longer than for ACPA-positive RA, but here too the maturation of the autoimmunity seems to take place mainly in the asymptomatic phase. Based on this, we have proposed a new picture of RA development. This knowledge can guide the choice of treatment targets in future trials aimed at preventing RA.

INTRODUCTION

Therapeutic interception in individuals at risk for rheumatoid arthritis (RA) has become an area of interest as several trials have demonstrated the potential to modify disease progression in individuals at risk.[1] The trajectory to RA development is a multi-step process that can take a decade. Understanding which processes occur at which moment during this trajectory is crucial when designing interventions to prevent disease development. From a clinical perspective, the 'pre-RA period' can be roughly divided into a stage without symptoms and one with symptoms. This distinction is consistent with the practice of identifying people at risk for RA: people with symptoms seek medical help and can be found in clinical practice, while people without symptoms are typically identified by population screening. To support the inclusion of defined groups of at-risk individuals in future trials, a risk stratification methodology is currently under development by European Alliance of Associations for Rheumatology and American College of Rheumatology for both risk stages: one for people presenting with arthralgia in secondary care and one for persons in the general population identified by population screening. Although not studied yet, the pathophysiological processes occurring in the asymptomatic and symptomatic risk stages likely differ. Visual representations of RA development often display the maturation of the autoimmune response as a continuum occurring in the symptomatic risk phase or relatively short before RA development, but evidence underlying this notion is limited.[2 3] To obtain more detailed insights into this aspect, we now reviewed the literature, summarised the results, and interpreted the current knowledge of the temporal sequences of immune processes in the asymptomatic and symptomatic risk stages of RA development. We will discuss anti-citrullinated protein antibodies (ACPA)-positive and ACPA-negative disease separately because pathophysiological processes may differ. For ACPA-positive disease, we studied the period after the appearance of ACPA in the systemic circulation. We will also shortly refer to previous meta-analyses of risk factors and review what is known about the timing of when these risk factors may exert their effect on RA development.

APPROACH TO FIND EVIDENCE

Reliable data on timing or temporal sequence of pathophysiological processes require longitudinal studies, in which patients are followed over time, while sampling the patient at multiple time points and monitoring the development of symptoms and clinical arthritis. In order to identify these studies, we established the following primary inclusion criteria: (1) longitudinal and prospective studies; (2) studies reporting serially obtained samples; (3) studies that analysed serially obtained samples as such and (4) studies with explicit information on the presence/development of symptoms. Symptoms could be described as clinically suspect arthralgia (CSA), musculoskeletal symptoms or arthralgia. Studies that did not fulfil the primary inclusion criteria but that were relevant for the overview of evidence were divided into 'second-best' and 'third-best' categories. 'Second-best' studies included those that were not prospective, but retrospective or nested case–control studies. These studies still had to include serial measurements within patients and had to report information on the asymptomatic or symptomatic phase. As a 'third-best' option, studies were included without serial measurements and/or clear information on symptoms that attempted to inform about the timing of events by relating the moment of serum sampling to the moment of RA development. To find studies, we searched Medline, Embase and Web of Science for evidence on the timing of occurrence and changes in the systemic autoantibody and immune response before RA develops. A detailed method regarding the literature search, inclusion and exclusion criteria, and the studies fulfilling the primary or the 'second and third-best' criteria are provided in online supplemental material.

THE SYMPTOMATIC RISK STAGE OF ACPA-POSITIVE RA

12 studies fulfilled the primary inclusion criteria, of which 7 reported on ACPA maturation and 6 on other aspects of autoimmunity maturation (eg, course of cytokines, T-cell and B-cell subsets) (online supplemental table S3). All of them were executed in patients with symptoms, defined as either CSA, musculoskeletal symptoms or arthralgia. Studies consistently reported that IgG ACPA levels remained stable from the onset of symptoms to the onset of clinically apparent arthritis, as did the number of ACPA isotypes and citrullinated peptides recognised.[4–9] Also, the ACPA IgG variable domain glycosylation profile seemed stable, although the number of patients studied with serial samples was relatively low.[10] Regarding the immune response, a study on the expression of 37 cytokines reported stable levels from symptom onset to the onset of clinical arthritis.[11] Different B-cell and T-cell subsets were also studied from symptom onset to clinical arthritis development. Although a relatively low number of subjects were studied, overall, stable lymphocyte subsets were observed.[4 12]

THE ASYMPTOMATIC RISK STAGE OF ACPA-POSITIVE RA

The appearance of ACPA can precede RA by up to 10 years or more. Since symptoms generally occur around 6–12 months before RA development, the ACPA-positive asymptomatic stage could cover the period of 10 to 1 year before RA diagnosis. None of the studies on the asymptomatic risk stage fulfilled the primary inclusion criteria. Also, none of the studies fulfilled the criteria for 'second-best' studies since no study described both serial measurements that were analysed in a serial manner and described the timing of symptom onset (online supplemental table S4). 32 studies were 'third-best'; these were mostly nested case–control studies with measurements at one point in time before RA onset (or analysed as such) and a few longitudinal studies in first-degree relatives of RA patients with serial measurements but without information on symptom onset. From these, we attempted to deduce the sequence of events between the occurrence of ACPA and the onset of symptoms. The mean ACPA levels, number of isotypes and autoantibody reactivities increased approximately 5 years before diagnosis (range 8–3 years before diagnosis).[13–17] Cytokine levels seem to rise approximately 3 years before diagnosis. One study that investigated both ACPA maturation and cytokine changes also reported an expansion of the ACPA response, followed by the appearance of changes in systemic inflammation.[15] Finally, a study that mapped longitudinal changes in a proteomic signature over time showed that these changes paralleled increases in ACPA-titres.[18]

THE ASYMPTOMATIC AND SYMPTOMATIC RISK STAGES OF ACPA-NEGATIVE RA

The time between the presentation of symptom complexes such as CSA and RA development is several months longer in ACPA-negative than in ACPA-positive RA.[19] Few studies have been performed on the autoimmune processes that precede the development of ACPA-negative RA. One study categorised as 'third-best' suggested that cytokines start to increase 2–3 years before RA diagnosis.[15] Another study evaluated cytokine expression in paired samples at CSA-onset and RA-development and observed stable levels.[11]

These studies defined ACPA negativity as a negative anti-CCP2 test.[11 15] ACPA negativity is not similar to auto-antibody negativity. Studies in established RA have revealed that ACPA-negative patients can be positive for other antibodies, such as anti-modified protein antibodies (AMPAs).[20] Especially anti-Carp and anti-APAA have been studied in RA risk groups.[9 17] The frequency in ACPA-negative patients seemed to be relatively low,[17] but since these studies did not measure an entire

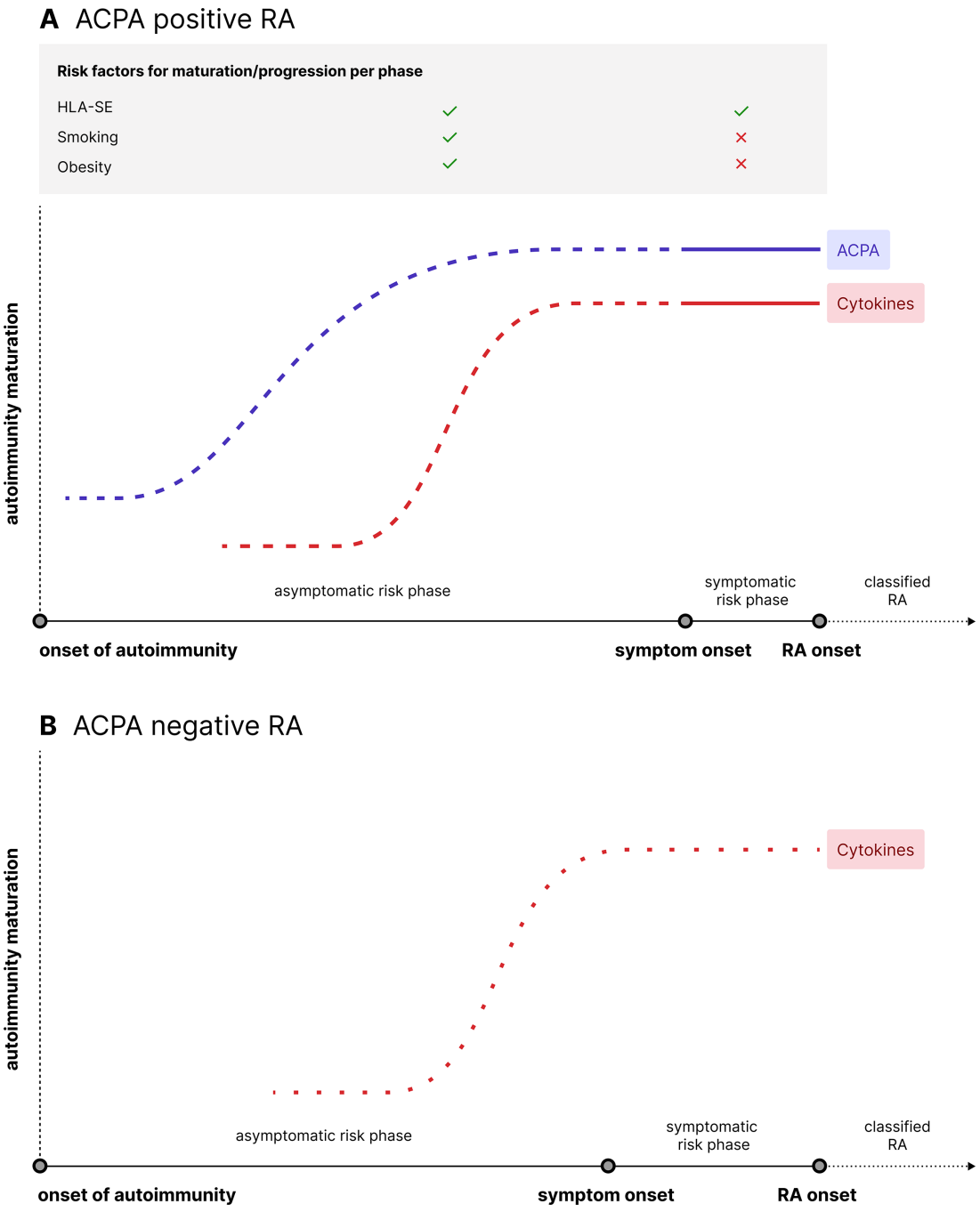

Figure 1 Maturation of the autoimmune response from the onset of autoimmunity and during the development of RA. A schematic representation of the maturation and progression of the immune response in the asymptomatic and symptomatic at-risk phases of RA. The onset of autoimmunity starts up to 10 years before the onset of RA with the appearance of ACPAs (not visualised). In ACPA-positive RA (A), the maturation of the ACPA response occurs in the asymptomatic phase and is enhanced by HLA-shared epitope presence, obesity and smoking. This is followed by a rise in cytokines. In the symptomatic at-risk phase, no further maturation of ACPA occurs, and HLA-SE associated with the progression to clinical arthritis. The level of scientific evidence in the symptomatic phase is stronger (straight line) than in the asymptomatic phase (dotted line). In ACPA-negative RA (B), cytokines seem to increase around 2 years before diagnosis. The lack of evidence about the development of ACPA-negative RA is represented by the dotted line. ACPA, anti-citrullinated protein antibody; HLA-SE, human leucocyte antigen shared epitope; RA, rheumatoid arthritis.

ACPA-negative risk population, no firm conclusions can be drawn about the prevalence of AMPA-positivity in ACPA-negative people at risk for RA. Furthermore, there were no studies that reported on the time course of AMPA's in ACPA-negative risk groups. The fact that a proportion of ACPA-negative at-risk individuals may be positive for other autoantibodies (and thus could be classified as auto-antibody positive) may not affect the observation of the stable expression levels of cytokines during the course of the symptomatic risk stage, as stable levels

have been observed in ACPA-positive patients during the trajectory to RA.

GENETIC AND ENVIRONMENTAL RISK FACTORS AND TIMING OF ASSOCIATIONS

The maturation of autoimmune responses may be influenced by genetic and environmental factors. For an overview regarding the associations of the well-known risk factors HLA-shared epitope, smoking and obesity during the symptomatic and asymptomatic risk stages, we refer to recent meta-analyses.[21 22] The meta-analysis on HLA-shared epitope and smoking was based on four studies from Northern Europe, one from Japan and one from the USA.[22] It revealed that, in the trajectory of ACPA-positive RA development, smoking associated with the development of ACPA and maturation of the ACPA response, but not with progression from the symptomatic risk stage to RA. In contrast, the HLA-shared epitope was not associated with ACPA development but did associate with progression of the autoantibody response and with progression from arthralgia to RA.[22] The HLA-shared epitope also tended to associate in a dose-dependent manner with progression to clinically apparent arthritis in the symptomatic risk stage of ACPA-negative RA.[22] The effect size appeared to be somewhat smaller than in ACPA-positive arthralgia, which is consistent with findings from genome-wide case–control studies reporting that the HLA locus conferred risk for ACPA-negative RA, but with a lower effect size.[23 24] Obesity portrays the same time pattern as smoking: it seemed to confer risk for ACPA presence in the asymptomatic risk stage, but not with progression to clinical disease in the symptomatic risk stage.[21]

CONCLUSIONS

To summarise, our interpretation of the current literature on the autoimmune processes preceding RA is that ACPA can appear ten years before RA diagnosis; this may be promoted by smoking and possibly by obesity. Maturation of the ACPA response occurs approximately 5 years before diagnosis and is enhanced by genetic factors (particularly HLA-shared epitope) and smoking. This is followed by a rise in cytokines, on average 3 years before diagnosis. Symptoms often occur later, ~6 months before clinical arthritis occurs. Autoantibody characteristics and cytokines are stable in this symptomatic phase until RA develops. This current knowledge is summarised in figure 1; the scientific evidence for the findings in the symptomatic stage is stronger than that in the asymptomatic stage, which is highlighted by straight and dotted lines, respectively.

The data we found were about the risk-contributing role of ACPA. Protective factors should also be considered in the developmental stages of RA, as protective ACPAs have been reported in mouse studies.[25 26] However, in our literature search, we focused on humans, and we did not find data on protective ACPAs in patients.

Much remains to be explored regarding the trajectory of ACPA-negative RA development. Cytokines seem to increase ~2 years before diagnoses in the asymptomatic stage. Subsequently, cytokine levels seem constant during the symptomatic risk stage (figure 1). However, these data are limited to the cytokines measured. It cannot be excluded that performing serial measurements of a broader set of cytokines or other systemic markers could provide different results. These results show that the development of ACPA-negative disease is a relatively understudied area compared with the number of studies on the development of ACPA-positive disease.

The broad range of autoimmune response characteristics that was studied during the transition from ACPA-positive arthralgia to RA showed stable levels. This finding, together with the observation that ACPA-positive arthralgia patients who did not develop RA had a similar ACPA response as those who developed RA, implies that the process critical for actual RA development in predisposed ACPA-positive at-risk individuals is still unknown.[5 9] This also applies to ACPA-negative RA. There too, a link is still missing that can point to the ultimately decisive processes. The ultimate critical process or 'hit' may be related to yet unmeasured characteristics of the systemic autoimmune response. Alternatively, the crucial final processes could not be present in the systemic circulation but occur locally, around or in the joint. Interestingly, prolonged work-related physical strain promotes subclinical joint inflammation (particularly tenosynovitis) and the progression from subclinical joint inflammation to clinical arthritis and RA.[27] Interestingly, this risk factor was independent of ACPA and could potentially point to a relevant process that is shared between the two RA subsets. Future studies at the tissue level of subclinical joint inflammation in symptomatic risk individuals who do and do not progress to RA are needed to gain more insight into the time course of the processes that ultimately lead to RA.

In conclusion, further research is needed at different risk stages to decipher the immunological processes crucial for the development of RA. This knowledge may guide the choice of treatment targets in future trials aimed at preventing RA.

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ORCID iDs
Judith W Heutz http://orcid.org/0000-0002-2126-7922
René E M Toes http://orcid.org/0000-0002-9618-6414
Annette H M van der Helm-van Mil http://orcid.org/0000-0001-8572-1437

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