

THE LEIDEN EARLY ARTHRITIS CLINIC: CURRENT CONCEPTS IN THE PATHOGENESIS AND TREATMENT OF EARLY ARTHRITIS

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ABSTRACT

In 1993 a special Early Arthritis Clinic (EAC) was established at the Department of Rheumatology of the Leiden University Medical Center in order to detect and treat inflammatory disorders early in the disease state, especially early rheumatoid arthritis. Patients with confirmed arthritis of recent onset (less than two years) were included by rheumatologists and trained research nurses. Parameters of first and follow-up visits (3, 6 and 9 months and yearly) that were entered in the EAC-database include the medical history, physical diagnostic examination, laboratory tests, questionnaires, radiographic joint scores and diagnosis. This database enables us to conduct research on arthritis, with an emphasis on rheumatoid arthritis, in many ways. Physicians and basic scientists have studied cellular immunology and genetic, environmental and clinical risk factors in order to determine the pathophysiologic mechanisms of inflammatory arthritis. The present article is a review on reports published from the EAC. Over the past ten years, these reports have been highly relevant for both daily clinical practice and research. Present and planned future studies, as described in this article, reconfirm the importance of an EAC framework to ensure that research continues on this disease in the Leiden EAC area.

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease. It is a chronic inflammatory disorder of unknown etiology and multifactorial pathogenesis that affects joints and other tissues. RA is characterized by a symmetric polyarthritis involving the small joints of the hands and feet, and most frequently affecting the metacarpophalangeal, proximal interphalangeal and wrist joints. Clinical articular and peri-articular manifestations include joint swelling and tenderness to palpation, with morning stiffness and severe motion impairment in the involved joints.

RA is a clinical diagnosis. In order to classify patients for studies, the American College of Rheumatology (ACR) has generated classification criteria. The most commonly used criteria are the ACR 1987 classification criteria, which include the following criteria: morning stiffness, arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, serum rheumatoid factor (RF), rheumatoid nodules, and radiographic changes. A patient is classified as having RA if he or she satisfies at least 4 of the 7 criteria for at least 6 weeks. RA has a wide clinical spectrum, ranging from self-limiting disease to progressive chronic disease with extra-articular manifestations.

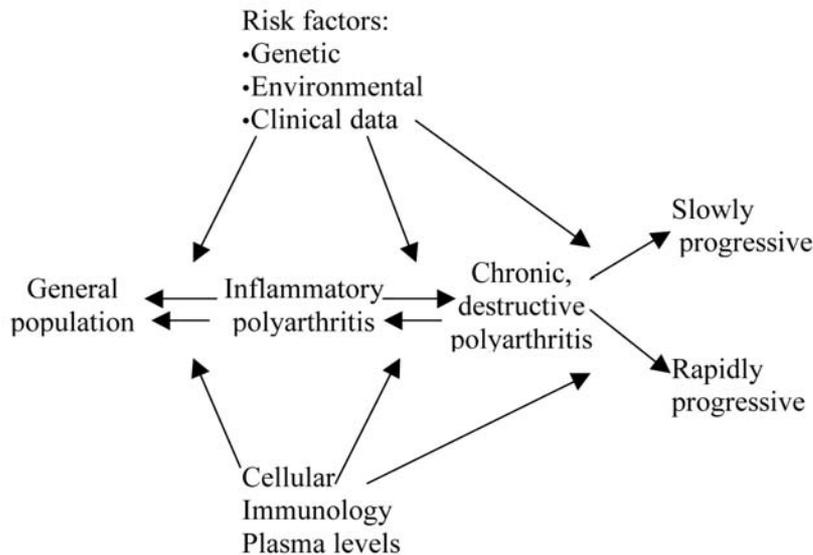


Figure 1. Research model for mechanisms involved in inflammatory arthritis

A UNIQUE POPULATION - BASED INCEPTION COHORT

The Leiden Early Arthritis Clinic (EAC) was started in 1993 in order to detect and treat inflammatory disorders early in the disease state, especially early RA (1, 2). In order to obtain early referrals by general practitioners (GPs), a campaign was started among GPs to refer patients with suspected arthritis as soon as possible to the rheumatology department of the Leiden University Medical Center. Our rheumatology outpatient clinic is the only center for rheumatic disease patients in a semi-rural area with more than 300, 000 inhabitants. Patients can be seen at the EAC within two weeks. They are asked to be included in the EAC if the suspected arthritis is confirmed by a rheumatologist and the symptoms of arthritis do not exceed two years. Second opinions are excluded. All parameters, ranging from history-taking, physic-diagnostic examination (general physical examination and a painful and swollen joint count), laboratory tests and questionnaires to radiographic joint scores are obtained by rheumatologists and trained research nurses. These data are entered into the EAC-database by encoded number. Based on the test results, a diagnosis is recorded at the second visit, two weeks later, and is revised during the follow-up visits after 3 months, 6 months and yearly. EAC follow-up was ended, if arthritis had not been observed by a rheumatologist for one year without

the use of disease-modifying antirheumatic drugs (DMARDs) or in case of posttraumatic arthritis, pseudo-gout or gout.

The major purpose of these cohorts was at that time partly epidemiological, i. e. , to see which fraction of patients with early arthritis would go on to develop RA. But it had also a scientific purpose. The researchers started collecting data at baseline from these patients in the hope to find markers of disease progression into RA. The term 'early' RA, however, is not precisely defined in the literature, and has become a moving target over the years as the striving for effective intervention became more and more ambitious.

The presumed steps in the pathogenesis of RA are presented in **Figure 1**. Our research has been focused on two major categories: risk factors (genetic, environmental and clinical) and cellular immunology (autoantibodies, T cells, synoviocytes, cartilage degrading products and cytokines). The interactions between these two categories and the course of inflammatory arthritis are presented in **Figure 1**.

Moreover, given the fact that many patients are seen before they fulfill the ACR criteria, this cohort is ideally suited to study disease dynamics. To this end we will discuss the definition of undifferentiated arthritis (UA), the natural course of UA, clinical characteristics that predict the progression from UA to RA and pathophysiological differences between UA and RA.

DEFINITIONS OF EARLY ARTHRITIS AND UA

The published trials evaluating treatment strategies in RA all include patients classified according to the 1987 ACR-criteria for RA. These criteria are generally accepted and are developed by experts that compared characteristics of patients with longstanding 'classical' RA (mean disease duration 8 years). In clinical practice, patients presenting with an early arthritis frequently have an undifferentiated disease that in time may progress to a polyarthritis fulfilling the ACR-criteria for RA or may have a more benign disease course. The ACR criteria have been criticized as they have low discriminative ability in patients presenting with recent onset arthritis (3-6). This is not surprising considering the method by which the criteria were formulated and the components of the ACR-criteria. One of the criteria is the presence of erosions on the radiographs of hands and wrists. In the early phases of RA only 13% of the patients have erosive disease (7). Additionally, erosions often initially present in the small joints of the feet and appear at a later point in the disease course in the small joints of the hands (8). Also rheumatoid nodules are very rare in the early phases of RA and rheumatoid factor is present in only 50% of the patients with early RA (9). This indicates that at present a set of criteria is needed that applies to early UA to differentiate the UA patients that will progress to RA from those that will have a more benign disease course. Before the characteristics that predict the disease outcome in UA patients can be identified, a general acceptance on the definition for early UA is needed. In the literature several terms that refer to arthritis of recent onset are used, but they refer to distinct categories of patients and should therefore be separated. Most frequently used are the terms 'early arthritis', 'early RA' and undifferentiated arthritis. *Early arthritis* is the description of a state in which there is a (mono-, oligo- or poly) arthritis that has a recent onset. In case of early arthritis the disease can be undifferentiated or differentiated. For example, about 20% of the patients that present with an early arthritis directly fulfill the ACR-criteria and thus can be classified as RA. This indicates that in *early RA* per definition the ACR-criteria for RA are fulfilled. Since the ACR criteria also state that the patients fulfill the criteria for at least 6 weeks, shorter disease duration than six weeks is by definition impossible in case of early RA. Patients with an early arthritis may also fulfill classification criteria

for other diagnoses. Finally, those early arthritis patients that can not be classified according to ACR-criteria and in whom the arthritis is not septic or reactive in origin have per exclusionem an *undifferentiated arthritis*. Discerning UA from early arthritis and early RA is relevant when comparing studies that describe models that predict the disease outcome. This is also relevant for studies that assess therapeutic efficacy as the generalizability of these studies depends on the patient group that is included. UA patients may provide an opportunity as it is to be expected that the process that drives chronicity can be influenced more effectively when it is less established.

NATURAL DISEASE COURSE OF UA

The natural disease course of UA is variably reported in several inception cohorts. This is not only due to the use of different definitions for UA, but is also a result of differences in inclusion criteria for several early arthritis cohorts. For example, inclusion in the Norfolk Arthritis Registry (UK) required the presence of at least two swollen joints (10), whereas for inclusion in the Leeds EAC (UK) (11) or the arthritis cohort from Wichita (USA) the presence of synovitis was not required (12). On the other hand, some EAC did not include patients with UA but only patients that fulfilled the criteria for RA (13, 14). Inclusion criteria from early arthritis cohorts differ not only in the presence/absence of arthritis, but also in the required symptom duration. Patients could be included in the NOAR when the arthritis was present for at least four weeks, whereas symptom duration of more than 12 weeks was an exclusion criteria for the early arthritis cohort from Birmingham. Different inclusion and exclusion criteria instigate the enrolment of different groups of patients and clarifies that different results are observed when the natural disease course is studied.

Early arthritis cohorts that included all patients with at least one swollen joint reported that at initial presentation about 20% of the patients fulfilled the criteria for RA and that 35%-54% of the patients presented with UA (15, 16). In case of UA the disease course was diverse: 40-55% remitted spontaneously (16-19), 35%-50% (7, 15) developed RA and the remaining patients developed other diagnoses or remained undifferentiated.

These data also illustrate that when evaluating studies on UA patients the duration of symptoms are of importance for the outcome of the patient group. In

Form to calculate a patient's prediction score

1. What is the age?	Multiply by 0. 02	
2. What is the gender?	In case female:	1 point
3. What is the distribution of involved joints?	In case small joints hands and feet:	0.5 point
	In case symmetric	0.5 point
	In case upper extremities	1 point
Or:	in case upper and lower extremities	1.5 points
4. What is the length of the VAS morning stiffness (range 0-100 mm)?	In case 26-90 mm	1 point
	In case > 90 mm	2 points
5. What is the number of tender joints?	In case 4-10	0.5 point
	In case 11 or higher	1 point
6. What is the number of swollen joints?	In case 4-10	0.5 point
	In case 11 or more	1 point
7. What is the C-reactive protein level (mg/L)?	In case 5-50	0.5 point
	In case 51 or higher	1.5 points
8. Is the Rheumatoid factor positive?	If yes	1 point
9. Are the anti-CCP antibodies positive?	If yes	2 points
		Total score

Figure 2A.

other words, an UA from recent onset (several weeks) has a different natural course than an arthritis that after one year of follow-up is still unclassified (persistent UA). In the Leiden EAC, patients that after one year of follow-up had persistent UA developed only in a minority (10%) RA later on in the disease course.

Intriguingly, the reported rates of spontaneous remission patients in case of UA are importantly different from those in RA. Whereas remission was achieved in 40-55% of the patients with recent onset UA, the remission rate in RA is at most 10-15% (20, 21). Apparently, the chance to achieve a natural remission becomes smaller when the disease process is more matured. This supports the notion that chronicity might be more easily reversed in the phase of UA.

PREDICTING PROGRESSION FROM UA TO RA

As UA has a variable disease course and DMARD-therapy is potentially toxic, only the UA patients that have a high chance to develop RA are preferentially treated with DMARDs, whereas the patients that will achieve a spontaneous remission will preferentially not receive these drugs. This un-

derlines that a model that is able to predict the disease outcome in individual patients with UA is needed. Initial attempts to define such prognostic criteria have been made by Visser *et al.* based on the Leiden EAC (22). This model predicts disease persistency and erosiveness. For the development of this model all early arthritis patients were included and not only patients with UA. Consequently, patients that at first presentation were classified as e. g. reactive arthritis or RA were also included. However, the natural course of these diseases, already known as reactive arthritis is in most cases remitting and RA is in most cases a persistent disorder. This indicates that patients with a diagnosis of which the disease course is well-known may skew a model that predicts the disease outcome. As the model of Visser *et al.* was not developed using specifically patients with UA, this model is not optimal to guide individualized treatment decision in UA. Recently, a model that predicts the disease outcome in individual patients with UA was developed also based on the Leiden EAC (23). From a total cohort of 1700 early arthritis patients, 570 patients presented with UA. After one year of follow-up 31% of the UA patients had progressed to RA. The remaining two-thirds had developed other diagno-

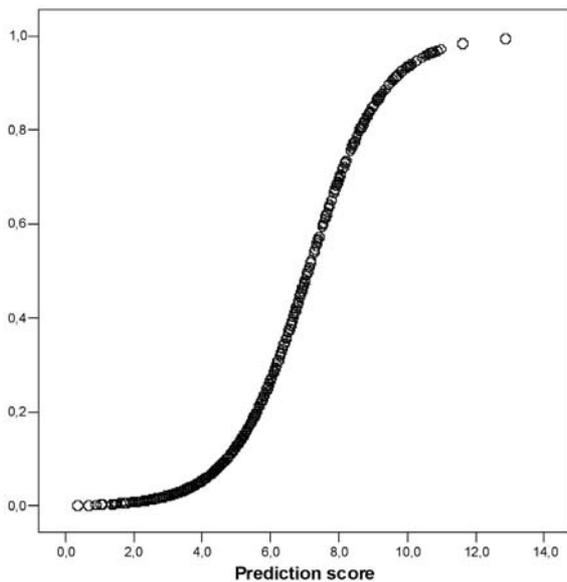


Figure 2B. The subjects' prediction scores plotted versus the predicted risk to develop RA.

ses (16%), had achieved spontaneous remission (26%) or remained unclassified (26%). Clinical characteristics between the UA-patients that had and had not developed RA were compared and using logistic regression analysis the variables that were independent predictors for the development of RA were selected. This resulted in the construction of a prediction rule as well as a graph on one could easily read the probability to develop RA as a value between 0 and 1 (Figure 2A and 2b) (23). The discriminative ability of this prediction rule was assessed by the area under the receiver operator curve, which was 0.89 for the derivation cohort and 0.97 for the replication cohort. The total prediction score ranged between 0 and 14. All patients with a score < 4 did not progress and all patients with a score > 10 did progress to RA. With the cutoff levels ≤ 6 and ≥ 8 the negative and positive predictive values were 91% and 84% respectively. As this prediction rule consists of 9 variables that are regularly assessed at the outpatient clinic (age, gender, distribution of involved joints, morning stiffness severity, number of tender and swollen joints, C-reactive protein (CRP), RF and anti-CCP antibodies), this prediction rule can be easily applied in daily practice. Moreover, as the prediction rule estimates the chance for an individual patient to prog-

ress to RA in a percentage, application of this rule might facilitate the involvement of patients themselves in treatment decision-making.

BIOLOGICAL MECHANISMS IN UA AND RA

Subsequently, the question arises which biological mechanism is responsible for the progression from UA to RA. The identified nine risk factors may provide clues. Therefore possible mechanisms underlying the association with each of these variables and RA-development are shortly discussed.

1. Age

Ageing is associated with a decline in a large number of physiological functions as well as immune function. Impairment in cellular, humoral and innate immunity might predispose persons with an increasing age to amongst others RA. Relevant changes in the innate immune system are an altered phagocyte function and an increased production of pro-inflammatory cytokines such as IL-1, TNF- α and IL-6 (the latter is responsible for the increase in CRP that is seen in elderly persons) (24). Modification of the adaptive immune system is exemplified by the development of a polyreactive antibody production at higher age (25). The immunosenescence is further discussed in reference 26 (26) but might predispose to arthritis or mediate an aggressive disease course.

2. Gender

Sex hormones influence the predisposition to autoimmune diseases. In general, men are less prone than women. This might be caused by anti-inflammatory effects of androgens. Recently it was demonstrated that PPAR γ , a gene in CD4 $^+$ T cells, is sensitive to androgen levels and is higher expressed in males, which induced higher levels of Th2 cytokines and consequently a lower susceptibility to Th1-mediated autoimmune diseases (27). Estrogen is also able to suppress arthritis in mouse models (28) and the use of oral contraceptives might be associated with a lower risk on RA development (29). However, this finding was not replicated in

the Nurses' Health study (30). Additionally, both estrogen and androgen inhibit bone resorption (31). Moreover, sex hormones may have local effects which seem to consist mainly in modulation of cell proliferation and cytokine production (i. e. , TNF- α , IL-1). Altogether, these data suggest that postmenopausal women exhibit a pro-inflammatory cytokine profile that might contribute to the higher incidence of RA in these women.

3. Distribution of involved joints

RA particularly affects the small joints of the hands and feet, whereas in some other rheumatologic diseases the large joints are preferentially inflamed. At present the reason for this predilection is not clear. It has recently been suggested that differential accumulation of regular T cells in different joints may dictate the anatomic spectrum seen in arthritis syndromes (32). However this hypothesis is based on animal models and whether this might explain the distribution of inflamed joints in human is not known.

4. Severity of morning stiffness

Although in clinical practice the presence of morning stiffness is a specific marker for RA, the anatomical substrate causing morning stiffness is ample examined. Straub *et al.* proposed that the symptom stiffness is due to edema formation mediated by circulating pro-inflammatory cytokines (33). The observations that the pro-inflammatory cytokines TNF- α and IL-6 exhibit a circadian rhythm and that these levels peak around 6. 00-7. 00 hour in RA patients might support this hypothesis and explain why stiffness is most severe in the early morning.

5. C-reactive protein, number of tender and swollen joints.

As already discussed, IL-6 enhances the hepatic production of CRP, explaining that in situations in which IL-6 is increased (older age, inflammation) CRP levels are elevated. Therefore, the CRP level directly reflects the level of pro-inflammatory cytokines. Additionally, also the number of tender joints

and the number of swollen joint may mirror the level of the pro-inflammatory processes. It is reasonable to suggest that in case of increased (local) pro-inflammatory activity the biological processes that generate RA are boosted.

6. Rheumatoid factor and anti-CCP antibodies

The association between most of the above mentioned factors and RA are (in part) mediated by an increase in pro-inflammatory cytokines, and thus reflect a quantitative trait. The last two items of the prediction model, the presence of autoantibodies, are primarily a qualitative trait. Although it is still uncertain whether these autoantibodies are of pathophysiological importance or the result of a bystander effect, the specificity of anti-CCP antibodies for the development of RA is extensively reported. A recent study revealed that not only the presence of anti-CCP antibodies, but in case of anti-CCP positivity also the level of these antibodies, is correlated with an increased risk on progressing from UA to RA (34). Moreover, not only the level but also the nature of the autoantibody response is different in UA and RA. Patients with UA have a lower number of anti-CCP isotypes than patients with RA and, similarly, the UA patients that progressed to RA had a higher number of isotypes compared to the UA patients that did not develop RA (35). Furthermore, a recent study by van der Linden *et al.* (36) suggested that the isotype anti-CCP-2 remains the most powerful serologic test for predicting the development of RA and that anti-CCP-2 antibodies were also a marker of severe disease. This information is especially important, because the rheumatology community has increasingly recognized the value of earlier diagnosis and treatment of RA.

In conclusion, the biological mechanisms underlying UA and RA differ both in quantity (e. g. level pro-inflammatory cytokines) and quality (e. g. autoantibody response). Apparently, UA patients that have more of these quantitative or qualitative traits have a concomitant higher risk to progress to RA.

CLINICAL INTERVENTION STUDIES

Presently, early arthritis trials are embedded in the EAC follow-up structure in order to ensure long

term follow-up of these patients. The “BeSt” trial is a multi-center randomised trial in which four different, disease activity score (DAS)-steered, dynamic (including tapering to drug-free remission) treatment strategies are compared (37, 38). Two groups (group 1, sequential monotherapy, and group 2, step-up combination therapy) started with methotrexate (MTX) monotherapy, with introduction of combination therapy with infliximab or prednisolone in case of insufficient response to at least three conventional DMARDs. The other two groups started with combination therapy (group 3, initial combination therapy with MTX, salazopyrine (SSZ) and prednisolone, and group 4, initial combination therapy with MTX and infliximab). The initial combination therapy groups showed an earlier improvement in DAS, HAQ and quality of life (39), earlier remission and less radiological progression compared with the initial monotherapy groups. The dynamic study design aiming at a DAS 2.4 or less resulted in comparable results in functional ability in the four treatment groups from the end of the first year of treatment onwards, meanwhile enabling most patients in the initial combination therapy groups to taper their medication and most patients in the initial monotherapy groups to increase or change their medication. Despite only a brief period of clinical differences in response early in the trial between the treatment arms, patients treated with initial combination therapy still had significantly less joint damage progression after five years as compared with the initial monotherapy groups. After five years, 48% of patients are in clinical remission, defined as a DAS less than 1.6 (40). Fourteen, 16, 10 and 19% of patients had by then successfully discontinued all antirheumatic drugs. The patients in sustained drug-free remission (>one year) barely showed radiological progression after the discontinuation of DMARDs. The BeSt study showed that, with continuous steering at low disease activity, a comparable disease state could be achieved in all four groups, independent of initial treatment.

The effective management of patients with recent onset UA is difficult. Early initiation of MTX has been shown to be effective in slowing progression to RA and in reducing the level of joint damage at a group level (41). However, the rate of spontaneous remission in early UA is considerable (40–50%) and only one-third of patients with UA will develop RA (17-19). Thus, the ability to accurately predict outcome at an individual patient level, to allow accurate

individualized treatment decision-making, is an important goal.

Since little is known on the outcome and treatment of UA, a double blind, placebo-controlled trial the “PROMPT” study was conducted in Leiden (41). This study is a double-blind, placebo-controlled, randomized, multicenter trial involving 110 patients with UA who fulfilled the American College of Rheumatology (ACR) 1958 criteria for probable RA. Treatment started with MTX (15 mg/week) or placebo tablets, and every three months the dosage was increased if the DAS was > 2.4. After 12 months, the study medication was tapered and discontinued. Patients were followed up for 30 months. When a patient fulfilled the ACR criteria for RA (primary end point), the study medication was changed to MTX. Joint damage was scored on radiographs of the hands and feet. In 22 of the 55 patients (40%) in the MTX group, UA progressed to RA compared with 29 of 55 patients (53%) in the placebo group. However, in the MTX group, patients fulfilled the ACR criteria for RA at a later time point than in the placebo group ($P=0.04$), and fewer patients showed radiographic progression over 18 months ($P=0.046$). This study provided evidence for the efficacy of MTX treatment in postponing the diagnosis of RA, as defined by the ACR 1987 criteria, and retarding radiographic joint damage in UA patients.

ACPA POSITIVE AND ACPA NEGATIVE RA: DIFFERENT DISEASES?

The main genetic risk factor for RA, the HLA region, has been known for 25 years. Previous research has demonstrated, within the RA population, an association between HLA-DRB1 alleles carrying the shared epitope (SE) and anti-CCP antibodies. For the Leiden EAC, the odds ratio (OR) describing the association of two copies of the SE allele with anti-CCP positivity (using no copies of the SE allele in the healthy control group as the referent) was 11.79 ($P < 0.0001$), while the OR for one SE allele was 4.37 ($P < 0.0001$). No association with the SE was observed in the Dutch anti-CCP negative RA patients. For an American genetic study in multicase families, the “NARAC”, linkage and association analysis revealed the SE to be associated only with anti-CCP positive disease and not with anti-CCP negative disease. Stratified analyses indicated that

anti-CCP antibodies primarily mediated association of the SE with joint damage or disease persistence. Therefore, HLA-DRB1 alleles encoding the SE are specific for disease characterized by antibodies to citrullinated peptides, indicating that these alleles do not associate with RA as such, but rather with a particular phenotype.

Antibodies to citrullinated proteins are highly specific for RA and precede the onset of disease symptoms, indicating a pathogenetic role for these antibodies in RA. We showed that distinct genetic risk factors are associated with either anti-CCP positive disease or anti-CCP negative disease. These data are important as they indicate that distinct pathogenic mechanisms are underlying anti-CCP positive disease or anti-CCP negative disease. Likewise, these observations raise the question of whether anti-CCP positive RA and anti-CCP negative RA are clinically different disease entities. We therefore investigated whether RA patients with anti-CCP antibodies have a different clinical presentation and disease course compared with patients without these auto-antibodies. In a cohort of 454 incident patients with RA, 228 patients were anti-CCP positive and 226 patients were anti-CCP negative. The early symptoms, tender and swollen joint count, and CRP level at inclusion, as well as the swollen joint count and radiological destruction during four years of follow-up, were compared for the two groups. There were no differences in morning stiffness, type, location and distribution of early symptoms, patients' rated disease activity and CRP at inclusion between RA patients with and without anti-CCP antibodies. The mean tender and swollen joint count for the different joints at inclusion was similar. At follow-up, patients with anti-CCP antibodies had more swollen joints and more severe radiological destruction. Nevertheless, the distribution of affected joints, for swelling, bone erosions and joint space narrowing, was similar. In conclusion, the phenotype of RA patients with or without anti-CCP antibodies is similar with respect to clinical presentation but differs with respect to disease course.

Also the synovitis in patients with anti-CCP positive RA differs from that in patients with anti-CCP negative RA, notably with respect to more infiltrating lymphocytes in the synovium in anti-CCP positive patients. These anti-CCP positive patients were also associated with a higher rate of local joint destruction as shown in a synovial tissue biopsy study

performed by Oosterhout *et al.* (42). Furthermore, there was more fibrosis and increased synovial lining layer present in the anti-CCP negative RA patients and these differences were already present early in the disease.

In the PROMPT study, subgroup analysis revealed that the beneficial outcomes were most pronounced in UA patients with anti-CCP. In striking contrast, in the anti-CCP negative subgroup, the effect of MTX on the development of RA, the radiographic progression, and even on the signs and symptoms, was not demonstrable. Although these groups were small, a post hoc analysis suggested that only anti-CCP positive UA patients, who have the highest risk of developing RA, had benefit from early MTX treatment. Also this supports the growing evidence that anti-CCP positive and anti-CCP negative UA are different disease entities that should be approached differently.

It has been suggested that the Leiden EAC patients may not be representative of RA patients seen in community practices, since there is a high rate of spontaneous remission in this cohort, possibly due to the pattern of very early referral of patients with arthritis to the clinic. The Leiden EAC has therefore his limitations concerning the applicability of results from this cohort for other countries. However, the Leiden EAC cohort has a valuable contribution to our understanding of the pathogenesis of RA and has helped us distinguish patients with UA whose disease will progress to full-blown RA.

CONCLUSION

This brief review has given an impression on the past, present and future work performed on the Leiden Early Arthritis Clinic. The EAC enables us to conduct research on arthritis in many ways. Physicians and fundamental scientists have studied cellular immunology and genetic, environmental and clinical risk factors in order to determine pathophysiologic mechanisms of inflammatory arthritis. Over the past years, reports on the EAC have been highly relevant for both daily clinical practice and research. The studies described in this article, reconfirm the importance of an EAC framework to ensure continuous research of the Leiden EAC area.

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