

The Leiden Early Arthritis Clinic

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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 2 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 pathophysiological 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.

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 rheumatoid arthritis (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 Early Arthritis Clinic within 2 weeks. They are invited to be included in the EAC if the suspected arthritis is confirmed by a rheumatologist and the symptoms of arthritis do not exceed 2 years. Second opinions are excluded. All parameters, ranging from a medical history, physical-diagnostic examination (general physical examination and painful and swollen joint counts), 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 numbers. Based on the test results, a diagnosis is recorded at the second visit, 2 weeks later, and is revised during the follow-up visits after 3 months, 6 months (in cases of probable or definite RA) and yearly.

A detailed follow-up schedule is shown in Table I. The EAC follow-up procedure was terminated if arthritis had not been observed by a rheumatologist for 1 year without the use of disease-modifying antirheumatic drugs (DMARDs) or in cases of post-traumatic arthritis, pseudo-gout or gout. The tenth anniversary of the EAC was marked this year, and during this period over 1600 patients have been enrolled in the inception cohort and over 2000 variables have been measured in each patient. Table II presents some of the baseline characteristics of 1000 patients included in this cohort, who had completed one year of follow-up. The age at diagnosis, duration of symptoms and delay in referral by the GP are reported for each diagnosis at 1 year.

From the diagnosis at first visit to the diagnosis at 1 year, the number of "RA" and "arthritis of unknown cause" diagnoses increased, while the number of "probable RA" diagnoses decreased. This finding appears to be consistent with the course of probable RA. As ex-

Table I. Follow-up schedule of the Leiden Early Arthritis Clinic.

EAC visit number	1 inclusion	2 weeks	3 months	(6 months)	4 1 year	5 2 years	6 3 years etc.
Check-in / exclusion criteria	X						
Informed consent	X						
Visit rheumatologist	X	X	X		X	X	
Visit research nurse	X		X		X	X	
Joint assessment	X		X		X	X	
Laboratory assessment (including PBMCs*)	X		X		X	X	
HLA-typing	X						
Radiologic assessment	X			X	X	X	X
HAQ + AIMS questionnaires	X				X	X	
Assessment of ending					X	X	
EAC follow-up							

*PBMCs: Peripheral blood mononuclear cells.

pected, patients diagnosed with reactive arthritis, juvenile chronic arthritis, spondylarthropathy, sarcoid arthritis and lyme arthritis are quite young of age at the time of diagnosis. The duration of symptoms, recorded in days, is relatively long in those forms of arthritis with a remitting and relapsing character (i.e. RA, probable RA, palindromic RA, psoriatic arthritis, spondylarthropathy, SLE and osteoarthritis/arthritis). Another explanation for this phenomenon is that some of these diseases are difficult for the GP to recognize, as indicated by a relatively long

delay in referral.

In many disease states, deleterious characteristics are acquired during the course of disease. Examples can be found in oncology, where tumour cells spread from the original tumour to the regional lymphnodes and eventually disseminate to metastatic disease. The curative effect of a surgical or chemotherapeutical intervention depends heavily on the stage in which the disease is first treated. In RA, it is unknown if and when such deleterious characteristics are acquired during the course of the disease, although sequen-

tial events that take place in patients who develop RA have been suggested (3). These 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 this figure.

Genetic risk factors

Since the association between RA and HLA-DR4 was first described (4), genetic studies have implicated a role for specific HLA class II-dependent immune reactions in the pathogenesis of RA. The presence of HLA-DR Shared Epitope (SE) bearing alleles has been related to the severity of RA, with radiographic damage and rheumatoid factor positivity as measures of disease severity (5, 6). Genetic research in a group of female Dutch RA patients confirmed this association between the Shared Epitope and RA severity, reflected in the increased radiographic joint damage of this group (7), although this conclusion was challenged by several other groups (8, 9).

Genetic research has been conducted to

Table II. Some baseline characteristics of 1000 EAC patients. Values are the medians (25th-75th percentile).

Diagnosis	Age (years)	Duration of symptoms at 1 st visit (days)		Delay in referral (days)	1st visit (number)	1 year (number)	
Rheumatoid arthritis (RA)	57 (47, 68)	148	(77, 280)	78	(38, 148)	95	284
Probable RA	51 (35, 62)	131	(66, 266)	64	(20, 160)	254	53
Palindromic RA	50 (37, 60)	141	(96, 237)	223	(220, 225)	13	6
Septic arthritis	53 (33, 63)	10	(4, 15)	6	(4, 14)	35	10
Reactive arthritis	35 (30, 39)	13	(7, 28)	11	(6, 22)	72	45
Crystal induced arthritis	54 (47, 70)	11	(5, 76)	3	(1, 16)	105	86
Psoriatic arthritis	42 (34, 51)	189	(47, 373)	50	(22, 141)	63	52
Juvenile chronic arthritis	14 (13, 14)	70	(47, 92)	unknown		4	2
Spondylarthropathy	32 (23, 42)	204	(73, 360)	103	(50, 170)	22	18
Sarcoid arthritis	31 (28, 37)	21	(12, 29)	16	(8, 23)	56	44
Lyme arthritis	29 (24, 44)	26	(8, 129)	9	(2, 111)	3	8
Paraneoplastic arthritis	52 (43, 66)	49	(21, 85)	28	(3, 60)	10	12
Systemic lupus erythematosus	32 (28, 48)	95	(19, 221)	122	(95, 149)	1	11
MCTD/vasculitis	63 (46, 77)	69	(12, 152)	50	(11, 131)	12	11
Osteoarthritis/arthritis	59 (51, 70)	109	(44, 364)	63	(24, 288)	36	59
Post-traumatic arthritis	48 (34, 55)	29	(10, 94)	7	(6, 93)	10	12
Arthritis of unknown cause	45 (35, 56)	73	(18, 161)	19	(1, 68)	36	149
Other causes	44 (33, 58)	66	(29, 151)	25	(6, 87)	39	141

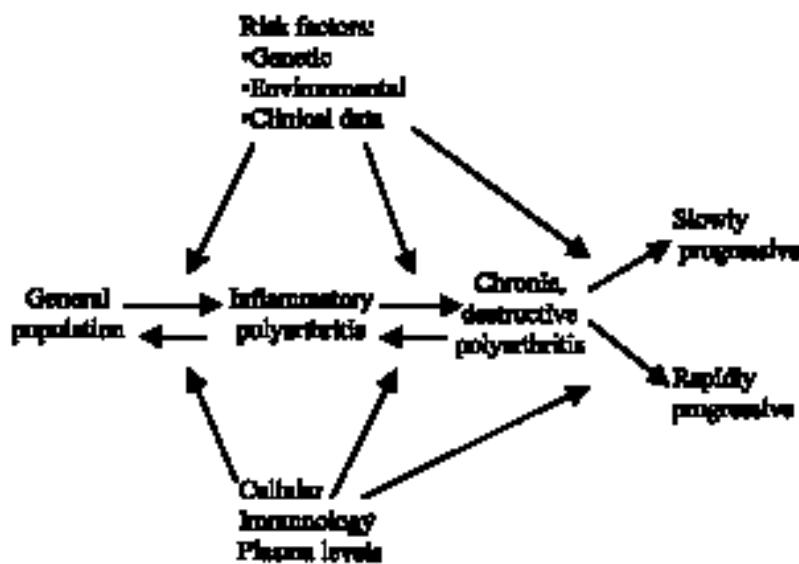


Fig. 1. Working model for the mechanisms involved in inflammatory arthritis.

explain susceptibility to RA (8, 10). A large population-based report on incident cases of RA demonstrated a limited contribution of HLA-DR-alleles, including the SE, to this susceptibility (11). Since not all (susceptibility and severity) questions could be solved with the Shared Epitope hypothesis, a new hypothesis was proposed in which different HLA class II alleles are associated with disease severity. In this so-called RA protection (RAP) model, certain DQ alleles (DQ3 and DQ5) predispose to RA, whereas certain DR alleles can modulate the effect of DQ by either enhancing or dominantly protecting against the DQ-associated predisposition. These protecting DR alleles share a common amino-acid motif "DERAA" in the HV3 region of the protein (12-14). Applying this model to our EAC-population, we confirmed the strong predisposition of DQ alleles to RA in DQ3 and DQ5 positive individuals. Moreover, if this DQ positivity was accompanied by the presence of DRB1 alleles bearing the "DERAA" motif, a dominant protective effect was observed (15, 16). In the EAC population, the RAP model was significantly better able to predict remission rates and erosion scores in early RA patients than the SE model (17).

In the search for other genetic determinants than HLA-DR4, several genes have gained interest, for example the

IL-1 and IL-10 gene cluster. IL-1 is secreted by activated macrophages and plays an important role in the progression of joint inflammation. Elevated serum levels of IL-1 in RA could be explained by a functional polymorphism in the IL-1 cluster gene. Genotyping for IL-1 α , IL-1 β and IL-1Ra single nucleotide polymorphisms (SNPs) in a group of 312 EAC patients revealed that the IL-1RN+2017 polymorphism is associated with susceptibility to RA. However, no significant associations could be demonstrated between IL-1 genotypes and disease severity (18). With regard to the immunoregulatory cytokine IL-10, different roles have been reported for the different IL-10 gene variants. A protective effect against RA has been described for both high and reduced levels of IL-10. Since IL-10 production is largely under genetic control (19, 20), the contribution of IL-10 gene variants to the pathophysiology of RA was studied by comparing the allelic frequencies of -2849G/A IL-10 promoter polymorphism of RA patients with other rheumatic disease patients from our EAC cohort. The results suggest that there is no association between the IL-10 genotype and RA incidence. A positive correlation was demonstrated for IL-10 gene polymorphism and disease severity, with high autoantibody production preceding the development of joint da-

mage (21). However, a direct role of autoantibodies in the pathogenesis of RA still remains to be established.

Currently, we are focusing on the role of genes located at 1q32 (i.e. IL-10 and its homologues) on the susceptibility and course of RA. Together with the group of Cornélis (GenHotel, Paris, France), the distribution of gene variants in well-defined patients with extremes of phenotypes is being studied by means of whole genome scans.

Environmental risk factors

In 1999, a double-blind pilot study was performed to determine the effect of adjuvant blood transfusion on disease activity in RA. This study was a follow-up from our genetic studies and showed that a DRB1-matched blood transfusion improved symptoms in several RA patients according to the ACR 20 response criteria (22). However, the effect of this treatment was moderate and short-term. Given the known risks of blood transfusions and the growing number of therapeutic alternatives for RA, no further studies have been conducted to examine this transfusion effect.

Together with the Department of Obstetrics, Gynaecology and Reproductive Medicine, we examined whether fecundity (time of unprotected intercourse until first pregnancy) and miscarriage are associated with the severity of joint destruction in RA. The results indicate that miscarriage prior to disease onset and not fecundity is associated with the progression of joint damage (23).

In various Early Arthritis Registries, an association between cigarette smoking and RA has been reported (24). Possible links between smoking and the development of RA have been demonstrated, especially in seropositive RA (25, 26). Currently, we are investigating the effect of smoking on the onset and course of RA in the Dutch EAC population.

Clinical risk factors

Clinical risk factors have been the subject of various investigations and range from referral by GPs to routine laboratory tests and treatment modalities. As

mentioned earlier, GPs are encouraged to refer patients with suspected arthritis to our Early Arthritis Clinic. When referral delays were analyzed, however, female patients had a significantly longer delay in referral than male patients for various possible reasons (27). The most commonly accepted clinical risk factors for severe erosive disease are rheumatoid factor and early radiographic damage (28), which have also been described for our EAC cohort (29). Over the last decade, early DMARD treatment has been advocated to improve both short and long term disease outcome. With regard to short term outcome it was observed that patients treated with DMARDs in an early phase of the disease (within 2 weeks after the first visit to the rheumatologist) had substantially less radiographic damage after two years compared to patients initially treated with analgesics (30). Radiographic evaluation of the same patients after four years however, showed no difference in the progression rate between the early and the delayed treatment group after the first year (31).

A problem frequently encountered in daily clinical practice is the outcome of undifferentiated arthritis. In order to predict arthritis outcome, a clinical prediction model was developed based on 22 potentially diagnostic determinants obtained at first visit (32). The final model of 7 variables (symptom duration, morning stiffness, arthritis of 3 or more joint areas, bilateral compression pain in the metatarsophalangeal joints, rheumatoid factor positivity, anti-cyclic citrullinated peptide antibody positivity and the presence of erosions) was based on the first 500 patients who were included in the Early Arthritis Clinic. Whether this model can be validated in another set of EAC patients, is currently being analyzed.

Beside (early) RA, other forms of arthritis have also been studied from the EAC population, for example sarcoid arthritis (33). By clustering the data of 55 EAC patients with sarcoid arthritis and comparing these to the data of 524 patients with other arthritides, it was possible to describe the exceptionally high diagnostic value of the presenting

clinical features, especially symmetrical ankle arthritis. When test positivity is defined as the presence of at least three of four criteria (symmetrical ankle arthritis, symptoms less than two months, age below 40 years and erythema nodosum), a high positive predictive value of 75% (PPV) and even higher negative predictive value of 99.7% provide a useful algorithm for the assessment of sarcoid arthritis in daily practice (34).

Cellular immunology

Current knowledge of the nature of inflammatory attack in joints, derived mainly from experimental animal models, has led to improvement of anti-inflammatory treatment of RA by using cytokine inhibitors, like anti TNF-alpha and anti IL-1. However, such treatments can have serious side effects, since they may affect the patient's ability to resist infections and malignancies. Cellular immunology studies are directed to more specific immuno-modulatory mechanisms as a target for new therapies. Several cell types are thought to be important in the pathophysiological mechanism leading to joint destruction in RA. In the research performed on EAC-material we focus on three cell types - B cells, T cells and synoviocytes.

B cells produce cytokines and autoantibodies. Rheumatoid factor (RF) was one of the first autoantibodies to be associated with RA and its severity. Lately, antibodies directed against Cyclic Citrullinated Peptides (CCP) have been reported to have a higher specificity for RA than RF (35, 36). In 936 EAC patients with recent onset undifferentiated arthritis, we observed that the presence of anti-CCP antibodies has a positive predictive value (PPV) of RA of 93% with a sensitivity of 50%, which is higher than the PPV of 75% and sensitivity of 41% when using RF (37). The presence of anti-CCP antibodies in early arthritis could be useful as a predictive marker for disease progression to RA.

T cells are thought to play an important role in RA, depending on the nature of the secreted cytokines (pro- or anti-inflammatory) and on their interaction

with other cells of the immune system. This way, T cells are able to increase and downregulate inflammation. In animal models, the induction or recruitment of so-called regulatory CD4+ T cells (Treg) has been proposed to actively downregulate inflammation. In humans, the presence of Treg cells has been shown, but their antigen-specificity, type of responses, molecular interactions and role in autoimmune disease such as RA are not known.

T cell research in our EAC cohort focuses on these subjects.

Other cells involved in joint inflammation are synoviocytes, in which two cell types can be distinguished: fibroblast-like synoviocytes and macrophages. Both types play a pivotal role in the destruction of cartilage in RA by producing cytokines, thereby promoting inflammation, and by producing cartilage degrading matrix metalloproteinases (MMPs). Preliminary data suggest that fibroblast-like synoviocytes from RA patients can invade healthy cartilage in a more aggressive manner than synoviocytes from healthy donors. The mechanism responsible for this phenomenon is currently being investigated in our department. Several MMPs have been suggested to correlate with disease activity and joint damage progression (38, 39). In an EAC cohort, we investigated whether serum levels of MMPs have a predictive value with regard to joint destruction. In this cohort, MMPs -3, -8 and -9 are associated with disease activity, while serum proMMP-3 levels are also predictive of radiographic joint damage progression in early RA (first two years of the disease), indicating a possible role for proMMP-3 as a predictor for progressive erosive disease (40).

A product of both T cells and synoviocytes is IL-16, which has been reported as a pro-inflammatory cytokine, as well as an anti-inflammatory cytokine in RA. In the EAC cohort, increased levels of IL-16 in recent-onset RA patients were observed, compared to IL-16 levels in patients with undifferentiated arthritis and healthy controls. Also, IL-16 levels of patients that presented with undifferentiated arthritis but developed RA over time, were increased com-

pared to those of healthy controls and persistent undifferentiated arthritis patients. The positive correlation between high IL-16 levels and radiographic joint destruction during a two-year follow-up suggests a broad function of IL-16 in predicting both progression to RA and radiographic damage (41).

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, a multi-center randomised trial, has been designed to determine the clinical and radiological outcome of four different treatment strategies: sequential monotherapy, step-up therapy, combination therapy including high-dose corticosteroids and initial treatment with anti TNF-alpha blocking agents. The uniqueness of this trial is demonstrated by the fact that it is the first trial to compare so many different treatment strategies with a long term follow-up (5 years). Since little is known on the outcome and treatment of undifferentiated arthritis, a double blind, placebo-controlled trial is currently being conducted to determine the effect of methotrexate-treatment on early undifferentiated oligo-arthritis. This "Probaat" trial will not only provide the best treatment strategy for probable RA, but will also indicate important predictors for disease progression to RA, by means of the discussed research strategies.

Work disability

Rheumatic diseases are a major cause of work disability and place a huge financial burden on the individual as well as on society. In addition, the non-economic impact of work disability on the individual and his or her family is substantial. As a considerable amount of rheumatic disease associated work disability occurs in the first years of the disease (42-44), more and more attention is being paid to the question how the development of work disability in these early stages can be prevented. Although permanent work disability is usually preceded by sick leave, little data on the occurrence of prior working problems and sick leave are available.

To gain more insight into the challenges encountered in the working situation resulting in sick leave or not, and into the complex process of vocational guidance, a prospective, observational study linked to the EAC was started.

Conclusion

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

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