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Determinants of disease course in rheumatoid arthritis

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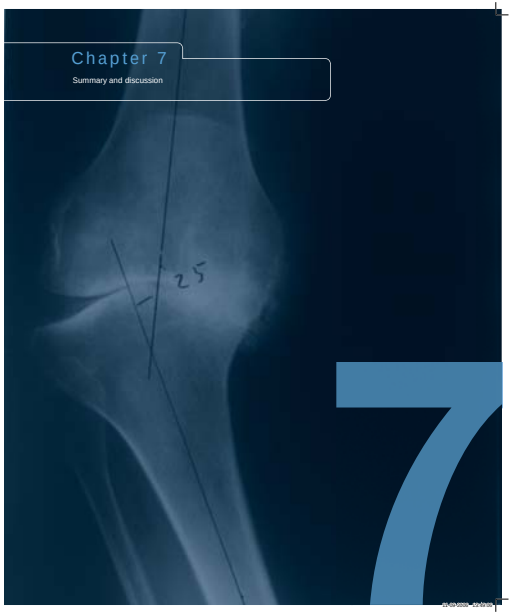

Chapter 7

Summary and discussion

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Rheumatoid arthritis (RA) is a common chronic inflammatory joint disease that may lead to loss of function, systemic illness and even premature death. In the past decade new therapeutic insights and the development of additional, effective disease modifying anti-rheumatic drugs (DMARDs) have greatly improved disease outcome for newly diagnosed RA patients. Recognizing RA early in its disease course and being able to predict which patient will develop severe erosive disease and which patient will not, has become very important given the successes of early treatment strategies[1, 2]. The purpose of this thesis is to elucidate factors that influence disease course in early and established RA.

Chapter 1

Chapter 1 gives an introduction to the stages that a patient may go through before and after developing arthritis. An autoantibody response is the first, asymptomatic step in developing RA in a large proportion of patients. When the first signs and symptoms are present, the disease is often classified as undifferentiated arthritis. There is a 50% chance of achieving remission in patients who present with undifferentiated arthritis. The remaining 50% will develop RA or other diseases that are associated with arthritis[25]. The patients who develop RA may have a mild to severe disease course. Over time there is a 10% chance of achieving sustained remission[26].
In this chapter the factors that play a role in the development of RA and subsequent disease course are discussed. The following subjects are reviewed:

Epidemiology

The incidence and prevalence of RA
The prevalence of RA is 0.5-1.1 per 100,000 inhabitants in most countries, but is subject to geographical variation. Incidence rates are around 0.02-0.07 per 100,000 inhabitants, and are lower in some geographical areas[30].

Gender distribution
The male: female distribution in RA is around 3:2. Severity of RA is not significantly different between male and female patients. Men are more likely to achieve spontaneous remission. Sex hormones play a role in disease course and onset (the influence of pregnancy, breast-feeding and menopause is well-documented)[8, 31].

Age
The mean age of onset is around 55 years.
RA of later onset is associated with lower frequencies of Rheumatoid Factor and more polymyalgia rheumatica-like symptoms [8, 9].

Environmental factors

Diet may play a role in the aetiology of auto-immune disease. The role of vitamin D and selenium, an essential trace element, is currently a topic of interest, but has not yet been established [12-14]. The Mediterranean diet, especially the anti-oxidant effect of olive oil may playe a role in preventing RA [34]. The influence of fruit and (red) meat are currently studied. Fat fish consumption is associated with a 49% reduction of RA incidence [34-37].
Smoking is a well-established risk factor for developing RA and for severity of RA (positive RF, erosions, rheumatoid nodules)[38-52].

Socio-economic factors and coping strategies

RA patients from socially deprived areas and patients with a lower level of formal education have been described to have increased morbidity and mortality from RA.
Negative coping strategies (e.g. avoidance, resigning) negatively influenced disease outcome, pain control and psychological adjustment compared to positive coping (e.g. ignoring pain, illness acceptance)[22-24].

Serological markers

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are often present in the sera of RA patients before disease onset[53-56]. RF and anti-CCP antibodies have also been linked to disease severity in RA[29-31].

Genetic factors

The HLA class II locus plays an important role in susceptibility for RA. The HLA-DRB1 shared epitope alleles are the best studied example. The knowledge on this subject is growing rapidly and new genes such as PTPN22 that are associated with RA have been described in different populations[32].

Gene-environment interactions

The only gene-environment interaction that has been identified in RA at this moment is the interaction between smoking and HLA-DRB1 shared epitope alleles, this combination is a risk factor for carrying RF and anti-CCP antibodies in patients with RA[39-39].

Chapter 2

Chapter 2 discusses the predictive value of anti-cyclic citrullinated peptide (anti-CCP) antibodies in patients with arthritis who can not be readily classified (undifferentiated arthritis, UA) for the development of RA (according to the American College of Rheumatology [ACR] 1987 criteria, table 1). Recognizing the importance of early diagnosis of RA, the ACR criteria, in which the rheumatoid factor (RF) plays a major role, may not be sufficient for diagnosing RA in an early stage. In previous studies, anti-CCP antibodies have been demonstrated in sera of persons who have later developed RA (25-29). Given the low prevalence of RA (~1%), testing of the general population is of no clinical benefit. However in individuals at higher risk for RA, like patients with UA, this may not hold true. Therefore, this prospective study was performed in 318 UA patients from the Leiden Early Arthritis Clinic (EAC) to investigate the value of anti-CCP antibodies in the development of RA.
The 318 UA patients were selected from 936 consecutive patients from the EAC. From these patients, 205 had RA and the remaining 413 patients had other diagnoses like psoriatic arthritis, reactive arthritis, spondyloarthropathy etcetera. The patients were followed for three years. After 3 years, 40% of the UA patients had developed RA. Almost all UA patients who were anti-CCP positive developed RA within three years (64: 69 patients= 93%). In the 249 patients who had no anti-CCP antibodies, 63 patients developed RA within three years (25%).
The odds ratio (OR) for developing RA within three years in UA patients with anti-CCP antibodies was 37.8 (95% confidence interval [95% CI] 13.8-111.9). The sensitivity of the anti-CCP antibody test was 50% (95% CI 41-59) and the specificity was 97% (95% CI 95-99). The positive predictive value for developing RA in UA patients with anti-CCP antibodies is 93% (95% CI 69-80). In other words: anti-CCP antibodies are 16.7 times more likely to be detected in UA patients who progress to RA than in UA patients who do not progress to RA.
Next, the performance of anti-CCP antibodies in conjunction with commonly used variables for diagnosing RA was assessed, performing multivariate analysis. Primary outcome variable was fulfilment of the ACR 1987 criteria for RA after one year follow-up. The ACR criteria and anti-CCP antibodies were possible explanatory variables. A model only including the ACR criteria showed an OR of

9.8 (95% CI 4.1-23.4) for IgM RF positivity. Other significant variables were symmetric arthritis, morning stiffness, polyarthritis and radiographic erosions. Additional multivariate analysis including anti-CCP anti-bodies resulted in the same significant predictors, except morning stiffness, and remarkably except IgM RF. The most important predictor for the development of RA in patients with UA was anti-CCP positivity (OR 38.6, 95% CI 9.9-151.0). In conclusion, the presence of anti-CCP antibodies proves to be an important predictor for the development of RA in patients with undifferentiated arthritis and a valuable addition to the ACR 1987 criteria for diagnosing RA and recognizing early RA.

Table 1

ACR 1987 criteria for rheumatoid arthritis

Morning stiffness > 1 hour
Arthritis of ≥ 3 joints
Arthritis of wrist, MCP or PIP joint
Symmetric involvement of joints
Rheumatoid nodules
Rheumatoid Factor positivity
Radiographic erosions

Chapter 3

In chapter 3 the predictive value of the distribution of inflamed joints at first presentation for the severity of the disease course in RA was studied in 285 patients from the Leiden Early Arthritis Clinic. The method of comparison of extremes of phenotypes was used: 28 patients who achieved sustained clinical remission were compared to the 28 patients with the most radiological damage (Sharp van der Heijde score) after 1 year follow-up.

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First, the distribution of inflamed joints was compared in the extremes of phenotype groups. Then, the association between the distribution of inflamed joints and the level of destruction of hands and feet in the whole group of RA patients was assessed using regression analysis. Comparison of the patients with extreme disease courses using univariate and logistic regression analyses revealed that arthritis of the large joints, in particular the knee, was associated with severe RA (p<0.05). In the whole group of RA-patients, the total number of swollen joints and the presence of knee arthritis associated independently with the level of destruction of the small joints (p=0.004). RA-patients with knee arthritis had higher C-reactive protein levels than patients without knee arthritis (mean 48 mg/l SD 35 mg/l versus mean 22.5 mg/l SD 2 mg/l, p< 0.001). Investigating the distribution of inflamed joints together with other variables yielded the number of swollen joints and knee arthritis as the presence of anti-CCP antibodies and symptom duration as predictors for RA severity.
It was concluded that arthritis of large joints, in particular the knee, at first presentation is associated with a destructive course of RA.

Chapter 4

In chapter 4 the question of remission in RA is addressed: What is remission and does it occur? The most difficult part of studying remission is the definition, or rather the lack of definition. In 1981, Pinals defined preliminary criteria for remission in RA. These criteria (Table 2)[35] have proven difficult to use because of the subjective items that are listed, especially the aspect of fatigue. Many suggestions of defining remission have been made since 1981, but no uniformity has been reached. Mostly, next to the Pinals criteria the disease activity score (DAS or DAS 28)[37,38] is used, bas it the cut-off point marking remission is still not agreed on, despite various studies that have been conducted with this goal[39,40]. Recently, the subject has been discussed in the OMERACT 2004 and 2005 meetings. This has resulted in the term minimal disease activity (MDA). Two preliminary equivalent definitions of MDA were stated, based on 60 profiles of RA patients, interpreted by 35 rheumatologists from Europe and the USA[40]. Further validation of these definitions will be needed in the near future. At the time that this study was undertaken, there was no OMERACT preliminary definition, and many definitions were used simultaneously.
The goal of our study was to determine clinical, serological and genetic factors associated with sustained remission in RA. Sustained clinical remission was defined as fulfillment of the preliminary Pinals criteria for remission for at least one year without DMARD treatment. From the EAC population 1009 consecutive patients were studied. From these patients, 285 developed RA within one year. During follow-up, 162 RA patients had no arthritis for at least one visit. 42 of these patients used no DMARD therapy. These patients' charts were reviewed and follow-up was completed by confirming the current state of disease activity with their family physician.
Eventually 29 patients were identified who had achieved sustained remission. The mean disease duration of the remitting patients was 3.7 years (range 210-3159 days, SD 852 days). Compared to the remaining RA patients, remitting patients were more often IgM rheumatoid factor (IgM RF) negative and anti-CCP negative (CI respectively 1.68-11.22 and 2.99-55.66). Other baseline parameters including male/female distribution, age, time to first visit, DAS score, ESR, EBP and presence of shared epitope were not different between both groups.
The data showed that sustained clinical remission without DMARD therapy was observed in around 16% of the RA patients from our EAC cohort. Remission is more likely to occur in patients who are IgM RF and anti-CCP negative. Clinical presentation at onset of disease did not differ from RA patients who do not remit.

Table 2 Pinals preliminary criteria for remission in RA

Five or more of the following requirements must be fulfilled for ≥ 2 months

Duration of morning stiffness ≤ 15 minutes
No fatigue
No joint pain (by history)
No joint tenderness or pain on motion
No soft tissue swelling in joints or tendon sheaths
ESR less than 30 mm/hour for a female and less than 20 mm/hour for a male

Exclusions:
Clinical manifestations of active vasculitis, pericarditis, pleuritis, myositis and unexplained recent weight loss or fever attributable to RA will prohibit a designation of remission.

Chapter 5

Smoking is an established risk factor for development and severity of RA[18-21]. A gene-environment interaction between smoking and shared epitope was previously described by Padyukov et al for the risk having positive rheuma-oid factor (RF)[24]. In this chapter studies the gene-environment interaction between smoking (tobacco exposure = past or present smoker, TE) and the presence of auto-antibodies (RF, anti-CCP antibodies) is studied in patients with RA and UA.
The HLA class II alleles which share the conserved amino acid sequence are called the shared epitope (SE). This is the most important genetic risk factor for RA. The shared epitope hypothesis postulates that the SE motif itself is directly involved in the pathogenesis of RA by allowing the presentation of a peptide to arthritogenic T-cells[18]. Recently, it was demonstrated in populations from the USA and from Europe that HLA DRB1 alleles are only a risk factor for RA in people who have anti-CCP antibodies, but not in people without these antibodies[41]. This suggests that different pathogenic pathways are exploited in anti-CCP positive and anti-CCP negative RA. To establish whether the interaction between tobacco exposure and shared epitope is also present in UA patients or if it is specific for RA, arthritis patients who could not readily be classified were also analyzed. The underlying pathogenesis is probably different in UA patients. If the TE-SE interaction is specific for the patho-genesis in RA, it is likely not to be found in patients with UA.
For this study, 1305 consecutive patients from the EAC were analyzed. From these patients, within 2 weeks, 276 were diagnosed with RA and 486 with UA. From these UA patients, after one year, 131 patients developed RA. Baseline parameters between RA patients diagnosed at 2 weeks and one year were comparable. UA patients were younger, more often male and less often RF and anti-CCP positive. In all categories TE was around 50%. Odds ratios for positive RF and anti-CCP antibodies were determined by Chi-square analysis on 2x4 tables. Stratified analysis was undertaken for anti-CCP positive and negative and for RF positive and negative strata. A strong interaction between tobacco exposure and shared epitope was found in patients with both RA for anti-CCP antibodies (OR 5.27, 95% CI 2.37-11.80, p<0.001) and for RF (OR 3.23, 95% CI 1.54-6.81, p<0.001). Stratified analysis to exclude influence of overlap between RF and anti-CCP positive patients showed no significant interaction between between tobacco exposure and shared epitope in relation to the presence of RF.
These data suggest that the interaction between tobacco exposure and shared epitope primarily associates with positive anti-CCP antibodies and not with positive RF in patients with RA. In patients with UA no interaction was found between tobacco exposure and shared epitope, confirming our hypothesis that this interaction is specific for RA.

Chapter 6

Chapter 6 describes a theory on the decreased incidence of RA. A decline in incidence of RA has been observed throughout the years[157]. The decline can be observed all over the western world. This could be caused by either an environmental effect or by a change in the population genome. The latter is proposed to have occurred for the following reason: In previous times, reproductive success was very unevenly distributed: a minority of very fertile women gave birth to the majority of newborns. This is no longer the case since currently, both fertile and less fertile women have a limited number of children[38, 39]. Fertility is associated with higher levels of IL-10. The genetic composition of the population that was born from these fertile women favours high IL-10 production[158]. The IL-10 R3 haplotype is associated with lower IL-10 production as well as with a lower risk for RA[160].
The fact that women with the IL-10 R3 locus, who are less fertile contribute relatively more to the new generations, makes it likely that this haplotype is more generally present. This genetic shift might contribute to the declined incidence of RA.

In conclusion

This thesis attempts to unravel parts of a puzzle concerning the aetiology of a multifactorial disease. The fact that RA has a multifactorial aetiology, complicates drawing conclusions, because there may always be a confounding factor. For example: if one states that smoking is a risk factor for the severity of RA, one needs to correct for established risk factors like rheumatoid factor, anti-CCP antibodies, early radiographic erosions, female gender and disease duration. With the increasing knowledge on genetics in RA, this factor should also be included in the analysis, like in chapter 5, where a gene-environment interaction between smoking and anti-CCP antibodies has been described only in the presence of the shared epitope. In this thesis, a large population of patients from the Leiden area with early arthritis is studied. The fact that so many factors are registered on these patients, facilitates the task of drawing conclusions on clinical remission, the predictive value of anti-CCP antibodies in patients with undifferentiated arthritis, the influence of smoking in RA and the value of clinical presentation for further disease course in RA.
In the past few years, many others have studied similar subjects. The cumulative information gathered in these studies has lead to an increase in knowledge on the aetiology and disease course in RA. For example:

- Anti-CCP antibodies have become firmly established predictors of RA in patients with early arthritis and are strongly associated with adverse disease outcome.
- The influence of smoking in RA was already described 15 years ago, but recent studies have made it possible to associate smoking with anti-CCP antibodies.

Implications in clinical practice

A possible clinical implication of these examples is that a patient presenting with an oligoarthritis and anti-CCP antibodies will be strictly monitored for developing RA, so early treatment will not be delayed, which will improve the prognosis. Second, the fact that smoking is associated with severity in RA should lead to stronger recommendations from rheumatologists to stop smoking. This fact should also be known in the general population as a preventive measure.

Suggestions for future studies

On pathogenesis in RA
How does the process of citrullination influence disease course in RA? What is the influence of smoking on this process. Do oxygen radicals play a role? Can citrullination be influenced by medication?

On aetiology
What is the influence of environmental changes and pollution on the development of RA? Should we all eat a mediterranian diet to prevent RA, or is the genetic make-up of the people in the Mediterranean countries different as an explanation of lower prevalence of RA in these countries?

On disease course
Does quitting smoking influence disease course in early arthritis or early RA? Does the level of anti-CCP antibodies correlate with disease activity? Now that a good and uniform definition of remission in RA is coming closer: can our data on remission be confirmed with this definition? These and many other questions will most likely be answered in the near future and may have new implications for the way we treat patients with early RA.

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