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Determinants of disease course in rheumatoid arthritis

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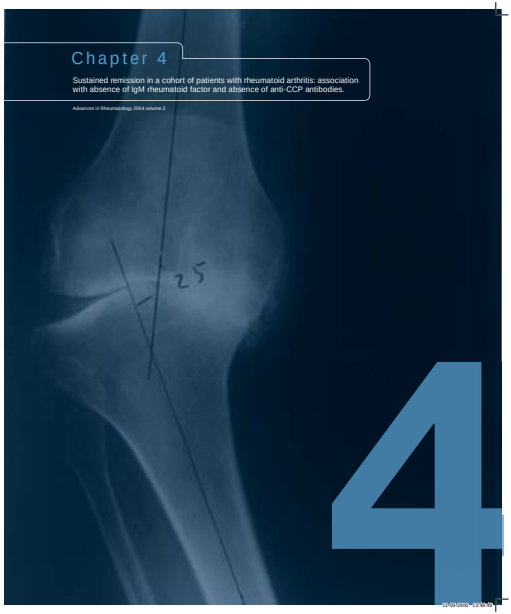

Chapter 4

Sustained remission in a cohort of patients with rheumatoid arthritis: association with absence of IgM rheumatoid factor and absence of anti-CCP antibodies.

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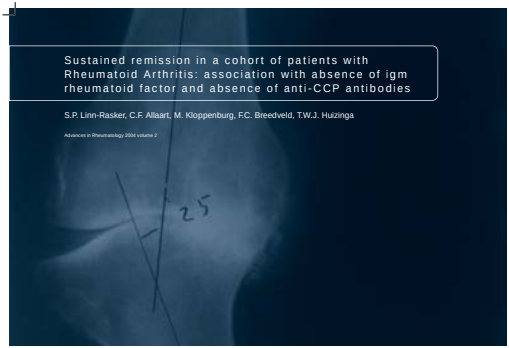

Sustained remission in a cohort of patients with Rheumatoid Arthritis: association with absence of igm rheumatoid factor and absence of anti-CCP antibodies

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Abstract

Objective **To determine the clinical, serological and genetic factors associated with sustained remission in rheumatoid arthritis.**
Methods **In a population-based inception cohort of 1009 patients with newly diagnosed arthritis of whom at least four-year follow-up data were present, the subpopulation of RA patients was selected. Within this cohort the patients fulfilling the Pinals preliminary criteria for remission at the time of assessment in RA were identified. Sustained remission was defined as fulfilling these criteria for at least one year without DMARD treatment.**
Results **29 out of 285 RA patients fulfilled this definition of sustained remission. The average duration of follow-up was 8.2 years; the average duration of remission was 4.6 years.**

Clinical parameters at onset of disease did not differ significantly between the RA patients with sustained disease activity versus those who achieved sustained remission. At onset, remitting patients were more frequently characterized by absence of IgM rheumatoid factor (OR 3.13 - 95% CI 1.26-7.98) and absence of anti-CCP antibodies (OR 9.52 - 95% CI 2.66-40.65).
Conclusions **Patients who are IgM rheumatoid factor and anti-CCP negative are more likely to achieve sustained clinical remission.**

Introduction

Rheumatoid arthritis (RA) is a systemic illness with chronic symmetric polyarthritis and variable disease course as its most characteristic clinical features. Often the disease course is very severe with progressive, destruction of joints, loss of function and decreased quality of life. On the other hand the disease course can also be mild and patients may achieve remission with or without treatment. The recognition of these two patient categories is important, both for informing the patient on prognosis and because of availability of effective and often expensive therapies.
In order to study the course of chronic polyarthritis, inception cohorts and cohorts of patients with recent onset inflammatory arthritis have been established since decades and have shown the dynamics of the disease process in RA[1-14]. Different cohorts of patients with early arthritis have shown that from all patients included, a number present with undifferentiated polyarthritis and a number already fulfil the ACR criteria for RA at presentation. Follow-up data from our early arthritis cohort have demonstrated that from the patients with undifferentiated arthritis 28% progress to polyarthritis fulfilling the ACR criteria for RA, 30% continue to have undifferentiated arthritis and 42% achieve remission.
Many studies have focused on the question whether the abovementioned range of outcome also persists after patients have fulfilled the ACR criteria for RA. In different cohorts, the number of patients that achieve sustained remission after being diagnosed with RA ranges from some to one third[15-18]. Presumably this depends on the inclusion criteria of the cohorts and on the definition of remission, varying from DAS scores to Pinals criteria[19-22], Table 1.
In the first long term prospective study, the Bath (UK) study, only patients were included who fulfilled the 1958 ACR criteria of definite or classical RA. In this study a 10% remission rate after 10 years was observed.
This study had the same entry criteria as the present series: at least one year of active disease, still fulfilling the ACR criteria for definite or classical RA after one year[15].
A Swedish study included 183 subjects with early RA (less than 24 months of symptoms) recruited in the 1980's [16]. In this study the Pinals criteria[19] were used – with the modification that fatigue was excluded – remission periods were observed that occurred during the first 5 years. 37 patients achieved remission periods of at least 6 months duration. The average length of remission was almost 2 years, but the remission persisted in 14 patients only[15, 23].
In two other cohorts, remission rates were 9.5% in early RA[1,17] and 18.8% in established RA[18].
In a prospective study of early RA patients, a 32% remission rate was found in Finland at six years follow up[18].
In a Dutch study of early RA patients, hardly any full remissions were found despite systematic DMARD therapy[24].
In a community-based cohort in Manchester (UK), Harrison et al found that 19% of patients that presented with polyarthritis were in clinical remission after 2 years. Remission was defined as 'no arthritis on examination and no DMARD or corticosteroid therapy within the previous 3 months'[25]. In cross sectional studies, remission rates were found of 27% at 2 years follow up, 7% after 3 years[26] and 7% at 7 years[14]. These studies used 'being symptom free' as a definition for remission[26, 32].
The phenomenon of sustained clinical remission in RA patients raises the question if the disease process in RA can be altered or even cured.
The objective of this study was to identify factors in patients with RA that are associated with remission. This was done by studying the characteristics of patients with sustained clinical remission and of the patients that did not achieve remission in a population-based prospective cohort study. To avoid any misclassification in the RA group, only patients with a physician confirmed diagnosis of RA of at least one year were studied.
The remitting patients were described regarding clinical presentation, laboratory values and radiological damage and these were compared with those of non-remitting RA patients. Possible predictive variables for patients with remitting disease were analysed.

Patients and methods

Patients

The patients were selected from the Leiden Early Arthritis Clinic. In 1993 a special Early Arthritis Clinic (EAC) was started at the Department of Rheumatology of the Leiden University Medical Center, the primary referral center for rheumatic patients in an area with approximately 300.000 inhabitants in the West of the Netherlands. General practitioners were encouraged to directly refer patients when arthritis was suspected. All patients referred to the EAC were included in the study when a rheumatologist objectified arthritis and the symptoms had lasted less than 2 years. Second opinions were excluded[16].
Clinical remission was defined as: the patient satisfies the proposed ARA criteria for clinical remission and discontinued the use of DMARDs for at least one year. This definition was chosen because it reflects a state of complete and sustained absence of disease activity in RA patients.

Strategy to identify patients with long-term remission

The patients were included in the EAC cohort between February 1993 and January 1999. From this cohort potential remitting patients were identified by selecting patients from our database, who at one visit during follow-up had no swollen joints. From this group, patients were selected who did not take any DMARDs at the time that there was no disease activity. All patient charts of the selected patients were reviewed for fulfillment of the ACR 87 criteria for RA[39] within one year after inclusion and during follow up and for fulfillment of the Pinals criteria for clinical remission[24,25]. Also, the past use of DMARDs was documented. Since all remitting patients had been discharged from our outpatient clinic, their current disease activity state was confirmed by telephone calls with patients' family physicians.

Methods

At baseline and yearly thereafter all patients underwent physical examination including tender and swollen joint count[26], Health Assessment Questionnaire (HAQ)[27,28] and Arthritis Impact Measurement Scales (AIMS 1)[29-31].

Laboratory tests

Baseline laboratory examination included ESR, Hemoglobin, C-reactive protein (CRP), IgM rheumatoid factor Enzyme-Linked Immunosorbent Assay (ELISA) as previously described [32]. Anti- cyclic citrullinated peptide 2 (CCP2) antibody ELISA (Immunoscan RA Mark 2, Euro-Diagnostica, Arnhem, The Netherlands and Axis-Shield, Dundee, UK) was performed according to the manufacturer's instructions. Also, the presence of the shared epitope (SE) was determined as previously described.

Radiology

Radiological progression was monitored by radiographs of the hands and feet, obtained at study entry, 6 months and at yearly thereafter. Radiographic damage was scored according to the modified Sharp/van der Heijde method [33] by an experienced rheumatologist who was blinded to the clinical data.

Statistics

The Statistical Package for the Social Sciences (SPSS) version 11.0 was used to analyze the data. The differences between the groups are depicted with 95% confidence interval (CI). When 0 is not included in this interval, the difference reaches statistical significance at p<0.05. In case of small numbers the Fischer exact test was used.

Ethics

The study was approved by the hospital's ethics committee.

Results

Patients

Of 1009 patients, included in the EAC, 285 satisfied the ACR 1987 criteria for RA within the first year after inclusion. This group was selected for further analysis. Of these 285 patients, 162 had no swollen joints at one point during follow-up, but only 42 of these patients were without DMARD treatment at the same time. These 42 were identified as potential remitting patients.
After reviewing the individual patient charts, nine patients were excluded: Seven of these did not satisfy the remission criteria and two had resumed use of DMARDs.
After contacting the family physicians of the remaining 33 patients for information on their current disease status in July 2003, 29 patients were left who satisfied the remission criteria and currently had inactive disease while not using any DMARDs. The four remaining patients were excluded because of painful joints without arthritis[25] and re-activation of RA and use of DMARD's[20]. From the 29 patients who had sustained remission, two had died: one due to unrelated progressive neurological disease and one due to chronic obstructive pulmonary disease.
These patients were in remission for respectively three and four years before death.
The mean disease duration of the 29 patients described above before remission was 1350 days = 3.7 years (range 210-3159 days SD 852 days) and mean duration of remission was 1671 days = 4.6 years (range 426-3348 days SD 773 days). In the RA patients the mean disease duration was 2627 days = 7.2 years (range 1696-3797 days SD 590 days).
Of the 162 patients without swollen joints at one point during follow-up, 38 also had no swollen joints one year later while being treated with DMARDs.
None were lost to follow-up.

Baseline characteristics and clinical presentation

Baseline characteristics of the 29 remitting and the other RA patients were comparable regarding age and male / female distribution.
Ritchie, HAQ and AIMS 1 and DAS scores were comparable at baseline. The DAS scores were lower during follow-up in remitting patients compared to the non-remitting RA patients (Table 2).
In 14 patients the diagnosis of RA was confirmed within two weeks after the first visit. The other patients were initially classified as probable RA (11), undifferentiated polyarthritis (2) and psoriatic arthritis (2). In the remitting patient group, 16 had not used any DMARDs; 6 patients used HCQ, and the other patients were treated with Methotrexate, Sulphasalazine or combination therapies.

Laboratory parameters

At baseline the remitting patients were more frequently RF negative (p=0.0005) than those who achieved no remission. The relative risk for disease remission for IgM RF negative RA patients is three-fold compared to rheumatoid positive patients (Odds Ratio 3.1, 95% CI 1.3-8.0). The average level of IgM RF was lower in remitting patients, but this was not significant. There was a significant difference in anti-CCP positivity between the two groups (p=0.00003084). The relative risk for disease remission for anti-CCP negative patients is more than nine-fold compared to the anti-CCP positive patients (Odds Ratio 9.5, 95% CI 2.7-41).
The shared epitope was more frequently negative in the remitting group (p=0.050).

Follow-up parameters

During follow-up DAS scores improved significantly in the remitting patients compared to persistent RA patients (Table 3).
ESR improved in both patient groups, but did not differ between groups. Contrary to the persisting RA patients, the remitting patients showed stable hemoglobin levels and improvement of C-reactive protein compared to baseline.

Radiological damage

At baseline, Sharp scores were lower in the group of patients that achieved remission (2.7) compared to the group of patients that did not achieve remission (4.4), this difference was not significant (p= 0.504; 95% CI -6.7-3.3). During follow-up, Sharp scores remained low in most remitting patients. Four patients showed a slight rise in the first three years before these patients achieved remission. These four patients were responsible for the fact that when the data were analyzed for the increase in Sharp scores in both groups during the first three years, a significant rise was observed in both groups: 5.1 in the group of patients that would achieve remission and 23.0 in the patients that did not achieve remission (p=0.043; CI -35,4-0.60). These values compare average Sharp scores between remitting and persistent RA at baseline and three years follow-up.

Discussion

In this study we focused on 29 out of 285 RA patients who developed remission. Patients with no IgM rheumatoid factor and those who are anti-CCP negative have a better chance of achieving such a disease state.
Briefly, factors that may play a role in the disease course of RA were described by studying RA patients who achieve sustained clinical remission. The most rigorous definition for remission was used because our aim was to describe clinical variables that allow recognition of patients that will develop sustained remission. The previously described definitions of remission did not take into account the aspect of long term, DMARD-free remission.
Our findings demonstrate that a proportion of RA patients achieve sustained clinical remission lasting for several years, without treatment with DMARDs. At clinical presentation these patients do not differ from other RA patients in several aspects. Age and sex distribution are comparable as well as the Ritchie index, AIMS 1 and HAQ scores, the number of swollen joints and ESR.
However, the remitting patients differ significantly from other RA patients with respect to serological abnormalities such as a less frequent presence of IgM Rheumatoid Factor and anti-CCP antibodies.
In the patients that eventually achieved remission, a mild clinical course of disease was observed: Hemoglobin levels were stable, ESR was lower and if erosions were present, the progression of joint damage was significantly slower than in other RA patients (data not shown).
Although none of our patients, who eventually would develop remission, were in remission after one-year follow-up, the clinical picture at one year was mild compared to the other RA patients.
In the EAC cohort, all consecutive patients who presented to our outpatient clinic with arthritis were included. Since no other arthritis clinics are available in the health

care region of Leiden, it can be assumed that the large majority of the newly diagnosed RA patients were present in this cohort. This implies that no selection bias as to the severity of RA has occurred. This cohort is representative for most newly diagnosed RA cases.
It is unlikely that we have overestimated the number of patients with sustained clinical remission. The duration of follow-up was long and the persistent state of remission was checked. The method applied to identify cases of remission, may have led to an underestimation of sustained clinical remission: The database was used as a first indicator to find patients with no swollen joints at follow-up and one year later.
Another 38 patients also fulfilled this criterium but the physician decided to continue DMARD therapy in these cases. It can be expected that several of these patients would also have been in remission when DMARDs would have been discontinued. Assuming that this would be 50% of the patients, the total number of patients that achieve a state of remission without therapy would be 29 + 19 which is 16% of all patients.
Quite a few studies have addressed the issue of remission in RA patients, reporting remission rates varying from almost none to about one third. The comparison of these studies is not easy given the differences in definition of remission and the differences in patient referral and selection. Moreover, the practical use of the Pinals remission criteria is difficult. For example fatigue is hard to measure and is therefore often not used for measuring clinical remission. Thus, the definition for clinical remission remains a problem and there is a need for another standard. Some years ago, Prevoo et al suggested use of DAS 28 instead of the preliminary ARA criteria for determination of clinical remission because of its more reliable reproducibility[27]. The use of DAS 28 as a measurement for remission has received great attention, most recently during the 2004 OMERACT meeting[28,29,30].

The phenomenon of sustained clinical remission in RA patients also raises the question whether such a disease state can be induced by treatment. The patients in this study were included in a period when DMARDs were prescribed according to the traditional treatment pyramid schedule and the use of biologicals was still in an experimental phase. Recent studies that employed more aggressive treatments including TNF antagonists in early RA have reported the absence of swollen joints in ±40% of the patients in the first year of treatment. Long term follow-up is necessary to find out whether a state of long term remission as defined in this paper is being achieved more frequently at present.

Table 1

Proposed ARA criteria for clinical remission in rheumatoid arthritis (Pinals 1981)
Five or more of the following requirements must be fulfilled for ≥ 2 months
1 Duration of morning stiffness ≤ 15 minutes
2 No fatigue
3 No joint pain (by history)
4 No joint tenderness or pain on motion
5 No soft tissue swelling in joints or tendon sheaths
6 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 preclude a designation of remission.

In conclusion, the observations of this study suggest that sustained clinical remission without use of DMARDs at the time of remission is observed in around 16% of patients with RA who satisfy the 1987 ACR criteria at the time the diagnosis was made. A potential remitting RA patient cannot be recognized on clinical grounds at presentation although the disease course in the first year of presentation is mild. The results of this study serve to contribute that the patient category that will develop a remission at presentation is best characterized by the absence of IgM-RF and anti-CCP antibodies.

Table 2

Baseline characteristics			
	Remitting RA n=29	Non-remitting RA n=256	95% CI
Male (number)	11	89	
Female (number)	18	165	
Age (years)	60	56	-2.12-0.39
Time to first visit (days)	143	205	-1.30-7.82
DAS 28 baseline	3.7	3.6	-0.34-0.54
Richie baseline	12.2	12.0	-3.39-3.82
HAQ baseline	1.3	1.0	-3.56-0.59
AIMS baseline	0.9	0.9	-8.92-0.15
ESR baseline (mm/hr)	49	44	-6.29-6.65
C-reactive protein baseline	35	32	-10.60-15.66
IgM RF positive (%)	28	61	1.68-11.22
CCP positive (%)	10	52	2.99-55.66
Shared Epitope positive (%)	52	65	0.90-5.20

Table 3

Follow-up characteristics			
	Remitting RA n=29	Non-remitting RA n=256	95% CI
DAS baseline	3.7	3.6	-0.34-0.54
DAS 1 year	2.3	2.9	-1.31-5.88
DAS 2 years	1.5	2.5	-1.51-0.45
ESR baseline (mm/hr)	49	44	-6.29-6.65
ESR 1 year	37	39	-16.21-11.09
Hemoglobin (mmol/l) baseline	8.3	8.0	-6.36-0.55
Hemoglobin (mmol/l) 1 year	8.1	7.7	-5.99-0.73
C-reactive protein baseline	35	32	-10.60-15.66
C-reactive protein 1 year	18	33	-33.33-3.17

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