Predictive factors for outcome of rheumatoid arthritis

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CHAPTER 11

Repair of joint erosions in rheumatoid arthritis: prevalence and patient characteristics in a large inception cohort

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ABSTRACT

Background

Joint destruction in rheumatoid arthritis (RA) was until recently seen as an irreversible state. Lately, it was defined that repair of bone erosions occurs; however little is known about its prevalence. This study investigates the frequency of repair and patients characteristics associated with repair in an inception cohort.

Patients and methods

250 RA patients, included in the Leiden Early Arthritis Clinic between 1993-2000 and treated with conventional DMARD-therapy, were studied (mean follow-up 10.1 years). Yearly made radiographs were scored using the Sharp-van der Heijde method, initially aware of the chronology. Patients with a negative change in erosion scores on subsequent radiographs were selected and their series of radiographs were rescored with concealed time sequence by three readers. Repair was defined as agreement of two readers in having a negative change in erosion scores that persisted for at least two years.

Results

Repair was identified in 32 joints in 18 patients (7.2%). Patients with repair had more frequent autoantibodies (RF, ACPA) and a higher level of joint destruction. In the joints with repair arthritis was absent in the two years preceding repair.

Conclusions

Repair occurred in 7.2% of the RA patients, particularly in clinically inactive joints in patients with severe destructive disease.

INTRODUCTION

Rheumatoid arthritis (RA) often results in destruction of bone and cartilage, visualized on radiographs as erosions and joint space narrowing respectively. For a long time the bone damage was considered to be permanent.[1] Recently some studies sustained the possibility of radiological repair.[2-6] Dedicated research in the context of Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT),[7,8] along with recent literature reviews,[9,10] led to the conclusion that "repair does exist". This is of utmost clinical relevance because it demonstrated that the "repair machinery" is able to take away, at least partly, the consequences of damage by RA. If the biological basis of this phenomenon could be understood, it would allow the development of therapies specifically targeted to stimulate these repair mechanisms. This study aims to assess the frequency of repair in a large inception cohort of RA patients treated with conventional disease modifying antirheumatic drugs, and to characterize the patients expressing repair.

PATIENTS AND METHODS

Patients

250 RA patients, consecutively included in the Leiden Early Arthritis Clinic (EAC) between 1993 and 2000 were studied. The era 1993-2000 was chosen as it has the longest duration of follow-up (mean 10.1 years, SD=2.3), resulting in a real opportunity to express repair. Clinical and laboratory characteristics were yearly measured and radiographs of hands and feet were yearly taken.[11] Treatment strategies differed per inclusion period. Patients included between 1993-1995 were treated with delayed therapy (initially analgesics, subsequently chloroquine or salazopyrin) and between 1996-2000 with prompt initiation of chloroquine, salazopyrin or methotrexate. Biologicals or aggressive combination therapy were not applied.

Radiograph scoring

The radiographs were scored using the Sharp–van der Heijde method[12] by one reader, blinded to the clinical data, initially aware of the chronology. Patients with a negative change in erosion scores on subsequent radiographs were selected. Their series of radiographs were mixed with series of patients with stable or positive change in erosion scores, so that the readers were unaware of the scores that were assigned previously. These radiographs were rescored with concealed time sequence by three trained readers. The intrareader intraclass correlation coefficient for the status scores was 0.91. The intraclass correlation coefficient between reader 1 and 2 was 0.94, between reader 1 and 3 0.95 and between reader 2 and 3 0.93.

Definition of repair

Repair was defined as fulfilling all of the following three criteria a) presence of a negative change in erosion score on a joint level on two subsequent time points both when scored with known

and concealed time order, b) persistency of the lower erosion score ≥2 subsequent years, c) agreement on the negative change in erosion score between at least two of the three readers. In case data on two subsequent years were not available, all three readers had to agree with the negative change in erosion score.

Patient characteristics

Patients with and without repair were compared for several baseline characteristics and for the total Sharp-van der Heijde scores during follow-up. The achievement of sustained DMARD-free remission (the persistent (≥1 year) absence of arthritis after cessation of therapy with disease modifying antirheumatic drugs)[13] was evaluated in both groups. The annually assessed swollen joint count was studied in order to investigate whether the joints that showed repair had clinically detectable arthritis in the two years preceding the development of radiologically visible repair.

Statistical analysis

Differences in means were analyzed with the Mann-Whitney test. Proportions were compared using the chi-square test. The Statistical program for Social Sciences (SPSS) version 14 was used. P-values <0.05 were considered significant.

RESULTS

Prevalence of repair

Seventy of 250 RA patients had at least once a decrease in erosion score in any of the joints, evaluating all series of radiographs with known time-order. After rescoring with concealed time-order, 32 joints with repair were identified in 18 (7.2%) patients. Of these, 26 concerned small joints of the hands (8 MCP joints, 9 PIP joints and 9 radiocarpal joints) and 6 concerned MTP joints. Thirty joints showed persistency of the negative change in erosion score for ≥2 years and for 2 joints no data on two additional years were available but there was agreement of all three readers in the identification of repair. 61% of the patients showed repair in one joint; 11%, 17% and 11% expressed repair in 2, 3 and 4 joints respectively. The highest frequency of repair occurred after 4 to 6 years follow-up (Figure 1). The frequency of repair was 13.0% for inclusion between 1993 and 1995 and 5.2% for inclusion between 1996 and 2000.

Baseline characteristics of patients expressing repair

Patients with and without repair revealed no difference in age, gender, Ritchie score, swollen joint count, CRP level and total Sharp-van der Heijde score at baseline (Table 1). In contrast, patients with repair were more often RF-IgM positive (OR 3.7, 95%CI 1.2-11.5, p=0.025) and anti-CCP positive (OR 7.9, 95%CI 1.8-35.2, p=0.007) compared to the non-repair group.

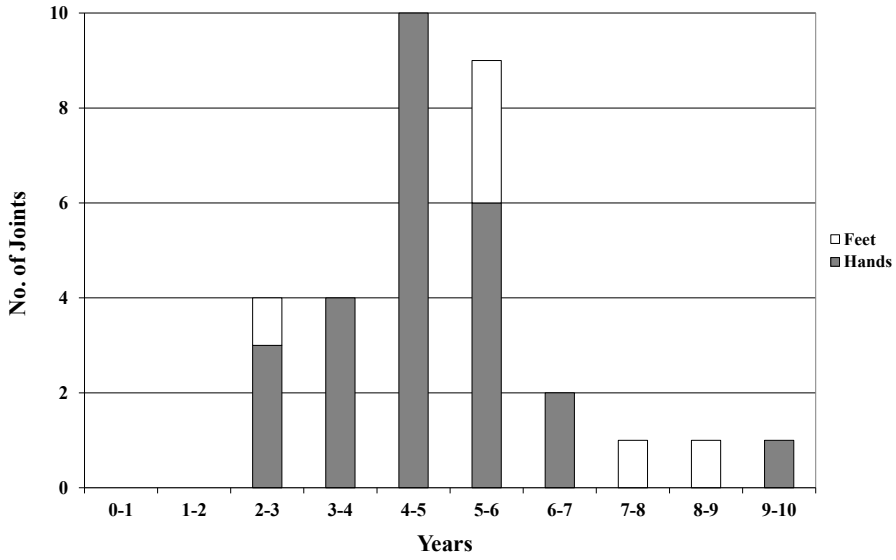

Figure 1. Frequency of repair during the years of follow-up, indicated for small joints of the hands and the feet separately. The total number of small joints assessed in the hands is 32 and in the feet is 12. The joints assessed in the hands are the proximal inter-phalangeal (PIP) joint in digits 1 to 5, the metacarpo-phalangeal (MCP) joint in digits 1 to 5 and 6 radio-carpal sites (base of metacarpal bone digit 1, trapezium, lunate, scaphoid, distal ulna and distal radius and in the feet are the inter-phalangeal (IP) joint digit 1 and metatarso-phalangeal (MTP) joint in digits 1 to 5

Table 1. Baseline characteristics of patients with and without repair

	Repair group N=18	Non-repair group N=232	P value
Age at baseline, mean (SD)	59.3 (9.3)	55.1 (16.9)	0.30
Female gender, No (%)	13 (72)	155 (67)	0.67
Ritchie score, mean (SD)	11.5 (8.0)	10.8 (7.8)	0.73
44 Swollen Joint Count, mean (SD)	5.9 (2.4)	6.0 (3.4)	0.86
ESR in mm/h, mean (SD)	44.2 (25.0)	41.6 (29.9)	0.68
CRP in mg/l, mean (SD)	26.4 (21.3)	29.4 (28.2)	0.59
RF-IgM positive, No (%)	14 (77.8)	112 (48.7)	0.025
Anti-CCP2 positive, No (%)	15 (88.2)	106 (48.8)	0.007
Total Sharp score, mean (SD)	8.1 (6.1)	7.5 (9.1)	0.79

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation date; RF, rheumatoid factor.

Disease course of patients expressing repair

Seventeen patients with repair (94%) had an increase in total Sharp score at the same time as showing repair in individual joints; only one patient showed a decrease in total Sharp-score, indicating that, next to repair, simultaneous progression was present in other joints.

During the disease course patients with repair had significant higher Sharp-van der Heijde scores compared to patients without repair (Figure 2A). A similar observation was done for the total erosion score (Figure 2B).

The achievement of sustained DMARD-free remission was compared for patients with and without repair. One patient of the repair group had clinical remission (5.5%), compared to 16 % (56 out of 232 patients) in the non-repair group (OR 0.15, 95%CI 0.01-1.37, p=0.07).

The presence of joint swelling for the 23 joints showing repair in the MCP, PIP or MTP-joints was evaluated at the two previous years. This showed that joint swelling was absent in 22 joints in two years preceding repair and in 1 joint swelling was absent one year preceding repair.

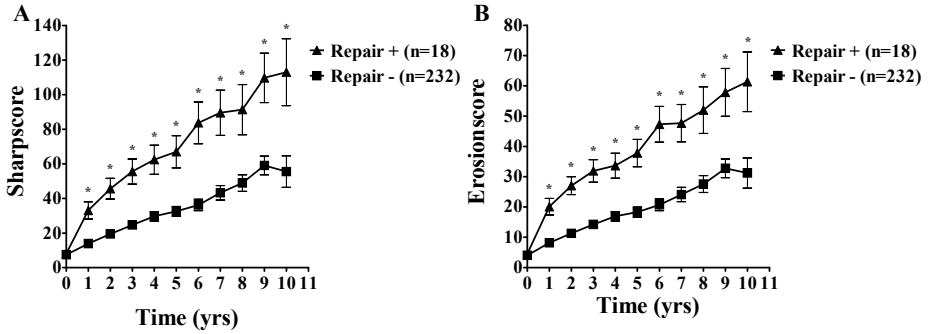

Figure 2. Total Sharp-van der Heijde scores (mean ± SEM) (A) and total erosion scores (mean ± SEM) (B) during follow-up in patients with and without repair. From the patients with repair, the number of radiographs available per year were: 18 at baseline, 18 after 1 year of follow-up, 18 after 2 years of follow-up, 15 after 3 years of follow-up, 14 after 4 years of follow-up, 17 after 5 years of follow-up and 12, 12 , 10, 8 and 8 after 6-10 years of follow-up respectively. *p<0.05

DISCUSSION

The present study investigated repair in an inception cohort with a long duration of follow-up. Previous studies concerned data from clinical trials or evaluated a selected set of RA patients.[2,5,6,14] Importantly, these studies formed the basis for the acceptance of the existence of repair. We now report on the prevalence in a large longitudinal cohort of RA patients treated with conventional treatment strategies. Our results show that, despite the absence of aggressive or biological anti-rheumatic therapy, repair occurs in part of the general RA population.

The prevalence of repair observed here (7.2%) is somewhat lower than reported previously (10.7%).[14] We have chosen a strict definition of repair to reduce the chance on false-positive findings; this may indicate that our prevalence is an underestimation. In addition, the comparison of erosion scores of individual joints between two consecutive time-points may have introduced misclassification, in some cases repair would have been more easily detected in case a larger interval between the radiographs was compared. Third, the finding of a lower prevalence may be caused by the fact that we studied a general RA population and not a selection of RA patients.

Interestingly, repair occurred preferentially in patients with severe joint destruction. This might seem surprising as it could be hypothesized that repair will predominantly be present in the patients with a low total level of joint destruction. Several possibilities may explain this observation. First, it may be a methodological issue based on the presumption that a refill is more easily detected in large erosions. If this is true, repair should predominantly be present in joints with a high erosion score. Our data are not supportive for this notion. The erosion score for individual joints ranges between 0 (no erosion) and 5 (maximum score). The majority of patients with repair showed a decrease in the erosion score from 2 till 1 or from 1 till zero, and thus did not reveal repair in joints that are particularly severely damaged. A second possibility is again methodological. In patients with a lot of damage, many joints show erosions and therefore in these patients more joints are 'at risk' for showing repair. A third possible explanation is biological. In general the human body tends to heal destruction and aims for homeostasis. It can be hypothesized that the more destruction is present, the more regenerating processes are activated. Then after the inflammation or the processes that drive the destruction of bone are disappeared, the enhanced regenerating mechanisms may result in repair.

At the same time repair occurred in some joints, the total Sharp-van der Heijde score increased, indicating progression in other joints. This is in concordance with a study performed by the OMERACT group,[4] and implies that repair is a localized process. The observed absence of joint swelling in the two years preceding repair is in line with similar findings in the TEMPO-trial.[15]

In conclusion, repair occurs in 7.2% of conventionally treated RA patients, particularly in clinically inactive joints in patients with severe destructive disease. Further studies on the biological basis of repair are challenging as they may allow the development of therapies specifically targeted to stimulate these repair mechanisms.

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