Repair of Erosions in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** The aim of this study was to examine the occurrence of repair in a cohort of conventionally treated patients with early rheumatoid arthritis over 8 years.

Methods. There were 395 patients included in the BARFOT study having radiographs of hands and feet at inclusion, and at 1, 2, 5, and 8 years, which were chronologically scored for erosions by the Sharp/van der Heijde method. An erosion with repair was defined as an erosion that has become partially or totally filled, with or without sclerosis.

Results. Erosions with repair were observed in 64 patients (16%) at 1 year, 113 (29%) at 2 years, 142 (36%) at 5 years, and 200 (51%) at 8 years. At the 1-year visit, 13% of the patients with at least 1 new erosion showed repair versus 3% of the patients with no new erosions ($p = 0.001$). At 2, 5, and 8 years the corresponding figures were 22% and 6%, 28% and 8%, and 39% and 11%, respectively (all $p = 0.001$). The sum of all repaired erosions correlated strongly with the sum of all erosions and with the sum of all erosion scores ($\rho = 0.79$ and 0.77). Presence of rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies (anti-CCP) was significantly associated with both new erosions and repair.

Conclusion. Repair was more common than previously described. The frequency of repair increased over time and was associated with the number of erosions. RF- and anti-CCP–positivity, patient age, and presence of erosions at baseline were independent predictors of repair. (First Release February 1 2019; J Rheumatol 2019;46:670–5; doi:10.3899/jrheum.180557)

Key Indexing Terms:
REPAIR OF EROSIONS RADIOGRAPHY SHARP/VAN DER HEIJDE METHOD
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The typical feature of joint destruction is erosions of periarticular cortical bone observed on conventional radiographs in patients with rheumatoid arthritis (RA). Radiographic progression of bone erosions is a commonly used outcome measure of RA in clinical trials, observational studies, and clinical practice[1,2,3]. Measurement of the degree of joint damage represents an important tool to assess disease progression and effectiveness of current treatments[4,5,6].

Radiographs of hands and feet can be easily performed and are relatively cheap. Validated scoring methods are available, and measuring progression is standardized. Radiographic damage is considered to reflect joint inflammation over time. Erosions result from excessive local bone resorption and inadequate formation leading to joint destruction and eventually to functional limitations.

Erosions are not irreversible; repair does occur[7,8]. However, the significance and determinants of repair have been debated[9]. The frequency of repair in patients with RA has only been addressed in a few studies, and in these reports the prevalence of repair of erosions in patients with RA has been estimated between 1.6% and 27% outside the smallest detectable change (SDC), depending on the imaging method used[9,10,11,12,13]. The course of RA varies considerably, from early and long-lasting remission to persistent disabling joint damage that might have an effect on repair[14,15,16]. It is known that the presence of rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies (anti-CCP) is associated with the development of erosions in RA[17].

The aim of our study was to examine the occurrence of repair of erosions in patients with early RA over 8 years and to look for possible factors linked to repair.

MATERIALS AND METHODS

Patients. Between 1993 and 2005, 1281 patients from 4 out of 6 participating centers were included in the BARFOT early RA inception cohort study[17]. All patients were 18 years or older, fulfilled the classification criteria for RA

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established by the American Rheumatism Association[18], and had a disease duration of ≤ 12 months.

This study comprises all 395 patients who had complete radiographs at baseline and at the 4 followup visits. The 886 patients who did not have radiographs from all followups and therefore were excluded were at baseline older and had a higher 28-joint count Disease Activity Score (DAS28).

No patient had received disease-modifying antirheumatic drug (DMARD) or prednisolone treatment prior to inclusion in the study.

Clinical, radiological, and laboratory assessments of the patients were performed at the time of inclusion in the study (baseline), and after 1, 2, 5, and 8 years of followup. RF was available in 383 patients, and anti-CCP in 191 patients at baseline. Disease activity was measured by C-reactive protein (CRP) and DAS28[19]. Remission was defined by the European League Against Rheumatism criterion as DAS28 < 2.6[20]. Sustained remission was defined as being in remission at all the followup visits[21].

Functional disability was assessed using the Swedish version of the Stanford Health Assessment Questionnaire (HAQ)[22].

Radiographic measurements. Posterior-anterior radiographs of the hands and feet were obtained at baseline, and 1, 2, 5, and 8 years. The radiographs were scored chronologically for erosions using the Sharp/van der Heijde scoring method by 1 experienced reader who was blinded to the clinical data[23]. The intrareader intraclass correlation coefficient was 0.94[24]. The SDC for erosion scores was assessed by a formula described by Bruynesteyn, *et al*[25]. The SDC for erosion scores at 1, 2, 5, and 8 years compared to baseline were thus calculated to 1.40, 1.45, 1.55, and 2.95, respectively. Repair of a single erosion was regarded to be present if the erosion was partially or totally filled, with or without sclerosis. All patients gave their informed consent and the Ethics Committees approved the study, which was performed in accordance with the Declaration of Helsinki (ethical approval: LU 326-93, Gbg 88:94, LU 368-94, Li 94-283).

Statistical analysis. Statistical analyses were performed using SPSS version 21.0 statistical software (IBM SPSS). To test the differences between groups, the Student t test was used for continuous variables, and the chi-square test was used for proportions. Spearman rank correlation coefficient was used to assess the relationships between 2 continuous variables. Baseline variables judged to be potential independent predictors of presence of repair at the end of the study were included in a logistic regression model. All significance tests were 2-tailed and conducted at the 0.05 level of significance.

RESULTS

The 395 patients having radiographs from baseline, 1, 2, 5, and 8 years participated in this study. Demographic and clinical characteristics at baseline are shown in Table 1. At baseline the mean age was 54 years, the mean disease duration was 7 months, 72% were women, 63% of 383 were RF-positive, and 56% of 191 anti-CCP–positive. The mean DAS28 was 4.9, and the mean HAQ was 0.91. Treatment was started at first visit (baseline) with prednisolone to 49% of the patients and with DMARD to 71% at baseline.

In total, 17,380 joints were examined on the 5 occasions and erosions were seen in 7661 joints.

Frequency of repair. One or more repaired erosions (repair) were observed in 64 patients (16%) at 1 year, in 113 (29%) at 2 years, 142 (36%) at 5 years, and in 200 (51%) at 8 years. At 1, 2, 5, and 8 years these patients had 121, 209, 328, and 708 repairs, respectively.

Repair occurred irrespective of whether a patient developed new erosions (Table 2).

Association of number of repairs with number of erosions and erosion scores. The sum of the number of erosions showing repair recorded at the followup visits (total repairs) was 1.366 and the corresponding sum of eroded joints (total eroded joints) and erosion scores (total erosion scores) was 6.998 and 10.810, respectively. Total repairs correlated strongly with total eroded joints and total erosion scores ($\rho = 0.79$, $p = 0.001$ and $\rho = 0.77$, $p = 0.001$).

Repair, RF, and anti-CCP. Compared with RF-negative patients, RF-positive patients had a significantly higher mean sum of all repairs and of all erosion scores (mean 4.0 vs 2.5, $p = 0.001$, and 33 vs 17, $p = 0.001$, respectively). Similarly, compared with anti-CCP–negative patients, anti-CCP–positive patients had a mean sum of all repairs of 4.4 versus 2.6 ($p = 0.005$) and a mean of all erosion scores of 35 versus 15 ($p = 0.001$), respectively.

Table 1. Demographic and clinical characteristics at baseline and treatment with prednisolone and/or DMARD started at first visit.

Characteristics	Mean	SD	%
Age, yrs	54	14	
Disease duration, mos	7	4	
Women			72
Current smokers			30
RF-positive			63
Anti-CCP–positive			56
DAS28 (0–9.4)	4.9	1.2	
CRP	28	34	
HAQ (0–3)	0.9	0.6	
Erosion score (0–280)	2.2	3.5	
Prednisolone			49
DMARD			
No DMARD			29.4
MTX			47.3
SSZ			17.7
Other cDMARD			2.8
Combination of cDMARD			2.5
bDMARD			0.3

Anti-CCP: anticyclic citrullinated peptide antibodies; CRP: C-reactive protein; DAS28: 28-joint count Disease Activity Score; RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; SSZ: sulfasalazine; cDMARD: conventional DMARD; bDMARD: biological DMARD.

Table 2. Patients with new erosions and repair at followup visits.

Variables	1 Year	2 Years	5 Years	8 Years	At All Visits
New erosions and repair	50 (13)	88 (22)	112 (28)	156 (39)	19 (5)
New erosions but no repair	156 (39)	102 (26)	115 (29)	83 (21)	2 (0.5)
No new erosions but repair	14 (3)	25 (6)	30 (8)	44 (11)	0 (0)
No new erosions and no repair	175 (44)	180 (46)	138 (35)	112 (28)	82 (21)

Values are expressed as n (%).

Patients with new erosions and repair at the 8-year followup visit were significantly more frequently anti-CCP-negative and RF-positive compared with the rest of the patients. Conversely, patients with no new erosions and no repair had these autoantibodies significantly less often (data not shown).

Repair, sex, smoking habits, disease activity, and remission. Neither sex nor smoking habits were associated with sum of repairs or sum of erosion scores (data not shown).

At 8 years, correlation between number of repairs and levels of DAS28 was weak ($\rho = 0.14$, $p = 0.009$). At 1, 2, and 5 years, the correlations were nonsignificant.

The mean DAS28 did not at any followup visit differ between patients with and without repair (data not shown).

Presence of repair was not associated with remission at any followup visit. Thus, at 1, 2, 5, and 8 years, patients in remission had repair and no repair in similar proportions (20% vs 13%, $p = 0.06$; 29% vs 26%, $p = 0.55$; 27% vs 36%, $p = 0.86$; and 48% vs 53%, $p = 0.29$, respectively). Sustained remission was rare and seen only in 14% of all patients. Repair was seen in similar proportions in patients with or without sustained remission. Thus, at 1 year, repair was present in 16% of the patients with sustained remission versus 20% in patients without ($p = 0.47$). At 2, 5, and 8 years, the corresponding figures were 22% and 30% ($p = 0.23$), 33% and 37% ($p = 0.57$), and 47% and 52% ($p = 0.53$), respectively.

The correlations between repair and CRP were weak at all followup visits.

Repair and function. There was no significant correlation between level of HAQ and number of repairs at any time. Thus, at 1 year, ρ was –0.07 ($p = 0.15$) and at 2, 5, and 8 years the corresponding figures were 0.04 ($p = 0.50$), –0.02 ($p = 0.69$), and 0.06 ($p = 0.22$), respectively.

The mean HAQ did not at any time differ between patients with and without repair (data not shown).

Repair and treatment. DMARD and prednisolone treatment had very little or no influence on the frequency of repair (data not shown).

Predictors of repair. Presence of anti-CCP emerged as an independent predictor of repair (OR 2.26, 95% CI 1.20–4.26; $p = 0.012$). Further, baseline erosion score and patient age independently predicted repair (OR 1.22, 95% CI 1.08–1.37, $p = 0.002$; and OR 1.03, 95% CI 1.00–1.06, $p = 0.013$, respectively).

SDC for the erosion score. SDC is the smallest change in score detectable with the instrument in individual patients. Repair has been defined by some[11,12] as a value outside the SDC. According to this definition, 3% of the patients had repair at one year, 4% at two, 5% at five, and 3% at 8 years.

DISCUSSION

Our present study aimed to evaluate the prevalence of repaired erosions in patients with RA over the first 8 years of disease. To our knowledge, this is the first study addressing repair of erosions in patients with RA during a longer time period.

Although repair has been described in RA since the 1960s, it has rarely been reported and its existence has been questioned. One possible reason for this is that it is still unusual to follow patients with radiography regularly in clinical practice. Another reason may be that clinical trials often are very limited in time. However, in a study by Sharp, *et al*, a panel of experts in the Outcome Measures in Rheumatology (OMERACT) Imaging Committee in 2 exercises agreed that repair of bone damage in RA does occur[7].

Different definitions of repair have been used in previous studies[7,8,11,26-31]. In some, a negative erosion score was used to define repair[10,11,12,26,32,33,34] and this has been recommended as a surrogate marker for repair[8]. Many cases of filling in (with only a small reduction in erosion size) will not result in a score reduction. For example, a reduction of a score from 1 to 0 requires a complete disappearance of the erosion, a reduction from 2 to 1 requires a reduction of a large erosion to a small one, and so forth. Therefore, it is more likely to find more cases of repair by observation of single erosions than by negative scores.

In our study the following definition was used: repair is considered present if an erosion becomes partially or totally filled with or without bone sclerosis, and the result is a change in erosion size. This definition was used already in the 1900s by several authors[27,30,35] and in more recent years not only on conventional radiographs but also with 3-D technique[11,13,28,33,36].

Repair was visualized by conventional radiography. Although newer techniques such as computed tomography and magnetic resonance imaging can give us a more detailed and precise picture of what is happening with erosions, our study shows that conventional radiographs are able to provide sufficient information on the development of repair.

In the present cohort of patients with early RA, repair of erosions occurred with increasing frequency during the 8-year study and repair was more common than previously described. Thus, we have shown repair in 51% of the patients at 8 years while van der Linden, *et al* (using negative erosion score) found repair in only 7.2% of 250 patients over a mean of 10 years[32]. Similarly, Ideguchi, *et al* found repair (defined by filled bone erosions with sclerosis on paired sequential radiographs of both hands and wrists) in only 10.7% of 122 patients with disease duration of mean 2.3 years[26].

The high incidence of repair in our study compared with that of earlier studies might be because we have looked at all patients with some repair including those with increasing erosion scores and those who developed new erosions during the 8 years. In addition, repair and new erosions were frequently observed in the same patient at the same time

(Table 2). This phenomenon has previously been described by Rau, *et al*, who defined repair as a negative score[31].

Notably, new erosions may appear simultaneously with repair, even in the same joint, which might result in unchanged or increased erosion score also in presence of repair.

Reactivation of an erosion was sometimes observed, exclusively in cases without sclerosis, suggesting that repair may be transient. This very intriguing question could not be addressed in this work but should be given priority in forthcoming studies.

In our present study, 3–5% of the patients had repair defined by a change score outside the SDC. This is in agreement with the results from a small number of previously published studies using radiography and showing SDC, in which the frequencies of repair above SDC were 1.8–9%[9,10,11].

Presence of anti-CCP or RF, baseline erosion score, and patient age emerged as independent predictors of repair. RF-positive and anti-CCP–positive patients had significantly more erosions and repair than had RF-negative and anti-CCP–negative patients. This is in agreement with a study of 250 patients with RA by van der Linden, *et al*, who found that patients with repair had a greater prevalence of autoantibodies (RF and anti-CCP)[32].

It has been suggested that effective control of inflammation is a prerequisite for inducing repair[8]. Accordingly, Ideguchi, *et al* found that patients in the repair group had lower mean disease activity and less progression of erosive changes[26]. However, in our present study the occurrence of repair was not affected by DAS28. Similarly, there were no differences in repair in patients with or without sustained remission. During the 8 years, all patients with repair also developed new erosions, independently of DAS28. Thus, it appears that the repair rate was not influenced by effective suppression of the inflammatory process, as measured by DAS28.

With the new treatment options [e.g., the biological DMARD (bDMARD)], improvements including repair of erosions might be expected. Thus, Silva *et al* described in a case report that anti-tumor necrosis factor (TNF) therapy in combination with methotrexate (MTX) in a woman with longstanding RA resulted in repair of erosions on radiographs after 2 and 3 years[37].

Some studies have shown that TNF inhibitor (TNFi) treatment was more likely to be associated with signs of repair than treatment with conventional DMARD (cDMARD).

For instance, Lukas, *et al*, using the TEMPO study, in which treatments with MTX only, TNFi only, or a combination of both drugs were compared, found that after 1 year of treatment with TNFi only or the combination, there was an association with repair not seen in the MTX group[34].

In a 1-year study comparing the amount of repair of erosions in patients treated with TNFi in combination with MTX or with MTX only, Finzel, *et al* found evidence of limited repair and no progression of erosions in patients treated with TNFi, whereas the size of erosions increased in the MTX-treated patients[28].

In a recent study over 6 months by Yue, *et al*, a posthoc analysis comparing the bone-healing effects of denosumab versus alendronate treatment for osteoporosis in 36 women with RA treated with cDMARD, repair of erosions was seen exclusively in the group of patients receiving denosumab[13].

It was not stated in these studies whether the increased frequency of repair in bDMARD-treated patients was a result of increased suppression of the inflammatory process or of decreased osteoclast activity. Our present study cannot contribute to solving this issue because it was performed when bDMARD were not available until sometime after inclusion of the patients.

A limitation of our study is that it is a posthoc analysis. Thus, when the BARFOT study was planned in the early 1990s, repair of erosions was not a recognized issue. Another limitation is that because the method for detecting anti-CCP was not in clinical practice until the beginning of the 2000s, anti-CCP was available in only 56% of the patients.

A strength is that all the participating patients had radiographs from all timepoints.

In light of the highly effective and rapidly acting antirheumatic drugs available today, it might be interesting to use scoring methods that also take repair into account. Van der Heijde, *et al* stated that incorporating repair in a scoring system would improve recognition of repair, particularly in patients with both repair and radiographic progression[8]. However, the current scoring methods using conventional radiographs are not designed to describe reparative changes. Lillegraven, *et al* suggest a simplified method for scoring radiographs, which may serve many clinical purposes[38]. Such a method may conceivably be designed to detect repair of erosions.

The definition of repair should apparently be based on observation of changes in single erosions. Therefore, repair could not easily be included in current scoring methods. However, we should encourage counting erosions with repair complementary to the scoring method used.

In this cohort of patients with early RA, repair was more common than previously described. Repair of erosions occurred with increasing frequency during the 8-year study, was strongly associated with the number of eroded joints and with erosion scores, and was associated with RF and anti-CCP positivity. Further studies are needed to clarify the potential value of recording repair in clinical practice.

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