Chapter 4

Repair of erosions occurs almost exclusively in damaged joints without swelling

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ABSTRACT

Background: Negative radiographic change scores obtained under blinded time-sequence conditions suggest that repair of joints may indeed occur. It is likely that, if repair truly exists, it would be preferentially seen in clinically inactive joints from patients treated with drugs with well-known structural efficacy.

Objective: To determine whether repair is associated with both the absence or improvement of swelling and with treatment.

Patients and methods: Radiographs from patients of the TEMPO trial were scored twice by two readers according to the Sharp–van der Heijde score, blinded to both treatment and true time sequence. Single-joint change scores in erosions were coupled with single joint swelling scores obtained from clinical examination.

Consistency of observed improvement across readers and repeat reads was described, and factors expected to increase the likelihood of occurrence of both worsening and improvement of erosion were tested by generalized estimating equations (GEE) modeling.

Results: In all of the four independent reads, the mean change in erosion score was statistically significantly negative only in the subgroup of joints with absent or improved swelling, when erosions were present at baseline. Multivariate analysis showed that worsening of the erosion score in a joint was significantly increased if that joint was already damaged at study entry, clinical swelling persisted and methotrexate was used instead of etanercept. Repair was associated with improvement of swelling and use of etanercept ($p<0.007$ for all associations).

Conclusion: Repair of erosions almost exclusively occurs in joints with improvement or absence of swelling, in patients treated with etanercept. Progression is seen more frequently in joints with persistent swelling, in patients receiving methotrexate monotherapy, primarily if damage is already present.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by pain and swelling of peripheral joints and destruction of the affected skeletal structures, leading to functional disability within several years of disease [1]. It is obvious that inflammation drives radiographic progression, both at the patient and at the individual joint level [2]. The development of effective 'targeted' treatments has dramatically changed the approach and main aims of treatment in RA. Gradually, better drug efficacy and intensification of treatment has resulted in improved symptomatic and structural outcome as measured by 'clinical remission' and 'zero radiographic progression'.

A matter of debate has been the negative radiographic progression scores that have been found in recent clinical trials pointing to the concept of 'repair' [3-6]. However, because scoring methods have not been specifically designed to perform measurement of change in structural damage in opposite directions (progression vs improvement), the potential influences of measurement error, reading sequence and others should be evaluated before adopting the concept of repair. A subcommittee of Outcome Measures in Rheumatology (OMERACT) has conducted several exercises concluding that repair of erosions can indeed occur in RA, but morphological features considered to be specific for repair (sclerosis, cortication, filling-in, remodelling and restoration) did not help in the differentiation between joint damage progression and repair in blinded reads [7,8]. Moreover, in one of the exercises it was shown that the Sharp–van der Heijde scoring (SHS) method could identify joints with repair in agreement with the global judgment of the experts.

In addition, the description of the relationship between clinical disease activity and radiographic progression at a single-joint level has indicated that progression of damage preferentially occurs in joints with both damage and swelling present [9]. Assuming that repair is the opposite of progression (eg, filling-in of erosions), a prerequisite for a putative repair mechanism to be switched on by drug treatment is the resolution of inflammation by that treatment. Since measurable repair can only occur in joints that are measurably damaged, and since trained readers may detect a change in the size of erosions rather than repair or progression [10], our hypothesis here is that repair is associated both with absence or improvement of swelling and with treatment [4].

METHODS

We used the 1-year data from the Trial of Etanercept and Methotrexate with radiographic Patient Outcomes (TEMPO trial) [4], which compared 12-month clinical and radiographic outcomes of patients with RA treated with either methotrexate only (MTX), etanercept only (ETA) or the combination of both drugs (COMBI).

Assessment of repair

Radiographs of hands and feet at baseline and after 12 months of treatment from patients included in this trial were independently read and scored under blinded time-sequence conditions using the SHS method [11], first by a pool of three readers, with each of them reading one-third of the included patients, and several months later again by two of the three readers, so that for approximately two-thirds of the patients each joint was scored on four independent occasions. Patient identity, treatment allocation and true time sequence were randomised and blinded to the readers. Only joints with at least three of the four change scores present were included in the analysis. Only the joints for which swelling scores were available (12 joints of the wrists, 10 metacarpophalangeal joints, eight proximal interphalangeal joints, two interphalangeal joints of the hands, 10 metatarsophalangeal joints and two interphalangeal joints of the feet) were included in the analyses.

Repair in a single joint was considered present if at least one of the four potential reads showed a negative change in erosion score, while the remaining reads showed no change.

Assessment of swelling

Swelling was assessed using the clinical trial data collected at baseline and 1-year follow-up visits using a 66-joint count score, which ranged from 0 (absence of synovitis) to 3 (major swelling). Change scores were obtained by subtracting the value given at the 12-month follow-up visit from the baseline swelling score. A negative change score in swelling means an improvement in swelling of that particular joint. Evolution in clinical swelling score over time was then compared between joints with 'repair' versus 'no repair' by means of a Fisher's exact test.

Analysis of the association between swelling and repair

Joints were classified into four subgroups defining the radiographic and the clinical status as follows: First, two categories describing the observed clinical

response in a joint (worsening or persistence of swelling (category 'A') versus improvement or absence of swelling (category 'B')). Second, two categories describing the level of radiographic damage at baseline: erosions absent (category 1) versus erosions present (category 2). Categories describing clinical response and baseline erosions were then combined.

An actual analysis included the comparison across subgroups of mean change in erosion score between baseline and 1-year follow-up for each of the four reads.

In order to test the robustness of the findings in the actual analysis, data were modelled by generalised estimating equations (GEE) for binomial outcomes that allow adjustment of within-readers correlation in the change in erosion score as well as adjustment for potential confounders. Two distinct GEE models were designed, one modelling the probability of progression of erosion (ie, a positive change score, ΔSHS erosion score ≥1 unit), and a second model estimating the probability of a negative change score (ΔSHS erosion score ≤1 unit) given by the reader. An unstructured correlation matrix (which best fitted our data) was assumed, and three independent categorical factors were tested in each model: the treatment group (three categories: MTX, ETA or COMBI); the clinical evaluation of swelling (two categories: improvement or absence of swelling at both time points versus worsening or persistent swelling at both time points); and the baseline radiographic status of the joint, (two categories: normal or eroded).

RESULTS

In total, 20 489 joints with at least three change scores available were analyzed. These joints pertained to 495 patients, of whom 150 were included in the MTX group, 169 in the ETA group and 176 in the COMBI group. Of all 20 849 joints, 883 (4.3%) individual joints fulfilled the criterion for 'consensual repair' (a negative change score in at least one read and no change in all remaining reads).

Table 1 presents the joints by change in swelling scores and whether or not they met the repair criterion. Far more joints showed clinical improvement (n=10 258; 50.1%)—including 9290 with a complete resolution of swelling—than worsening of swelling (272 joints; 1.33%). Repair occurred in 512of the 10 258 joints with any improvement of swelling (5.45%) and in only five of the 272 joints with any worsening (including two with persistent swelling and three with onset of doubtful swelling) of swelling (1.87%). Statistical testing con-

Table 1. Numbers (percentage) of joints with repair or no-repair as a function of change in swelling score over 1 year

	Change in swelling score							Total
	(Improvement)			Stable no swelling	Stable swelling	(Worsening)		
	-3	-2	-1	0		1	2	3	
Repair	25 (2.8%)	165 (18.7%)	322 (36.5%)	329 (37.3%)	37 (4.2%)	5 (0.6%)	0 (0%)	0 (0%)	883 (100%)
No repair	369 (1.9%)	2455 (12.5%)	6922 (35.3%)	8531 (43.5%)	1062 (5.4%)	246 (1.3%)	20 (0.1%)	1 (<0.005%)	19606 (100%)

firmed that the distribution of joints in each category was unequal (p<0.0001 for the contingency table), suggesting that improvement rather than worsening or persistence of swelling was associated with repair.

In addition, of the 366 joints with repair that showed a stable swelling score, 329 (89.9%) did not have swelling present at baseline. And of the 512 joints with repair that showed improvement in swelling score, 449 (87.7%) no longer had soft tissue swelling at the final visit (scored '0'), or had minimal residual swelling (scored '1')—(N=61, 13.6%)—that is, 510/512 (99.6% cumulative frequency). Any improvement in swelling score was associated with repair in comparison with joints that had not changed (relative risk (RR) (95% CI): 1.36 (1.19 to 1.55), and in comparison with joints that had shown worsening in swelling (RR=2.72 (1.14 to 6.50)).

Tables 2 and 3 summarize the results of the GEE models, which confirmed the results of the actual analysis. As a proof of concept, we have demonstrated that worsening of erosive damage was related to an inappropriate clinical response in the respective joint of interest: persistent synovitis, or onset of inflammatory signs in a previously quiescent joint, were shown to increase the

Table 2. Probability of erosion **progression** over time in a single joint (GEE model, taking the correlation of 4 repeated reads into account as within-subject variation source)

Compared conditions		OR [95% CI]	p
Treatment	MTX	1 (reference)	
	ETA	0.54 [0.45-0.65]	<0.001
	MTX+ETA	0.32 [0.26-0.39]	<0.001
Swelling	Improvement/none	1 (reference)	
	Worse/persistent	2.13 [1.69-2.69]	<0.001
Baseline erosions	Normal	1 (reference)	
	Eroded	2.00 [1.68-2.39]	<0.001

ETA, etanercept only; GEE, generalised estimating equations; MTX, methotrexate only; OR, odds ratio.

risk of deterioration twofold (p<0.001). A joint already eroded at study entry had a similarly increased probability of progression (p<0.001). On the other hand, the use of ETA as monotherapy or in combination with MTX was significantly different from the use of MTX alone; the combination of etanercept plus methotrexate was most protective (table 2). Further, we showed that both improvement and the use of ETA were independently associated with repair (table 3). However, although the point estimate was somewhat higher with the combination of MTX and ETA versus ETA monotherapy, suggesting a higher probability of occurrence of repair in a joint for a patient treated with the combination of the drugs, there was no statistically significant difference between the two drug regimens.

Table 3. Probability of erosion **"repair"** over time in a single joint (GEE model, taking the correlation of 4 repeated reads into account as within-subject variation source)

Compared conditions		OR [95% CI]	p
Treatment	MTX	1 (reference)	
	ETA	1.28 [1.07-1.53]	0.007
	MTX+ETA	1.33 [1.12-1.58]	0.001
Swelling	Worse/persistent	1 (reference)	
	Improvement/none	1.57 [1.16-2.14]	0.004
Baseline erosions	Normal	1 (reference)	
	Eroded	∞	N/A

ETA, etanercept only; GEE, generalised estimating equations; MTX, methotrexate only; NA, not applicable; OR, odds ratio.

DISCUSSION

The results of these analyses suggest that an improvement in erosion score preferentially occurs in joints in which clinical swelling is either absent or has decreased over time, and is associated with the use of ETA, an anti-tumour necrosis factor (TNF) agent.

Studies focusing on structural changes at the joint level have rarely been conducted. As stated earlier, Boers *et al* demonstrated that persistent swelling and baseline damage in a joint were both independent determinants of damage progression in that particular joint [9]. Our hypothesis was that if a negative change score could be regarded as a surrogate for a real structural repair, it should be preferentially seen in joints showing good clinical response, or in patients treated with anti-TNF agents, because the latter have clearly demonstrated a potential to halt progression of radiographic damage in RA. So

far, no analogous examination of potential improvement of the damage over time had been conducted, although several reports have suggested that clinical remission—a more global approach in the individual patient—is related to the detection of repaired erosions [12-19]. Ideguchi *et al* recently reported on a study in which radiographs of 122 patients with RA were examined to detect any sign of erosion repair [20]; when comparing clinical assessments of the 13 patients with at least one repaired joint versus those without any, the authors found that the repair group had a better clinical response during the observation time (lower mean DAS28-3 score at final time point ($p<0.005$)). Their conclusion—namely, that observation of structural repair is coupled with adequate clinical response, as well as the conclusions from the others cited earlier, are consistent with ours, in that improvement of erosions can occur in patients with RA, and preferentially in those who have responded satisfactorily to treatment. However, this is the first study to have investigated the relation between clinical activity and repair at the joint.

Limitations in our study can be summarised as follows: in principle, reliability of the scoring system implies a summation of effects in single joints (out of 64 that are assessed in the SHS method) to obtain a reproducible total score. However, because opposite change scores in different joints within the same patient may result in at least partial neutralisation of effects, a more extensive insight was required to ensure sufficient sensitivity in detecting 'repaired' joints [10]. Consequently, in order to ensure satisfactory accuracy in our definition of 'repair', we based our first descriptive analyses on consistency of four independent reads made with unknown time sequence. Our first criterion for 'repair' relied on relative agreement only across readers (excluding discrepant values—that is, opposite change scores for observed change), because absolute agreement was not considered to be a realistic outcome. Indeed, obtaining a similar score across the four different reads turned out to be very rare (this applies to both positive and negative change scores); however, in spite of a lack of absolute agreement, truly opposite results were also very rare, and most of the joints were scored 'no change' by the other reader [10]. Moreover, validity of this 'single-joint effect' is supported by the highly consistent results that were obtained from the four independent reads, which showed homogeneous results (see figure 1A-D). This 'artificial' definition of repair on a joint level, could be viewed as a limitation of our study, although given the variability in scoring joints this can hardly be avoided completely.

Another limitation of our analyses relates to the fact that we used data based on detailed clinical examination of joints, applying an ordinal score to estimate the extent of the swelling. Assessment of soft tissue swelling, however, remains

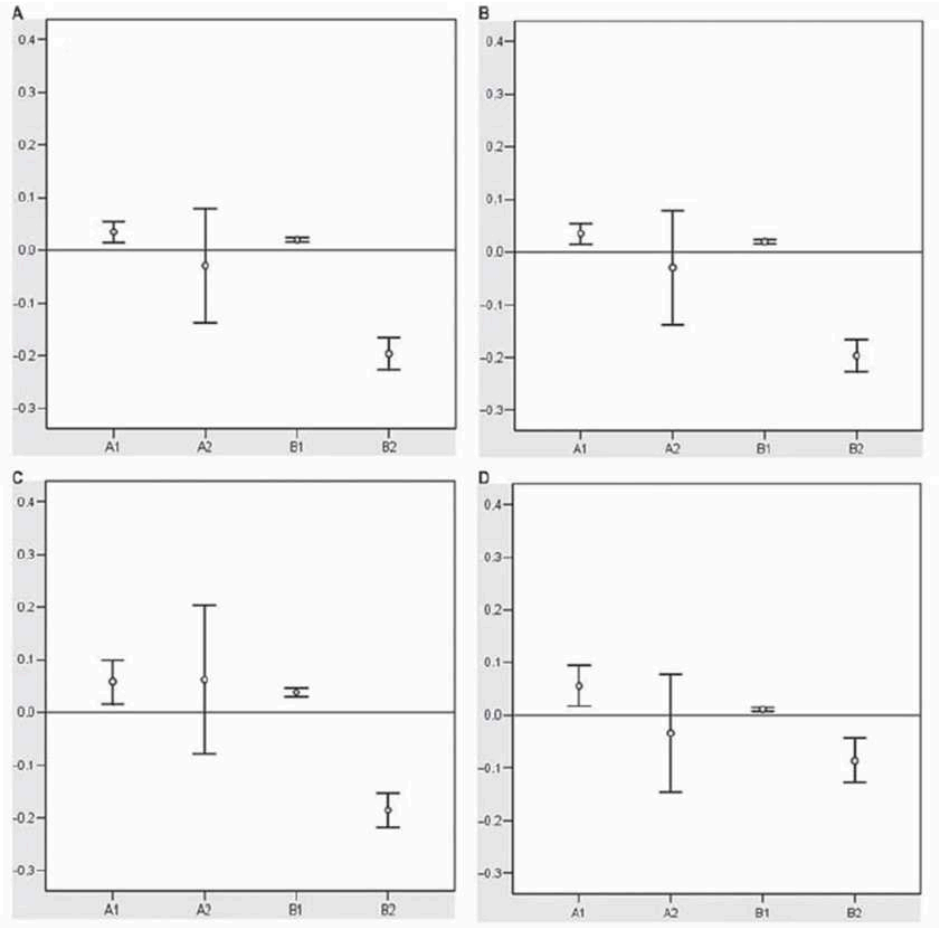

Figure 1. Mean erosion change score and 95% CI in the four defined subgroups (A1, A2, B1, B2) of individual joints, from each of the four independent readings (A–D).
A1: Swelling persistent; NO baseline damage.
B1: Swelling absent or improving; NO baseline damage.
A2: Swelling persistent; baseline damage.
B2: Swelling absent or improving; baseline damage.

a difficult task when applied to patients with longstanding RA, since differentiating an active synovitis from a chronic swelling due to severe damage of the underlying joint can be difficult, potentially leading to overestimated scores in most circumstances. On the other hand, some authors argue that clinical examination underestimates the level of clinical involvement in comparison with, for example, ultrasound. Further studies may apply a more accurate definition of 'active synovitis', based on ultrasonography with power Doppler or on MRI. These techniques may be able to more precisely determine whether

a particular joint has a low likelihood of structural improvement (ie, active synovitis) or a high likelihood of repair (either absence of synovitis or 'inactive' swelling of the joint as often seen in severely damaged joints) [21].

The study population included in our investigations had a high average disease activity, which may limit the generalisability of our results for patients with moderate or low disease activity. However, since we have shown that repair is associated with clinically inactive joints (no or improved swelling), in clinical practice it may actually be more common.

In conclusion, the results of this work have added evidence supporting repair as a true phenomenon rather than a measurement artefact, by showing that in light of the fact that inflammation and progression are coupled, absence or reduction of inflammation independently is associated with the occurrence of repair. This hypothesis is strengthened by the methodological aspects that were used in our work: scoring of the radiographs was obtained at the single-joint level, under blinded conditions for both treatment allocation and true time sequence, in four independent reads, and coupled to clinical data which had also been independently collected. Confirmation of this relevant connection between appropriate clinical response, use of anti-TNF treatment in this case ETA, and observation of negative change scores can thus be regarded as another piece of circumstantial evidence of repair of erosions seen on radiographs.

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