Repair of joint damage in patients with rheumatoid arthritis does not relate to previous suppression of inflammation: a subanalysis after 8 years treat-to-target in the BeSt-trial

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ORIGINAL RESEARCH

Repair of joint damage in patients with rheumatoid arthritis does not relate to previous suppression of inflammation: a subanalysis after 8 years treat-to-target in the BeSt-trial

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ABSTRACT

Objectives To investigate whether repair of erosions and joint space narrowing (JSN) in rheumatoid arthritis (RA) occurs and whether clinical variables predict this.

Methods Eight-year follow-up data of the BeSt-study were used. Patients with recent onset RA (1987 criteria) were randomised to four treatment strategies and treated-to-target (Disease Activity Score (DAS)≤2.4). Yearly radiographs of hands and feet were scored in non-chronological order by four independent readers, using the Sharp/van der Heijde score (SHS). Damage repair was defined as a negative ΔSHS in an individual joint, seen by ≥3 out of 4 readers and persisting ≥2 consecutive years. Associations between repair and DAS, prednisone use, infliximab use, anticitrullinated protein antibody, gender, age, body mass index, symptom duration and randomisation arm were investigated with logistic regression analyses, corrected for mean SHS.

Results Repair was seen in 17 patients (5.3%); 10 had regression of JSN, 7 of erosions, none had both. There were no significant associations in any of the regression analyses.

Conclusion After 8 years of treatment to target DAS≤2.4 in 508 patients with recent onset RA, repair of JSN and erosions was seen in 17/320 patients (5.3%). Probably due to the rarity of repair, we found no associations with suppression of disease activity or other predictors and repair.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In patients with rheumatoid arthritis, suppression of inflammation is associated with arresting damage progression. In small numbers of patients with sufficient disease suppression, repair of joint erosions has been described.

WHAT THIS STUDY ADDS

⇒ We found that repair of joint space narrowing also occurs, but due to small numbers of patients with repair, we found no associations with clinical variables. There were trends towards fewer patients with repair in increasing symptom duration, if initial therapy included infliximab and with lower body mass index.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Suppression of damage progression should be the focus of clinical care, due to the rarity of damage repair.

INTRODUCTION

Inflammation in rheumatoid arthritis (RA) is associated with (progression of) joint damage in the form of bone erosions and damage to cartilage, visible on radiographs as joint space narrowing (JSN).[1] Progressive damage is associated with irreversible loss of functional ability.[2] Suppression of inflammation is associated with arresting damage progression.[3–5] In small numbers of patients with RA, joint damage repair has been described, in particular of erosions, primarily in joints where persistent suppression of inflammation was achieved.[6 7]

In RA, repair in the form of regression of JSN, suggestive of cartilage repair, has not been previously described, and damage to cartilage is generally seen as irreversible. However, in osteoarthritic knees, under the right circumstances, restoration of cartilage may occur.[8] Due to improved treatment options in RA, profound suppression of inflammation is becoming more common. We hypothesised that in patients with RA with previous damage where subsequently

disease activity is sufficiently suppressed, repair of erosions as well as cartilage damage may be seen.

In the current study, we investigated the occurrence of and potential predictors for repair of joint damage in the BeSt cohort (Dutch acronym for Treatment Strategies, 'BehandelStrategieën'). In this cohort of patients with severe early RA, high percentages of patients over time achieved low disease activity and remission.[9]

METHODS

Data of the BeSt-study were used; a multicentre randomised clinical trial (trial register ISRCTN32675862). A full description of the study has previously been published.[10] Patients with early RA (ACR 1987 criteria, arthritis symptoms <2 years) were included between March 2000 and August 2003 and randomised to four treatment arms: sequential monotherapy with initial methotrexate (MTX); step-up combination therapy with initial MTX; initial combination therapy with MTX, sulfasalazine and prednisone or initial combination therapy with MTX and infliximab. Patients were treated-to-target, based on 3 monthly assessments of the 44/53-joint count Disease Activity Score (DAS), treatment target ≤2.4. For each group, treatment adjustments were specified in the protocol in case of an inadequate response to therapy.

Radiographs of the joints were taken yearly and damage was assessed using the Sharp/van der Heijde score (SHS). Radiographs were scored in random time order, blind for patient identity and treatment arm by two independent readers every 2 years. We used the scores of four independent readers until year 8 (years 9 and 10 were scored only by the last two readers) and calculated the interclass correlation coefficient (ICC) for agreement. To minimise the possibility of finding repair due to random variations in scoring, we conservatively defined repair as a reduction of ≥1 SHS point (negative ΔSHS) at the individual joint level compared with the previous available X-ray, present in ≥2 consecutive visits and with ≥3 out of 4 readers agreeing. In accordance with the recommendations of the OMERACT subcommittee on healing, we focused on repair of damage of individual joints and not on regression of total SHS scores.[11] Furthermore, we used the conventional SHS scoring method (originally developed for identifying progression) for assessing repair, also as advised by OMERACT.[11]

T-tests were applied to parametric data, Mann-Whitney-U tests to non-parametric data and χ^2 tests to count data. Logistic regression analyses were performed in the groups with damage for associations between achieving repair and maximum duration of previous remission, mean DAS until repair, previous prednisone use, previous infliximab use, anticitrullinated protein antibody (ACPA) positivity, age, gender, body mass index (BMI), symptom duration and randomisation arm. All models were adjusted for mean joint damage over time until repair. In the group without repair, models were adjusted for mean damage over time until mean time point of repair in the group with repair.

RESULTS

In 7/508 patients, no radiographs were taken and 12 had radiographs taken only once. These patients were excluded from the current analyses, since consecutive repair could not be assessed. Online supplemental table 1 shows the availability of radiographs over time. In 169/489 patients, no damage developed over time; in 320 patients, there was damage in at least 1 joint with ≥3 readers agreeing. In the patients with damage, the median progression in SHS after 8 years was 5.5 (IQR 2.25 to 19, range −1.5 to 242), and the mean (SD) DAS from month 3 to year 8 was 1.93 (0.95).

In 343 patients, at least one reader scored a negative change in SHS ('repair') in at least one joint at ≥1 time point (101 patients with a negative change in JSN, 53 patients with a negative change in erosions, 189 with a negative change in both). Despite the high ICC among the four readers (ICC 0.989), it was increasingly more rare to have>1 reader identify the same negative changes. Table 1 shows the numbers of patients with damage/repair, depending on the required number of readers agreeing. Ultimately, repair by our strict definition was present in 17 of 320 patients (5.3%), over time. Mean (SD) time to repair was 38.8 (17.1) months from baseline. Ten out of 17 patients with repair had a negative change in JSN, 7 in erosions, none had both. In 14 patients, repair was seen in 1 joint, 3 had repair in 2 joints, of which 2 at the same

Table 1 Number of patients with damage and/or repair per number of readers agreeing

	Total N with damage	Total repair, N (%)	JSN repair, N (%)	Erosion repair, N (%)	Both, N (%)
≥1 reader (one time point)	462	343/462 (74.2)	101/343 (29.4)	53/343 (15.5)	189/343 (55.1)
≥2 readers (one time point)	393	141/393 (35.9)	70/141 (49.6)	44/141 (31.2)	27/141 (19.1)
≥3 readers (one time point)	320	51/320 (15.9)	32/51 (62.7)	13/51 (25.5)	6/51 (11.8)
≥3 readers (two consecutive time points)	320	17/320 (5.3)	10/17 (58.8)	7/17 (41.2)	0 (0.0)

JSN, joint space narrowing.

Table 2 Baseline characteristics in groups with and without damage and with and without repair

	No damage (*n=169*)	Damage, no repair (*n=303*)	Damage, repair (*n=17*)	P^{α}	P^{β}
Demographic					
Age, mean (SD)*	51.4 (13.5)	55.7 (13.6)	53.4 (48.2–70.0)	<0.001	0.917
Gender, male, n (%)†	54 (32)	99 (32.7)	11 (64.7)	0.85	0.823
Smoking, n (%)†	59 (35.1)	104 (34.4)	8 (47.1)	1.00	0.289
BMI, mean (SD)*	26.6 (4.4)	25.7 (3.90)	25.1 (4.38)	0.02	0.555
Randomisation arm, n (%)†				0.69	0.173
Sequential monotherapy	45 (26.6)	70 (23.1)	7 (41.2)		
Step-up combination therapy	46 (21.3)	74 (24.4)	5 (29.4)		
Initial combination with prednisone	41 (24.3)	81 (26.7)	4 (23.5)		
Initial combination with infliximab	47 (27.8)	78 (25.7)	1 (5.9)		
Disease-related					
Symptom duration in days, median (IQR)‡	21.9 (13.6–41.7)	27.0 (13.9–56.3)	18.9 (15.0–20.4)	0.13	0.012
RF-positive, n (%)†	86 (50.9)	217 (71.6)	14 (82.4)	<0.001	0.336
ACPA-positive, n (%)†	73 (43.7)	208 (71.5)	13 (81.3)	<0.001	0.397
DAS, mean (SD)*	4.5 (0.9)	4.40 (0.84)	4.48 (0.92)	0.44	0.681
SJC44, median (IQR)‡	14 (9–20)	14 (10–18)	12 (10–17)	0.82	0.982
RAI, median (IQR)‡	13 (9–19)	13 (9–18)	13 (11–17)	0.095	0.597
ESR, median (IQR)‡	30 (16–45)	38 (21–59)	51 (32–72)	<0.001	0.116
CRP, median (IQR)‡	16 (6–34)	25 (10–63)	34 (12–73)	<0.001	0.683
Global health, median (IQR)‡	53 (45–69)	50 (37–64)	50 (34–63)	0.016	0.905
HAQ, median (IQR)‡	1.4 (1–1.9)	1.4 (0.875–1.88)	1.4 (1–1.63)	0.73	0.712
tSHS, median (IQR)‡	0 (0–0)	2 (0–5)	2 (0–5)	<0.001	0.773

P^{α}: p value for comparison between two groups with damage and without damage, grouping 'damage, no repair' and 'repair' together.
P^{β}: p value for comparison between two groups with repair and without repair, in the patients with damage.
*Student's t-test (parametric data).
†Pearson χ^2 test was applied (binary data).
‡Mann-Whitney-U test (nonparametric data).
ACPA, anticitrullinated peptide antibody; BMI, body mass index; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RAI, Ritchie Articular Index; RF, rheumatoid factor; SJC44, 44 Swollen Joint Count; tSHS, total Sharp/van der Heijde score.

time point and 1 in consecutive years. The mean (range) change in local SHS compared with the previous X-ray was −1.13 (−0.5 to −2) SHS points. After initial repair, 10 out of 20 joints showed local damage progression, with a mean (range) of 1.17 (0.25 to 2) SHS points. Details of the joints are shown in online supplemental table 2. At the time point of repair, mean DAS was 2.13 (range 0.47–3.86), all relevant joints were non-swollen and 2/20 joints were tender. At the previous visit, none of the joints were swollen or tender.

Patients with damage were significantly older, less overweight, more often seropositive, and their inflammatory parameters, global health and total damage were higher (table 2). None of the baseline characteristics were significantly different among patients with missing data and patients with complete follow-up (data not shown). Symptom duration was significantly shorter in patients with repair, and other numerical differences were not statistically significant.

After adjustment for mean SHS until repair, we found no associations between achieving repair and mean DAS until repair, duration of previous remission, gender, age, randomisation arm, presence of ACPA or previous exposure to prednisone or infliximab (table 3). Of the 17 patients with repair, 6 (35.3%) had received previous infliximab, compared with 131 of 303 patients without repair (43.2%) before the mean time of repair in the other group, for comparison. Treatment over time in the 2 years preceding repair at the patient level can be found in online supplemental table 3. There were trends towards fewer patients showing repair with increasing symptom duration, initial treatment including infliximab and with lower BMI.

DISCUSSION

This 8-year subanalysis of the BeSt study is the first to report the occurrence of repair of both erosions

Table 3 Logistic regression models to investigate associations with repair (n=17)

	OR	95% CI	P value
Duration of previous remission	1.005	0.802 to 1.26	0.963
Symptom duration at baseline (weeks)	0.972	0.95 to 1.00	0.051
Mean DAS from month 3 to time of repair	0.82	0.40 to 1.63	0.566
Previous prednisone	1.09	0.385 to 3.09	0.871
Previous infliximab	0.599	0.206 to 1.74	0.347
ACPA	1.51	0.413 to 5.53	0.533
Gender	1.13	0.401 to 3.16	0.822
Baseline age	1.01	0.975 to 1.05	0.548
BMI	1.03	1.00 to 1.05	0.056
Randomisation arm			
Sequential monotherapy	Ref	–	–
Step-up combination therapy	0.798	0.231 to 2.75	0.721
Initial combination with prednisone	0.597	0.158 to 2.26	0.448
Initial combination with infliximab	0.147	0.0173 to 1.25	0.080

All models were adjusted for mean Sharp/van der Heijde score until repair.
ACPA, anticitrullinated peptide antibody; DAS, disease activity score.

and JSN in rheumatoid arthritis to our knowledge. We have demonstrated that repair can be seen on radiographs, but it is rare and occurs in 5.3% of patients, based on our most conservative definition. Repair of bone erosions occurred in only 2.2% of our patients. Previously, a prevalence of erosion repair of 7.2% was reported in the Leiden Early Arthritis Cohort (EAC).[12] In the EAC, there was on average more joint damage and thus more potential for repair, and the definition for repair was less strict in that study than the current one. In both studies, radiographs were scored (in chronological order in the EAC, in non-chronological order in the BeSt study) with the aim of detecting progression, however with the connotation that repair might also occur. Since repair of joint damage is such a rare phenomenon, there is no minimal clinically important difference (MCID) to take into account. For damage progression, the MCID of the SHS is 5, but this concerns the total SHS score for all joints. In the current substudy, we investigated whether repair occurred at the individual joint level. 'Repair' of JSN has not previously been reported in patients with RA. Despite some reports on various techniques aiming at cartilage repair in osteoarthritis, it remains questionable whether cartilage regeneration is possible.[8 13 14] We have to consider that JSN repair in our study may have been coincidental and/or related to over time differences in joint alignment on the radiographs, since no moulds were used to fixate the hands and wrists. On the other hand, this may be the first identification of a new phenomenon, not previously reported because there have been few previous RA cohorts where, due to targeted treatment, inflammation and radiographic damage progression have been so adequately suppressed. In the BeSt study, only yearly radiographs were available. It has been shown that MRI and ultrasonography (US) can detect more erosions than are visible on radiographs. No studies have been published to specifically report on erosion repair on MRI or US in comparison to radiographs and/or clinical outcomes. However, one study in 32 patients with RA showed that US appeared most sensitive to finding erosion regression after 12 months of treatment with adalimumab, reporting regression of the US erosion score in MCP 2–5 in 52% of patients, compared with 24% with regression on MRI and 23% on radiographs (all techniques were assessed by different single scorer).[15]

TNF inhibitors have the ability to almost fully halt damage progression.[16] In addition, they have been linked to erosion repair in numerous case reports and in the TEMPO-trial.[17–19] Unpublished results of this trial (mentioned in Ref. 1) indicate repair of JSN may likewise be associated with use of anti-TNF and suppression of local swelling. In contrast, in the current study, prior treatment with infliximab was not associated with repair, and in fact, we saw a trend for fewer repair in patients in the study arm treated with initial infliximab. This may be a first indication that exposure to TNF-inhibition in RA may suppress inflammation and osteoclasts and osteoblasts.[20]

In general, small numbers may have restricted our analyses, requiring us to perform multiple regression models, corrected for only one confounder, when ideally we would have implemented one multivariable regression model to adjust for all confounders and predictors at the same time. Thus, although at baseline there were some numerical differences between the groups, we found no clear associations in subsequent analyses, except for a borderline association between symptom duration and repair, which may have occurred by chance through multiple testing. It can be speculated that earlier in the disease course, processes that later on prove more chronic can still be reversed.

In conclusion, during 8 years of targeted treatment, repair of JSN and erosions was seen in a small number of patients. This supports that repair occurs in early RA. However, repair is a rare phenomenon, and we could not identify predicting factors.

Contributors JAvdP analysed the data and drafted the manuscript. GA, MvdB, LD and IMM scored radiographs and were sub-investigators of the trial. PK, WFL, TWJH and CFA contributed to data acquisition (patient inclusion), CFA was the principal investigator. All authors critically revised and approved the final version

of the paper. All authors accepted responsibility to submit the manuscript for publication.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by BeSt: Medisch Ethische Toetsingscommissie Leiden P02.189. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request.

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