Early Local Swelling and Tenderness Are Associated with Large-joint Damage After 8 Years of Treatment to Target in Patients with Recent-onset Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To assess whether early swelling and tenderness in large joints in patients with rheumatoid arthritis (RA) is predictive of later local damage and whether this leads to functional disability.

Methods. Two-year clinical and 8-year radiological followup data from the BeSt study (trial numbers NTR262 and NTR265), a randomized controlled treat-to-target trial, were used. The association between early local joint swelling and/or tenderness (at least once, or for ≥ 2 consecutive visits) and later large-joint damage (Larsen score ≥ 1) was assessed using generalized estimating equations. The association between large-joint damage and functional ability [by Health Assessment Questionnaire (HAQ)] was assessed using logistic and linear regression analysis.

Results. Clinical and 8-year radiological data were available for 290 patients. Concomitant local joint swelling and tenderness at least once in the first 2 years was independently associated with damage of the large joints (OR 2.5, 95% CI 1.7–3.6), as was swelling without tenderness (OR 2.0, 95% CI 1.1–3.6). Stronger effects were seen for persistent swelling and/or tenderness. Other independent predictors for joint damage were baseline erythrocyte sedimentation rate (OR 1.01, 95% CI 1.01–1.02) and the presence of rheumatoid factor and/or anticitrullinated protein antibodies (OR 2.5, 95% CI 1.5–4.1; and OR 2.2, 95% CI 1.3–3.8, respectively). Patients with large-joint damage had a higher HAQ score after 8 years than patients without (difference 0.15).

Conclusion. Early local swelling and tenderness are independent predictors of later joint damage in these joints after 8 years of Disease Activity Score-guided treatment in patients with RA. This suggests that suppression of local inflammation could help prevent local damage and functional disability. (First Release April 1 2013; J Rheumatol 2013;40:624–9; doi:10.3899/jrheum.121248)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TREAT TO TARGET LARGE-JOINT DAMAGE
SYNOVITIS LARSEN SCORE

Swelling and tenderness in the small joints are associated with radiological damage in these joints in patients with rheumatoid arthritis (RA)[1,2]. Clinical synovitis of the large joints, especially the knees, has also been shown to be predictive of small-joint damage, possibly because the presence of a large area of inflamed synovium is correlated with higher systemic levels of proinflammatory cytokines[3]. One would assume that large-joint inflammation results in local joint damage, but to our knowledge this has never been investigated. In older cohorts, large-joint damage was associated with worse functional ability[4,5]. It is unclear whether this association is still present in patients optimally

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treated to target. We investigated a large cohort of patients with systematic joint evaluations during 8 years of targeted treatment aimed at low disease activity.

MATERIALS AND METHODS

Patients. Data from patients from the BeSt study (trial numbers NTR 262 and NTR 265) who had radiographs after 8 years of followup of ≥ 2 different large joints were used. The BeSt study is a multicenter randomized controlled trial that included 508 patients with recent-onset RA according to the 1987 American College of Rheumatology criteria[6]. All patients gave written informed consent and the study was approved by the local medical ethics committees of all participating centers. Patients were treated according to a dynamic protocol starting with initial methotrexate monotherapy (sequential or stepwise), combination therapy with prednisone, or combination therapy with infliximab, with treatment adjustments based on assessments of the Disease Activity Score (DAS) performed every 3 months. Treatment was intensified or changed in case of insufficient response (DAS > 2.4). If the DAS was ≤ 2.4 for ≥ 6 months, medication was tapered to maintenance dose. Starting 2 years after inclusion, patients receiving monotherapy maintenance dose with a DAS < 1.6 for ≥ 6 months were allowed to taper and stop their last disease-modifying antirheumatic drug (DMARD). A detailed description of the study protocol has been published[7].

Study endpoints. Tenderness in the shoulders, elbows, wrists, hips, knees, and ankles was assessed every 3 months by trained research nurses, blinded for treatment allocation, using the Ritchie Articular Index (RAI). It was recoded for the purpose of these analyses as absence (RAI = 0) or presence of tenderness (RAI = 1, 2, or 3). With the exception of the hips, joints were also scored for swelling (absent or present). Clinical data from the first 2 years after starting treatment was chosen because disease activity was highest in these years, while radiological damage in the small joints was still relatively low. Thus, it is unlikely that symptoms in the large joints were due to radiological damage, but we have no baseline radiographs of the large joints to confirm this. Largely owing to logistic limitations, radiographs of the large joints were carried out in only 290 out of 347 patients who were still in followup after 8 years. Missing data for at least 1 joint were found in 76 patients, either because no radiographs were available or because they had a prosthesis and no information about the reason for the prosthesis was present. The distribution of missing joints has been described[8]. At baseline, patients still in followup who did not have large-joint radiographs were statistically significantly older (56 vs 52 years), but they had slightly better functional ability [mean Health Assessment Questionnaire (HAQ) score 1.1 vs 1.3]. Other baseline characteristics were not statistically different (data not shown). Joint damage in the shoulders, elbows, wrists, hips, knees, and ankles consistent with effects of rheumatoid inflammation or secondary arthritis was scored by an experienced musculoskeletal radiologist (HMK) using the Larsen score for large joints[9], ranging from 0 (no damage) to 5 (total destruction). Ten percent of all joints were rescored to assess reliability, with the same score in 93%. A total Larsen score of all 12 joints (maximum 60) was calculated for all patients who had a maximum of 2 missing joint scores. Functional ability was assessed using the HAQ. Disability was defined as HAQ score ≥ 1[10].

Statistical analysis. The relation between symptoms of local inflammation in the first 2 years of treatment and any local joint damage after 8 years (defined as a Larsen score ≥ 1, to include minimal damage into the analysis) was evaluated for "ever signs of inflammation" and next for "persistent signs of inflammation" by calculating attributable risks. Attributable risks indicate the fraction of added risk in the presence of a certain risk factor, but do not imply causality. Next, we calculated OR using generalized estimating equations with an exchangeable covariance structure. This type of analysis takes into account the correlation between different joints within the same patient. The presence or absence of swelling and tenderness was assigned into 4 categories: no swelling or tenderness; tenderness but not swelling; swelling but no tenderness; and swelling and tenderness. As swelling could not be determined in the hips, these were not included in the analyses. The models were adjusted for baseline age, erythrocyte sedimentation rate (ESR), body mass index (BMI), sex, treatment strategy, rheumatoid factor (RF) or anticitrullinated protein antibodies (ACPA) or a combination of these variables, and time-averaged DAS of Year 0–2. The correlations between HAQ and total Larsen score and between HAQ and DAS after 8 years of treatment were assessed using the Spearman rank correlation test. Then the association between having damage in any large joint (total Larsen score ≥ 1) and the HAQ score was determined using a linear regression analysis. Subsequently we used logistic regression analysis to investigate whether patients with a total Larsen score in the highest tertile had greater risk of a HAQ score ≥ 1 compared to patients with a total Larsen score in the lowest tertile. Both estimates were adjusted for DAS at Year 8, baseline age, ESR, BMI, sex, treatment strategy, the presence of RF or ACPA, or a combination of these variables.

DAS over 8 years was compared for patients with and without any large-joint damage using linear mixed models with a Toeplitz covariance structure, adjusted for baseline age, DAS, BMI, sex, treatment strategy, the presence of RF or ACPA, or a combination of these variables. This analysis was repeated to compare systemic inflammation over 8 years for these patients, with ESR as outcome, adjusted for the same variables, but with baseline ESR instead of baseline DAS.

RESULTS

Radiographs of the large joints were available for 290 patients, 84% of all patients still under followup in the BeSt study (baseline characteristics are shown in Table 1). Patients with radiological data still in followup were younger than the 218 patients no longer in followup or without radiographs (mean age at baseline 52 vs 58 years, respectively; $p < 0.001$) and were more often treated with combination therapy with infliximab (30% vs 19%) compared to combination therapy with prednisone (24% vs 29%; $p = 0.01$) and step-up monotherapy (21% vs 28%; $p = 0.003$). They had a baseline DAS of 4.3 compared to 4.5 ($p = 0.02$) and a baseline HAQ of 1.3 compared to 1.5 ($p = 0.01$) in the group of patients without data.

Table 1. Baseline characteristics for all patients with radiological data of at least 2 different large joints after 8 years of treatment (n = 290).

Characteristics	
Male sex, %	33
Age, mean (SD) yrs	52 (12)
Initial treatment, %	
Sequential monotherapy	25
Step-up monotherapy	21
Combination with prednisone	24
Combination with infliximab	30
ACPA+ or RF+, %	24
ACPA+ and RF+, %	51
Smoker, %	33
Body mass index, mean (SD)	26 (4)
Disease Activity Score, mean (SD)	4.3 (0.9)
Health Assessment Questionnaire, mean (SD)	1.3 (0.6)
Sharp-van der Heijde score, median (IQR)	2.0 (0.0–5.6)

ACPA: anticitrullinated protein antibodies; RF: rheumatoid factor; IQR: interquartile range.

Larsen score ≥ 1 was observed in 64/532 shoulders (12%), 51/538 elbows (10%), 146/563 wrists (26%), 67/521 hips (13%), 95/528 knees (18%), and 39/544 ankles (7%). A Larsen score ≥ 1 in at least 1 joint was found in 64% of 290 patients, and a Larsen score ≥ 2 in at least 1 joint in 37%. Tenderness at least once was observed in 60% of all large joints, at least twice consecutively in 27%. Swelling was observed at least once in 46% and at least twice consecutively in 15%. Patients with radiological damage of large joints (Larsen score ≥ 1 in at least 1 large joint) were older at baseline than patients without (age 54 years compared to 48 years; $p < 0.001$) and they had more small-joint damage, with a median Sharp-van der Heijde score (SHS) of 3.0, compared to 0.8 ($p < 0.001$).

Swelling and tenderness. Swelling, in either the presence or absence of tenderness, showed an association with any local joint damage after 8 years (OR 2.5, 95% CI 1.7–3.6; and OR 2.0, 95% CI 1.1–3.6, respectively; Table 2). The association between tenderness without swelling and any local damage was less strong (OR 1.4, 95% CI 0.97–2.1). These associations were independent of baseline age, ESR, BMI, sex, treatment strategy, RF or ACPA or both, and time-averaged DAS of Year 0–2.

Persistent swelling and/or persistent tenderness (present during at least 2 consecutive visits) in the first 2 years showed an even stronger association with any local joint damage after 8 years. Other independent predictors of large-joint damage after 8 years in this model were higher baseline ESR (OR 1.01, 95% CI 1.01–1.02) and the presence of RF or ACPA (OR 2.2, 95% CI 1.3–3.8), or both (OR 2.5, 95% CI 1.5–4.1).

The attributable risk of tenderness was small, but for swelling (with or without tenderness) it varied from 8 to 25 per 100 joints, depending on the duration of swelling (Table 3). When stratified for autoantibody status, the attributable risk of having tenderness and swelling was 17 per 100 joints in ACPA-positive and RF-positive patients compared to 3 in ACPA-negative and RF-negative patients if it was observed at least once, and 26 per 100 joints versus 4 in ACPA-negative and RF-negative patients if swelling and tenderness were observed twice consecutively (Table 4).

Functional ability and disease activity. The median total Larsen score, which could be calculated for 262/290 patients, was 1 (IQR 0–4). Total Larsen score showed a weak but significant correlation ($R_s = 0.2$, $p = 0.001$) with the HAQ score at Year 8. In comparison, small-joint damage (by total SHS) at Year 8 showed no correlation with the HAQ score in these patients. The DAS score showed a correlation with the HAQ score at Year 8 of 0.5 ($p < 0.001$). The difference in HAQ scores after 8 years between patients with and those without joint damage in ≥ 1 joint was not clinically relevant: 0.15 (95% CI 0.02–0.28). Patients with a higher total Larsen score (highest tertile, Larsen score ≥ 4) had a higher risk of functional impairment (HAQ ≥ 1) compared to patients in the lowest tertile (Larsen score = 0), with an OR of 2.5 (95% CI 1.01–6.1; Table 5).

Over 8 years of DAS-guided treatment, there was a small difference in disease activity between patients with and those without damage in any large joint of 0.19 (95% CI 0.05–0.3; Figure 1A). ESR over 8 years was not significantly different for patients with and without damage in any large joint (Figure 1B).

DISCUSSION

Swelling, persistent swelling, and persistent tenderness in individual large joints during the first 2 years of treatment in patients with recent-onset RA were independently associated with joint damage after 8 years in the same joints. Although there was little radiological damage in the large joints, large-joint damage showed a statistically significant association with functional ability, whereas small-joint damage did not.

The association between clinical signs of synovitis and joint damage in large joints is in agreement with evidence for damage in small joints[1,2]. Local suppression of inflammation may also result in local prevention of damage. This was suggested by the finding that fewer erosions on magnetic resonance imaging occurred in metacarpophalangeal joints that were treated with intraarticular corticosteroids on top of systemic treatment[11]. Other independent predictors of later large-joint damage were higher baseline ESR, as an indication of systemic inflammatory activity, and presence of ACPA and RF autoantibodies, also previously associated with damage progression in general[12,13]. If local treatment of swelling and tenderness could prevent later joint damage, this would be especially beneficial in high-risk patients. Attributable risk of having swelling and pain at least once is only 3 per 100 joints in

Table 2. Number of joints with swelling and/or pain at least once in Years 0–2 per joint.

Feature	Elbow		Ankle		Knee		Wrist		Shoulder	
	R	L	R	L	R	L	R	L	R	L
No swelling or pain	130	128	75	62	101	88	44	39	94	66
Pain no swelling	56	75	61	59	63	60	38	44	140	156
Swelling no pain	20	16	13	17	15	22	10	12	5	5
Pain and swelling	84	71	141	152	111	120	198	195	51	63

Table 3. The association between local swelling, tenderness, or swelling and tenderness with joint damage in shoulders, elbows, wrists, knees, and ankles. Data are numbers, as attributable risks per 100 joints.

	At Least Once			Twice Consecutively		
	No. with Damage/ No. at Risk (%)	Attributable Risk, %	Adjusted OR (95% CI)	No. with Damage/ No. at Risk (%)	Attributable Risk, %	Adjusted OR (95% CI)
No swelling or tenderness	70/770 (9.1)	ref	ref	190/1793 (10.6)	ref	ref
Tenderness, no swelling	74/703 (10.5)	1.4	1.4 (0.97–2.1)	74/509 (14.5)	3.9	1.6 (1.2–2.2)
Swelling, no tenderness	23/133 (17.3)	8.2	2.0 (1.1–3.6)	31/88 (35.2)	24.6	3.8 (2.2–6.6)
Swelling and tenderness	228/1099 (20.7)	11.6	2.5 (1.7–3.6)	100/315 (31.7)	21.1	3.2 (2.2–4.8)

Table 4. Baseline and attributable risk per 100 joints of (persistent) swelling and tenderness stratified for autoantibody status.

Status	At Least Once		Twice Consecutively	
	Baseline Risk (%)	Swelling and Tenderness Attributable Risk, %	Baseline Risk (%)	Swelling and Tenderness Attributable Risk, %
ACPA- and RF-negative	7/138 (5.1)	2.7	23/394 (5.8)	3.7
ACPA- or RF-positive	18/199 (9.0)	12.4	43/446 (9.6)	26.6
ACPA- and RF-positive	43/418 (10.3)	16.6	120/923 (13.0)	26.3

ACPA: anticitrullinated protein antibodies; RF: rheumatoid factor.

Table 5. Association between total Larsen score (in tertiles) and disability (Health Assessment Questionnaire score ≥ 1).

	OR (95% CI)
Larsen 0	ref
Larsen 1–3	1.4 (0.6–3.3)
Larsen ≥ 4	2.5 (1.01–6.1)

ACPA- and RF-negative patients, compared to 17 per 100 joints in ACPA- and RF-positive patients. This means that if the effects of swelling and tenderness on joint damage could be prevented, a risk reduction would occur of 17% in autoantibody-positive patients compared to 3% in autoantibody-negative patients.

A high correlation between large-joint damage and functional ability was found in 2 older cohorts[4,5]. Although (possibly because of DAS-guided treatment) there was less severe damage in the patients who did show damage (median Larsen score 1) than in older cohorts (median Larsen score 3 in the Drossaers-Bakker cohort[4]), we found a statistically significant correlation between large-joint damage and functional ability. Probably related to our finding that damage per joint was less severe than in the older cohorts, the difference in HAQ scores between patients with and those without large-joint damage was not above the clinically significant level of 0.19–0.24[14]. As suggested by the analyses by tertile, this difference would most likely be bigger when a more stringent cutoff for

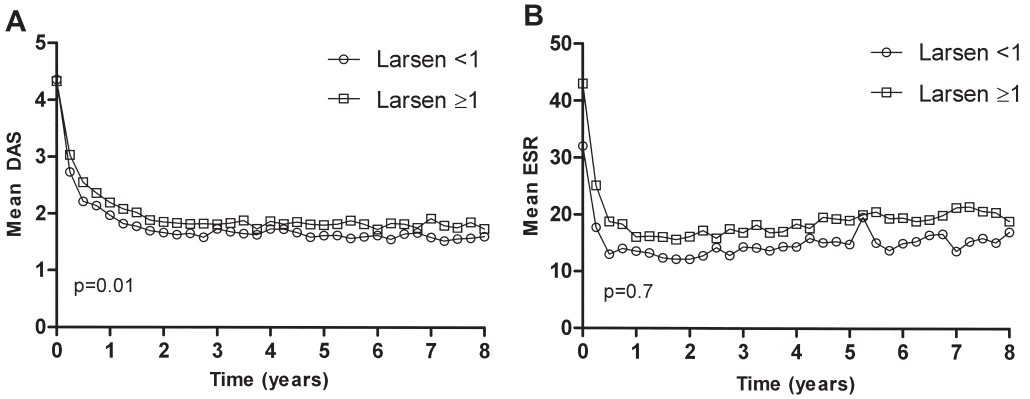

Figure 1. Mean Disease Activity Score (DAS) and erythrocyte sedimentation rate (ESR) over time for patients with and those without any large-joint damage.

large-joint damage is used. The difference we found was largely attributable to damage of the wrists (data not shown), because most daily activities assessed in the HAQ require use of the wrists. In small joints, the association between joint damage and functional ability increases with time[15], so perhaps this 8-year evaluation comes too soon to detect disabling joint damage.

Because baseline radiographs of the large joints or radiographs after 2 years were not available in this study, we could not determine when joint damage occurred. In theory, tenderness or swelling recorded in the first 2 years of the study might have been the result of early large-joint damage. However, since large-joint damage usually occurs later in the disease course and is usually preceded by small-joint damage[15,16,17], which was limited at baseline in our study, swelling and tenderness in the first 2 years after diagnosis are most likely to be the result of local synovitis and not joint damage. Of all large joints, 18% were damaged after 8 years without showing any signs of clinical synovitis in the first 2 years of treatment. This may indicate that such damage was the result of inflammation that occurred later in the disease stage, or perhaps the result of inflammation with subclinical synovitis[11]. We cannot confirm this, because no other imaging techniques were part of the study protocol. Our experienced musculoskeletal radiologist differentiated between signs consistent with secondary osteoarthritis (OA) and signs consistent with primary OA, but it is possible that there are joints in the database that received a score of 1 because of signs of primary OA. There was a small but statistically significant difference in disease activity over 8 years of followup between patients with and those without any large-joint damage. However, this was not found for systemic inflammation as represented by the ESR.

Another potential limitation is that these data from the BeSt cohort are based on a selection of patients who had radiographs available and remained under followup. There was no significant difference in large-joint swelling and tenderness over 8 years between patients who remained in followup with or without radiographs. This indicates that we have no evidence of selection bias, which might influence the association between early large-joint swelling and tenderness and later large-joint damage. Compared to patients who remained in followup, patients no longer in followup in the BeSt study were, on average, older and had slightly higher disease activity at baseline. It is likely that these patients would have had worse functional ability, but also possible that they had more large-joint damage at Year 8 than the patients still under followup. This would not affect the association between large-joint damage and functional ability that we found.

In this treat-to-target cohort, early local signs of inflammation were independently associated with local damage in the same large joints after 8 years, although disease activity over 8 years was similar, for both patients with and those without large-joint damage. More than small-joint damage, large-joint damage is associated with functional disability. This suggests that better suppression of local inflammation could prevent future damage and disability, which would be especially relevant in autoantibody-positive patients, because they have an increased risk of large-joint damage. Additional studies to determine the longterm effects of local treatment are needed to give more insight into whether this can indeed prevent large-joint damage and disability.

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