Benefits and risks of targeted treatment in rheumatoid arthritis

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CHAPTER 7.

Early local swelling and tenderness are independent predictors of large joint damage after 8 years of DAS steered treatment in recent onset RA patients

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ABSTRACT

Objective

To assess if early swelling and tenderness in large joints in patients with rheumatoid arthritis (RA) is predictive of later local damage and to assess the association between large joint damage and functional disability.

Methods

Two-year clinical and 8-year radiological follow-up data from the BeSt study, a randomized controlled disease activity steered 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 (HAQ) was assessed using logistic and linear regression analysis.

Results

Clinical and 8-year radiological data were available in 290 patients. Local joint swelling at least once in the first 2 years was independently associated with joint damage of the large joints, with an OR of 1.8 (95%C.I. 1.3-2.3), as were persistent swelling and persistent tenderness (≥2 consecutive visits): ORs 2.5 (1.8-3.4) and 1.4 (1.05-1.9). Other independent predictors for joint damage were baseline ESR (OR 1.01 (1.01-1.02)) and the presence of RF and/or ACPA (OR 2.5 (1.5-4.1) and 2.2 (1.3-3.8), respectively). Patients with large joint damage had a higher HAQ 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 DAS-steered treatment in patients with RA. This suggests that suppression of local inflammation could help prevent local damage. Patients with large joint damage had worse functional ability.

INTRODUCTION

Swelling and tenderness in the small joints are associated with radiological damage in these joints in RA patients.(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 pro-inflammatory cytokines.(3) In older cohorts, large joint damage is associated with worse functional ability.(4;5) It is unclear whether this association is still present in patients optimally treated with DAS steered therapy. One would assume that large joint damage is a result of local inflammation, but to our knowledge it has never been investigated whether early local swelling and/or tenderness of the large joints are associated with later radiological damage in the same joints. This is what we set out to investigate in a cohort of patients with recent onset RA who have been treated with DAS steered therapy for 8 years. We also reassessed the possible association between large joint damage and functional ability, disease activity and systemic inflammation.

METHODS

Patients

Data from patients from the BeSt study who had radiographs after 8 years of follow-up of ≥2 different large joints were used. The BeSt study is a multi-center randomized controlled trial, in which 508 patients with recent onset RA according to the 1987 American College of Rheumatology criteria were included. 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 three-monthly assessments of the disease activity score (DAS). 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 on monotherapy maintenance dose with a DAS <1.6 for ≥6 months were allowed to taper and stop their last disease modifying anti-rheumatic drug (DMARD). A more detailed description of the study protocol has been published previously.(6)

Study endpoints

Tenderness in the shoulders, elbows, wrists, hips, knees and ankles was assessed every three 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 of tenderness (RAI 0), or presence (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. Mostly due to logistic limitations, only of 290/347 patients still in follow-up after 8 years radiographs of the large joints were made. At baseline, patients still in follow-up who did not have large joint radiographs were older (56 vs. 52 years), but they had slightly better functional ability (mean HAQ 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 (HK) using the Larsen score,(7) 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 Health Assessment Questionnaire. Disability was defined as a HAQ $\geq$1.(8)

Statistical analysis

The relation between symptoms of local inflammation in the first 2 years of treatment and local joint damage after 8 years (defined as a Larsen score of $\geq$1) was evaluated for 'ever signs of inflammation' and next for 'persistent signs of inflammation' using generalized estimating equations with an exchangeable covariance structure. Four different models were used; 1: swelling versus no swelling, 2: tenderness versus no tenderness, 3: swelling versus no swelling and tenderness versus no tenderness as independent predictors, 4: swelling but no tenderness, or tenderness but no swelling and simultaneous swelling and tenderness versus no swelling or tenderness. The models were adjusted for baseline age, erythrocyte sedimentation rate (ESR), body mass index (BMI), gender, treatment strategy, rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) or a combination of these variables and time-averaged DAS of year 0-2. Next, these analyses were repeated for persistent signs of

inflammation, using tenderness, swelling, tenderness and swelling as independent predictors and simultaneous swelling and tenderness for at least 2 consecutive visits in the first 2 years of treatment.

The correlations between HAQ and total Larsen score and between HAQ and DAS after 8 years of treatment were assessed using the Spearman's rank correlation test. Then, the association between having damage in any large joint (total Larsen score ≥1) and the HAQ score was explored using a linear regression analysis. Subsequently we used logistic regression analysis to investigate if patients with a total Larsen score in the highest tertile had a 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, gender, 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, gender, 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

X-rays of the large joints were available in 290 patients, 84% of all patients still under follow-up in the BeSt study. Patients with radiological data were younger than the 218 patients without (mean age at baseline 52 versus 58, $p<0.001$) and more often treated with combination therapy with infliximab (30 versus 19%) when compared to combination therapy with prednisone (24 versus 29%, $p=0.01$) and step-up monotherapy (21 versus 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.

A Larsen score ≥1 was observed in 64/532 (12%) shoulders, 51/538 (10%) elbows, 141/541 (26%) wrists, 67/521 (13%) hips, 95/528 (18%) knees and 39/544 (7%) ankles.

A Larsen score ≥1 in at least 1 joint was found in 64% of 290 patients, a Larsen score of ≥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 one large joint) were older at baseline than patients without (54 years old

compared to 48, p<0.001) and they had more small joint damage, with a median Sharp v/d Heijde score (SHS) of 3.0, compared to 0.8 (p<0.001).

Swelling and tenderness

Joints that in the first 2 years of treatment were swollen at least once, more often showed joint damage of the large joints after 8 years than joints that were never swollen, independent of baseline age, ESR, BMI, gender, treatment strategy, rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) or both and time-averaged DAS of year 0-2, and independent of tenderness. The odds ratio was 1.8 (95%C.I. 1.3-2.3). (table 2) The association between tenderness at least once with large joint damage was not independent of swelling, OR 1.4 (95%C.I.0.99- 1.9). Both persistent swelling and persistent tenderness (present during at least 2 consecutive visits) were independently associated with large joint damage with ORs of 2.5 (95%C.I 1.8-3.4) and 1.4 (95%C.I. 1.05-1.9) respectively. Other independent predictors of large joint damage after 8 years in this model were higher baseline ESR (OR 1.01, 95%C.I. 1.01-1.02) and the presence of RF or ACPA (OR 2.2, 95% C.I. 1.3-3.8), or both (OR 2.5, 95% C.I. 1.5-4.1). The interaction term between swelling and tenderness was not significantly associated with joint damage. Joints that were swollen and tender simultaneously had a higher odds ratio for joint damage than joints that were either swollen or tender (neither swelling nor tenderness as reference category), with odds ratios of 2.5 (95%C.I. 1.7-3.7) and 1.5 (95%C.I. 1.05-2.3) respectively. Similar results were seen for persistent swelling and/or tenderness.(table 2)

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-value 0.001) with the HAQ score at year 8. In comparison, small joint damage (total Sharp v/d Heijde score) at year 8 did not show a correlation with the HAQ score, but DAS score and HAQ score at year 8 showed a correlation of 0.5 (p-value <0.001). The difference in HAQ score after 8 years between patients with and without joint damage in ≥1 joint was not clinically relevant: 0.15 (95% C.I 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 of 0), with an odds ratio of 2.5 (95% C.I. 1.01-6.1).(table 3) Over 8 years of DAS steered treatment, there was a small difference in disease activity between patients with and without damage in any large joint of 0.19 (95% C.I. 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. Overall, possibly due to DAS-steered treatment in this cohort, there was little radiological damage in the large joints. Large joint damage after 8 years showed a statistically significant association with functional ability, whereas small joint damage did not.

The association that was found between clinical signs of synovitis and joint damage in large joints is in line with what was found for damage in small joints.(1;2) Local suppression of inflammation may also result in local prevention of damage. Previously, MRI data showed that less erosions occurred in metacarpophalangial joints that were treated with intra-articular corticosteroids on top of systemic treatment.(9) We have insufficient data on intra-articular injections in our cohort, so this hypothesis could not be further investigated. However, we may assume that if intra-articular injections were given, this would have been done in joints with signs of inflammation, and a possible protective effect of this on the joints would mean that we have underestimated rather than overestimated the association between early signs of inflammation and late damage.

In contrast to our previous findings in the small joints, persistent tenderness in large joints was not associated with an increased risk of damage when compared to tenderness at least once. Possibly, large joint tenderness is less specific for rheumatoid synovitis than large joint swelling.

Other independent predictors of later large joint damage were higher baseline ESR as indication of systemic inflammatory activity, and presence of autoantibodies ACPA and rheumatoid factor, previously also associated with damage progression in general.(10;11)

A limitation of this study is that baseline X-rays of the large joints or X-rays after 2 years are not available, nor were we able to use other imaging techniques as part of the study protocol. Therefore, we cannot determine when joint damage occurred, or in what form. 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, (12-14) swelling and tenderness in the first 2 years after diagnosis are most likely to be the result of synovitis, and not of joint damage. Of all large joints, 18% was 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 of inflammation with subclinical synovitis.(9) There was a small but statistically significant difference in disease activity over 8 years follow-up between patients with and without any large joint damage. However, this was not found for systemic inflammation as represented by the ESR. Since we have no baseline radiographs of the large joints we cannot determine at which point in time damage occurred. In theory, early joint damage could be the cause of early signs of inflammation. The association between early inflammation and later damage would be still there. However, since small joint damage usually precedes large joint damage, small joint damage was limited at baseline, and small joint damage progression over time was suppressed by DAS steered treatment in the BeSt study, it is more likely that signs of inflammation were present before damage. This we cannot prove, nor did we set out to do so.

In two older cohorts (4;5) a high correlation between large joint damage and functional ability was found. In our DAS-steered cohort, we found a weaker correlation between large joint damage and functional ability. The proportion of patients with a Larsen score of ≥1 in our cohort was similar (64%) to that found by Drossaers-Bakker (70%), but in the older study the median total Larsen score was 3, compared to 1 in the BeSt cohort. Patients with a Larsen score of at least 4 in the BeSt cohort did show more disability. In the cohort described by Kuper, X-rays of the large joints were only taken in symptomatic patients, and joints without X-rays were considered not damaged. This might have resulted in an overestimation of the association between large joint damage and HAQ after 6 years. On the other hand, the data in the BeSt cohort are also based on a selection of patients. Patients no longer under follow-up 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 it is also possible that they have more large joint damage at year 8 than the patients still under follow-up. Thus the association between HAQ and damage could be influenced either way if we had no missing data. As it is, the difference in HAQ between patients with or without large joint damage was not above the clinically significant level of 0.19-0.24.(16) The difference we found was largely attributable to damage of the wrists (data not shown), as most daily activities inventoried in the HAQ require use of the wrists. In small joints, the association between joint damage and functional ability increases in time,(12) so maybe this 8 year evaluation comes

too soon to detect disabling joint damage. Since the HAQ score during 8 years of follow-up in our cohort was stable where older studies found gradual deterioration,(12) it remains to be seen whether or when the correlation will increase after longer follow-up.

In conclusion: in this DAS-steered cohort, early local signs of inflammation are 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 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. Additional studies to determine the long term clinical and radiological effects of local treatment are needed.

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

Male gender, %	33
Age, mean (SD)	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
Smoking, %	33
BMI, mean (SD)	26 (4)
DAS, mean (SD)	4.3 (0.9)
HAQ, mean (SD)	1.3 (0.6)
SHS, median (IQR)	2.0 (0.0-5.6)

ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor; BMI, body mass index; DAS, disease activity score; HAQ, health assessment questionnaire; SHS, Sharp v/d Heijde score

Table 2: The association between local swelling, tenderness or swelling and tenderness with joint damage, presented as odds ratio's (95% C.I.).

	At least once	At least 2 consecutive
1. No swelling	*ref*	*ref*
Swelling	2.0 (1.5-2.6)	2.9 (2.1-3.9)
2. No tenderness	*ref*	*ref*
Tenderness	1.7 (1.2-2.2)	1.9 (1.4-2.5)
3. No Swelling	*ref*	*ref*
Swelling	1.8 (1.3-2.3)	2.5 (1.8-3.4)
No Tenderness	*ref*	*ref*
Tenderness	1.4 (0.99-1.9)	1.4 (1.05-1.9)
4. No Swelling or tenderness	*ref*	*ref*
Swelling or tenderness	1.5 (1.05-2.3)	1.9 (1.5-2.6)
Swelling and tenderness	2.5 (1.7-3.7)	3.3 (2.3-4.9)

Table 3: The association between total Larsen score (in tertiles) and disability (HAQ ≥1).

	Odds ratio (95% C.I.)
Larsen 0	*ref*
Larsen 1-3	1.4 (0.6-3.3)
Larsen ≥4	2.5 (1.01-6.1)

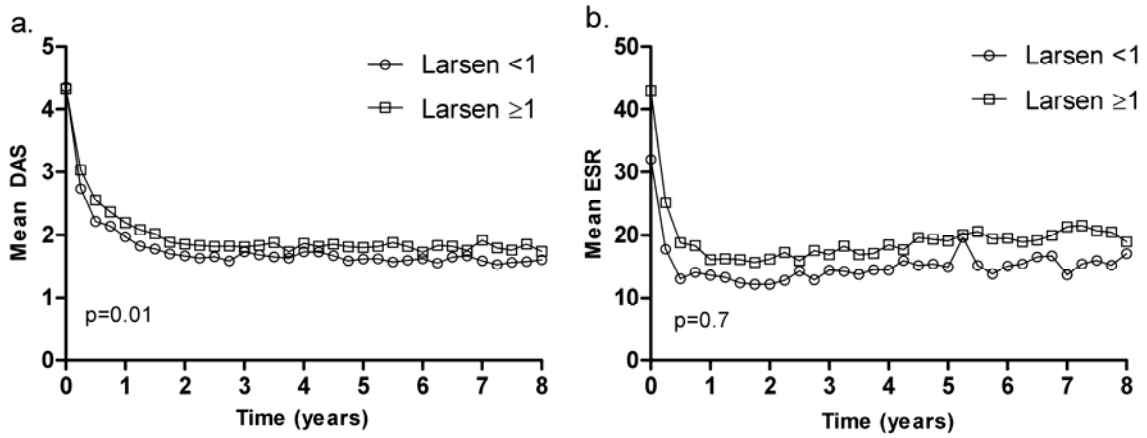

Figure 1: Mean DAS (A) and ESR (B) over time for patients with and without any large joint damage.