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## Benefits and risks of targeted treatment in rheumatoid arthritis

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## CHAPTER 6.

### **Large joint damage in patients with early rheumatoid arthritis and its association with treatment strategy and damage of the small joints**

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## **ABSTRACT**

### **Objective**

To determine the prevalence of large joint damage and the association with small joint damage in patients with rheumatoid arthritis (RA) after eight years of low disease activity score ( $DAS \leq 2.4$ )-targeted treatment with different treatment strategies.

### **Methods**

Radiological data of 290 patients participating in the BeSt study, a randomized trial comparing initial monotherapy and initial combination therapy strategies, were used. Radiographs of large joints were scored using the Larsen score, of the small joints using the Sharp-vanderHeijde (SHS) score. With multivariate logistic regression analysis an association between total damage of the small joints and of the large joints was investigated.

### **Results**

After 8 years of treatment, damage was observed in 12% of shoulders, 10% of elbows, 26% of wrists, 13% of hips, 18% of knees and 7% of the ankles. Damage in  $\geq 1$  large joint was found in 64% of patients, with a median score of 1. No difference was found between initial monotherapy or combination therapy strategies. There was a significant association between damage progression in small joints and damage of  $\geq 1$  large joint (OR 1.02, 95%CI: 1.00-1.04).

### **Conclusion**

After 8 years of DAS-targeted treatment in early RA patients, large joint damage was found in 64% of the patients and was associated with small joint damage. Continued DAS-targeted treatment is probably more important in damage suppression than initial treatment strategy. Patients with more damage of hands and feet also have more damage of the large joints.

## **INTRODUCTION**

Radiographic damage in the small joints (hands and/or feet) occurs in most patients with rheumatoid arthritis (RA) in the early years of disease [1-3]. Damage of the large joints (shoulders, elbows, hips, knees and ankles) usually has a later onset [4, 5]. Since damage of the large joints has an even larger impact on functional ability than small joint damage [6, 7] prevention of large joint damage is a relevant goal in RA treatment. However, large joints are not routinely monitored for damage progression in RA.

In older cohorts, damage progression in small and large joints was highly correlated [6, 7]. It is not known if this is still the case, now that disease activity targeted treatment strategies and new (combinations of) anti-rheumatic drugs have shown to adequately suppress damage progression in small joints in many patients [8-10].

Therefore, we looked at the prevalence of radiological damage in large joints in a disease activity score (DAS)-targeted treatment cohort of RA patients with 8 years of disease duration and investigated whether there is still a relation with damage progression in small joints, and we investigated whether such a relation depends on small joints erosiveness or joint space narrowing and whether it was influenced by the initial therapy.

## **METHODS**

### **Patients**

All data were collected in the BeSt study, a randomized clinical trial comparing four different treatment strategies in patients with recent onset RA (revised 1987 American College of Rheumatology (ACR) criteria). The ethics committees of all participating centers approved the study protocol and patients gave their written informed consent.

Patients were randomized to one of four treatment strategies: (1) sequential monotherapy, (2) step-up therapy, (3) initial combination therapy with tapered high-dose prednisone or (4) initial combination therapy including infliximab. Every three months, treatment adjustments were made based on the DAS (original DAS, based on a 44 swollen and 53 tender joint count) and treatment aimed at a  $DAS \leq 2.4$ . More details on the BeSt study design were previously published [11, 12]. At year 8, radiographs of the large joints were

made for 290/347 patients who were still under follow-up. In 57/347 of the patients radiographs were not made, mostly due to logistic reasons in the different hospitals (including study personnel who failed to organize the radiographs and radiology personnel who failed to follow protocol and did not take radiographs of all required joints), but also because ten patients refused.

### **Assessment of radiological damage**

Radiographs of the shoulders, elbows, wrists, hips, knees and ankles were scored by an experienced musculoskeletal radiologist (HK) using the Larsen score (range 0-5 per joint) [13]. Only joints showing specific signs of damage caused by rheumatoid arthritis inflammation or secondary osteoarthritis, not primary osteoarthritis, according to HK were scored as having damage. Intra-reader reliability was determined based on a rescore of a random 10% of all radiographs, separately for each joint, with intraclass correlation coefficients of 0.78 for the shoulders, 0.98 for the elbows, 0.89 for the wrists, 0.96 for the hips, 0.98 for the knees and 0.65 for the ankles. Overall, 93% of all rescored radiographs were given the same score twice. Large joint damage was defined as a total Larsen score  $\geq 1$  (at least one joint with damage  $\geq 1$  point). For the total Larsen score, all separate joint scores of patients who had no more than 2 joint scores missing were added up (maximum 60). Radiographs of the hands and feet were taken at baseline and yearly up to year 8 and scored according to the Sharp-van der Heijde Score (SHS) [14]. Two independent readers (LD and MB) scored these radiographs blinded for time order and patient identity and the mean progression score of the two readers was used for the analysis. The inter-observer intraclass correlation coefficient (ICC) was 0.96. Two thresholds of radiological damage progression of the small joints of hands and feet were defined: an increase in SHS scores  $\geq 5$  points (based on the smallest detectable change) or an increase of  $\geq 15$  points (the highest 20%) over eight years time.

### **Statistical analysis**

Demographic and clinical baseline characteristics for patients with and without damage  $\geq 1$  point total Larsen were compared. Differences were tested using the chi-square test for categorical data and either the students T-test or Mann Whitney U test for continuous

data, depending on the distribution of the tested variable. The distribution of damage in the individual large joints was analyzed with a cluster analysis (TreeView, version 16) in order to identify whether specific patterns of joint involvement occur.

Subsequently, a multivariate logistic regression analysis was performed to identify an association between damage in the large joints and radiological damage progression in the small joints over eight years time. For these analyses the wrists were not included in the large joints score (Larsen) but only in the SHS. In the analysis small joint damage was entered first as a continuous variable and next as a dichotomous variable with cut-offs of  $\geq 5$  points SHS and  $\geq 15$  points SHS. Estimates were adjusted for gender, treatment strategy, rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA) or a combination of RF and ACPA, and baseline age, erythrocyte sedimentation rate (ESR) and SHS. In addition, multivariate logistic analyses were repeated for narrowing and erosions separately and simultaneously to determine if narrowing or erosion scores were independently associated with damage in the large joints. Estimates were adjusted for gender, treatment strategy, RF, ACPA or a combination of RF and ACPA, and baseline age, ESR and narrowing and/or erosion score. To analyze the data, SPSS version 17.0 software (SPSS, Chicago, IL, USA) was used. All tests were two-tailed and  $p < 0.05$  was considered to be statistically significant.

## **RESULTS**

Patient characteristics, separately for patients with and without damage of the large joints, are shown in table 1. Patients were on average 52 years old, most were female (67%), had an average BMI of 26 and 67% and 60% of the patients were RF and ACPA positive, respectively. At baseline, disease was active with a mean DAS of 4.3, mean ESR of 41 mm/hr, and the mean HAQ was 1.3. In 40% of the patients erosive disease of the small joints was present, and the median SHS score at baseline was 2 points.

The 290 patients with large joint radiographs were younger (52 versus 58 years) and had a slightly lower DAS (4.3 versus 4.5) and HAQ (1.3 versus 1.5) and a higher median SHS (2.5 versus 2 points) than the 218 other patients in the BeSt cohort who were no longer under follow-up or did not have large joint radiographs made. Further, more patients with

large joint radiographs had been treated with initial combination therapy with infliximab and less with initial combination therapy with prednisone or with step-up combination therapy.

### **Radiological damage in the large joints**

Joint damage ( $\geq 1$  point Larsen) was observed in 64/532 (12%) of the shoulders, 51/538 (10%) of the elbows, 141/541 (26%) of the wrists, 67/521 (13%) of the hips, 95/528 (18%) of the knees and 39/544 (7%) of the ankles. Sixty-four percent of the patients had damage in at least 1 large joint. Of the patients with damage, 31% had damage in only one joint, 24% in 2 joints, 13% in three joints and 32% in four or more joints (figure 1). Mean (SD) total Larsen score was 2.7 (3.7) and median (IQR) total Larsen score was 1 (0-4). The cluster analysis identified clusters of bilateral damage in the wrists, the knees, hips and elbows (right wrist clusters with left wrist, right knee with left knee, etc.), showing that symmetrical involvement in RA extends to symmetrical damage of the large joints.(figure 2).

Seven percent of the patients (n=21) had one or more joint prostheses; two elbows, two wrists, 15 hips, 14 knees and one ankle prosthesis. Most patients (n=11) had one prosthesis, seven patients had prostheses in two joints and three patients had prostheses in three joints. In 17 cases prostheses were placed because of degenerative joint disease (primary osteoarthritis), in 12 cases because of secondary osteoarthritis, in 4 cases due to other reasons such as fracture or dysplasia and in one case the reason was unknown.

There was no significant difference in median total Larsen scores between patients initially treated with monotherapy and patients initially treated with combination therapy. The median (IQR) total Larsen in the initial monotherapy group was 1.5 (0-5), 2 (0-4) in the step-up group and 1 (0-3) both in the initial combination therapy with prednisone group and the initial combination therapy with infliximab group.

Seventy-two percent of the 290 BeSt patients in this analysis had radiological damage ( $>0.5$  point) of the small joints after 8 years. Thirty-three percent of the patients had progression  $\geq 5$  points SHS and 19% had progression  $\geq 15$  points SHS in 8 years. Mean ( $\pm$  SD) damage progression was highest in the first year ( $2.7 \pm 1.1$ ) and stabilized thereafter with a mean (SD) progression of 1.2 (4) SHS points per year in these patients. Patients

with large joint damage (total Larsen without wrists  $\geq 1$ ) had more small joint damage progression per year than patients without large joint damage (figure 3), but the difference was only significant in the first year of treatment: mean (SD) SHS progression in patients with large joint damage 4 (13) and in patients without large joint damage 1 (4) ( $p < 0.05$ ).

Radiological damage progression in small joints (SHS) was significantly associated with damage of the large joints with an odds ratio (OR) of 1.02 (95% CI: 1.00-1.04). Radiological damage progression  $\geq 5$  points and  $\geq 15$  points SHS were both independently associated with damage  $\geq 1$  total Larsen score in the large joints, with ORs of 2.0 (95% CI: 1.1-3.8) and 2.6 (95% CI: 1.2-5.6), respectively. (table 2) Thus, patients with more damage progression in small joints had a higher risk of damage of the large joints.

Both an increase in joint space narrowing and an increase in erosion score over 8 years were significantly associated with damage of the large joints (OR 1.04, 95% CI: 1.00-1.07 and OR 1.05, 95% CI: 1.01-1.09, respectively), but when both were entered in one model, neither was independently associated with damage of the large joints (OR 1.03, 95% CI: 0.97-1.09 and OR 1.02, 95% CI: 0.97-1.07, respectively).

## **DISCUSSION**

After 8 years of treatment, 64% of the patients with RA have developed radiological damage in the large joints, despite tight control DAS-targeted therapy adjustments aimed at low DAS ( $\leq 2.4$ ). The percentage we found (64%) is similar to what was reported in non-DAS-targeted treated historical cohorts but the per patient severity is less [6, 7, 15]. In patients from our Rheumatoid Arthritis Patients in Training (RAPIT) trial who were matched for 8 years symptom duration, the percentage of patients with large joint damage was 79% [15]. Since patients in the BeSt cohort were selected based on active disease at baseline, the observed difference may be the result of earlier and DAS-targeted treatment in our cohort. Similar results were previously found for small joint damage [8]. Further, in the RAPIT cohort radiographs of the tarsus and not of the wrists were used for the total Larsen score, while in the BeSt cohort radiographs of the wrists and not the tarsus were used. However, since in the BeSt cohort the wrists were most often and severely

damaged, it is unlikely that we underestimated the total large joint damage in that cohort. Although in the BeSt cohort more patients had been treated with initial combination therapy including prednisone or infliximab, it is unlikely that this explains the difference in large joint damage between the cohorts, since in a separate analysis in the BeSt cohort we found no difference in large joint damage between patients initially treated with monotherapy (sequential or step-up) and patients initially treated with combination therapy (including either prednisone or infliximab). This was different in the FIN-RACo study, where after 11 years of treatment there was less large joint damage in the initial DMARD combination therapy group than in the DMARD monotherapy group [16]. In the first 2 years of FIN-RACo, there were less treatment adjustments than in the first years of the BeSt study, resulting in a considerable difference in clinical response still after 1 year of treatment. In the BeSt study there was a statistically significant difference in small joint damage progression between the initial monotherapy groups and the initial combination therapy groups in the first years of treatment, but in the following years this difference is lost due to the larger effect of similar low disease activity in all treatment groups, as a result of continued frequent DAS-targeted treatment adjustments [12, 17]. For large joint damage, the effect of initial treatment strategy may be similar as for small joint damage, but since large joint damage tends to occur later in the course of the disease, when disease activity in the BeSt study was well suppressed, the continued DAS-targeted treatment may be even more effective [4, 5].

In contrast to previous studies [6, 7], our cohort was treated according to a DAS-targeted protocol, resulting in significantly better suppression of damage progression in the small joints [8, 12, 17, 18]. Therefore we expected also little damage in the large joints, resulting in a smaller or even absent association between small and large joint damage. However, we did find in this DAS-targeted BeSt cohort that total small joint damage progression is associated with large joint damage. Neither small joint erosions nor small joint space narrowing score were independently associated with damage in the large joints. To our knowledge we are the first to examine these features of joint damage separately.

Interpreting radiographic damage in the large joints can be difficult since damage may also be caused by primary degenerative processes or osteoarthritis, which may be found

in a substantial number of older patients, or secondary osteoarthritis due to other causes than RA [19, 20]. Experienced musculoskeletal radiologists such as HK recognize patterns of damage both within and between large joints as primary degenerative damage or as rheumatoid damage. Nevertheless, we cannot rule out the possibility of an overestimation of large joint damage in our cohort. The fact that patients with large joint damage were on average older may suggest this. Still, including non-rheumatic damage in our analysis would result in an underestimation of the association between small and large joint damage rather than an overestimation. Therefore, we do not think that this possibility undermines our conclusions.

In 7% of the evaluated patients in this cohort joint replacement surgery had occurred, which is a similar prevalence as previously reported [6, 21]. This would suggest that severely damaged joints occurred as often as in older cohorts. Since we have excluded the joints with a replacement from our analysis, one might even argue that we have underestimated large joint damage. However, the medical records showed that the majority of joint replacements were due to osteoarthritis and not rheumatoid arthritis. And it is likely that, in comparison to older cohorts, patients in the BeSt cohort had joint replacement surgery in relatively less damaged joints, due to advanced technical possibilities, shorter waiting lists and changed insights in timing of joint replacements.

In conclusion, after 8 years of DAS-targeted treatment, a similar percentage of patients with some damage, and a similar percentage of joint replacements was found as was reported in historical cohorts. However, per patient large joint damage appeared to be less severe. Possibly reflecting the benefit of 8 years of targeted treatment, no difference in large joint damage between patients initially treated with monotherapy and patients initially treated with combination therapy was found. As in older cohorts, large joint damage was found to be associated with damage in small joints of the hands and feet. This implies that monitoring small joint damage is sufficient to guide treatment decisions in order to also prevent large joint damage and long term disability.

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Table 1. Baseline characteristics of 290 out of 508 recent-onset RA patients in the BeSt study. Patients were categorized with and without damage  $\geq 1$  point of the total Larsen score in the large joint.

<b>Baseline characteristics</b>	<b>All patients (n=290)</b>	<b>Patients without large joint damage (n=104)</b>	<b>Patients with large joint damage (n=186)</b>	<b>p-value</b>
Age, mean $\pm$ SD years	52 (12)	48 (12)	54 (12)	<0.001
Female gender, no. (%)	195 (67)	69 (66)	126 (68)	0.808
Symptom duration, median (IQR) weeks	23 (14-52)	22 (13-51)	24 (14-53)	0.422
DAS, mean $\pm$ SD	4.3 (0.9)	4.4 (0.9)	4.3 (0.8)	0.824
HAQ, mean $\pm$ SD	1.3 (0.6)	1.3 (0.6)	1.4 (0.7)	0.258
BMI, mean $\pm$ SD	26 (4)	26 (4)	26 (4)	0.740
ESR, mean $\pm$ SD	41 (27)	32 (14)	43 (29)	<0.001
SHS, median (IQR)	2 (0-6)	1 (0-4)	3 (0-7)	<0.001
Total Larsen score, median (IQR)	1 (0-2)	0 (0-0)	3 (1-5)	<0.001
RF positive, no (%)	192 (67)	64 (62)	128 (69)	0.209
ACPA positive, no (%)	173 (60)	54 (52)	119 (66)	<0.05
Smoking yes, no (%)	95 (33)	38 (37)	57 (31)	0.279
Treatment strategy, no (%)				0.795
Sequential monotherapy	73 (25)	23 (22)	50 (27)	
Step-up therapy	60 (21)	21 (20)	39 (21)	
Initial combination with prednisone	70 (24)	28 (27)	42 (23)	
Initial combination with infliximab	87 (30)	32 (31)	55 (30)	

SD, standard deviation; DAS, disease activity score; HAQ, health assessment questionnaire; BMI, body mass index; ESR, erythrocyte sedimentation rate; SHS, Sharp-van der Heijde Score rheumatoid arthritis; IQR, inter-quartile range; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies.

Table 2. Associations between radiological damage progression in the small joints (model 1 with delta SHS, model 2 with  $\geq 5$  and model 3 with  $\geq 15$  points SHS) and damage  $\geq 1$  point in at least one large joint, presented in odds ratios (OR) and their 95% CI.

		Crude odds ratio (95% C.I.)	Adjusted odds ratio (95% C.I.)
Model 1	Delta SHS 0-8	1.03 (1.01-1.05)	1.02 (1.00-1.04)
Model 2	<5	Ref	
	$\geq 5$	2.6 (1.5-4.4)	2.0 (1.1-3.8)
Model 3	<15	Ref	
	$\geq 15$	3.3 (1.7-6.7)	2.6 (1.2-5.6)

\* Adjusted for gender, treatment strategy, RF/ACPA/combination of RF and ACPA, baseline SHS, age and ESR

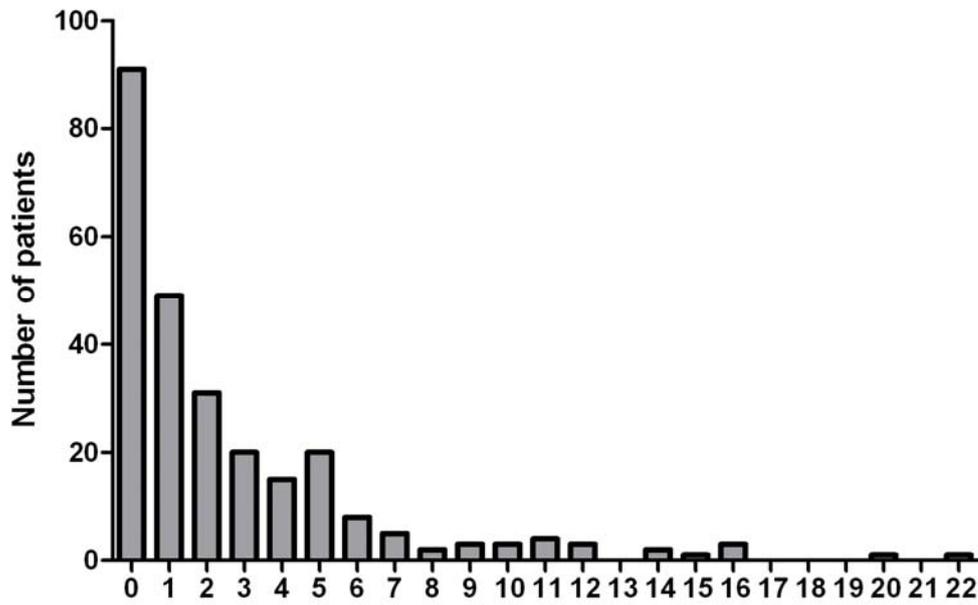


Figure 1: Frequencies of total Larsen scores of 290 patients, after eight years of treatment.

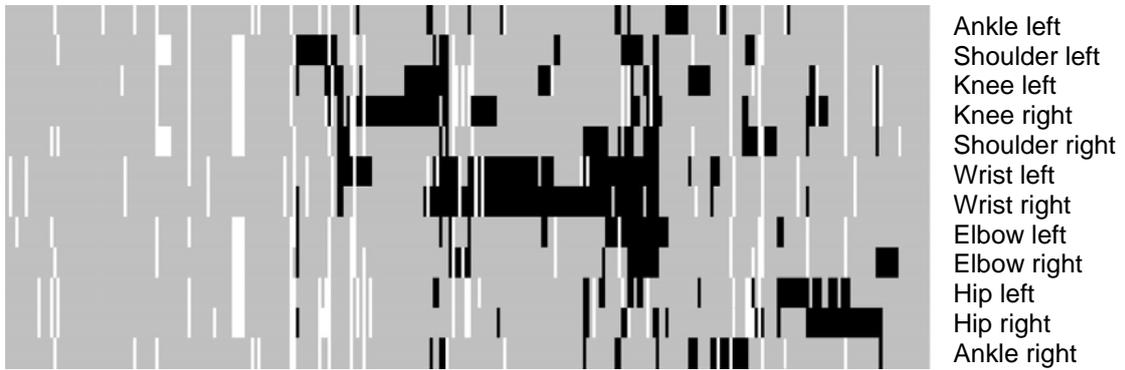


Figure 2. Cluster analysis to identify specific patterns of joint involvement. Each column represents a specific patient and each row a specific joint. Black indicates that a patient has damage ( $\geq 1$  point Larsen score) in that specific joint, grey indicates no damage and white indicates that a joint score is missing.

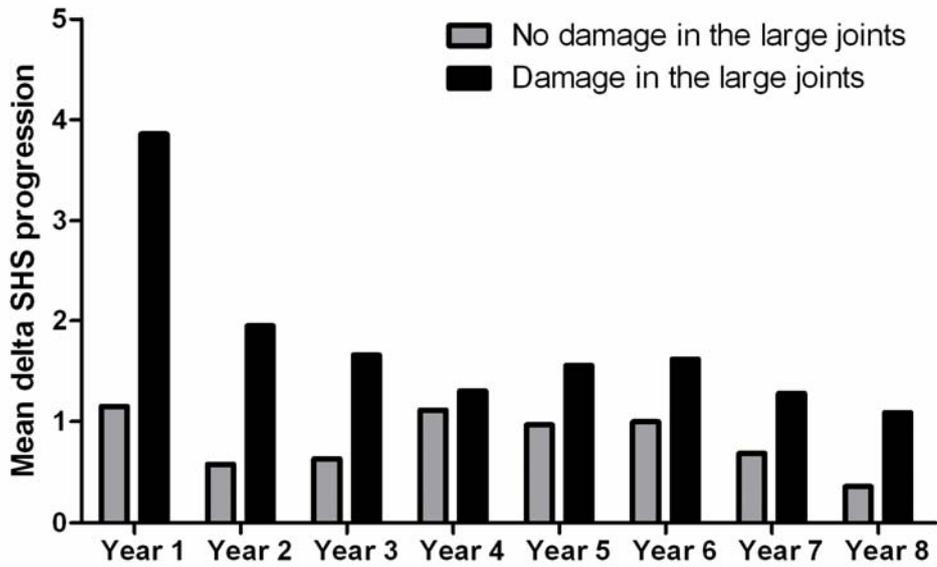


Figure 3. Mean radiological damage progression (SHS) of the small joints per year, separately for patients with and without large joint damage at t=8 years (shoulders, elbows, hips, knees and ankles).