Objective. To determine the prevalence of large-joint damage and the association with small-joint damage in patients with RA after 8 years of low DAS (≤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 and of the small joints using the Sharp/van der Heijde 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 one or more large joints 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 to one or more large joints (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 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 to hands and feet also have more damage to the large joints.

Key words: RA, joint damage, treatment.

Introduction

Radiographic damage in the small joints (hands and feet) occurs in most patients with 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]. Because 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 whether this is still the case now that disease activity-targeted treatment strategies and new (combinations of) anti-rheumatic drugs have been 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 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-joint erosiveness or joint space narrowing and whether it was influenced by the initial therapy.

Methods

Patients

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

Patients were randomized to one of four treatment strategies: (i) sequential monotherapy, (ii) step-up therapy, (iii) initial combination therapy with tapered high-dose prednisone or (iv) initial combination therapy including infliximab. Every 3 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 ≤ 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 of 347 patients who were still under follow-up. In 57 of 347 patients, radiographs were not made, mostly for logistical 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 10 patients refused.

Assessment of radiological damage

Radiographs of the shoulders, elbows, wrists, hips, knees and ankles were scored by an experienced musculoskeletal radiologist (H. K.) using the Larsen score (range 0–5/joint) [13]. Only joints showing specific signs of damage caused by RA inflammation or secondary OA, not primary OA, according to H. K. 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 intra-class 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 of ≥ 1 (at least one joint with damage ≥ 1 point). For the total Larsen score, all separate joint scores of patients who had no more than two 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 (L. D. and M. B.) 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 intra-class correlation coefficient was 0.96. Two thresholds of radiological damage progression of the small joints of the hands and feet were defined: an increase in SHS scores of ≥ 5 points (based on the smallest detectable change) or an increase of ≥ 15 points (the highest 20%) during the 8-year period.

Statistical analysis

Demographic and clinical baseline characteristics for patients with and without damage ≥ 1 point total Larsen score were compared. Differences were tested using the χ² test for categorical data and either the Student 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 analysed with a cluster analysis (TreeView, version 16) 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 during the 8-year period. For these analyses, the wrists were not included in the large-joint score (Larsen), 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 ≥ 5 points SHS and ≥ 15 points SHS. Estimates were adjusted for gender, treatment strategy, RF, ACPA or a combination of RF and ACPA and baseline age, ESR and SHS. In addition, multivariate logistic analyses were repeated for narrowing and erosions separately and simultaneously to determine whether 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 analyse 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, a mean ESR of 41 mm/h and a mean HAQ of 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 vs 58 years) and had a slightly lower DAS (4.3 vs 4.5) and HAQ (1.3 vs 1.5) and a higher median SHS (2.5 vs 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.
### Table 1 Baseline characteristics of 290 of 508 recent-onset RA patients in the BeSt study

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All patients (n = 290)</th>
<th>Patients without large-joint damage (n = 104)</th>
<th>Patients with large-joint damage (n = 186)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>52 (12)</td>
<td>48 (12)</td>
<td>54 (12)</td>
<td>-.001</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>195 (67)</td>
<td>69 (66)</td>
<td>126 (68)</td>
<td>.808</td>
</tr>
<tr>
<td>Symptom duration, median (IQR) weeks</td>
<td>23 (14–52)</td>
<td>22 (13–51)</td>
<td>24 (14–53)</td>
<td>.422</td>
</tr>
<tr>
<td>DAS, mean (s.d.)</td>
<td>4.3 (0.9)</td>
<td>4.4 (0.9)</td>
<td>4.3 (0.8)</td>
<td>.824</td>
</tr>
<tr>
<td>HAQ, mean (s.d.)</td>
<td>1.3 (0.6)</td>
<td>1.3 (0.6)</td>
<td>1.4 (0.7)</td>
<td>.258</td>
</tr>
<tr>
<td>BMI, mean (s.d.)</td>
<td>26 (4)</td>
<td>26 (4)</td>
<td>26 (4)</td>
<td>.740</td>
</tr>
<tr>
<td>ESR, mean (s.d.)</td>
<td>41 (27)</td>
<td>32 (14)</td>
<td>43 (29)</td>
<td>-.001</td>
</tr>
<tr>
<td>SHS, median (IQR)</td>
<td>2 (0–6)</td>
<td>1 (0–4)</td>
<td>3 (0–7)</td>
<td>-.001</td>
</tr>
<tr>
<td>Total Larsen score, median (IQR)</td>
<td>1 (0–2)</td>
<td>0 (0–0)</td>
<td>3 (1–5)</td>
<td>-.001</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>192 (67)</td>
<td>64 (62)</td>
<td>128 (69)</td>
<td>.209</td>
</tr>
<tr>
<td>ACPA positive, n (%)</td>
<td>173 (60)</td>
<td>54 (52)</td>
<td>119 (66)</td>
<td>.05</td>
</tr>
<tr>
<td>Smoking yes, n (%)</td>
<td>95 (33)</td>
<td>38 (37)</td>
<td>57 (31)</td>
<td>.279</td>
</tr>
<tr>
<td>Treatment strategy, n (%)</td>
<td>0.795</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential monotherapy</td>
<td>73 (25)</td>
<td>23 (22)</td>
<td>50 (27)</td>
<td></td>
</tr>
<tr>
<td>Step-up therapy</td>
<td>60 (21)</td>
<td>21 (20)</td>
<td>39 (21)</td>
<td></td>
</tr>
<tr>
<td>Initial combination with prednisone</td>
<td>70 (24)</td>
<td>28 (27)</td>
<td>42 (23)</td>
<td></td>
</tr>
<tr>
<td>Initial combination with infliximab</td>
<td>87 (30)</td>
<td>32 (31)</td>
<td>55 (30)</td>
<td></td>
</tr>
</tbody>
</table>

Patients were categorized with and without damage ≥ 1 point of the total Larsen score in the large joint.

Radiological damage in the large joints

Joint damage (≥ 1 point Larsen score) was observed in 64 of 532 (12%) shoulders, 51 of 538 (10%) elbows, 141 of 541 (26%) wrists, 67 of 521 (13%) hips, 95 of 528 (18%) knees and 39 of 544 (7%) ankles. Sixty-four per cent of the patients had damage in at least one large joint. Of the patients with damage, 31% had damage in only one joint, 24% in two joints, 13% in three joints and 32% in four or more joints (Fig. 1). Mean (s.d.) total Larsen score was 2.7 (3.7) and median (interquartile range) (IQR) total Larsen score was 1 (0–4). The cluster analysis identified clusters of bilateral damage in the wrists, 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 (Fig. 2).

Seven per cent of the patients (n = 21) had one or more joint prostheses: 2 elbows, 2 wrists, 15 hips, 14 knees and 1 ankle. 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 OA), in 12 cases because of secondary OA, in 4 cases for other reasons such as fracture or dysplasia and in 1 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 per cent of the 290 BeSt patients in this analysis had radiological damage (≥ 0.5 point) of the small joints after 8 years. Thirty-three per cent of the patients had progression of ≥ 5 points SHS and 19% had progression of ≥ 15 points SHS in 8 years. Mean (s.d.) damage progression was highest in the first year [2.7 (11)] and stabilized thereafter with a mean (s.d.) progression of 1.2 (4) SHS points per year in these patients. Patients with large-joint damage (total Larsen without wrists ≥ 1) had more small-joint damage progression per year than patients without large-joint damage (Fig. 3), but the difference was only significant in the first year of
treatment: mean (s.d.) SHS progression in patients with large-joint damage was 4 (13) and in patients without large-joint damage was 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 of \( \geq 5 \) points and of \( \geq 15 \) points SHS were both independently associated with damage of \( \geq 1 \) 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 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]. As 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, whereas in the BeSt cohort, radiographs of the wrists and not the tarsus were used. However, because 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 more patients in the BeSt cohort 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, as 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 Finnish Rheumatoid Arthritis Combination Therapy (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].
Radiological damage progression of the small joints is defined as ΔSHS in model 1, ≥ 5 points SHS in model 2 and ≥ 15 points SHS in model 3. Damage of the large joints is defined as ≥ 1 point in at least one large joint. Results are presented as ORs and their 95% CIs. Adjustments were made for gender, treatment strategy, RF/ACPA/combination of RF and ACPA, and baseline SHS, age and ESR.

In the first 2 years of FIN-RACo there were fewer treatment adjustments than in the first years of the BeSt study, resulting in a considerable difference in clinical response even 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, owing 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 because 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 also expected little damage in the large joints, resulting in a smaller or even absent association between small- and large-joint damage. However, in this DAS-targeted BeSt cohort we did find that total small-joint damage progression is associated with large-joint damage. Neither small-joint erosions nor small-joint space narrowing 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 because damage may also be caused by primary degenerative processes or OA, which may be found in a substantial number of older patients, or secondary OA due to causes other than RA [19, 20]. Experienced musculoskeletal radiologists, such as H. K., 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. Because 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 OA and not RA. It is likely that, in comparison with the older cohorts, patients in the BeSt cohort had joint replacement surgery in relatively fewer damaged joints, owing 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 were found, as 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 the small joints of the hands and feet. This implies that monitoring small-joint damage is sufficient to guide treatment decisions to also prevent large-joint damage and long-term disability.

**Rheumatology key messages**

- This is the first study describing large-joint damage in RA patients treated with a treat-to-target approach.
- In RA, continued treat-to-target treatment seems more important in damage suppression than initial treatment.
- With treat-to-target treatment, large- and small-joint damage are associated in RA patients.

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References


