# Chapter 4

## Rapid radiological progression in the first year of early RA is predictive of disability and joint damage progression during 8 years of follow-up: post hoc analyses from the BeSt study

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## ABSTRACT

**Objective** Several prediction models for rapid radiological progression (RRP) in the first year of RA have been designed to aid rheumatologists in their choice of initial treatment. We assessed the association between rapid radiological progression and disability and joint damage progression in 8 years.

**Methods** Patients from the BeSt cohort were used. RRP was defined as an increase of ≥5 points Sharp-van der Heijde Score (SHS) in year 1. Functional ability over 8 years, measured with the Health Assessment Questionnaire (HAQ), was compared for patients with and without RRP using linear mixed models. Joint damage progression from year 1-8 was compared using logistic regression analyses.

**Results** RRP was observed in 102/465 patients. Over 8 years, patients with RRP had worse functional ability: difference in HAQ score 0.21 (0.14 after adjustment for DAS over time). RRP was associated with joint damage progression ≥25 points SHS in year 1- 8: odds ratio 4.6.

**Conclusion** Rapid radiological progression in year 1 is a predictor of worse functional ability over 8 years, independent of baseline joint damage and disease activity. Patients with RRP have more joint damage progression in subsequent years. This makes RRP a relevant outcome to base the initial treatment decision on.

## INTRODUCTION

Minimizing joint damage (progression) to prevent disability is an important treatment goal of rheumatoid arthritis.[1] Several prediction models have been designed to identify patients at risk of rapid radiological progression in the first year of treatment (RRP), in order to individualize initial treatment strategies.[2,3] But is there clinical relevance in whether or not a patient has rapid radiological damage progression? To our knowledge, it has not been investigated whether RRP is associated with functional disability in subsequent years. Therefore we asked whether patients with RRP in year one, defined as an increase in Sharp-van der Heijde Score (SHS) of ≥5,[4] had worse functional ability in the first 8 years of treatment. Secondly we investigated whether RRP is a predictor of subsequent joint damage progression.



## METHODS

*Patients*

All patients with radiological data at baseline and after 1 year of treatment from the BeSt cohort were analyzed (465/508). Patients included in the BeSt study, a randomized controlled trial, were treated according to 4 treatment strategies, aimed at a disease activity score (DAS) ≤2.4. Initial therapy was sequential or step-up monotherapy (starting with methotrexate) or combination therapy with prednisolone or with infliximab. If the DAS was ≤2.4 for ≥6 months, medication was tapered to monotherapy. Details of the BeSt study were published previously.[5]

*Study endpoints*

To evaluate radiological progression, the Sharp-van der Heijde score was used. Radiographs from baseline and year 1 were scored by two readers, blinded for patient identity and time order. The average progression score of these readers was used to classify patients as with RRP (change in SHS ≥5) or without (change <5). This threshold is similar to the smallest detectable difference (SDD) of the first study year.[5] Radiological progression from year 0-8 was assessed by two other readers according to the same method, using radiographs of years 0-1-2-3-4-5-6-7-8. The inter-observer intraclass correlation coefficient was 0.96. Functional ability and disease activity were measured every 3 months using the Health Assessment Questionnaire (HAQ) and DAS respectively.

*Statistical analysis*

The HAQ score over 8 years was compared for patients with and without RRP using linear mixed models, to incorporate missing patient data, with a Toeplitz covariance structure.

The estimate was adjusted for treatment group, baseline ESR, HAQ, SHS and the presence of rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) or both. To assess the contribution of disease activity to functional ability over time, the analysis was repeated adjusted for these variables and for DAS over time. The mean HAQ over time was calculated using these models and depicted in a graph. Because the definition of RRP was relatively arbitrary, we investigated if patients with even more progression in year 1 would also show more disability. We divided all patients into deciles of SHS change in year 1. The lowest score of the 9$^{th}$ and 10$^{th}$ decile were 5.5 and 9.5 respectively. We used data driven cut-offs to avoid multiple testing. HAQ over time was compared for patients with a progression score of <5.5 or ≥5.5 and for patients with a progression score of <9.5 or ≥9.5, using linear mixed models as described above. To compare disease activity over time for patients with and without RRP, linear mixed models with a Toeplitz covariance structure were used. The analysis was adjusted for treatment group, baseline DAS, SHS and RF, ACPA or RF and ACPA. Adding age and gender to this model or the models with HAQ did not change the results, nor did adding an interaction term between RRP and treatment group.

Joint damage progression from year 1-8 was compared for patients with and without RRP using the Mann-Whitney U test. Logistic regression analyses were then used to compare risk of damage progression of ≥5 (SDD) and ≥25 points (progression in the 10% of patients with highest progression scores in years 1-8), adjusted for treatment group, baseline ESR and SHS and RF/ACPA or RF and ACPA.

## RESULTS

RRP was observed in 102/465 (22%) patients. Patients with RRP were more often ACPA and RF positive and treated with initial monotherapy. Patients with RRP had a higher baseline ESR (54 versus 37 mm/hr, p-value <0.001) and CRP (60 versus 31, p-value <0.001). They had worse functional ability (HAQ 1.5, versus 1.4, p-value 0.04) and more radiological damage: median baseline SHS 5.8 versus 1.5, p-value <0.001.(*table 1*) The number of treatment steps patients had failed on and the number of patients failed on all protocol steps after 8 years was higher in patients with RRP, p-values 0.001 and <0.001. At year 8, 133/465 patients were lost to follow-up: 29% of patients without RRP, 27% of patients with RRP, p=0.6. Differences in baseline characteristics for patients without and with radiological progression ≥9.5 in year 1 were comparable to these results.(*table S1*)

### *Functional ability*

Over 8 years, there was a statistically significant difference (0.21 (95% CI 0.10;0.33)) in HAQ score for patients with and without RRP.(*figure 1*) For groups 1 and 2 the difference was 0.20

**Table 1:** baseline characteristics of patients with and without RRP after 1 year of DAS-targeted treatment

| | Without RRP (n=363) | With RRP (n=102) | p-value |
|---|---|---|---|
| Female gender, % | 67 | 72 | 0.3 |
| Age | 54 (13) | 55 (13) | 0.5 |
| Symptom dur., wks, median (IQR) | 24 (14-52) | 24 (14-58) | 0.5 |
| ACPA pos, % | 57 | 77 | <0.001 |
| RF pos, % | 60 | 82 | <0.001 |
| Smoker, % | 35 | 36 | 0.9 |
| Initial treatment, % | | | <0.001 |
| Sequential monotherapy | 20 | 40 | |
| Step-up monotherapy | 21 | 33 | |
| Combination with pred | 29 | 16 | |
| Combination with ifx | 31 | 11 | |
| BMI | 26 (4) | 26 (4) | 0.9 |
| DAS | 4.4 (0.8) | 4.5 (0.9) | 0.07 |
| ESR | 37 (24) | 54 (33) | <0.001 |
| CRP | 31 (37) | 60 (56) | <0.001 |
| HAQ | 1.4 (0.7) | 1.5 (0.7) | 0.04 |
| SHS, median (IQR) | 1.5 (0.0-4.0) | 5.8 (2.0-11.5) | <0.001 |
| Treatment steps failed on, median (IQR) | 1 (1-3) | 3 (1-5) | 0.001 |

*ACPA* anti-citrullinated protein antibodies, *RF* rheumatoid factor, *BMI* body mass index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HAQ* health assessment questionnaire score, *SHS* Sharp-van der Heijde Score
Data are presented as mean (SD), unless stated otherwise

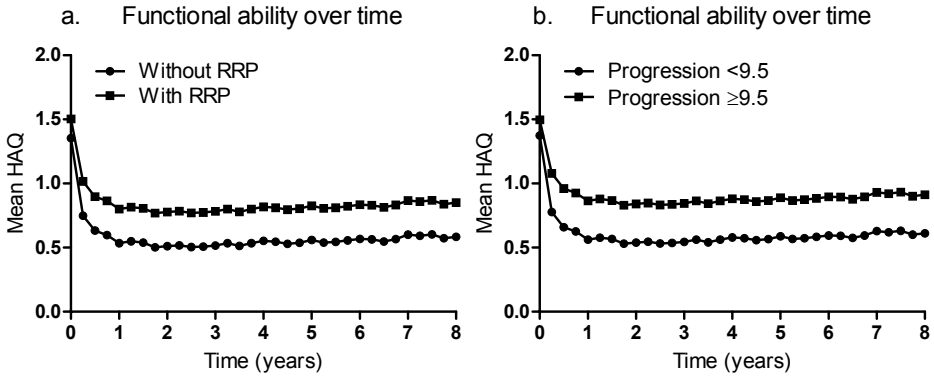


**Figure 1:** Mean Health Assessment Questionnaire score (HAQ) over 8 years for patients with and without rapid radiological progression SHS ≥5 in year 1 (RRP) (a) and for patients with progression <9.5 or ≥9.5 points in year 1 (b)
Adjusted for baseline HAQ, treatment strategy, baseline ESR and Sharp-van der Heijde Score and presence of RF and/or ACPA (using linear mixed models, which take into account missing patient data)

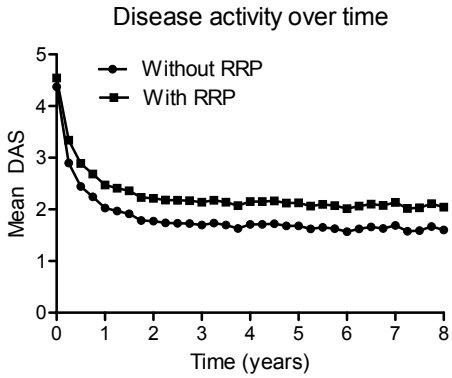


**Figure S1:** Disease activity over time for patients with and without rapid radiological progression in year 1, mean estimated values from linear mixed models

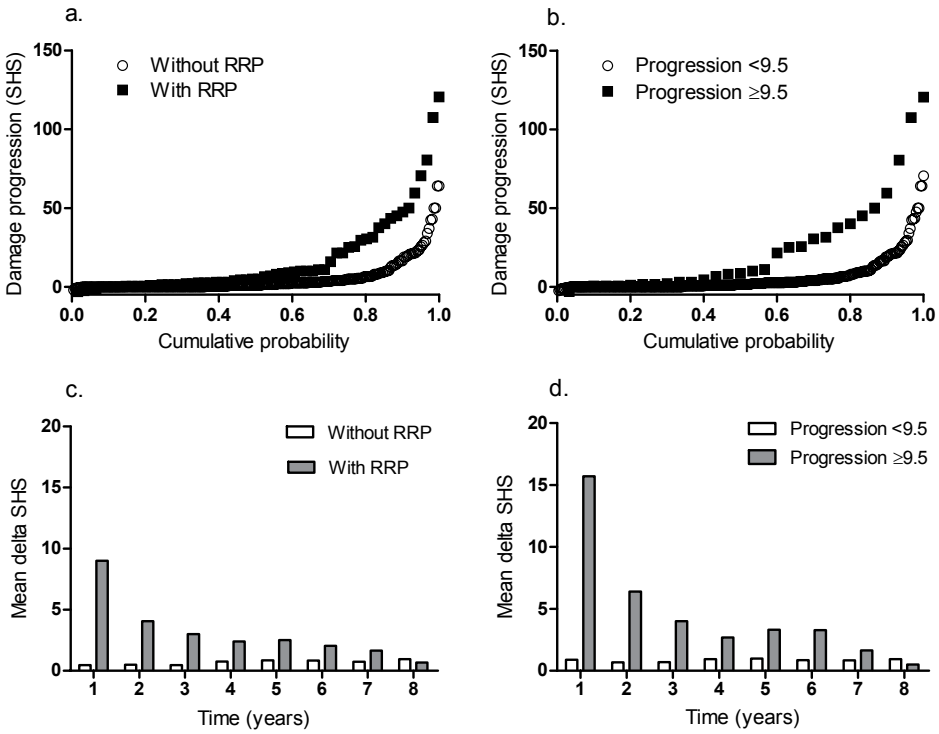


**Figure 2:** Joint damage progression in year 1-8 and yearly joint damage progression over time for patients with and without rapid radiological progression SHS ≥5 in year 1 (RRP) (a and c), and for patients with <9.5 or ≥9.5 points progression in year 1 (b and d)
n (no RRP/RRP) yr 1: 363/102, yr 2: 326/85, yr 3: 305/81, yr 4: 296/82, yr 5: 272/78, yr 6: 236/64, yr 7: 221/61, yr 8: 216/61

**Table S1:** a comparison of baseline characteristics for patients with <9.5 and ≥9.5 points (SHS) damage progression in the first year of treatment

| | <9.5 points progression (n=421) | ≥9.5 points progression (n=44) | p-value |
|---|---|---|---|
| Female gender, % | 68 | 66 | 0.8 |
| Age, mean (SD) | 54 (13) | 54 (13) | 0.7 |
| Symptom duration, wks, median (IQR) | 24 (14-51) | 23 (13-71) | 0.4 |
| ACPA pos, % | 59 | 84 | 0.001 |
| RF pos, % | 62 | 86 | 0.001 |
| Smoker, % | 34 | 46 | 0.2 |
| Initial treatment, % | | | <0.001 |
| Sequential monotherapy | 22 | 48 | |
| Step-up monotherapy | 24 | 30 | |
| Combination with pred | 27 | 14 | |
| Combination with ifx | 28 | 9 | |
| BMI, mean (SD) | 26 (4) | 25 (4) | 0.2 |
| DAS, mean (SD) | 4.4 (0.9) | 4.6 (0.8) | 0.1 |
| ESR, mean (SD) | 38 (25) | 66 (37) | <0.001 |
| CRP, mean (SD) | 35 (14) | 66 (51) | <0.001 |
| HAQ, mean (SD) | 1.4 (0.5) | 1.5 (0.7) | 0.4 |
| SHS, median (IQR) | 2.0 (0.0-6.0) | 5.8 (1.3-10.9) | 0.003 |

*ACPA* anti-citrullinated protein antibodies, *RF* rheumatoid factor, *BMI* body mass index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HAQ* health assessment questionnaire score, *SHS* Sharp-van der Heijde Score
Data are presented as mean (SD), unless stated otherwise

(95% CI 0.05;0.34), for groups 3 and 4: 0.27 (95% CI 0.08;0.45). DAS over time in RRP patients was also higher than in non-RRP patients: difference 0.33 (95% CI 0.18;0.48).(*figure S1*) After adjustment for DAS over time, the difference in HAQ score was statistically, but not clinically significant: 0.14 (95% CI 0.05;0.24). The difference in HAQ score between the 10% of patients with the highest progression score in year 1 and the other 90% was 0.27 (95% CI 0.12;0.41), 0.20 (95% CI 0.08;0.33) after adjustment for DAS over time. The difference in HAQ score for patients with and without damage progression ≥5.5 (top 20% of progression scores versus the other 80%) was 0.15 (95% CI 0.06;0.25) after adjustment for DAS over time.

*Joint damage*

Patients with RRP in year 1 had more joint damage progression in year 1-8,(*figure 2*) with a median progression score of 5.0 (IQR 1.5-25.3) compared to 1.0 (IQR 0.0-5.0) for patients without RRP (p<0.001). The OR of ≥5 points progression was 2.0 (95% CI 0.96;4.2). Patients with RRP had an increased risk of damage progression ≥25 in year 1-8: OR of 4.6 (95% CI 1.6;12.7). Of the patients without RRP, 5% had more than 25 units progression in years 1-8. The mean yearly progression score was never higher than the SDD (5) in either group.

When comparing the 10% of patients with the highest progression score in year 1 to the other 90% (cut-off 9.5), similar results were seen for progression ≥5 in year 1-8: OR 1.8 (95% CI 0.7;4.5). The risk of being in the top 10% of progression scores again in years 1-8 (progression ≥25) was higher: OR 6.6 (95% CI 2.2;19.8). The median progression score in year 1 in these patients was 15.5 points SHS (IQR 12.5-22.0).

## DISCUSSION

Rapid radiological progression, defined as an increase of ≥5 points in Sharp-van der Heijde score in the first year of treatment, is associated with worse functional ability in later years and more radiological damage progression. This can only be partly explained by higher disease activity in these patients. Our results show that rapid radiological progression is a clinically relevant outcome to be used in prediction models that can help choose the best initial treatment for patients with newly diagnosed RA.

The impact of rapid radiological progression with this threshold on functional ability is relatively small. Based on an estimated minimally important difference (MID) of the HAQ score of 0.20-0.24,[6] the statistically significant difference in HAQ over 8 years explained by RRP, not disease activity, was not clinically relevant. Probably this is because the follow-up period of 8 years is still short. More importantly, after the first 1-2 years yearly damage progression in all patients is much lower and shows a tendency to decrease with time.(*figures 2c and 2d*) This is most likely due to the continuous three-monthly DAS ≤2.4 steered treatment adjustments in the BeSt cohort, resulting in low disease activity in the vast majority of patients. Still, yearly progression in patients with RRP continues to be higher than in patients without RRP, who hardly progress at all. We found that patients with RRP have an increased risk of subsequent joint damage progression. Combined with the effect of ageing,[7] after a longer follow-up period, this continuous damage progression may lead to significantly more functional disability. Our results also show that the 10% of patients who had an increase of ≥9.5 points SHS in the first year have even worse functional ability after 8 years. We found a clinically meaningful difference in mean HAQ score between these 10% and the other patients after adjustment for disease activity over time.

In conclusion, rapid radiological progression in the first year of treatment is an independent predictor of later functional disability and thus not only a radiologically but also a clinically relevant early outcome to base the initial choice of treatment on. This may mean that, as earlier studies have shown[2,3], patients with a low risk of RRP require less intensive initial therapy to prevent radiological damage progression than patients with a high risk, provided that this therapy offers early symptom relief and provided treatment remains 'treat to target'.

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