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## Disease flares in rheumatoid arthritis are associated with joint damage progression and disability: 10 year results from the BeSt study

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## ABSTRACT

### Objective

Flares in patients with rheumatoid arthritis (RA) are suggested to sometimes spontaneously resolve. Then, targeted therapy could entail possible overtreatment. We aimed to determine the flare prevalence in patients who are treated-to-target and to evaluate associations between flares and patient-reported outcomes and radiographic progression.

### Methods

508 patients in the BeSt study were treated-to-target during ten years. After initial treatment adjustments to achieve disease activity score (DAS)  $\leq 2.4$ , a flare was defined from the second year of follow-up onwards, according to three definitions. The first definition is a DAS  $> 2.4$  with an increase of  $\geq 0.6$  regardless of the previous DAS. The other definitions will be described in the manuscript.

### Results

The flare prevalence was 4 – 11% per visit. 67% of the patients experienced  $\geq 1$  flare during 9 years of treatment (median 0 per patient per year). During a flare, functional ability decreased with a mean difference of 0.25 in health assessment questionnaire (HAQ) ( $p < 0.001$ ), and the odds ratios (95% CI) for an increase in patients' assessment of disease activity, pain and morning stiffness of  $\geq 20$  mm on a visual analogue scale were 8.5 (7.3 – 9.8), 8.4 (7.2 – 9.7) and 5.6 (4.8 – 6.6), respectively, compared to the absence of a flare. The odds ratio for radiographic progression was 1.7 (95% CI 1.1 – 2.8) in a year with a flare compared to a year without a flare. The more flares a patient experienced, the higher the HAQ at year 10 ( $p < 0.001$ ) and the more radiographic progression from baseline to year 10 ( $p = 0.005$ ).

### Conclusions

Flares were associated with concurrent increase in patient's assessment of disease activity, pain and morning stiffness, functional deterioration and development of radiographic progression with a dose-response-effect, both during the flare and long-term. This suggests that intensifying treatment during a flare outweighs the risk of possible overtreatment.

## INTRODUCTION

Despite current effective treatment of patients with rheumatoid arthritis (RA), episodes of increased disease activity still may occur.<sup>1,2</sup> These episodes are generally referred to as 'flares'. What constitutes a flare can be a matter for debate. This partly hinges to the fact that patients may experience a flare which for logistic or other reasons cannot be registered as an increase in disease activity. Therefore the notion of a flare is challenging.<sup>1-3</sup> It is generally understood, though, that flares are associated with concurrent deterioration of patient-reported outcomes. When the increase in disease activity is registered, flares are often managed with treatment intensification.<sup>3-6</sup> Following a treat-to-target strategy, treatment should be adjusted when a predefined target has not been achieved or maintained. It has proven to be effective in trials,<sup>7,8</sup> and is under the concept of 'tight control' also adopted in the recommendations for daily practice.<sup>9,10</sup> However, flares may also spontaneously resolve. In that case, targeted therapy entails the possibility of overtreatment.

In the BeSt study, treatment was targeted at low disease activity (DAS  $\leq 2.4$ , using the original disease activity score based on a 53/44 joints assessment), with three-monthly DAS measurements during ten years. In this post hoc-analysis, we aimed to examine the prevalence of flares defined by increases in disease activity, and to determine the short-term and long-term effects of these flares on radiographic progression, function and patient-reported outcomes.

## PATIENTS AND METHODS

### Study design

The multicenter, clinical trial BeSt (Dutch acronym for treatment strategies) with ten year follow-up enrolled 508 patients with recent-onset, active RA according to the 1987 criteria.<sup>11</sup> Treatment adjustments were made based on three-monthly DAS measurements, targeted at low disease activity (DAS  $\leq 2.4$ ). If DAS was  $>2.4$ , medication was intensified. As long as the DAS was  $\leq 2.4$  (for at least six months), combination therapy was tapered to monotherapy (usually methotrexate monotherapy), and then monotherapy was tapered to a maintenance dose. When DAS was  $<1.6$  for at least six months during a maintenance dose, medication was discontinued, but as soon as DAS increased to  $>1.6$ , the last effective medication was restarted and when DAS increased to  $>2.4$ , treatment was further intensified. The study protocol was approved by the medical ethics committees of all participating centers and all patients gave written informed consent. More details on the BeSt study protocol were previously published.<sup>12</sup>

### Study end points

During year 1, initial treatment adjustments were made to achieve the target of low disease activity in most patients. From the second year on, the presence or absence of a flare was

defined per visit. No unambiguous definition of a flare is yet established, but recently, a flare definition based on the DAS28 was validated.<sup>5</sup> From this definition, we derived three definition of flare based on the 44-joint DAS. Our definitions are partially overlap, but were always tested separately. 'Flare A' was defined as DAS >2.4, with an increase in DAS of at least 0.6 from a previous DAS of any value. A 'minor flare B' was defined as DAS >2.4, from a previous DAS  $\leq$ 2.4 with an increase of DAS of <0.6, and a 'major flare B' as DAS >2.4 from a previous DAS  $\leq$ 2.4 with an increase in DAS of  $\geq$ 0.6.

The cut-off for DAS of 2.4 was chosen based on the target of the BeSt study. The cut-off for difference in DAS of 0.6 was based on the European League Against Rheumatism (EULAR) criteria, where a decrease of >0.6 in DAS is stated as (clinically relevant) response.<sup>13</sup> Consequently, we classified  $\geq$ 0.6 increase in DAS as a (clinically relevant) deterioration. It is unknown whether we should take into account the absolute value of the previous DAS (thus, not only the change in DAS) when defining a flare. Therefore, flare A and major flare B were distinguished.

Functional ability was measured three-monthly using the health assessment questionnaire (HAQ, range 0 – 3).<sup>14</sup> An improvement of 0.22 in HAQ is considered to represent a clinically relevant improvement.<sup>15</sup> Hence an increase of 0.22 was considered to be a clinically relevant deterioration. At every visit, patients filled in several visual analogue scales (VAS, range 0 – 100 millimeter, mm), assessing general health (VASgh), disease activity (VASda), pain (VASpain) and morning stiffness (VASms). As VASgh is part of the DAS calculation,<sup>16</sup> this score was not used for further analysis. A clinically relevant cut-off for an increase in VAS of at least 20 mm difference, as proposed by Khan *et al*,<sup>17</sup> was used to test whether patients during a flare report higher VAS scores than in situations without a flare.

Joint damage progression was assessed on radiographs of hands and feet using the Sharp/van der Heijde score (SHS, range 0 – 448).<sup>18</sup> Radiographs were obtained yearly and were scored in one session, in random order, by two blinded readers. Radiographic progression was defined as an increase in SHS of >0.5 during a year.

During the trial, treatment adjustments were registered in a separate 'monitoring database'. Due to different formats the 'general' and 'monitoring databases' cannot be readily connected for analysis. Therefore, three samples of 100 patients who experienced a flare A, minor flare B and major flare B, were randomly selected and for these patients data from both databases were manually combined to explore the relationship between occurrences of flares and previous and subsequent treatment adjustments.

## Statistical analysis

Descriptive statistics were used to determine the frequency of flares.

All analyses were performed separately for the several definitions of flare. Patients with flare A were compared to patients without flare A; patients with major flare B were compared to patients with minor flare B and patients with no flare B. Associations between flares and functional ability, joint damage and VAS were tested using mixed models, a robust method since it takes into account all patients and can also handle missing data not completely

at random. HAQ was compared over time between patients with and without a flare per visit, with a linear mixed model (LMM). Flare, time and its interaction term were entered as determinants. A Toeplitz covariance matrix was used, because this best fitted the data based on the log likelihood ratio test.

To evaluate long-term and dose-response effects of the occurrence of a flare, patients were categorized according to the number of flares experienced during follow-up (none, 1, 2, or  $\geq 3$  flares for each definition of flare). Mean HAQ during follow-up was compared between the categories, as well as the HAQ at year 10 (based on a completers analysis). A Kruskal-Wallis test was performed because of a non-Gaussian distribution of the outcome variables. Cumulative probability plots for mean HAQ during year 2 to 10 and radiographic progression over 10 years were created to visualize the differences between these categories.

For each VAS type, the difference between two subsequent scores was calculated. Percentages of patients with an increase of  $\geq 20$  mm between two subsequent visits were reported.<sup>17</sup> A generalized linear mixed model (GLMM) was used to calculate the odds ratio for an increase of  $\geq 20$  mm in VAS score (from the preceding visit) during a flare. Flare and time were entered as determinants. Separate GLMM were performed for an increase of  $\geq 20$  mm (yes/no) in VASda, VASpain and VASms as outcomes. Covariance matrices were chosen based on their fit to the data, resulting in the Toeplitz covariance matrix for VASda and the Identity covariance matrix for VASpain and VASms.

SHS progression was evaluated yearly. In every patient, for every year the occurrence of a flare was checked. We tested whether the occurrence of a flare was associated with radiographic progression (defined as an increase in SHS  $>0.5$  during that year, yes/no). A GLMM with an Identity covariance matrix was used. Flare, time and its interaction term were again entered as determinants. To compare SHS progression over ten years in patients who ever had a flare with those who never experienced a flare, a Kruskal-Wallis test was used (based on a completers analysis). Also, radiographic progression was compared between the categories based on the numbers of flares per patient (none, 1, 2,  $\geq 3$  flares).

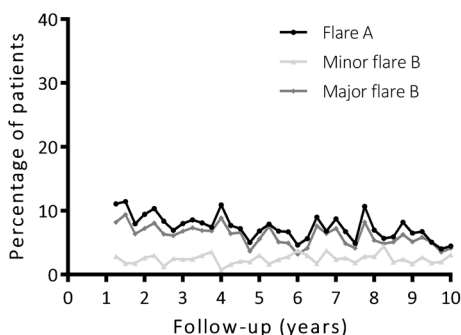
## RESULTS

### Frequency of flares

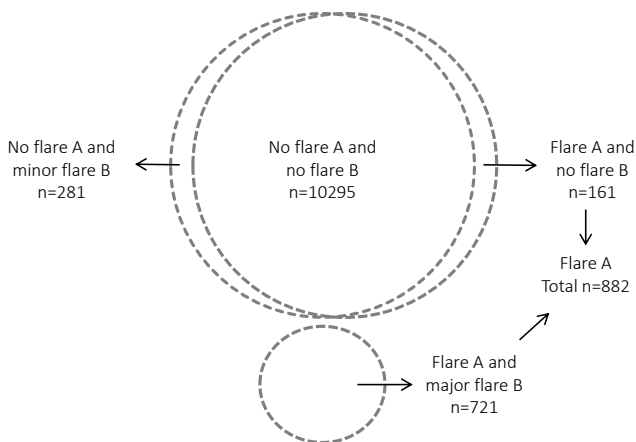
In 480 patients sufficient follow-up data were available to define presence or absence of a flare during at least one visit. At baseline, patients had active disease with a mean (SD) DAS of 4.4 (0.9) and a mean (SD) HAQ of 1.4 (0.7). During the first year of follow-up, disease activity was increasingly suppressed. At the first visit during year 2, patients had a mean (SD) DAS of 2.0 (1.0), a HAQ of 0.6 (0.6), and 320/480 patients (67%) had achieved a DAS  $\leq 2.4$ .

During year 2 to 10, the majority of patients experienced one or more flares. The prevalence of flares in accomplished study visits decreased over time, for all three definitions (Figure 1). We found a prevalence of flare A of 4 – 11% per visit over time. Comparable frequencies were found for major flare B (prevalence 4 – 9%) and a minor flare B occurred less often

(prevalence 1 – 6%). Flare A occurred at least once in 321/480 patients (67%). A minor flare B ever occurred in 159/480 patients (33%) and a major flare B in 304/480 patients (63%). In patients who experienced at least one flare A, the median (IQR) number of flares during follow-up was 2 (1 – 4). For a minor flare B, this was 0 (0 – 1) and for major flare B 2 (1 – 3). When evaluating the percentage of patients who ever achieved remission or low disease activity during total follow-up, comparable percentages were found in patients ever having a flare and patients never having a flare (regardless of definition of flare, data not shown).



**Figure 1.** Percentage of patients with a flare per performed visit over time. Flare A: from any DAS to DAS >2.4 with an increase in DAS of  $\geq 0.6$ ; Minor flare B: from DAS  $\leq 2.4$  to DAS >2.4 with an increase in DAS of  $< 0.6$ ; Major flare B: from DAS  $\leq 2.4$  to DAS >2.4 with an increase in DAS of  $\geq 0.6$ . Note: flares are defined from year 2 to year 10.



**Figure 2.** Total number of flares during year 2 to year 10 in all patients (n=480), according to the following definitions; Flare A (n=882/11458): from any DAS to DAS >2.4 with an increase in DAS of  $\geq 0.6$ ; Minor flare B (n=281/11458): from DAS  $\leq 2.4$  to DAS >2.4 with an increase in DAS of  $< 0.6$ ; Major flare B (n=721/11458): from DAS  $\leq 2.4$  to DAS >2.4 with an increase in DAS of  $\geq 0.6$ . It indicates the concordance and discordance between the definitions of flare. Note: More than one flare according to the same definition or according to another definition can occur in the same patient.

Table 1 shows the number of patients that experienced none, 1, 2 and  $\geq 3$  flares during follow-up according to all definitions. The circles in Figure 2 represent the total of visits in which presence or absence of flares was defined, indicating the concordance and discordance between the definitions.

### **Treatment**

Exploration of three samples of 100 random selected patients with flare A, minor flare B and major B, demonstrated that only approximately 25% of flares were preceded by medication tapering. Although the study protocol dictated to change medication or to increase the dose in case of  $\text{DAS} > 2.4$ , this was done only in  $\pm 60\%$  of flares. In particular, in 11% of cases of a minor flare B, rheumatologists scheduled an extra visit one month later, hoping to find that the flare had resolved spontaneously. This indeed occurred in 73% of those situations. At the next evaluation following a flare, a  $\text{DAS} \leq 2.4$  was achieved again in 60% of patients. According to our definition of flare, the remaining 40% of patients could have a flare A at this evaluation, not a flare B (as this definition required a previous  $\text{DAS}$  of  $\leq 2.4$ ).

### **Functional ability**

The mean (SD) HAQ in patients at a visit with a flare A was 1.04 (0.63), and in patients at a visit with no flare A 0.53 (0.56). Patients with a minor flare B and a major flare B had a mean (SD) HAQ of 0.85 (0.55) and 0.96 (0.60), respectively, compared to 0.53 (0.57) for patients with no flare B. Following the linear mixed models, compared to the absence of a flare, a flare A was associated with an increase in HAQ of 0.251 ( $p < 0.001$ ). Compared to the absence of a flare, a minor flare B was associated with an increase in HAQ of 0.059 ( $p = 0.001$ ), while a major flare B was accompanied by an increase in HAQ of 0.226 ( $p < 0.001$ ). The difference in functional ability at the time of a minor flare compared to a major flare was small (mean difference in HAQ 0.167,  $p < 0.001$ ).

The more flares a patient experienced over time, the higher the mean HAQ over time and the HAQ at year 10 (Table 1 and Figure 3).

### **Visual analogue scales**

Increases in each type of VAS were higher in patients with a flare than in patients without a flare, regardless of definition (Table 2). The odds ratios for an increase in VAS of  $\geq 20$  mm during a flare are reported in Table 2.

### **Joint damage progression**

Over ten years, SHS progression in completers was lowest in patients without any flare during follow-up, and increased with the number of flares A and major flares B (Table 1 and Figure 4). Proportions of patients without any radiographic progression can be derived from Figure 4.



**Table 1.** Dose-response effect of the number of flares on functional ability and radiographic progression.

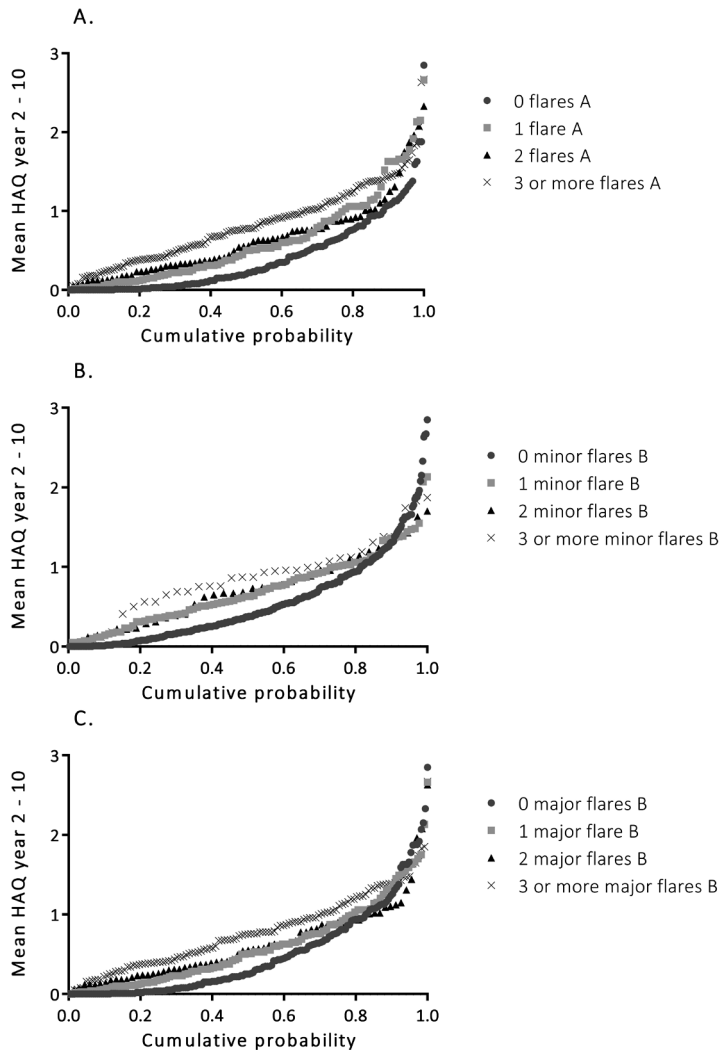
	Frequency, n (%) patients Total n=480	HAQ year 2 – year 10 median (IQR)	HAQ at year 10 median (IQR)	SHS progression baseline – year 10 median (IQR)
<b>No. of flare A</b>				
0	159 (33)	0.2 (0.0 – 0.6)	0.0 (0.0 – 0.5)	1.3 (0.0 – 3.1)
1	100 (21)	0.5 (0.2 – 0.9)	0.4 (0.0 – 0.9)	2.3 (0.5 – 9.6)
2	73 (15)	0.6 (0.3 – 0.9)	0.6 (0.1 – 0.9)	3.0 (0.0 – 10.0)
≥3	148 (31)	0.8 (0.4 – 1.1)	0.8 (0.4 – 1.3)	4.3 (0.5 – 20.1)
p value		<0.001	<0.001	0.005
<b>No. of minor flare B</b>				
0	321 (67)	0.4 (0.1 – 0.8)	0.3 (0.0 – 0.9)	2.0 (0.0 – 6.9)
1	89 (19)	0.6 (0.4 – 1.0)	0.6 (0.3 – 1.0)	6.0 (0.5 – 26.0)
2	37 (8)	0.7 (0.3 – 1.1)	0.8 (0.3 – 1.1)	4.5 (0.1 – 26.8)
≥3	33 (7)	0.9 (0.6 – 1.1)	0.8 (0.4 – 1.3)	1.0 (0.0 – 13.5)
p value		<0.001	<0.001	0.026
<b>No. of major flare B</b>				
0	176 (37)	0.3 (0.0 – 0.8)	0.0 (0.0 – 0.8)	1.5 (0.0 – 3.5)
1	114 (24)	0.5 (0.2 – 0.9)	0.4 (0.0 – 0.9)	2.0 (0.5 – 10.3)
2	68 (14)	0.6 (0.3 – 0.9)	0.6 (0.1 – 0.9)	3.5 (0.5 – 17.0)
≥3	122 (25)	0.8 (0.4 – 1.1)	0.8 (0.3 – 1.1)	4.5 (0.3 – 17.3)
p value		<0.001	<0.001	0.009

Note: Due to drop out, not all patients had a HAQ at year 10 available, or a SHS progression score from baseline to year 10.

IQR, interquartile range; No., number; HAQ, health assessment questionnaire; SHS, Sharp/ van der Heijde score.

'Flare A' defined as DAS >2.4, with an increase in DAS of at least 0.6 from a previous DAS of any value. 'Minor flare B' defined as DAS >2.4, from a previous DAS ≤2.4 with an increase of DAS of <0.6. 'Major flare B' defined as DAS >2.4 from a previous DAS ≤2.4 with an increase in DAS of ≥0.6.

Over time, during a year where a flare A occurred, the adjusted OR of developing SHS progression was 1.74 (95% CI 1.07 – 2.85,  $p=0.027$ ), compared to no flare A as reference category. Patients with a minor flare B had an adjusted OR of 2.11 (95% CI 0.87 – 5.13,  $p=0.101$ ) to develop SHS progression and patients with a major flare B had an adjusted OR of 1.72 (95% CI 1.01 – 2.91,  $p=0.044$ ), both compared to the absence of a flare B.



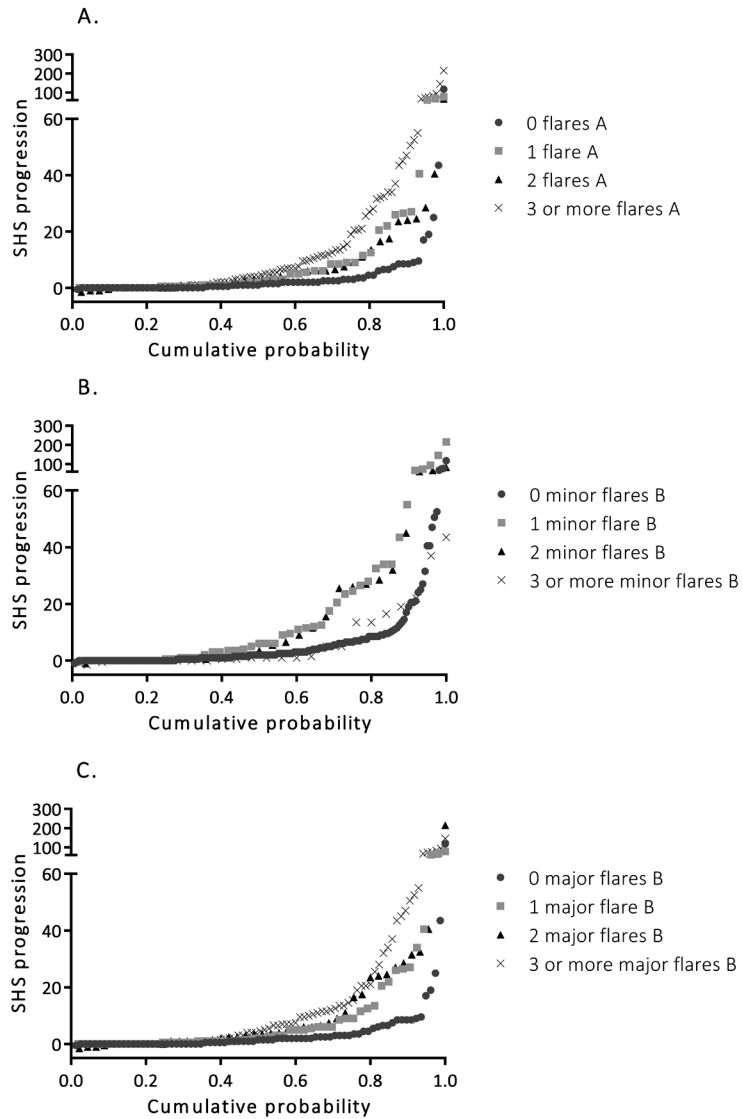
**Figure 3.** Cumulative probability plots of the mean functional ability (measured with the health assessment questionnaire, HAQ) during year 2 to year 10 of follow-up, stratified for definition and number of flares. (A) According to the definition of flare A (DAS >2.4, with an increase in DAS of at least 0.6 from a previous DAS of any value), (B) According to the definition of minor flare B (DAS >2.4, from a previous DAS ≤2.4 with an increase of DAS of <0.6), (C) According to the definition of major flare B (DAS >2.4 from a previous DAS ≤2.4 with an increase in DAS of ≥0.6). HAQ, health assessment questionnaire.

**Table 2.** Changes in patient's assessments of disease activity, pain and morning stiffness and odds ratios for an increase of at least 20 millimeter in visual analogue scales for these outcomes during the presence of a flare, compared to the absence of a flare (reference category).

	Change in VASda			Change in VASpain			Change in VASms		
	Median	IQR	IQR	Median	IQR	IQR	Median	IQR	IQR
No flare A	0	-8 - 5	-8 - 5	0	-8 - 5	-8 - 5	0	-8 - 6	-8 - 6
Flare A	17	3 - 40	3 - 40	17	3 - 35	3 - 35	11	0 - 29	0 - 29
No flare B	0	-8 - 5	-8 - 5	0	-8 - 5	-8 - 5	0	8 - 6	8 - 6
Minor flare B	7	-4 - 20	-4 - 20	5	-4 - 18	-4 - 18	5	-5 - 16	-5 - 16
Major flare B	18	4 - 41	4 - 41	18	3 - 37	3 - 37	12	0 - 31	0 - 31
Increase in VASda*									
	OR*	95% CI	95% CI	OR*	95% CI	95% CI	OR*	95% CI	95% CI
No flare A	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Flare A	8.47	7.30 - 9.83	7.30 - 9.83	8.35	7.20 - 9.69	7.20 - 9.69	5.63	4.84 - 6.55	4.84 - 6.55
No flare B	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Minor flare B	3.10	2.35 - 4.07	2.35 - 4.07	2.84	2.15 - 3.75	2.15 - 3.75	2.32	1.73 - 3.12	1.73 - 3.12
Major flare B	8.76	7.46 - 10.28	7.46 - 10.28	8.59	7.32 - 10.08	7.32 - 10.08	5.90	5.01 - 6.94	5.01 - 6.94

\*Increase of  $\geq 20$  millimeter from the previous VAS, \*Adjusted for time.

95% CI, 95% confidence interval; OR, odds ratio; *ref*, reference category; VASda, visual analogue scale of disease activity; VASpain, visual analogue scale of pain; VASms, visual analogue scale of morning stiffness.



**Figure 4.** Cumulative probability plots of radiographic progression (measured with the Sharp/ van der Heijde score, SHS) during 10 year follow-up, stratified for definition and number of flares. (A) According to the definition of flare A (DAS >2.4, with an increase in DAS of at least 0.6 from a previous DAS of any value), (B) According to the definition of minor flare B (DAS >2.4, from a previous DAS ≤2.4 with an increase of DAS of <0.6), (C) According to the definition of major flare B (DAS >2.4 from a previous DAS ≤2.4 with an increase in DAS of ≥0.6). SHS, Sharp/ van der Heijde score.

## DISCUSSION

In this post hoc-analysis of the BeSt study, we determined the short-term and long-term effects of flares defined using the original disease activity score. During a flare, functional ability decreased and patients reported higher VAS for disease activity, pain and morning stiffness. In addition, joint damage progression occurred more often when a patient experienced a flare during that year. Long-term assessments showed a higher loss of functional ability and more radiographic progression in patients who had suffered a flare, and there was a dose-response relation with the number of flares over time.

The definition of a flare in RA is still in development.<sup>1-3</sup> There may be transient periods of symptoms for which patients don't contact their rheumatologist. It is however determined that flares involve a deterioration of patient-reported outcomes, such as functional ability and VAS of general health, pain and morning stiffness.<sup>4,6</sup> It has also been suggested that the 28-joint DAS is a useful instrument to define flares,<sup>5</sup> and that registration of a flare should be followed by treatment intensification.<sup>3-6</sup> However, treatment intensification for a flare that may spontaneously resolve might constitute overtreatment. Therefore we monitored short- and long-term disease outcomes in relation to the occurrence of flares in the BeSt study.

We formulated three definitions of a disease flare based on the original DAS as obtained in the BeSt study. Over ten years, besides the DAS measurements, functional ability was assessed three-monthly using the health assessment questionnaire and patient's assessments of pain, disease activity and morning stiffness on a VAS were registered. Comparable prevalence of flare A and major flare B were found, as a result of overlapping definitions (Figure 2). Minor flares B occurred less often. This might be explained by the rather strict definition, which required an increase of DAS to above 2.4 but of less than 0.6 compared to the previous DAS. Still there was a statistically significant increase in HAQ in case of a minor flare B, although this was not a clinically relevant increase, and a trend was seen for increasing number of flares with decreasing functional ability (Table 1 and Figure 3). In 11% of minor flares B, rheumatologists did not adjust medication. In 73% of these cases the next DAS was again  $\leq 2.4$ . This appears to illustrate that (minor) flares will spontaneously remit and need no additional therapy. We have to stress however that these are very small numbers and if true, than only for minor flares. Numerically there appeared to be slightly more joint damage progression in patients who suffered a minor flare B, compared to patients who never experienced a minor flare B (Figure 3), although a dose-response relationship could not be demonstrated. The dose-response relationships should be interpreted carefully anyhow, as individual patients may have various types of flares in various frequencies.

The treatment protocol required stepwise tapering and discontinuation of antirheumatic drugs if the DAS was  $\leq 2.4$  during at least three consecutive visits. We wondered if reducing medication could have triggered flares. Only in 25% of the flares, by whichever definition, medication had been tapered at the preceding visit. This could be linked to our finding of a higher flare prevalence during the early years of follow-up and decreasing prevalence in the later years (Figure 1). It was previously reported that during year 1 and 2 of follow-up,

when a low DAS was achieved, and particularly if DAS was  $\leq 2.4$  twice in a row, there was a high probability that the next DAS will also be  $\leq 2.4$ .<sup>19</sup> During later years of follow-up, this probability was even higher, up to 95% (data not shown). The decrease shown in Figure 1 can be either an overestimation or an underestimation, as patients with sustained (drug-free) remission are more likely to drop out,<sup>20</sup> and although patients were instructed to visit their rheumatologist at the moment of a flare, flares between two study visits might have been missed. Despite this, we suggest that when a treat-to-target strategy is adopted from the start and continued over time, rheumatoid arthritis may become relatively indolent in most patients. Since a dose-response relationship between the number of flares and the degree of long-term functional disability and joint damage was demonstrated, one could also hypothesize that targeted treatment should be even stricter than required in the BeSt study. Rheumatologists need to be further encouraged to adjust medication each time a flare is registered rather than hope for a spontaneous improvement. In addition, on the condition that protocol violations would not occur even more often, the treatment target may be set lower, for instance at (DAS-)remission.<sup>10</sup> The over time disease activity may then be lower and episodes of high disease activity more rare. However, this comes with a risk of overtreatment and potentially, with higher turnover of medication in some patients, considerable costs. Setting the treatment target lower will also influence the definition of flare.

A recent study examined the frequency of flares in a cohort of patients with established RA.<sup>21</sup> Flares were self-reported by the patients through six-monthly questionnaires. During three years of follow-up, 99% of the patients reported at least one flare, with a frequency of 54 – 74% per evaluation. These percentages suggest a higher flare frequency than in our study (67 – 69% of our patients had at least one flare during nine years; frequency 4 – 11% per visit). Possibly, the notion of a flare as experienced by patients does only partially overlap with our DAS-based flare definitions. Also, the reported flares were inventoried retrospectively, whereas we relied on DAS increases as measured at the time of the study visits. Since Bykerk *et al* reported that patients with higher disease activity tended to report more flares,<sup>21</sup> the fact that the majority of our patients had low disease activity during most of the observation time may have conditioned a reduced flare frequency.<sup>22</sup>

We may have underestimated the prevalence of flares, as we missed short-term subjective flares by focusing on three-monthly DAS measurements for our flare definition. This will, however, not affect the associations found between the presence of flares and functional ability loss, increase in VAS scores, and joint damage progression. Another limitation of our study could be the amount of missing data. Patients have dropped out of the study (up to 38% at year ten) or may have missed some visits. To avoid the influence of missing data, we performed mixed models. This approach takes into account the correlation of repeated measurements within a patient and between variables when handling the missing data.

In conclusion, in patients with rheumatoid arthritis a flare in disease activity is associated with functional disability, more pain and morning stiffness, and more radiographic progression, both in the short-term and the long-term. Therefore, it seems worth to intensify therapy after

each flare. Any risk of overtreatment in case of a disease flare that *would* spontaneously remit, may be less serious than the risk of undertreatment resulting in long-term disability and joint damage. Continued targeted therapy might reduce the frequency of flares, suggesting that with an adequate treatment strategy rheumatoid arthritis may become more indolent. In that case, it is possible that tight monitoring in patients who achieved persistent low disease activity may be exchanged for longer monitoring intervals, under the condition that patients who suspect a flare can be readily assessed and treatment can be adjusted if necessary.

## REFERENCES

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