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CHAPTER 6

Simplified versions
of the original disease
activity score

Validation in the BeSt trial

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ABSTRACT

Objective: To evaluate three disease activity score (DAS) alternatives without the Ritchie articular index (RAI). To compare the use of patient's global assessment of disease activity (PGA) versus global assessment of health (GH) in DAS, DAS alternatives and DAS28.

Methods: Data from the BeSt study were used, a treatment strategy trial in early rheumatoid arthritis patients aiming at a DAS ≤ 2.4 . DAS alternatives were DAS 0–1, with the RAI (0–3) reduced to a no–yes (0–1) score, DAS tender joint count 53 (DAS TJC53), with a 0–1 TJC in 53 separate joints and DAS TJC44 in 44 joints. Correlation patterns, mean difference from original DAS, classification differences in disease activity level and patient percentages with radiological damage progression per level were determined for all scores.

Results: In the majority of patients the scores were equal and correlation was high. Mean differences with the DAS at year 1 were -0.03 for DAS 0–1, 0.18 for DAS TJC53 and 0.11 for DAS TJC44. Classification agreement between scores was high (k year 1 0.76 – 0.98). Patient percentages with joint damage progression were similar for all scores. DAS, DAS alternative and DAS28 perform similarly using either PGA or GH.

Conclusion: DAS variants without the RAI perform comparably to the original DAS and may be chosen as alternatives. PGA can replace GH in the DAS, the alternatives and DAS28.

INTRODUCTION

Measuring disease outcome in rheumatoid arthritis (RA) is important to evaluate response to treatment. Recent recommendations for the management of RA propose measurement by validated composite scores including joint counts.^{1,2}

The disease activity score (DAS) was the first composite measure developed to assess and compare disease activity in patients and patient groups. The DAS includes a swollen joint count in 44 joints, the Ritchie articular index (RAI)³ for evaluation of joint tenderness in 53 joints, erythrocyte sedimentation rate (ESR) and a visual analogue scale (VAS) for patients' global assessment of disease activity (PGA) or of general health (GH).⁴ However, the DAS with VAS–PGA is not yet validated. The DAS28 was introduced as a simplification with a no–yes swollen and tender joint count (TJC) in 28 individual joints.⁵

Although in general the usefulness and importance of the DAS and DAS28 are well accepted,⁶ implementation in daily practice remains challenging. Some find that the DAS28 unjustly neglects the feet, but other scores might be too time consuming.^{7,8} The RAI may be subjective and complicated, as it is a 0–3 graded evaluation of the severity of tenderness and uses joint groups of which only the highest score per group counts. Alternatives to the DAS, including more than 28 joints without the RAI, might be more attractive to use in daily routine or clinical trials. This study aims to evaluate three variations of the DAS compared with the original DAS. In addition, we compared DAS, DAS variations and DAS28 using VAS–GH or VAS–PGA.

PATIENTS AND METHODS

Data from the BeSt trial were used, a randomised clinical trial with 3-monthly assessments aiming at a DAS of 2.4 or less by subsequent treatment adjustments.⁹ All follow-up visits included a full 68/66 graded joint count for tenderness and swelling, as well as measurements of VAS–GH, VAS–PGA and ESR. The current analysis was performed based on 467 patients with complete data at 1 year follow-up.

The DAS and DAS28 were calculated using the following formulae: $DAS = 0.5398\sqrt{(RAI)} + 0.06465(SJC44) + 0.330\ln(ESR) + 0.00722(VAS)$ and $DAS28 = 0.56\sqrt{(TJC28)} + 0.28\sqrt{(SJC28)} + 0.70\ln(ESR) + 0.014(VAS)$.

DAS alternatives were derived as follows: the DAS 0–1 was calculated by the substitution of a RAI greater than 0 with '1', while the RAI '0' score remained '0', resulting in a maximum TJC of 26. The DASTJC53 was calculated with a '0'=no/'1'=yes TJC in the 53 joints originally assessed within the RAI, but without grouping, resulting in a maximum TJC of 53. The DAS TJC44 was calculated with a TJC of '0'=no/'1'=yes in the same 44 joints that are assessed for swelling in the DAS. All DAS variations, as well as the original DAS and DAS28, were calculated with VAS–PGA and VAS–GH.

Pearson's correlation coefficients were calculated between the original DAS and DAS alternatives. The mean of these two measurements and the mean difference was calculated at year 1 and displayed in Bland–Altman plots with limits of agreement of $1.96 \times SD$

mean difference. Patients were categorised according to previously published cut-offs into remission, low disease activity (LDA), moderate disease activity (MDA) or high disease activity (HDA).^{10–14} Percentage agreement and κ statistics were calculated to assess agreement between categorisation.

An area under the curve (AUC) DAS was calculated between 3 and 12 months for all scores separately using the formula: $(0.5 \times \text{DAS}_{3\text{ months}} + \text{DAS}_{6\text{ months}} + \text{DAS}_{9\text{ months}} + 0.5 \times \text{DAS}_{12\text{ months}}) / 3$. Baseline scores were excluded from the analysis to avoid skewness due to required HDA at inclusion.

The AUC DAS results, indicating disease activity over time, were categorised into remission, LDA, MDA and HDA. Next, the percentages of patients with a greater than 5 point Sharp van der Heijde score (SHS) progression between baseline and year 1 (consistent with the smallest detectable change and indicating rapid radiological progression) were compared in all categories for all disease activity scores. Finally, the ability of DAS alternatives to detect treatment differences at 3 months follow-up was assessed using the difference in scores between baseline and 3 months.

RESULTS

All patients had early (<2 years) RA and active disease at baseline with a mean (SD) DAS of 4.4 (0.9). At year 1 (n=467) median (range) RAI was 3.0 (0–52), RAI 0–1 3.0 (0–23), TJC53 4.0 (0–50), TJC44 3.0 (0–44) and TJC28 2.0 (0–28).

Correlation was high for all DAS alternatives compared with the original DAS, and ranged between 0.96 and 0.99 (p≤0.01) at baseline and between 0.97 and 1.00 (p≤0.01) at year 1. Correlation between VAS–PGA and VAS–GH at five time points was limited (P=0.5–0.8, p≤0.01). Nevertheless, for the original DAS, DAS alternatives and DAS28, all versions with VAS–GH correlated excellently to corresponding versions with VAS–PGA (range r=0.99–1.00, p≤0.01), both at baseline and year 1.

Figure 1 illustrates high agreement between DAS alternatives and the original DAS. DAS 0–1 shows a high accordance with the original DAS, whereas DAS TJC53 and DAS TJC44 are occasionally higher, as demonstrated by the higher mean difference and broader agreement limits. However, most scores remain unchanged compared with the original DAS. DAS, DAS alternatives and DAS28 perform similarly using either VAS–PGA or VAS–GH. Categorisation of all patients by different DAS is presented in table 1. The percentage of overall agreement for all separate DAS at year 1 was high (range 82.9–98.5%), chance corrected agreement as calculated by Cohen’s k ranged from 0.76 to 0.98. Significant disagreement between categorisation, for example LDA versus HDA or remission versus HDA was very rare (table 1). Chance corrected agreement for all scores with VAS–GH versus VAS–PGA ranged from 0.85 to 0.94. Both correlation and (chance corrected) agreement between the original DAS and alternatives using either VAS score did not change over time (data not shown).

The percentages of patients with rapid radiological progression (RRP; >5 points SHS in year 1) are represented in table 2. All DAS alternatives show comparable percentages of

TABLE 1 Classification of patients per disease activity category at year 1 according to the different indices, as compared with the original DAS (n=467)

		DAS			
		Remission	LDA	MDA	HDA
DAS PGA	Remission	143	7	0	0
	LDA	5	152	3	0
	MDA	0	2	123	0
	HDA	0	0	3	29
DAS 0-1 GH	Remission	148	2	0	0
	LDA	0	159	3	0
	MDA	0	0	126	2
	HDA	0	0	0	27
DAS 0-1 PGA	Remission	143	8	0	0
	LDA	5	151	6	0
	MDA	0	2	122	2
	HDA	0	0	1	27
DAS TJC53 GH	Remission	142	0	0	0
	LDA	6	126	1	0
	MDA	0	35	105	0
	HDA	0	0	23	29
DAS TJC53 PGA	Remission	138	6	0	0
	LDA	10	118	0	0
	MDA	0	37	102	0
	HDA	0	0	27	29
DAS TJC44 GH	Remission	142	5	0	0
	LDA	6	125	3	0
	MDA	0	31	105	0
	HDA	0	0	21	29
DAS TJC44 PGA	Remission	139	11	0	0
	LDA	9	118	4	0
	MDA	0	32	101	0
	HDA	0	0	24	29
		DAS28			
		Remission	LDA	MDA	HDA
DAS28 PGA	Remission	172	12	1	0
	LDA	6	76	11	0
	MDA	1	5	137	3
	HDA	0	0	9	36

DAS, disease activity score; GH, patient’s assessment of general health on a visual analogue scale; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; PGA, patient’s global assessment of disease activity on a visual analogue scale; TJC, tender joint count.

patients with RRP within categories of disease activity level using either VAS. Overall, there are few patients with RRP in patients categorised as in remission or LDA by all composite scores. Differences in disease activity between treatment arms (eg, treatment groups 1 and 2 vs 3 and 4) could be confirmed with all indices.

DISCUSSION

The original DAS is sometimes criticised for being complicated because it includes the RAI. We compared three alternatives with the original DAS, with various tender joint

TABLE 2 Percentage (numbers) of patients with rapid radiological damage progression (SHS >5 points) in the first year of the study categorised according to the ‘mean’ disease activity level between 3 months and 1 year for all indices (n=386)

	Remission	LDA	MDA	HDA
DAS	9.9 (8/81)	11 (13/118)	19 (28/146)	39 (16/41)
DAS PGA	10 (8/78)	12 (14/118)	18 (27/147)	37 (16/43)
DAS o-1 GH	9.9 (8/81)	11 (13/119)	21 (31/151)	37 (13/35)
DAS o-1 PGA	10 (8/78)	12 (14/121)	20 (30/150)	35 (13/37)
DAS TJC53 GH	9.1 (6/66)	12 (13/106)	17 (25/151)	33 (21/63)
DAS TJC53 PGA	10 (7/68)	11 (12/105)	17 (26/150)	32 (20/63)
DAS TJC44 GH	11 (8/73)	11 (12/108)	19 (28/147)	29 (17/58)
DAS TJC44 PGA	10 (8/75)	12 (12/104)	18 (26/147)	32 (19/60)
DAS28	12 (13/102)	8.3 (5/60)	17 (29/169)	36 (18/50)
DAS28 PGA	11 (12/107)	8.2 (5/61)	18 (30/167)	35 (18/51)

DAS, disease activity score; GH, patient’s assessment of general health on a visual analogue scale; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; PGA, patient’s global assessment of disease activity on a visual analogue scale; TJC, tender joint count.

scores and patient’s assessment (by VAS) of either disease activity or GH. We found very small differences in performance of all scores. Correlation between all alternatives and the original DAS is high. All scores classify patients similarly in remission, LDA, MDA and HDA. Differences in disease activity between treatment arms could be confirmed with all indices. The percentage of patients with RRP is comparable for original and alternative scores in different disease activity levels.

Our results on the use of VAS–PGA and VAS–GH demonstrate that either can be used and affirm the single study on this subject by Khan, et al.¹⁵ Although individual VAS scores itself correlate only moderately, which indicates that they cover a different concept, when used as part of the DAS, DAS alternatives or DAS28 the total effect is negligible, mostly because of the limited weight that is given to this component. When categorising patients in disease activity levels we see that DAS TJC53 and DAS TJC44 are classifying more MDA and HDA, less LDA and similar remission percentages. This can be explained because both DAS TJC53 and DAS TJC44 assess more joints separately, causing a small shift to a higher disease activity category. However, the vast majority of remission patients have none to one painful joint in which disease activity by any score, and thus remission percentages, remain the same. DAS28 shows a different pattern with more patients assessed as being in remission and consequently a smaller LDA group, in line with discussions about the remission definition of DAS28.¹⁶ The percentage of patients with RRP in DAS28 remission was higher compared with the (alternative) DAS. The slightly higher disease activity measured with both DAS TJC44 and DAS TJC53 with corresponding higher classification leads to less radiological damage in the HDA group of these scores. Differences are nonetheless very small. The percentages of patients with RRP were not influenced by the use of VAS–PGA or VAS–GH, neither in the alternative DAS nor in the original DAS28.

A limitation of the current study is caused by the rapid reduction in disease activity in

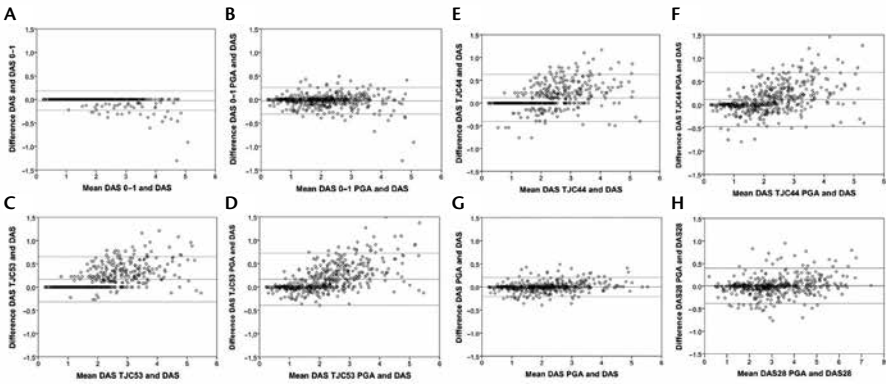


FIGURE 1 Bland-Altman plots illustrating the agreement between the DAS variants and the original DAS (A-G) and between DAS28 and DAS28 PGA (H). Mean of the two measurements (x-axis) versus the mean difference between the two values (y-axis) at year 1 (n=467). (A) Disease activity score (DAS) o-1 global health (GH). (B) DAS o-1 patient’s global assessment of disease activity (PGA). (C) DAS tender joint count in 53 joints (TJC53). (D) DAS TJC53 PGA. (E) DAS tender joint count in 44 joints (TJC44). (F) DAS TJC44 PGA. (G) DAS PGA. (H) Disease activity score in 28 joints (DAS28) PGA versus DAS28 GH.

this early severe RA population, leading to an infrequency of graded joint scores above one, which explains the overlap between DAS o-1 and DAS. If in daily practice RAI scores of 3 are more prevalent, we expect a greater difference between the original DAS and alternative versions in higher activity levels. In modern practice, in which treatment is aimed at achieving remission (or at least LDA), high grading may become rare. All our results regarding the DAS28 and DAS variants are valid at the group level and for the vast majority of patients; however, for some individual patients differences between scores may be larger.

In conclusion, we have shown that scoring the presence or absence of tenderness in individual joints to calculate a disease activity score performs as well as scoring a graded tenderness score in joint groups. In daily practice or clinical studies, using a DAS alternative may be much easier than the original DAS with RAI. The score based on the assessment of tenderness in the same 44 joints assessed for swelling may be most practical.

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