Disease Activity Score 28 as an Instrument to Measure Disease Activity in Patients with Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine the influence of components of the Disease Activity Score 28 (DAS28) [tender joint count (TJC), swollen joint count (SJC), patient's general health (GH), and erythrocyte sedimentation rate (ESR)] on the total DAS28 score, and overlapping of the 4 individual components in rheumatoid arthritis (RA) patients with low, moderate, or high disease activity.

Methods. The effect of each component was studied in the FIN-RACo trial patients at 6 months and in a "theoretical model," where each component of the DAS28 ranged as follows: TJC and SJC from 0 to 28, GH from 0 to 100, and ESR from 1 to 100, while the other 3 components were 0 (ESR1). Overlapping of the components was studied in the FIN-RACo trial patients at 6 months with low (DAS28 ≤ 3.2), moderate (DAS28 > 3.2 and ≤ 5.1), and high (DAS28 > 5.1) disease activity. The higher limit for overlapping was defined as the highest SJC in the low disease activity group, and the lower limit as the lowest SJC in the high disease activity group; the percentage of patients who fall between these limits represent overlapping in SJC. Overlapping was calculated similarly concerning TJC, ESR, and GH.

Results. ESR had the greatest effect on DAS28, followed by TJC, GH, and SJC, while in the "theoretical model" TJC had the greatest effect on the DAS28, followed by ESR, SJC, and GH. At 6 months, overlapping was present in 54%, 45%, 49%, and 31% of patients in SJC, TJC, GH, and ESR, respectively.

Conclusion. In real-life patients, ESR had the greatest effect of the 4 components of DAS28 on the total DAS28 score. The values of the individual components of DAS28 overlap considerably among the 3 disease activity groups. (First Release July 1 2007; J Rheumatol 2007;34:1987–91)

Key Indexing Terms:
DISEASE ACTIVITY SCORE 28 RHEUMATOID ARTHRITIS DISEASE ACTIVITY

There is an increasing need to measure clinical disease activity in patients with rheumatoid arthritis (RA) both in randomized controlled trials and in clinical practice. This is partly due to the need to show the efficacy and to regulate the use of expensive new treatments for RA[1].

The disease activity of RA cannot unambiguously be presented by using a single clinical measure, but various composite scores have been developed to measure overall disease activity. The Disease Activity Score (DAS)[2,3] was developed for that purpose originally in the late 1980s. A modified version of the DAS including 28 joints (DAS28) was subsequently developed[4]. DAS28 contains 4 components weighed individually: number of tender joints (TJC), number of swollen joints (SJC), general health (GH), and erythrocyte sedimentation rate (ESR).

The rationale for a composite instrument is to record multiple dimensions of a phenomenon in one score. DAS28 reflects disease activity of RA utilizing clinical examination, patient self-report, and a laboratory test. It is widely used in clinical trials and the use of DAS28 has been extended into clinical practice. Our clinical observation that some patients with several swollen joints have low disease activity on DAS28 led us to study the influence of the individual DAS components on the total DAS28 score and overlapping of the 4 components of DAS28 in RA patients with low, moderate, and high disease activity.

MATERIALS AND METHODS

Study population. In the FIN-RACo study[5], a total of 195 patients with recent onset RA were randomized to receive either disease modifying antirheumatic

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Accepted for publication April 16, 2007.

drug (DMARD) combination therapy with prednisolone or DMARD monotherapy with or without prednisolone. Patients were required to have early active disease with duration of symptoms less than 2 years, active disease with ≥ 3 swollen joints, and at least 3 of the following: ESR ≥ 28 mm/h or C-reactive protein (CRP) > 19 mg/l, morning stiffness ≥ 29 min, > 5 swollen joints, and > 10 tender joints. All patients had to fulfil the American Rheumatism Association criteria for RA[6]. The study has been described in detail[5].

The FIN-RACo study was done according to the Declaration of Helsinki. The protocol was approved by the national health authorities and ethics committees in all 18 participating hospitals. All the patients gave informed written consent.

Methods. In our study, the 6-month data of the FIN-RACo study were analyzed. Clinical assessments included TJC (28 and 68 joints), SJC (28 and 66 joints), GH on visual analog scale (VAS, 0–100 mm), and ESR.

DAS28 was calculated with a formula $0.56 \times \sqrt{}$(tender joints 28) + $0.28 \times \sqrt{}$(swollen joints 28) + $0.70 \times \ln$ (ESR) + $0.014 \times$ GH[7].

In the real-life (FIN-RACo) patient population the effect of the 4 individual components of DAS28 on the total DAS28 score was examined according to the DAS28 formula. The sum of 1 to 4 was calculated: (1) the mean of $0.56 \times \sqrt{}$(tender joints 28); (2) the mean of $0.28 \times \sqrt{}$(swollen joints 28); (3) the mean of $0.70 \times \ln$ (ESR); and (4) the mean of $0.014 \times$ GH of the 169 patients. The summation of parts 1 to 4 is the total DAS28 score of the study patients. The percentage of parts 1 to 4 of the total DAS28 score was considered as the weight of each component on the DAS28 score in the study population. Higher percentage therefore means a greater effect of an individual component on the DAS28.

In a "theoretical model" the effects of the individual components of DAS28 (TJC, SJC, ESR, and GH) were calculated according to the DAS28 formula as well. It was presumed that the other 3 components remained 0 (ESR 1), while the value of the component studied varied from 0 (ESR 1) to its clinically relevant maximum (SJC and TJC from 0 to 28). The effect of TJC was calculated as follows: $0.56 \times \sqrt{}$(range from 0 to 28) + $0.28 \times \sqrt{}$ 0 + $0.70 \times \ln 1 + 0.014 \times 0$; the effect was calculated similarly concerning the other 3 components. Higher value means a greater effect on the total DAS28 score (Figure 1).

Disease activity was graded as follows: low disease activity DAS28 ≤ 3.2, moderate disease activity DAS28 > 3.2 and ≤ 5.1, and high disease activity DAS28 > 5.1[8].

Overlapping was calculated as follows. The higher limit for overlapping was defined as the highest SJC (on a 66-joint count) in the low disease activity group, and the lower limit as the lowest SJC in the high disease activity group; the percentage of patients who fall between these limits represent overlapping in SJC. Overlapping was calculated similarly for the TJC (on a 68-joint count), ESR, and GH.

The results were presented as mean and median, standard deviation (SD) or interquartile range (IQR), percentages, and 95% confidence intervals.

RESULTS

Study population. The study included 169 patients with complete data at 6 months. The mean age of patients was 47 years, 63% were female, 71% were rheumatoid factor-positive, and 49% of the patients had erosions in hand and/or foot radiographs at baseline (Table 1).

Effect of the 4 individual components of DAS28 on the total DAS28 score. The mean value of the DAS28 was 2.78 at 6 months. The relative contribution of the mean values of the component variables on the total DAS28 score according to the DAS28 formula was as follows: (1) the mean of ($0.56 \times \sqrt{}$ TJC) was 0.71, while the median TJC was 2 (range 0–24); (2) the mean of ($0.28 \times \sqrt{}$ SJC) was 0.23, while the median SJC was 0 (range 0–20); (3) the mean of [$0.70 \times \ln$(ESR)] was 1.56, while median ESR was 10 (range 1–65); and (4) the mean of ($0.014 \times$ GH) was 0.28, while median GH was 15 (range 0–77). Thus the sum of parts 1 to 4 (0.71 + 0.23 + 1.56 + 0.28) was 2.78 (the total DAS28 score). Therefore, in this patient population ESR had the greatest impact on the DAS28

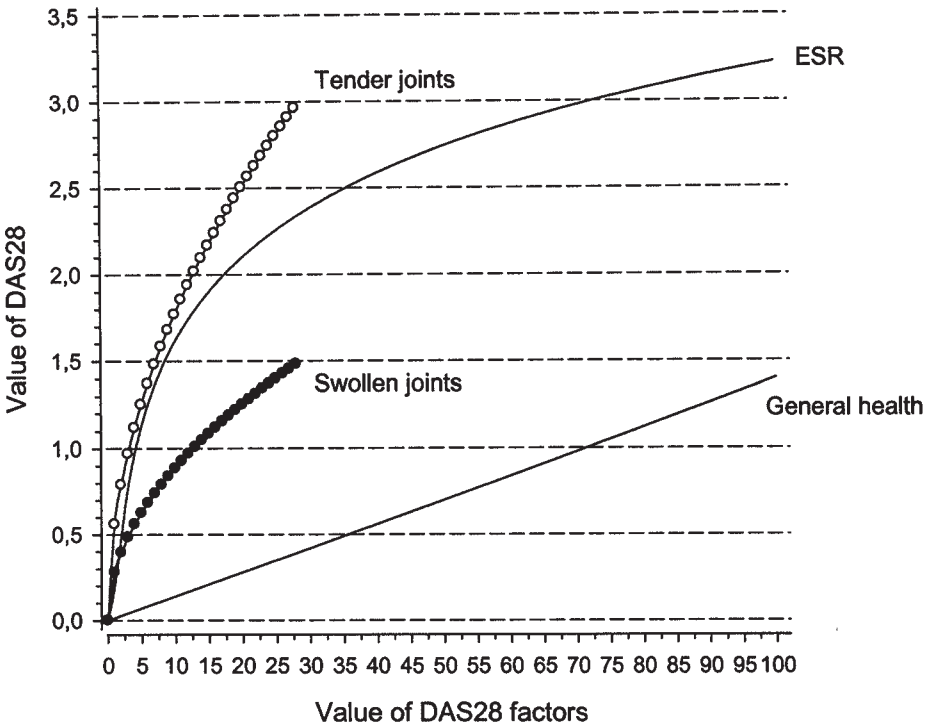

Figure 1. Influence of each component of DAS28 in the "theoretical model"; tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR), and patient's general health on DAS28, presuming that the remaining 3 components are 0 (ESR 1).

Table 1. Demographic variables and disease characteristics of 169 patients with early rheumatoid arthritis in the FIN-RACo study.

Characteristic	169 Patients
Mean age, yrs (SD)	47 (10)
Female sex (%)	106 (63)
Patients with positive rheumatoid factor (%)	120 (71)
Patients with erosions (%)	83 (49)
Duration of symptoms before diagnosis, months, median (interquartile range)	6 (4, 10)

score, with 56% of the total DAS28 score, followed by TJC (26%), GH (10%), and SJC (8%).

In the "theoretical model," the TJC (28 joint count) shows the greatest effect on the total DAS28 score: when TJC rises from 0 to 28, DAS28 increases from 0 to 2.94, provided that the other components remain 0 (ESR 1). Accordingly, ESR has the second largest effect on DAS28: when ESR rises from 0 to 20, DAS28 goes from 0 to 2.1. Further, when ESR rises to 100, DAS28 increases to 3.22. ESR exceeds the effects of all the other components when its value is above 70. SJC has the third most powerful effect on DAS28, followed by GH, with similarly calculated values of DAS28 of 1.5 and 1.42, respectively (Figure 1).

Overlapping of TJC, SJC, ESR, and GH values in the 3 DAS28 disease activity groups using the 66/68 joint count. Of the 169 patients, 107 (63%) had DAS28 ≤ 3.2 (low disease activity), 51 (30%) had DAS28 > 3.2 and ≤ 5.1 (moderate disease activity), and 11 (7%) had DAS28 > 5.1 (high disease activity) at 6 months.

In the high disease activity group the lowest SJC on a 66-joint count was 1, while the highest SJC in the low disease activity group was 11. In the low disease activity group 42 patients had a SJC from 1 to 11 and in the moderate and high disease activity groups 43 and 7 patients, respectively. In the whole patient population 92 of 169 patients had a SJC between those limits, so the overlapping rate was 92/169 (54%). The similarly calculated overlapping rates for GH, TJC (68-joint count), and ESR were 49%, 45%, and 31%, respectively (Table 2, Figures 2 and 3).

DISCUSSION

Composite scores of disease activity such as the DAS28 are of great value in RA clinical trials in the evaluation of treatment response. However, measures with good discriminatory power in groups of patients may not be optimal in individual patients. In our study a substantial proportion of the patients with low, moderate, and high disease activity defined by DAS28 had overlapping values with the other disease activity groups with respect to all 4 disease activity components (TJC, SJC, GH, and ESR).

The Ritchie index has a major effect on the original DAS score, followed by SJC, ESR, and GH[2]. Similarly, we found in the theoretical model that the TJC had the greatest effect on the DAS28, followed by ESR, SJC, and GH. The finding that GH had a minor effect on the DAS28 score is not compatible with the fact that GH closely correlates with pain, and pain has a substantial impact on the quality of life and function of patients with RA[9,10]. In our patient population, ESR showed the greatest effect on DAS28 at 6 months, although the median ESR was only 10.

Analyses of overlapping data provide an interesting view of the distribution of the DAS components in patients who have low, moderate, or high disease activity. In our patient population, more than half the patients with low disease activity had as many swollen joints as patients with moderate and high disease activity at 6 months when a 66-joint count was used.

The DAS was developed almost 2 decades ago[3] during an era with different medication options and treatment goals compared to the present. Therefore, definitions of levels of the DAS (and DAS28) disease activity may reflect that era. However, we used those levels, recognizing that in the future the cutoff points of low, moderate, and high disease activity may become lower because of more aggressive therapy of RA.

The British Society of Rheumatology guidelines for prescribing tumor necrosis factor (TNF) blockers recommend the restriction of biologicals only to patients with active disease defined as DAS28 > 5.1[11]. In The Netherlands, the activity requirement to start TNF blockers is only DAS28 > 3.2[12]. However, categorical application of DAS28 in the clinical

Table 2. The median (IQR) number of swollen and tender joints, ESR, and general health, of RA patients with low (DAS28 ≤ 3.2), moderate (DAS28 > 3.2 and ≤ 5.1), and high disease activity (DAS28 > 5.1), and the percentage of patients who have overlapping in the 4 individual components of the DAS28 in the 3 disease activity groups.

	Group 1 DAS28 0–3.2, median (IQR)	Group 2 DAS28 > 3.2 and ≤ 5.1, median (IQR)	Group 3 DAS28 > 5.1, median (IQR)	Overlap Between Groups 1, 2, and 3, %
No. of swollen joints	0 (0, 2)	4 (2, 7)	11 (7, 25)	54
No. of tender joints	1 (0, 4)	9 (4, 14)	15 (8, 25)	45
ESR	6 (3, 11)	19 (10, 28)	40 (18, 52)	31
General health	7 (2, 17)	29 (19, 40)	37 (25, 66)	49

IQR: interquartile range; ESR: erythrocyte sedimentation rate; DAS: Disease Activity Score.

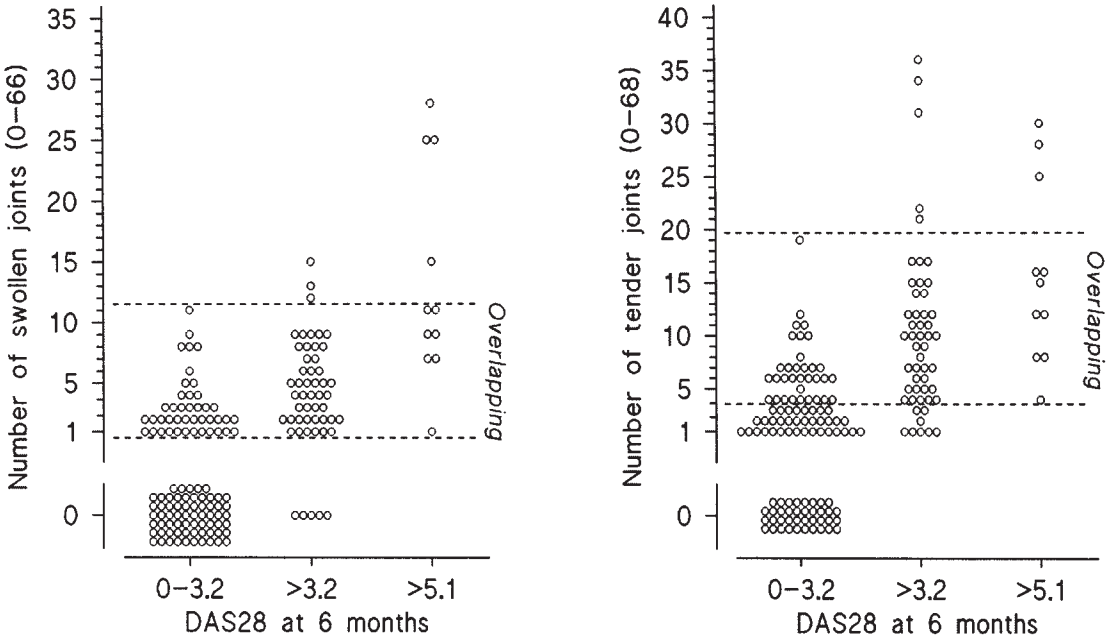

Figure 2. Overlap of the number of swollen and tender joints on a 66/68-joint count in RA patients with low (DAS28 ≤ 3.2), moderate (DAS28 > 3.2 and ≤ 5.1), and high disease activity (DAS28 > 5.1) according to DAS28. Each point represents one patient of the FIN-RACo trial.

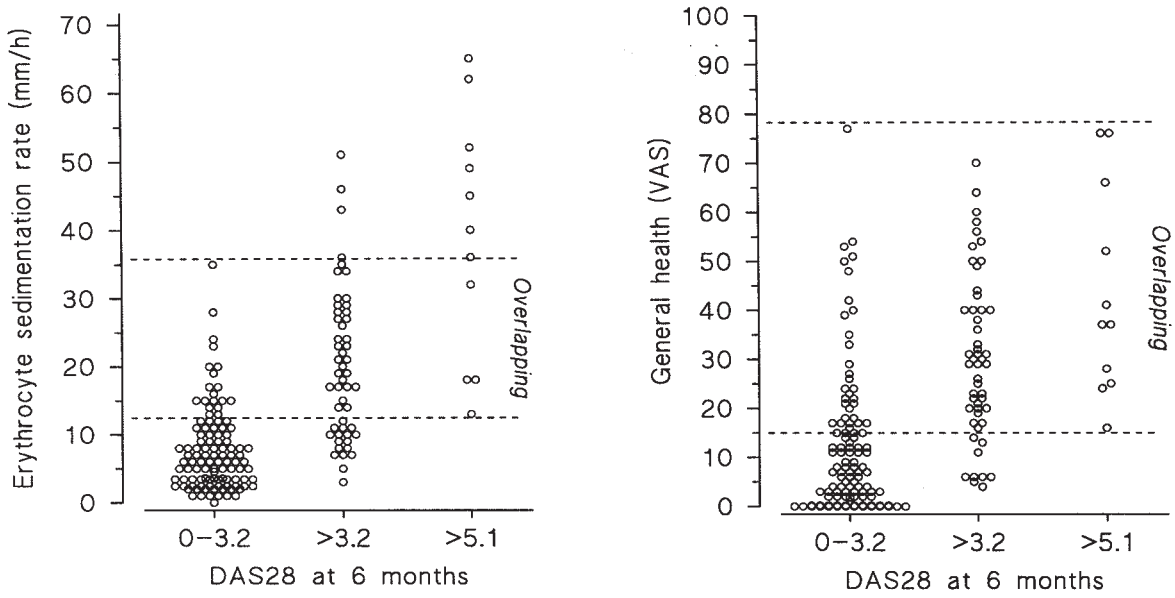

Figure 3. Overlap of the ESR and patient's general health in RA patients with low (DAS28 ≤ 3.2), moderate (DAS28 > 3.2 and ≤ 5.1), and high disease activity (DAS28 > 5.1) according to DAS28. Each point represents one patient of the FIN-RACo trial.

decision making may be unfeasible and inappropriate, as best illustrated by real-life patients. One patient in our cohort had 21/11 tender joints (68-joint count/28-joint count) and 12/11 swollen joints (66-joint count/28-joint count), ESR of 5, and GH of 60. Her DAS28 score was 4.76, indicating only moderate disease activity. Similarly, another patient had 4/1 tender and 11/8 swollen joints, ESR of 5, and GH of 4, with DAS28 score of 2.54 indicating DAS28 remission. It might be desirable that in addition to DAS28, a patient's function and potential radiographic joint damage[13] should routinely be taken into account in adjusting therapies for RA. We agree with the statement of Wolfe, *et al* that DAS28 is not suitable as the sole criterion for initiation and evaluation of therapy with biologics in a clinical setting[1].

Development of DAS and DAS28 has been an enormous step forward in evaluation of disease activity in RA both in

clinical trials and in clinical settings. The use of DAS28 as an aid for decisions regarding intensifying or decreasing medication in RA has been shown to lead to lower disease activity and even cost savings[14-16]. However, patients in remission according to DAS28 may still have many tender and/or swollen joints[17,18] and individual patients may have low disease activity according to DAS28, despite a raised SJC. Further, the cutoff values between low, moderate, and high disease activity are questionable[18]. According to our observations there is substantial overlapping in TJC, SJC, GH, as well as in ESR, between various DAS28 activity categories. DAS28 does not account for the activity in the joints of ankles and feet. Finally, the important aspects of the patients' clinical course — radiographic progression and patient's function — are omitted when applying only the DAS28 in clinical decision making.

ACKNOWLEDGMENT

We thank the other members of the FIN-RACo Trial group: Markku Hakala, MD, PhD; Heikki Julkunen, MD, PhD; Kaisa Vuori, MD; Leena Paimela, MD, PhD; Leena Laasonen, MD, PhD; Martti Nissilä, MD, PhD; Urpo Yli-Kerttula, MD, PhD; Kirsti Ilva, MD; Ilppo Pälvimäki, MD; Jari Ahonen, MD; Mikko Hakola, MD; Olli Koivisto, MD; Heikki Piirainen, MD, PhD; Pentti Järvinen, MD; Kalevi Koota, MD, PhD; Claes Friman, MD, PhD; Oili Kaipiainen-Seppänen, MD, PhD; Harri Blåfield, MD; Per Franzen, MD; Tapani Helve, MD, PhD; Juhani Koski, MD, PhD; Sinikka Forsberg, MD; Marianne Gripenberg-Gahmberg, MD, PhD; and Riitta Luosujärvi, MD, PhD.

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