
DAS remission cut points

J. Fransen, P. L.C.M. van Riel

Department of Rheumatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500HB Nijmegen, The Netherlands.

Japp Fransen, PhD, Prof. P. L.C.M. van Riel, MD, PhD.

Please address correspondence to:
Prof. P.L.C.M. van Riel, Department of Rheumatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500HB Nijmegen, The Netherlands.
E-mail: P.vanRiel@reuma.umcn.nl

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ABSTRACT

The Disease Activity Score (DAS) and DAS28 are continuous measures of rheumatoid arthritis (RA) disease activity. Values of DAS <1.6 and DAS28 < 2.6 correspond with an increased likelihood of being in remission. This review presents development of the DAS and DAS28 remission cut points and their interpretation.

Introduction

The Disease Activity Score (DAS) (1) and its modified version, the DAS28 (2), have been developed because disease activity in rheumatoid arthritis (RA) is not adequately represented by a single measure (3). Both disease activity scores combine information from tender and swollen joints, acute phase reactant such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and a global health assessment and, as a result, they are more informative for assessment of RA disease activity than any of the components individually.

An advantage of the DAS over a change measure like the American College of Rheumatology 20% improvement (ACR20)/ACR50/ACR70 criteria is that it is a measure of the disease state at any given point in time, reflecting at each time point the underlying RA disease activity. The ACR scoring system, on the other hand, provides a change score – that is, the difference compared to a prior assessment. For judgment of disease activity and for prognosis, state rather than change is most useful in clinical practice. For both DAS versions, cut points have been established that are equated with “low,” “moderate,” and “high” disease activity. Those cut points are used in the European League Against Rheumatism (EULAR) response criteria for disease-modifying antirheumatic drug (DMARD) trials (4-6). At the lower end of the DAS scales, cut points have been established that correspond with meeting of the

preliminary American Rheumatism Association (ARA) remission criteria (7-9).

Rather than defining clinical remission, the cut points on the DAS scale give meaning to “low disease activity scores”. This is an advantage for interpretation of the DAS and DAS28 because they are dimensionless scores, globally ranging from 0 to 10. These cut points, DAS < 1.6 and DAS28 < 2.6, are often called “DAS remission criteria.” However, when remission is interpreted as the total absence of signs and symptoms of disease activity, the DAS cut points correspond rather with “near-remission” or “partial remission.” The objective of this brief essay is to review the development of the DAS and DAS28 remission cut points and their interpretation.

Remission in RA

The availability of more effective treatments in RA has raised interest in the definition and assessment of the absence of disease activity or criteria for “low disease activity.” Remission is generally understood as the total absence of signs and symptoms of the disease, including the notion that sequelae of the disease will not develop during remission. In RA, a state of remission that can be maintained without medication may be regarded as “cure.” However, generally, medication will be needed to reach and maintain a state of remission. Remission is the ultimate goal of RA treatment, but it remains difficult to achieve in practice and in clinical trials. Furthermore, states of remission are often not maintained over long periods (8, 10-12). In current clinical practice, a more attainable goal is to induce and maintain at least a state of very low disease activity.

The Disease Activity Score

The DAS has been developed to provide a measure of RA disease activity that is more informative than the

several disease activity variables individually (1). The DAS combines information from swollen joints, tender joints, acute-phase response, and general health into one continuous measure of RA disease activity, according to the following formula:

$$\text{DAS} = 0.53938 \times \sqrt{\text{Ritchie}} + 0.06465 \times (\text{Swollen joints}) + 0.330 \times \ln(\text{ESR}) + 0.00722 \times (\text{General Health})^*$$

*Ritchie = Ritchie Articular Index, (Swollen joints) = 44 swollen-joint count, $\ln$ = natural log, ESR = erythrocyte sedimentation rate, (General Health) = patient's assessment of general health using a Visual Analog Scale (VAS) of 100 mm.

The DAS was developed using decisions on DMARD therapy as an external standard for defining "low" and "high" disease activity, in a data-driven process. The DAS formula includes the Ritchie Articular Index (0-78), which is performed on 53 joints (13), a 44 swollen-joint count (0-44), ESR, and a general health item using a VAS (0-100), in which higher scores mean worse health. The DAS28 includes 28 joint counts instead of the extended 53 (tenderness) and 44 (swelling)-joint count (2). The final form and development of the DAS28 mirrored development of the DAS (1, 2).

$$\text{DAS28} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times (\text{General Health})^*$$

*(TJC) = 28 tender-joint count, (SJC28) = 28 swollen-joint count; the other terms are defined as above.

The DAS is a continuous measure of disease activity state, which is clinically more useful than a measurement of change alone. Change measures, such as the change involved in the EULAR response criteria, can be derived from the DAS (4, 5). As the DAS and DAS28 are dimensionless scales, the question was raised whether the lower spectrum of the DAS scales correspond with being in remission – that is, with meeting the ARA remission criteria for RA (9).

DAS remission cut points

Data from the Nijmegen RA inception

Table I. ARA clinical remission.

Year	N	Total: n	Number of "remission visits" per patient: M (range)	Patients with ≥ 1 ARA "remission visit" n (%)	Patients with "remission visits" in a previous year n	Patients with ≥ 2 ARA consecutive "remission visits" n (%)
1	378	67	1 (1-4)	42 (11%)	—	17 (4%)
2	287	91	2 (1-4)	50 (17%)	24	25 (9%)
3	218	78	1 (1-4)	48 (22%)	22	21 (10%)
4	148	50	1 (1-4)	28 (19%)	17	13 (9%)
5	95	37	2 (1-4)	18 (19%)	11	10 (10%)
6	77	33	2 (1-4)	14 (18%)	12	9 (12%)

Occurrence of American Rheumatism Association (ARA) clinical remission in the Nijmegen rheumatoid arthritis cohort by years of follow-up. Meeting the the modified ARA criteria for remission at a single visit is noted as "remission visit." Year: follow-up year; N: number of patients; n: number of visits; M: median.

[From Fransen *et al.*: Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology (Oxford)* 2004; 43: 1252-5]

cohort were analysed to determine whether a cut point in the DAS could be found that corresponded with meeting the ARA remission criteria (14). This cohort included the patients whose findings were used to develop the DAS and DAS28. RA patients were included in the cohort immediately upon diagnosis according to the ACR criteria, if duration of RA symptoms was less than 1 year and patients had not been treated previously with DMARDs.

Cohort patients were evaluated at least every 3 months using standardised assessments. All visits of all patients

enrolled were included for a maximum of 6 years of individual follow-up time. Follow-up was censored for 1 of 3 reasons: 1) end of the observation period; 2) more than one consecutive visit missing; 3) lost to follow-up. With few exceptions, all patients were treated with DMARDs and/or biologic agents; when appropriate, nonsteroidal anti-inflammatory drugs and/or corticosteroids were added.

Because fatigue was not assessed in the cohort, a modification of the ARA remission criteria was used. A patient was classified as meeting remission criteria when 4 of the following 5 crite-

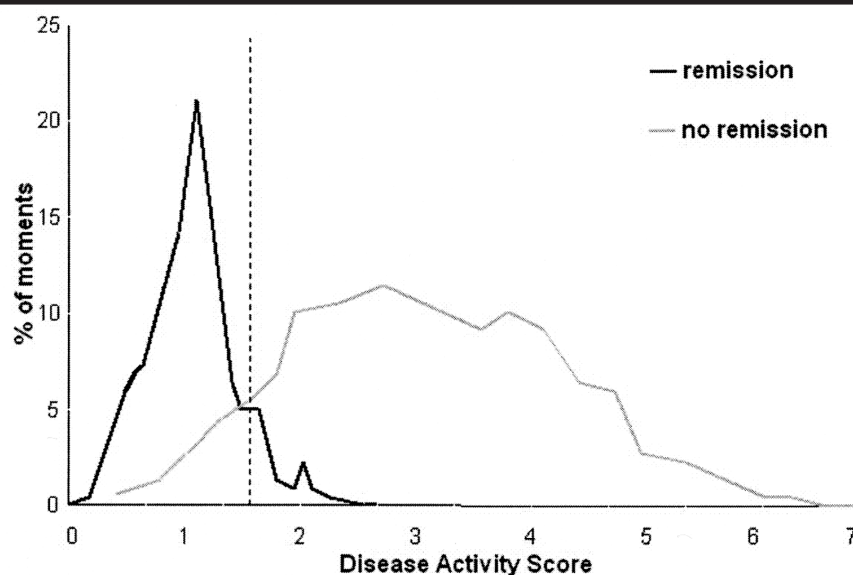


Fig. 1. Determination of the cut point in Disease Activity Score that is corresponding with fulfillment of the modified American Rheumatism Association remission criteria. A cut point of < 1.6 (broken vertical line) led to 10% misclassification in patients meeting the ARA criteria, as well as 10% misclassification in patient-moments not meeting the ARA criteria.

ria were met: morning stiffness ≤ 15 minutes, VAS pain ≤ 10 mm, 53 tender-joint count = 0, 44 swollen-joint count = 0, ESR < 30 for females or ESR < 20 for males. The number of patients meeting the modified remission criteria remained constant after the first 2 years of follow-up (Table I). For each visit of every patient, the DAS and DAS28 were calculated, and meeting of the modified ARA criteria for clinical remission was determined (7, 8). Analysis of sensitivity and specificity was performed to determine the cut points in the DAS and the DAS28 that corresponded to meeting of the modified ARA criteria. The results indicated cut points of DAS < 1.6 (Fig. 1) and DAS28 < 2.6 (Fig. 2).

Interpretation

These scores mean that almost all patients who met the modified ARA remission criteria had a DAS < 1.6 or DAS28 < 2.6 , and that patients who did not meet these criteria had a higher DAS. As can be seen in Fig. 3, DAS28 scores of patients who met the modified ARA criteria overlap considerably with those who did not. Indeed, a considerable proportion of the patients found to have a DAS28 < 2.6 do not fulfill the ARA remission criteria.

The reason for patients with DAS28 < 2.6 not meeting ARA remission criteria derives from the structure of the formula, which allows several ways to arrive at low DAS or DAS28 scores, which do not agree with the ARA criteria. Because of the way the weights are allocated, it is possible for patients to have a low DAS score resulting from a high number of swollen joints when they simultaneously have a (very) low ESR (Table II). As can also be seen in Fig. 2, the original DAS performs better than the DAS28, which may be a result of the weights and of the inclusion of more extended joint counts in the DAS. Whether exclusion of the feet in the 28-joint counts leads to much misclassification, which remains a possibility, is debated (15-17).

Use of the cut points in trials

Usually, ACR improvement criteria or EULAR response criteria are used as

Fig. 2. Receiver Operating Characteristic curve of the DAS (unbroken line) and DAS28 (broken line) for fulfillment of the modified American Rheumatism Association remission criteria.

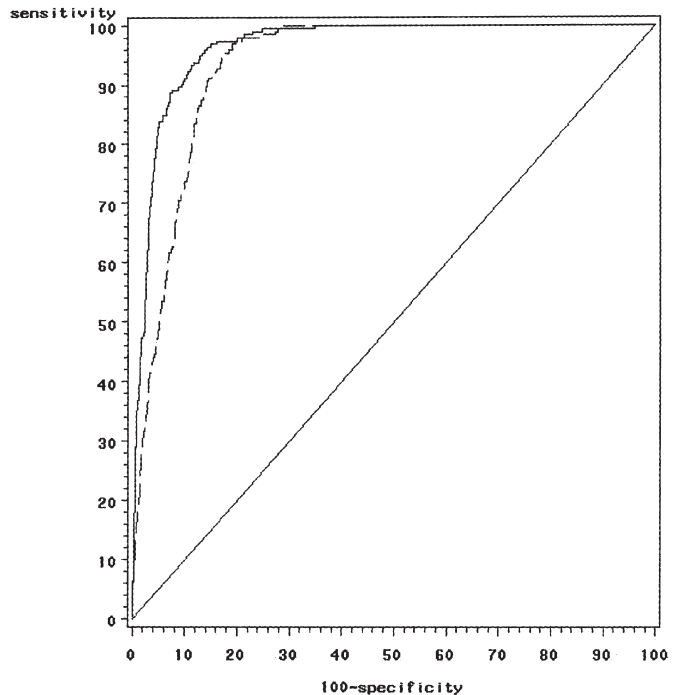
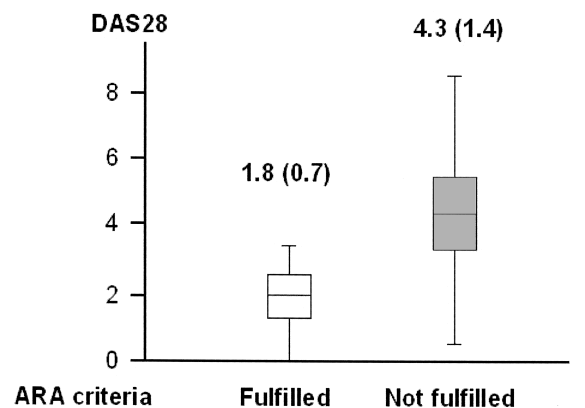


Fig. 3. Overlap in DAS28 scores between patient-moments in which the ARA preliminary remission criteria were fulfilled and not fulfilled, of RA patients (N = 378) in the Nijmegen rheumatoid arthritis cohort.



primary outcomes in randomised controlled trials of DMARDs or biologic agents. ACR improvement criteria are a measure of change in seven core-set measures; the EULAR criteria combine a magnitude of change in DAS (< 0.6 , $0.6-1.2$, > 1.2) and the level of the DAS reached (low, moderate, or high). The cut points in DAS or DAS28 have been used in several studies as a secondary endpoint (11).

The advantage of using the level of disease activity reached at the end of a trial is that it corresponds with the treatment goals in clinical practice. Sesin *et al.* reviewed the literature and showed that leflunomide and the combination of multiple DMARDs led to larger DAS or DAS28 remission rates (ranging from 13%-42%) than with

monotherapy, and that combinations of methotrexate (MTX) with tumor necrosis factor (TNF) inhibitors also led to high rates of remission defined by DAS or DAS28 (ranging from 31%-50%) (11). These data indicate that near-remission is an attainable goal for a relatively large group of patients at this time, using early treatment with agents which are now available.

Discussion

DAS and DAS28 are valid and useful measures of RA disease activity, with the advantage of being continuous measures of rheumatoid inflammation. DAS provides a maximum of information about rheumatoid inflammation using a minimal set of variables. For analysis, it is an advantage that the

Table II. Low values of the DAS28 and its components.

28 TJC	28 SJC	ESR	GH	DAS28
0	0	10	10	1.75
0	1	10	10	2.03
1	0	10	10	2.31
1	1	10	10	2.59
0	10	10	10	2.64
0	0	20	10	2.24
0	1	20	10	2.52
1	0	20	10	2.80
1	1	20	10	3.08

28TJC: 28 Tender-joint count; 28 SJC: 28 swollen-joint count; ESR: erythrocyte sedimentation rate; GH: General Health item on a Visual Analog Scale.

DAS show a Gaussian distribution. The DAS and DAS28 can be used in trials and in clinical practice, where they reflect the treatment goal of reaching low disease activity or even remission.

The cut points of DAS < 1.6 and DAS28 < 2.6 correspond with fulfillment of the ARA remission criteria. Most RA patients who meet ARA remission criteria have DAS falling below the cut point, and almost never higher. However, in the reciprocal situation, some patients with DAS below the cut point simultaneously do not fulfill the ARA remission criteria. The reason is that a low DAS does not necessarily coincide with ARA remission criteria - for example, having one swollen and one tender joint. Also, because of the weighting in the formulas, patients may have a high number of swollen joints with a coincident very low ESR. This matter is more pronounced for the DAS28, in which the weight for ESR is larger and the number of included joints is lower. Other studies also found cut points for meeting the ARA criteria for the DAS28 around 2.6 (18, 19). A similar cut score (DAS28 < 2.4) was found to correspond with physician opinion of remission when judging clinical profiles (20).

In conclusion, we do not feel that the DAS and DAS28 cut points should be used to "diagnose" clinical remission. Rather, the "remission" cut points are a refinement that gives meaning to low DAS. In our opinion, it does not

replace the cut points of DAS ≤ 2.4 and DAS28 ≤ 3.2 that are equated with "low disease activity." Cut points in continuous measures often appear biologically arbitrary. If they do not have prognostic or clinical meaning, the use of cut points is perhaps undesirable and should be avoided as much as possible. Furthermore, a cut point may change with an increase in knowledge concerning disease or a change in attitudes concerning appropriate treatment.

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