
The Disease Activity Score and the EULAR response criteria

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Clin Exp Rheumatol 2005; 23 (Suppl. 39): S93-S99.

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Key words: Rheumatoid arthritis, disease activity, response, clinical assessment.

ABSTRACT

In rheumatoid arthritis (RA), inflammatory activity cannot be measured using one single variable. For this reason the Disease Activity Score (DAS) has been developed. The DAS is a clinical index of RA disease activity that combines information from swollen joints, tender joints, the acute phase response and general health. The DAS-based European League Against Rheumatism (EULAR) response criteria were developed to measure individual response in clinical trials. The EULAR response criteria classify individual patients as non-, moderate, or good responders, dependent on the extent of change and the level of disease activity reached.

Introduction

The DAS, DAS28 and the EULAR response criteria have been extensively validated and are finding increasing use both in RA clinical trials and for monitoring individual RA patients. Major advantages of the DAS are that it is more valid than single measures alone, it has a continuous scale with a Gaussian distribution, its values are clinically interpretable, and it is sensitive enough to assess small effects. The DAS is used in the EULAR response criteria, which reflect a clinically meaningful target (reaching low disease activity) that has prognostic value for the progression of joint damage. When even more effective new drugs become available in the future, measures such as “time-to-low-disease-activity” or “time-in-low-disease-activity,” which can already be measured using the DAS and DAS28, may become useful as endpoints in clinical trials.

Clinical assessment of RA inflammation

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with peripheral synovitis as its main manifestation. The presentation of the disease and its course over time are highly

variable both within and between individuals. The symptoms and signs of RA may vary from joint complaints such as pain, stiffness, swelling and functional impairment to more constitutional complaints such as fatigue and loss of general health (GH). Because of this variety in disease expression, a selection of variables (core-set variables) is generally used to evaluate the status and course of RA disease activity, disability and joint damage (1,2). To provide a measure of RA disease activity that is more valid than the various existing disease activity variables individually, the disease activity score (DAS) was developed (3, 4).

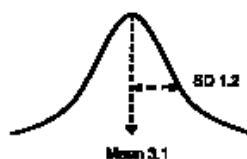
The DAS is based on an external standard of RA disease activity, and combines information from swollen joints, tender joints, the acute phase response and general health into one continuous measure of rheumatoid inflammation (Table I). Response criteria for RA clinical trials based on the core set variables were developed by the European League against Rheumatism (EULAR) and the American College of Rheumatology (ACR) (5-8). The EULAR response criteria use the individual change in DAS and the level of DAS reached to classify trial participants as good, moderate or non-responders (7). Despite their different constructions, the EULAR response criteria and the ACR improvement criteria were found to be in reasonable agreement in the same set of clinical trials (9).

The DAS and the EULAR response criteria have several advantages: (i) The continuous scale of the DAS reflects the extent of underlying inflammation, unlike a measurement of change such as the ACR20. (ii) The EULAR response criteria reflect a clinically meaningful target of disease modifying anti-rheumatic drug (DMARD) treatment (low disease activity). (iii) Because of the incorporation of a measure with an absolute value (the DAS), responses to treatments in clinical trials can be compared meaningfully, particularly in compara-

Table I. Anatomy of the Disease Activity Score (DAS). A typical distribution is shown at the left.

DAS4 = $0.53938 * \div (\text{Ritchie}) + 0.06465 * (\text{Swollen joints}) + 0.330 * \ln (\text{ESR}) + 0.00722 * (\text{General Health})$

- The DAS was developed using DMARD decisions on real RA patients as external standard of low and high disease activity.
- The DAS uses only **4 selected items**, to avoid double-counting of information
- The DAS uses **weights**, for the same reason
- The DAS uses the $\div$ and $\ln$ **transformations** to provide a Gaussian distribution.



Ritchie: Ritchie articular index; swollen joints: 44 swollen joint count; ESR: erythrocyte sedimentation rate (Westergren); GH: general health (100 mm VAS).

Table II. Computation of the Disease Activity Scores (3).

Disease activity score (4 variables):

DAS4 = $0.53938 * \div (\text{Ritchie}) + 0.06465 * (\text{Swollen joints}) + 0.330 * \ln (\text{ESR}) + 0.00722 * (\text{General Health})$

Disease activity score (3 variables):

DAS3 = $0.53938 * \div (\text{Ritchie}) + 0.06465 * (\text{Swollen joints}) + 0.330 * \ln (\text{ESR}) + 0.224$

Ritchie: Ritchie articular index; swollen joints: 44 swollen joint count; ESR: erythrocyte sedimentation rate.

tive/non-superiority trials. (iv) The DAS and the EULAR response criteria will also be useful in future trials of highly effective DMARDs. (v) Trial results can be expressed as a clinically meaningful outcome that may be applied in a clinical setting.

The main disadvantages of indices such as the DAS concern its validity and practical problems such as interpretation and computational difficulties (10). The validity of an index depends on the validity of the measures that are included and their appropriate weighting. The interpretation of an index becomes easier when more information from (e.g. discriminative or predictive) validity studies is available and when familiarity with an index increases. The objective of this overview is to describe the development and validation of the DAS and EULAR response criteria, and to describe their use in research and clinical practice. Parts of this manuscript have already been published (11).

The disease activity score (DAS)

The DAS as originally developed is an index containing the Ritchie articular index (RAI, range 0-78), a 44 swollen joint count (range 0-44), the erythrocyte sedimentation rate, and an optional general health assessment on a visual

analogue scale (range 0-100) (3, 4). A specially programmed DAS calculator, as well as a computer program which can be downloaded from the internet, are available to calculate the DAS (Table II). The DAS has a continuous scale ranging from 0-10, and usually shows a Gaussian distribution in RA populations (Table II). The level of disease activity can be interpreted as low (DAS ≤ 2.4), moderate ($2.4 < \text{DAS} \leq 3.7$), or high (DAS > 3.7) (7). A DAS < 1.6 corresponds to a state of remission according to the American Rheumatism Association (ARA) criteria (12). The DAS is reasonably well correlated with the patient's global assessment of disease activity (Fig.1), despite the scarce weight that the patient-assessed GH item receives in the DAS formula. Therefore the DAS also reflects patient-assessed disease activity.

Development of the DAS

The DAS was developed on the basis of a large prospective study in which the decision of rheumatologists to start a DMARD or to stop such treatment because of disease remission were equated with high and low disease activity, respectively (3, 4). The definition of high disease activity was: a) the start of a DMARD and b) termination of DM-

ARD treatment due to lack of effect. The definition of low disease activity was: a) the termination of DMARD treatment due to remission of the RA; b) not changing a DMARD for at least one year; and c) not starting DMARD treatment for at least one year. Various statistical methods were used to identify the clinical and laboratory variables that explained most of the variance in rheumatologists' decisions on DMARD treatment. These variables were then used to develop the DAS, by means of the following steps:

- 1) *Factor analysis.* A factor analysis was performed on the individual data, resulting in a 5-factor model. The factors could be grouped as follows: variables of inflammation in the blood (Factor 1: ESR, thrombocytes, hemoglobin, CRP, IgM-RF); variables from the joint examination (Factor 2: Ritchie score, tender joints, swollen joints); protein analysis (Factor 3: albumin and α -, β -, and γ -globulins); subjective complaints (Factor 4: Pain, general health, morning stiffness); and impairment (Factor 5: grip strength).
- 2) *Defining disease activity.* The rheumatologists' decisions regarding the start and termination of DMARD treatment were used as an external standard to define high and low disease activity as described above. The clinical assessments were performed by specially trained research nurses, and the rheumatologists made all decisions concerning second-line agents independently of these assessments. The rheumatologists were not aware that their decisions formed part of the investigation.
- 3) *Discriminant analysis.* The values of the 5 factors were entered into a discriminant analysis, using assessments during periods of high and low disease activity as defined above. Factors 3 and 5 were omitted, because grip strength also reflects destruction and protein analysis has low reproducibility. No discriminating power was lost by omitting these factors.
- 4) *Regression analysis.* A stepwise forward multiple regression analysis was used to determine which variables explained the greatest part of

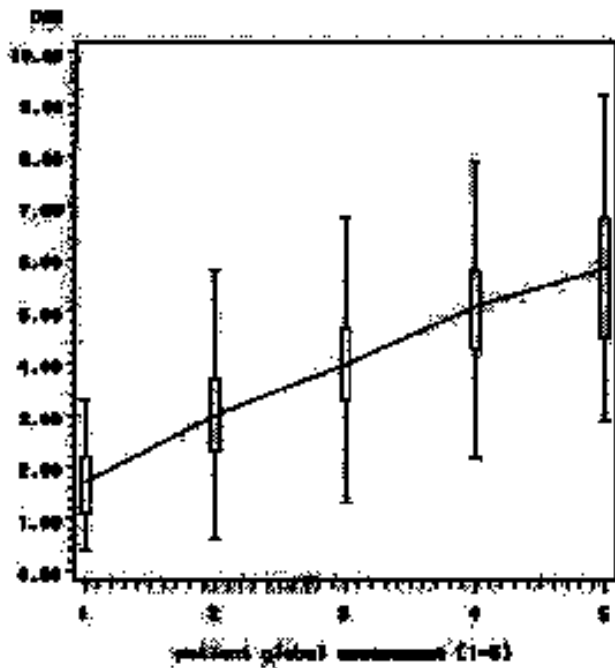


Fig. 1. The mean DAS increases with higher ratings on a 1-5 Likert scale for patient-assessed global disease activity in RA patients from a clinical trial (13).

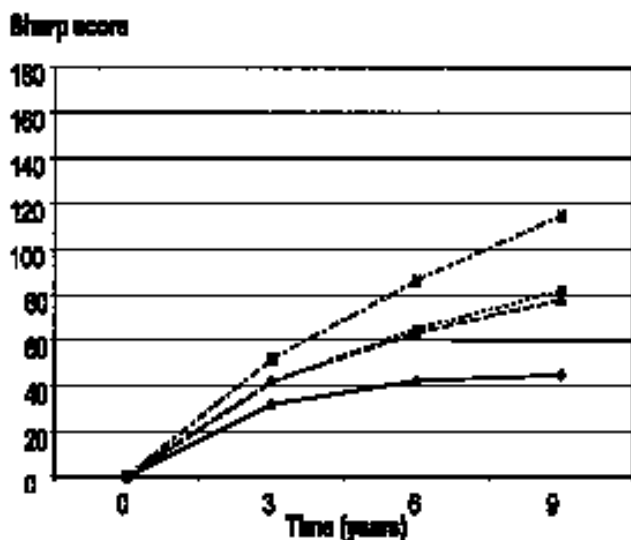


Fig. 2. Progression of joint damage is dependent on having a constant low DAS (lower curve), a fluctuating low DAS or constant high DAS (middle curves), or a fluctuating high DAS (upper curve) (20).

the discriminant function, with ESR, hemoglobin, thrombocytes, morning stiffness, number of tender joints, number of swollen joints, Ritchie score, pain, patient global assessment, CRP and IgM-RF as independent variables. Based on these results the DAS was composed using the Ritchie score, the number of swollen joints, ESR and the patient's global assessment (Table II).

- 5) **Reproducibility.** The reproducibility of the DAS was determined by an inter-period correlation matrix of repeated measurements over 5 months. The measurement – re-measurement

correlation was 0.89 for the DAS with 3 and 4 variables.

In early and established RA

The DAS was developed using data from patients with recent-onset (<3 years) RA. A new DAS formula was subsequently developed using the same procedure and the same cohort, with up to 9 years of follow-up (14). The resulting DAS was almost identical to the DAS as developed in the early-onset sample, which indicates that the disease duration did not influence the construction of the DAS and it was not necessary to replace the original DAS.

Validity of the DAS

The DAS includes measures from the 'core set' of measures that are used to assess the efficacy of DMARDs, but deliberately excludes measures of disability or joint damage (3). The DAS showed greater power than other indices or single variables to discriminate 'low' from 'high' disease activity as defined by DMARD changes (15), and also showed a good capability to discriminate between 'active RA' and 'partial or complete remission' in another study (16). Furthermore, the DAS showed the highest correlations with the single measures and other composite indices used to estimate disease activity (15,17), indicating that the combination of several variables into a single index was advantageous.

The DAS was also well correlated with disability as measured by the Health Assessment Questionnaire (HAQ) (15, 18) and an increase in the DAS was associated with an increase in disability over the same period (19). The value of the DAS over time correlated well with the increase in joint damage over the same time period (Fig. 2) (15,20). It was also shown that fluctuations in the DAS scores contribute to the progression of joint damage (20).

Development and validity of the modified Disease Activity Score (DAS28)

The DAS28 is an index similar to the original DAS, consisting of a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR, and an optional general health assessment on a visual analogue scale (range 0-100) (Table III) (14). Because of the use of reduced and non-graded joint counts, the DAS28 is easier to complete than the DAS. The DAS28 has a continuous scale ranging from 0 to 9.4, and usually shows a Gaussian distribution in RA populations. DAS and DAS28 values cannot be directly compared, but a formula to transform DAS28 into DAS values is available (8). The level of disease activity can be interpreted as low (DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), or high (DAS28 > 5.1) (8). A DAS < 2.6 corresponds to being in remission according to the ARA criteria

(21), meaning that nearly all RA patients in remission have a DAS28 < 2.6, but not all patients with DAS28 < 2.6 are in remission. A change of 1.2 (i.e., 2 times the measurement error) of the DAS28 in an individual patient is considered a significant change (8). The EULAR response criteria can also be applied using the DAS28 (8).

The DAS28 was developed following the same procedure as the DAS (14). The same cohort was used, but with more patients included and a longer duration of follow-up. It was concluded that no capacity to discriminate between 'low' and 'high' disease activity was lost by replacing the 2 comprehensive joint counts by the 28-joint count. The correlation of the modified disease activity score (DAS28) with the original DAS was 0.97.

The DAS28 was validated using the data from the same cohort and data from a very similar cohort (14). Similar correlations of the DAS and the DAS28 with the Mallya index, HAQ and grip strength were found, with no differences between the cohorts. The correlations of the DAS and the DAS28 with radiographically visible joint damage were also similar.

Development and validity of the EULAR response criteria

The efficacy of treatment in clinical trials has generally been determined by comparing group means of changes in disease activity variables. However, a significant difference between groups does not readily indicate the actual number of patients who responded to treatment. For example, in cancer treatment tumor shrinkage is often labeled as response. However, tumor shrinkage (a relative measure) is not prognostic for survival in cancer, but a tumor below the detection limit (an absolute measure) is. Similarly, in RA an absolute level of disease activity might improve the prognostic value for function and joint damage.

Therefore, the EULAR response criteria incorporate some amount of change, as well as a certain level of disease activity (7,22). The EULAR response criteria classify patients as good, moderate or non-responders, using the indi-

Table III. Computation of the modified Disease Activity Scores using 28 joint counts (14).

Modified Disease Activity Score (4 variables):

$$\text{DAS28-4} = 0.56 * \div (\text{TJC28}) + 0.28 * \div (\text{SJC28}) + 0.70 * \ln (\text{ESR}) + 0.014 * (\text{General Health})$$

Modified Disease Activity Score (3 variables):

$$\text{DAS28-3} = [0.56 * \div (\text{TJC28}) + 0.28 * \div (\text{SJC28}) + 0.70 * \ln (\text{ESR})] 1.08 + 0.16$$

TJC28: 28 tender joint count; SJC28: 28 swollen joint count; ESR: erythrocyte sedimentation rate.

Table IV. The EULAR response criteria using the DAS and DAS28 (7, 8).

DAS at endpoint	DAS28 at endpoint	Improvement in DAS or DAS28 from baseline		
		£ 1.2	> 0.6 and £ 1.2	£ 0.6
£ 2.4	£ 3.2	good	moderate	none
> 2.4 and £ 3.7	> 3.2 and £ 5.1			
> 3.7	> 5.1			

vidual amount of change in the DAS and the DAS value (low, moderate, or high) reached (Table IV) (7). A change of 1.2 (i.e., 2 times the measurement error) in a patient's DAS is considered indicative of a significant change (7). For example, a patient must show a significant change ($\Delta \text{DAS} > -1.2$), but must also reach low disease activity (DAS £ 2.4) to be classified as a good responder. The EULAR response criteria can also be applied using the DAS28 (Table IV) (8).

Development of the EULAR response criteria

The EULAR criteria were developed in

the RA cohort of the Radboud University Nijmegen Medical Centre (7, 8). Periods of low and high disease activity were defined using decisions on DMARD treatment as before (Fig. 3). To minimize overlap, the DAS was divided into the three categories of low, moderate and high disease activity. To define relevant change, the measurement error of the DAS was estimated using linear regression of the interperiod correlations, by estimating the measurement – remeasurement correlation r_0 (correlation between DAS measurements with intermediate time interval = 0). From r_0 the measurement error was calculated as 0.6.

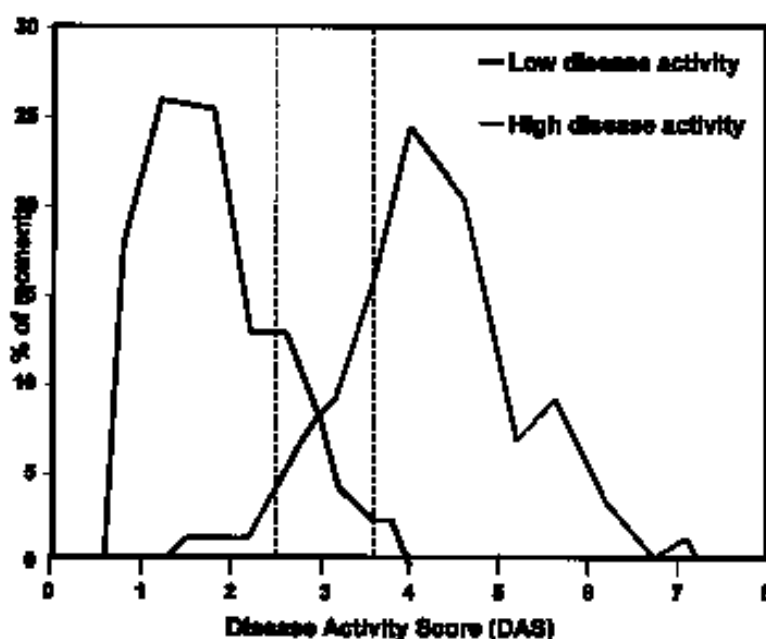


Fig. 3. Borders in the DAS discriminating low, moderate and high disease activity (7).

Validity of the EULAR response criteria

The resulting EULAR response criteria (Table IV) were validated in several clinical trials (7-9). The ACR improvement criteria and the EULAR response criteria agreed reasonably well. Patients who were good or moderate responders showed significantly more improvement in functional capacity and less progression of joint damage than patients with no response (Fig. 4) (7). The validity of the EULAR criteria was confirmed in a study analyzing nine well designed clinical trials that covered a range of responses and differences in response between treatment groups (9). It was concluded that the ACR and EULAR definitions of response in RA performed similarly in differentiating active or experimental treatment from placebo or control treatment. In addition, the ACR and EULAR definitions of response performed comparably in association with overall assessments of improvement and progression of joint damage.

Use of the DAS and EULAR criteria in clinical trials

Indices such as the DAS and the ACR criteria are used in RA clinical trials because it is difficult to objectively measure the underlying rheumatoid inflammation. These indices can thus be regarded as surrogate endpoints for a – currently immeasurable – definitive endpoint. Although the ACR improvement criteria and the DAS-based EULAR response criteria use different approaches, both perform quite well in discriminating placebo from active treatment and in discriminating between two types of active treatment (Table V) (9, 23).

The DAS-based EULAR response criteria were developed to compare treatments in clinical trials, but for this purpose the DAS can also be used as a continuous endpoint. Then the difference between two drugs or between a drug and placebo can readily be interpreted in terms of the DAS. The advantage of using a continuous DAS is that there is no loss of power due to categorization. Also, when no “success or failure” cut-off point is used, more

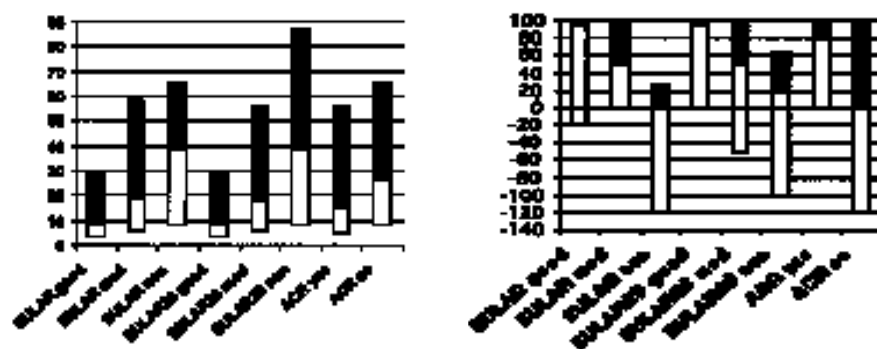


Fig. 4. Differences in (a) the progression of joint damage (Sharp) score and (b) %change in HAQ score between response categories. The bars show P10-P50-P90 (8).

Table V. Discrimination between two treatments in a clinical trial. *Combination treatment (n = 76) vs sulphasalazine treatment (n = 79). Higher chi-square (c^2) values point to stronger discriminative ability. Data from (23).

Criterion	Week 16 improved*	c^2	Week 28 improved*	c^2
ACR improvement				
20% threshold	72 vs 32%	25.7	72 vs 49%	8.6
50% threshold	43 vs 14%	16.6	49 vs 27%	8.1
70% threshold	16 vs 6%	3.6	29 vs 10%	8.8
EULAR response		20.2		13.4
Moderate	49 vs 41%		39 vs 39%	
Good	37 vs 15%		47 vs 24%	

precision is available to assess the benefits of very effective treatments. Especially when the response criteria are relatively “easy” to meet, the effectiveness of the treatment may be underestimated. When on the other hand the response criteria are “too difficult” to fulfill, none of the patients in the treatment arms may be responders and an actual difference between two treatments cannot be shown. However, cut-off points for continuous measures may be useful as (secondary) trial endpoints, when the categories have prognostic meaning and are clinically meaningful.

When using the DAS, cut-off points in the DAS may be chosen as a function of the trial objectives. One example is the use of the DAS in the EULAR criteria or the classification of the DAS to indicate low disease activity. One reason for adopting cut-off points is that measures of success or failure are generally more easily interpreted by clinicians than continuous measures. Interpretation of a response measure with two categories (“yes – no”) such as the ACR improvement criteria is easier

than when a response measure has 3 categories like the EULAR response criteria (“good – moderate – none”). Interpretation of the categories of a continuous measure is enhanced when the categories have prognostic meaning.

An advantage of the EULAR criteria over change criteria in relation to the progression of joint damage is illustrated in Figure 4. The reason is that in RA, it is not the change in rheumatoid inflammation, but low or absent inflammation that has the best prognostic value for the development of joint damage (20,24). As more effective new drugs are developed, measures like “time-to-low-disease-activity” or “time-spent-in-low-disease-activity” may become useful as endpoints in clinical trials. Such endpoints can already be measured using the DAS and DAS28, and lower cut-off points may be chosen when appropriate.

Use of the DAS in clinical practice

In clinical practice, there is general agreement that rheumatoid inflammation should be controlled as soon as

possible, as completely as possible, and that control should be maintained for as long as possible consistent with patient safety (25). Accepting that the goal of treatment is to reach optimal control of rheumatoid inflammation or even remission, it is clear that the management of RA should include systematic and regular quantitative evaluation of rheumatoid inflammation. Monitoring of the long-term effects, especially disability and joint damage, may also be useful in practice (26).

For the assessment of rheumatoid inflammation in daily clinical practice, the DAS and DAS28 offer certain advantages in that they are measures that can be used in clinical studies, especially clinical trials. This facilitates knowledge transfer or "evidence based practice", because it is easier to translate study results to one's own practice. Furthermore, as both the DAS and DAS28 are measures with absolute values, they can be used to determine and evaluate the status and course of disease activity in individual RA patients, in contrast to relative measures such as the ACR improvement criteria (26, 27). In practice, the DAS28 may appear to be more feasible than the DAS because of the reduced and non-graded joint counts. At the same time, it must be underlined that the DAS and DAS28 can support clinical decision-making, but they cannot replace careful patient examination and inquiry. Nonetheless, systematic monitoring of inflammatory activity may serve several goals in practice: e.g., to recognize whether the therapy chosen is necessary and effective, to ensure that rheumatoid inflammation remains under control, and to adjust DMARD dosage or therapy in the titration of disease activity (25, 26). Monitoring alone does not have an effect on health, but appropriate treatment may provide benefit.

A good example is the use of the DAS-28 to monitor response and adjust the dose in anti-TNF α therapy (28). Dose titration with these expensive therapies may prevent over-treatment as well as under-treatment, saving costs and probably also preventing long-term side effects. Besides dose adaptation, the treatment strategy may also be adjusted

using the DAS or DAS28.

In the TICORA study, the efficacy of a "tight control" treatment strategy including monitoring and protocolised increases in DMARD therapy was studied. DMARD therapy was steadily increased as long as the DAS exceeded 2.4. (low disease activity is defined as a DAS $\leq$ 2.4). Patients treated intensively showed a greater mean decrease in the disease activity score (DAS), were more likely to be in remission (65% vs. 16%), and had a greater reduction in disability and less progression of joint damage (29) compared with patients undergoing a "usual care" strategy. In a comparable monitoring trial (TRAC), the choice of treatment strategy was freely determined by the clinician, whereas the parameter of low disease activity according to the DAS28 (DAS $\leq$ 3.2) was strictly applied in the intervention group (30). The effect in the TRAC trial was much less marked than that in the TICORA trial, which could be explained by the less intense treatment that was employed in the TRAC study.

Conclusions

The DAS, DAS28 and EULAR response criteria have been extensively validated and are finding increasing use in RA clinical trials and to monitor individual RA patients. Several formulas are available for the calculation of the DAS, which may cause some confusion (31). Values of the DAS and DAS28 are not directly comparable, but a transformation formula is available.

Major advantages of the DAS are that: it contains more information than single measures alone, it has a continuous scale with a Gaussian distribution, its values are clinically interpretable, and it is sensitive to small effects. The DAS is used in the EULAR response criteria, which reflect a clinically meaningful target (reaching low disease activity) with prognostic value for the progression of joint damage. When even more effective new drugs become available in the future, measures such as "time-to-low-disease activity" or "time-in-low-disease-activity" may become applicable as endpoints in clinical trials; these possible endpoints can already be measured using the DAS and DAS28.

cal trials; these possible endpoints can already be measured using the DAS and DAS28.

The DAS can be used as a guide in the suppression of RA disease activity with DMARDs or "biologicals". However, even when the DAS is a useful guide for treatment decisions, it does not replace careful patient examination and inquiry. Self-assessment of RA disease activity by the patient may be less laborious for the physician than assessment of the DAS. Patient assessment of disease activity may complement but not replace the DAS (32).

Acknowledgement

We are grateful for the editing of the text by Mrs Aggie Smetsers, MA.

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