The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28)

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ABSTRACT

In rheumatoid arthritis, disease activity cannot be measured using a single variable.

The Disease Activity Score (DAS) has been developed as a quantitative index to be able to measure, study and manage disease activity in RA in daily clinical practice, clinical trials, and long term observational studies. The DAS is a continuous measure of RA disease activity that combines information from swollen joints, tender joints, acute phase response and patient self-report of general health. Cut points were developed to classify patients in remission, as well as low, moderate, and severe disease activity in the 1990s. DAS-based EULAR response criteria were primarily developed to be used in clinical trials to classify individual patients as non-, moderate, or good responders, depending on the magnitude of change and absolute level of disease activity at the conclusion of the test.

Introduction

Rheumatoid arthritis (RA) is a chronic systematic inflammatory disease with peripheral synovitis as its main manifestation. The presentation of the disease and the course over time is highly variable both within as well as between individuals. The symptoms and signs of RA may vary from joint complaints like pain, stiffness, swelling and functional impairment, to more constitutional complaints like fatigue and loss of general health. Because of this variety in disease expression a large number of variables have been used in the past decades to evaluate status and course of RA disease activity and its consequences (1).

Disease Activity Score

It was common to evaluate treatments in RA comparing the group means of changes in several individual variables, like the acute phase response and joint counts as a *gold standard* to assess disease activity did not exist. In the early 1980s, a need for individual response criteria in RA was recognised, also because a relationship was suggested between genetic factors (HLA antigens) and response to treatments (2). Some composite indices for disease activity were available, such as the Lansbury index and the Mallya index. However, these indices were quite comprehensive and not easily scored, and individual response criteria were not available (3). Based on the Mallya index, a 4 component Index of Disease Activity (IDA) was developed as well as the Percentage of improvement of the IDA (PIDA score). Individual response criteria were developed from the IDA and PIDA, and a relationship between response on parenteral gold treatment and response was found (4).

As a follow-up, the disease activity score (DAS) was developed (5). It was shown that the DAS, which combines information from swollen joints, tender joints, acute phase response and patient self-report of general health into one continuous measure of RA disease activity, had the best correlational, criterion and construct validity compared to several disease activity variables individually (6). Quite unique was that the DAS was developed using an external standard of RA disease activity, based on changes in disease-modifying antirheumatic drug (DMARD) therapy by the rheumatologist.

EULAR response criteria

Many efforts have been made in the past years to standardise the assessment of RA aiming to render study results interchangeable. Consensus has been reached about a minimal set of disease activity variables to be measured in clinical trials, known as the RA core data set (7). As a further step, re-

Competing interests: none declared.

sponse criteria based on these core-set variables have been developed by the European League against Rheumatism (EULAR) (8) and the American College of Rheumatology (ACR) (9).

Advantages

The DAS and the EULAR response criteria have several advantages:

1. The continuous scale of the DAS has absolute meaning making its value interpretable at any visit, unlike a change measure.
2. The EULAR response criteria reflect a clinical meaningful target of DMARD treatment (low disease activity).
3. Responses to treatments in clinical trials may be compared meaningfully, according to an absolute measure, especially in comparative/non-superiority trials.
4. Trial results may be expressed as a clinical meaningful outcome that can be translated into clinical use.

As a continuous measure with an absolute value and extensive validation, the DAS, and the DAS-based EULAR response criteria provide quite useful measures.

Development of the DAS

The starting point for the development of the DAS was that in clinical practice an opinion of disease activity in a patient with RA is formed from a combination of information, such as laboratory and clinical variables, and overall impression of the patient. In patients with RA it is not possible to measure disease activity with one single variable as none of these could serve as *gold standard* for disease activity. This is in contrast with for instance monitoring bloodpressure in patients with hypertension or measuring the cholesterol level in patients with hypercholesterolaemia (10). Formalising this clinical judgement into a quantifiable disease activity index would provide an opportunity to recognise, analyse, and influence the process of disease activity. In addition, such an instrument could be used to study and compare the efficacy of treatments in clinical trials.

The DAS was developed using a large prospective study, in which the decisions of rheumatologists to start a DMARD or to stop such treatment because of disease remission were equated with high disease activity and low disease activity, respectively (5, 6). The definition of high disease activity was a) start of a DMARD; b) termination of DMARD treatment due to lack of effect. The definition of low disease activity was:

a) termination of DMARD treatment due to remission of the rheumatoid arthritis;
b) not changing a DMARD for at least one year;
c) not starting DMARD treatment for at least one year.

The clinical and laboratory variables that explained most of the variation of the rheumatologists' decisions on DMARD treatment were composed into the disease activity score (DAS), using discriminant analysis and other statistical methods.

1. Factor analysis

A factor analysis was performed on the individual data, resulting in a 5-factor model. The factors are described in Table I and can be labelled as follows: variables of inflammation in the blood (factor 1), variables of the joint examination (factor 2), protein analysis (factor 3), subjective complaints (factor 4) and grip strength (factor 5).

2. Defining disease activity

The rheumatologists` decision on starting and terminating DMARDs was used as an external standard to define high and low disease activity as described above. The rheumatologists made all the decisions on starting and withdrawing the second line agents independently of the clinical assessments for the study, done by specially trained research nurses. The rheumatologists did not know that their decisions were part of the investigation.

3. Discriminant analysis

The factor values of the 5 factors were used in a discriminant analysis, using assessments during defined high and low disease activity. Factors 3 and 5 were omitted, because grip strength also reflects destruction and protein analysis has low reproducibility. No discriminating power was lost by omission of these variables.

4. Regression analysis

A stepwise forward multiple regression analysis was used to determine which variables explain the greatest part of the discriminant function, with ESR, hemoglobulin, 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, number of swollen joints, ESR and patient global assessment (Table II).

5. Reproducibility

The reproducibility of the DAS was determined by an interperiod correlation matrix of repeated measurements over five months. The measurement-re-

Table I. Five factor model of the individual data.
VAN DER HEIJDE *et al. Ann Rheum Dis* 1990; 49: 916-20.

Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
ESR	Ritchie score	Albumin	Pain	Grip strength
Thrombocytes	Painful joints	α_1-globulin	General health	
Haemoglobin	Swollen joints	α_2-globulin	Morning stiffness	
CRP		β-globulin		
IgM-RF		γ-globulin		

Table II. Computation of the Disease Activity Scores. VAN DER HEIJDE *et al. Ann Rheum Dis* 1990; 49: 916-20.

Disease activity score (four variables)=

DAS4=0.53938*√(Ritchie) + 0.06465*(Swollen joints) + 0.330*ln(ESR) + 0.00722*(General Health)

Disease activity score (three variables)=

DAS3=0.53938*√(Ritchie) + 0.06465*(Swollen joints) + 0.330*ln(ESR) + 0.224

Table III. Mean, standard deviation and standardised difference for high and low disease activity. VAN DER HEIJDE *et al*. *Ann Rheum Dis* 1992; 51: 177-81.

Variable	High disease activity		Low disease activity		
	Mean (n=129)	SD	Mean (n=115)	SD	Standardised difference
DAS	4.27	1.11	2.50	1.01	1.66
Mallya index	2.62	0.58	1.89	0.48	1.37
IDA	2.41	0.62	1.60	0.47	1.46
Pain	6.14	2.30	3.34	2.79	1.10
Tender joints	4.01	1.63	2.19	1.76	1.08
Swollen joints	12.60	7.25	4.16	4.93	1.35
Ritchie index	3.82	1.56	2.05	1.51	1.15
Morning stiffness	2.21	1.31	1.06	1.14	0.93
ESR	3.52	0.88	2.72	0.93	0.89
CRP	2.27	0.80	1.59	0.62	0.94
Haemoglobin	7.44	1.07	7.88	0.69	0.49
Grip strength	7.18	1.78	5.48	2.32	0.82

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

Validation of the DAS

As a first step, validity of the newly developed DAS was assessed against single variables and other indices used to measure disease activity in RA (10). A cohort from the University Hospital Groningen was studied to assess *criterion* validity. The RA patients were divided into two groups with low or high disease activity according to the same explicit rules as used in the development of the DAS (Table III). Among all available measures, the DAS had the highest discriminative power to distinguish between the 2 groups.

Construct validity

Construct validity of the DAS was assessed using data from the Nijmegen and Groningen clinics. The DAS and the Ritchie Index had the highest correlations with Health Assessment Questionnaire (HAQ) scores for physical disability. Further, correlations of the three indexes with other disease activity variables were comparable and substantially higher than of single variables. Correlations between increase in joint damage in periods of 6 months and mean clinical and laboratory variables over same period were also studied. It was shown that ESR, CRP, swollen joints and all three indexes had the highest correlations; all other variables were substantially lower (6, 10).

In support of the construct validity of the DAS, it was shown in early RA that in addition to the genetic markers HLA-DR2 and DR4, high disease activity, measured as ESR, CRP or DAS, at 0 and 6 months was significantly associated with radiographic damage at 2 years (11).

Long term studies

The DAS as measure of disease activity was also shown in a long-term study of the relationship between disease activity, joint destruction and functional capacity over 9 years of follow-up.

Using a general linear mixed model for longitudinal data (repeated measurement) it was shown that in early RA, functional capacity was most associated with disease activity, and in late disease with joint damage (12). Using mixed models for longitudinal data analysis (13), patients who had a constant low disease activity over time had about half the progression of joint damage as patients who had constant high disease activity (Fig. 1). Moreover, fluctuating disease activity added to progression of joint damage.

In early and established RA

The DAS was developed using data from patients with recent-onset (<3 years) RA. Later, a new DAS formula was developed using the same procedure and the same cohort, with up to 9 years follow-up (14). The resulting DAS was almost identical to the DAS as developed in the early-onset sample. Therefore, disease duration did not influence the DAS, and there was no need to replace the original DAS.

In conclusion, the DAS was developed using rheumatologists' judgements of disease activity in clinical practice. This DAS turned out to be one of the most valid measures of disease activity in comparison with widely used variables. This combination of a few variables, which have lesser value as single measurements, into an index, greatly enhances their validity. As the DAS was developed using clinical judgements, it also may be concluded that clinical judgement by rheumatologists

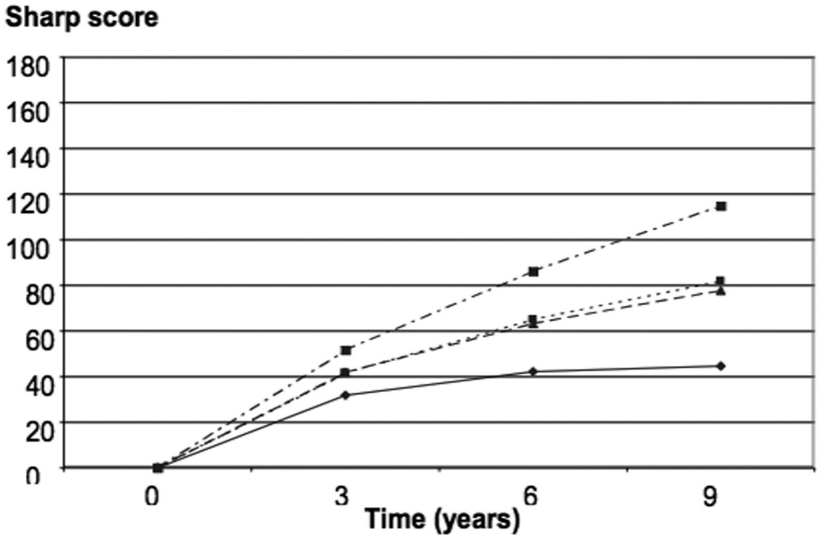


Fig. 1. Progression of joint damage is dependant of having a constant low DAS (lower curve), a constant high DAS (middle square curve), or a fluctuating high DAS (upper curve). WELSING *et al*. *Arthritis Rheum* 2004; 50: 2082-93.

correlate with clinical outcome, namely physical disability and joint damage.

Development and validation of the DAS28

The DAS includes 2 comprehensive joint counts, the Ritchie Articular Index (RAI) and a 44 swollen joint count, plus the erythrocyte sedimentation rate and a General Health assessment (VAS). It was shown that joint counts consisting of 28 joints are as valid and reliable as more comprehensive joint counts in clinical care (15) and in clinical trials, although all joints should be examined (in contrast to only some being measured). Therefore, a modified disease activity score was developed, using 28 joint counts (14).

Development

Development of the DAS28 mirrored the development of the DAS. A study was conducted in the outpatient department at the University Hospital Nijmegen of 227 patients who had RA according to ACR criteria, disease duration <1 year, and no prior DMARD therapy. Patients were systematically assessed by specially trained research nurses and were seen by rheumatologists at least once every three months. The development of the DAS28 involved the following steps:

1. Principal component analysis

Initially, principal component analysis was performed, resulting in 5 factors with an eigenvalue >1. These factors could be described as: "laboratory measures", "joint counts", "functional status measures", "subjective assessments by the patient" and "globulins".

2. Canonical discriminant analysis

To select the variables that best discriminate between high and low disease activity, canonical discriminant analysis was performed on all variables. This resulted in a discriminant function of 9 variables (pain, haemoglobin, ESR, grip strength, morning stiffness, 44 swollen joint count, RAI, α_2- globuline, β- globuline) with a canonical correlation of 0.81 (a DAS with 9 variables). When applying canonical discriminant analysis to the 4 variables RAI, 44-SJC, ESR, and GH, which are the components of the original DAS, this resulted in a function with also a canonical correlation of 0.81. As both correlations were equal, further analyses were conducted with these 4 measures.

3. Joint count replacement

In the next step, the 2 comprehensive joint counts were replaced by 28-joint counts and the discriminant function was recalculated. The resulting canonical correlation was 0.82, thus identical with the correlation using full joint counts. The correlation of the modified disease activity score (DAS28) with the original DAS was 0.97. The calculation of the DAS28 is shown in Table IV.

Validation

The DAS28 was validated using the data from the same cohort and data from a very similar cohort from the University of Groningen (14). Similar correlations of the DAS and the DAS28 with HAQ and grip strength were found, with no differences between the clinics. Both scores correlated identically with the IDA and the Mallya index. The correlations of the DAS and the DAS28 with radiograhically visible joint damage were also the same. In conclusion, the DAS28, including reduced joint counts, is a valid measure of disease activity. The features of the original DAS generally apply to the DAS28, due to the developmental procedure. However, the DAS and DAS28 values are not directly interchangeable. Next to this in an individual patient it might be clinically necessary to assess joints outside the 28 joint count for instance if the patient is complaining about the feet joints or to make sure in case of remission that no single active joint is present.

Table IV. Computation of the modified Disease Activity Scores using 28 joint counts. PREVOO MLL *at al*. *Arthritis Rheum* 1995; 38(1): 44-48.

Modified Disease Activity Score (four variables)=

DAS28-4=0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR) + 0.014*(General Health)

Modified Disease Activity Score (three variables)=

DAS28-3=[0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR)]1.08 + 0.16

Table V. The EULAR response criteria using the DAS and DAS28.

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		
>2.4 and ≤3.7	>3.2 and ≤5.1		moderate	
>3.7	>5.1			none

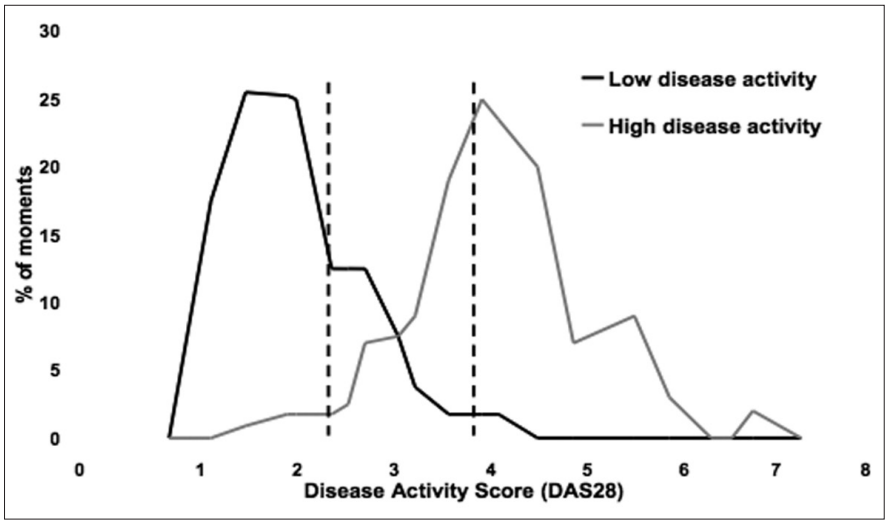


Fig. 2. Borders in the DAS discriminating high, moderate and low disease activity. VAN GESTEL *et al*. *Arthritis Rheum* 1996; 39(1): 34-40.

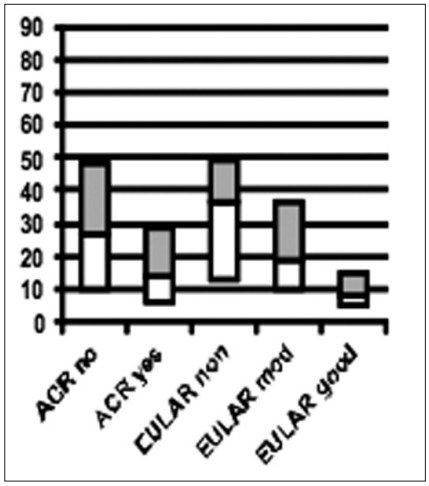


Fig. 3. Differences in progression of joint damage (Sharp) score between response categories. VAN GESTEL *et al*. *J Rheumatol* 1999; 26: 705-11.

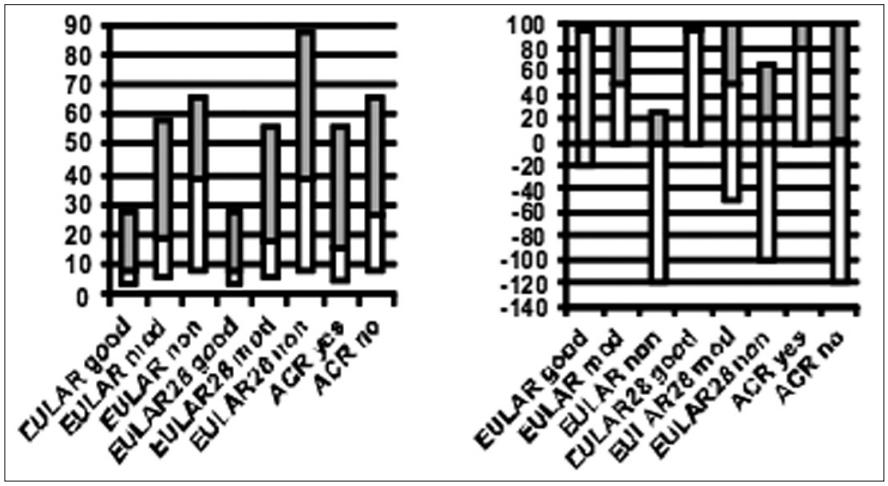


Fig. 4. Differences in progression of joint damage (Sharp) score (left figure) and % change in HAQ score (right figure) between response categories. The bars show P10-P50-P90. VAN GESTEL *et al*. *Arthritis Rheum* 1998; 41(10): 1845-50.

Development and validation of the EULAR response criteria

Efficacy of treatment 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, tumour shrinkage is often labelled as response. However, tumour shrinkage (a relative measure) is not prognostic for survival in cancer, but a tumour below detection limit (an absolute measure) is. Similarly in RA, response ideally should incorporate an absolute level of disease activity, to have prognostic meaning. Therefore, it was decided that response criteria should incorporate some significant amount of change as well as a certain level of low disease activity.

Development: high and low activity

The EULAR criteria were developed in the RA cohort of the University Hospital Nijmegen (7). Periods of low disease activity and high disease activity were defined using decisions on DMARD treatment as before (Fig. 2). To minimise overlap, the DAS was divided in three categories, of low, moderate and high disease activity.

Development: relevant change

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). The measurement error was calculated as 0.6. A good response was defined as a change of 1.2 (two times the measurement error), as well as reaching low disease activity (DAS≤2.4).

Validity of EULAR response

The resulting EULAR response criteria (Table VI) were validated in a 48 week double blind randomised clinical trial that comparedsulfasalazine *versus* hydroxychloroquine in 60 patients with recent-onset RA. The EULAR response criteria and ACR improvement criteria. showed good agreement (7, 17). Patients with a good EULAR response had significantly more improvement in functional capacity than patients with a moderate or no response (Fig. 3). Patients with no response had significantly more progression in joint destruction (p=0.0001) (Fig. 3). This difference in progression of joint destruction was less clear between ACR responders and non-responders (p=0.03). With the EULAR response criteria, patients in the sulfasalazine-treated group manifested a significantly better response, which was not seenby the ACR criteria. The WHO/ILAR criteria also did not indicate differences, similar to the ACR, but not EULAR criteria.

Validity with reduced joint counts

The validity of the EULAR response criteria using the DAS28 was studied using a randomised double-blind placebo-controlled trial of 105 patients treated with MTX, Sulfasalazine or both (16). Response was evaluated at week 52.

No significant differences between treatment groups were found using any criteria. There was a significant association of EULAR response with change in functional capacity (HAQ) and progression in joint damage (Sharp score), (Fig. 4). As the validation of the DAS and the DAS28 response criteria took place in a single trial (16). the validation was further analysed in nine well done clinical trials that covered a range of response and differences in response between treatment groups (17). It was concluded that ACR and EULAR definitions of response in RA performed similarly in differentiating active (or experimental) treatment from control (or placebo) treatment. In addition, the ACR and EULAR definitions of response performed comparably in association with overall assessments of improvement and progression of joint damage.

Overview of psychometric properties

Instruments aimed to measure a process, like the DAS, should be reliable, valid and responsive to change. In absence of a single *gold standard* measure applicable to all individual

patients, *criterion validity* cannot be assessed in an ideal manner. Therefore, assessment of validity is approached in several ways. *Content validity* refers to the appropriateness of the contents of a measure. *Concurrent validity* refers to the performance of a measure in comparison to measures applied with the same objective. *Construct validity* refers to the performance of a measure in the framework of a philosophical construct.

DAS and DAS28

Reliability: Test-retest reliability of the DAS was determined by an interperiod correlation matrix of RA patients with ≥3 years follow-up and 3-monthly assessments. The measurement-remeasurement correlation was r=0.80, and the measurement error was calculated as 0.6, as noted above (7). A significant change in DAS and DAS28 for individual patients was defined as 2 times the measurement error (2 x 0.6) = 1.2 (7, 16); changes that large are unlikely (*p*0.05) the result of random measurement error.

Criterion validity: In the absence of a 'gold standard' to judge RA disease activity, in development of the DAS and the DAS28, physician judgement of low and high disease activity was used as an external standard (5, 14). In a validation study, the DAS showed larger power than other indices or single variables to discriminate low from high disease activity (9, 10). The DAS showed a high predictive capacity (pc = 0.93) to discriminate'active RA' from 'partial or complete remission' in a similar validation study (18).

Content validity: The DAS and DAS28 include measures from the 'core set' of measures used to assess the efficacy of DMARDs. To avoid duplicationity (double counting of information from different variables), few items were selected from all possible disease activity measures and the 4 selected items were then weighted, using an external standard for high and low disease activity. The DAS and DAS28 deliberately exclude measures of disability or joint damage; these constructs should be measured separately from disease activity (5, 14).

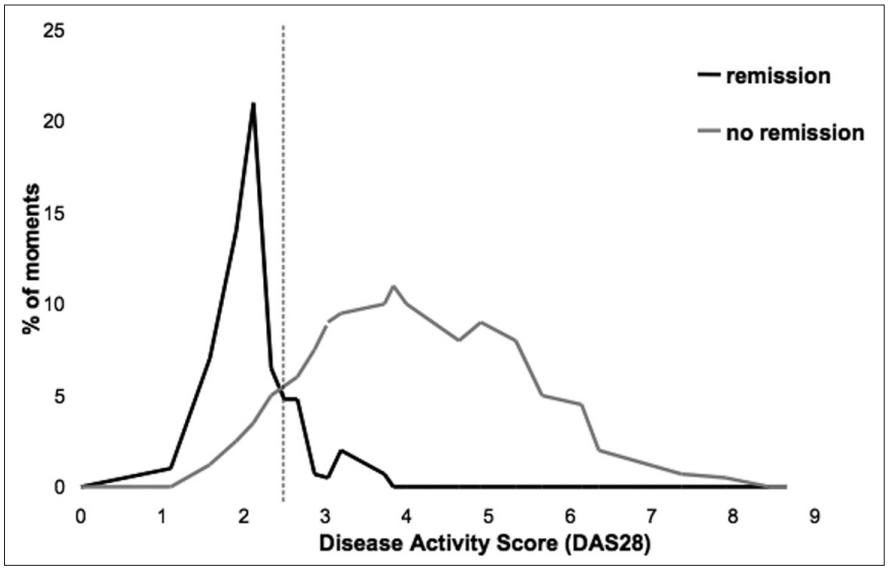


Fig. 5. A cut-off point of DAS28<2.6 is associated with being in remission according to the ARA criteria.

Concurrent validity: The DAS was well correlated (mean r=0.61) with 12 other common estimators of disease activity, and all composite indices showed higher correlations than the single variables (9, 10). In a study comparing several composite indices, the DAS and DAS28 had the highest correlations with assessor's (r >0.80) and patient's (r >0.60) global assessment of disease activity (19). The DAS28 was correlated at very high leves (r >0.94) with the original DAS, suggesting that measurement properties were virtually identical (14).

Construct validity: Analyses generally are conducted to determine if a process (disease activity over time) is associated with an expected outcome (disability and joint damage). The DAS is correlated significantly with disability as measured with the HAQ (10, 20). Although the HAQ is influenced both by disease activity as well as joint damage (and co-morbidities), this correlation remained fairly constant (r=0.51 – 0.68) throughout 12 years of disease duration (20). When evaluated over time using longitudinal data analysis an increase in the DAS was associated with an increase in disability over the same period (12). Cross-sectionally, the DAS28 was well correlated (r=0.49 and r=-0.46) with disability as measured with the HAQ or short form 36 SF-36 Physical Functioning scale (21). Joint damage may be regarded as the result of the activity of the RA disease process over time. The mean DAS and increase and fluctuations in the DAS were well related to increase in joint damage over the same time period (10, 13). Likewise, the time integrated DAS28 (area under the curve) was well related to increases in joint damage over the same time period (14).

Responsiveness to change: In a trial comparing sulfasalazine with a combination of methotrexate, sulfasalazine and prednisolone, all composite indices were more responsive than single core set measures. The ACR20% criteria were most responsive; the Standardised Response Mean (mean change divided by SD change) of the DAS was about half as large (22).

In another trial in which flares of disease activity were analysed, the standardised effect size (SES: difference of within-group changes divided by the pooled SD of change) of the DAS28 was 1.56, which was higher than its components (SES<1.18) or the HAQ (SES=1.16), but lower than patient assessed pain (SES=1.67) (23).

EULAR criteria

The EULAR response criteria make use of the DAS or the DAS28. The EULAR response criteria generally are evaluated for their performance in RCTs and their association with change

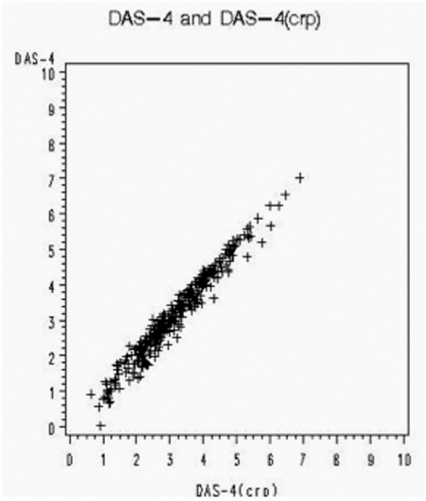


Fig. 6. Scatterplot of the DAS calculated using ESR (y-axis) and CRP (x-axis).

DAS formulas using CRP:
DAS28-CRP=0.56*√(TJC28)+0.28*√(SJC28)+0.36*ln(CRP+1)+0.014*(General Health)+0.96
DAS-CRP=0.54*√(RAI)+0.065(SJC44)+0.17*ln(CRP +1)+0.0072*(General Health)+0.45

in HAQ disability and radiographic joint damage.

Discriminative ability. It was shown that the EULAR response criteria performed equal (17, 22) or better (7) than the modified ACR or WHO/ILAR response criteria in discriminating the stronger treatment from control treatment in RCTs. No meaningful differences were found between ACR and EULAR criteria when using full or reduced joint counts (6).

Construct validity. Good responders according to the EULAR criteria showed significantly more improvement in pain (p<0.001) and disability (p<0.001) than moderate and non-responders. Joint damage progressed in moderate (p=0.005) and non-responders (p=0.01) but not in good responders (p=0.94) (24). Earlier studies also showed that the EULAR response criteria clearly are related to change in disability (7) and progression of joint damage (7, 16) and perform similarly or more effectively than than the ACR response criteria (25).

Assessment of remission

The ultimate goal of medical treatment in RA may be formulated as to reach a state of remission, which may be temporarily and often require ongoing therapy with DMARDs or *biological* agents. Next to halting radiographic progression and preserving function one assumes that this state would also lead to less RA related morbidity and mortality. Although progress has been made in recent years to find a uniformly acceptable definition of remission, there remain several criteria for remission in RA. Remission can be assessed clinically using the ACR/EULAR preliminary criteria, 26 which are very strict or by using the less stringent cut point of the Disease Activity Score (DAS or DAS28) (26, 27).

A DAS<1.6 or a DAS28<2.6 (Fig. 5) corresponds with being in remission according to the ARA criteria (28, 29). However, disease activity may not be regarded as an *on/off* phenomenon, and disease activity of an individual patient may fluctuate on a level of *no or minimal* disease activity. Accordingly, it may be desirable to express disease status of a patient as the cumulative amount of disease activity over a certain period of time, or the mean disease activity in a certain period, rather than classifying a patient as in remission or not at a given point in time (30).

Using CRP OR ESR?

C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28 (31). CRP is regarded as a more direct measure of inflammation than ESR, and more sensitive to short-term changes. Due to this, differences between ESR and CRP at a certain time point in the disease process may exist. Like ESR, CRP production is associated with radiological progression in RA, and is considered at least as valid as ESR to measure RA disease activity. Prospectively collected data from the Nijmegen University Hospital cohort of RA patients (n=334) were used to develop and test (split-sample) of DAS-CRP. As discussed above ESR and CRP are not identical, the relationship between transformations of ESR and CRP was imperfect, especially in the lower ranges. But the relationship was linear and did not change over time (Fig. 6).

New DAS and DAS28 formulas including CRP were devised using linear regression, with the purpose to give a good estimate of DAS values on group level (Fig. 6). However there was a considerable lack of individual agreement, therefore DAS28-ESR and DAS28-CRP scores are not interchangeable within individual patients. In general the DAS28-CRP scores are about 0.2 points lower than the DAS28-ESR scores (32, 33).

Use in daily clinical practice

For clinical practice, there is general agreement that rheumatoid inflammation should be controlled as early as possible, as completely as possible, and that control should be maintained for as long as possible, consistent with patient safety (34).

Accepting that the goal of treatment is to reach optimal control of rheumatoid inflammation or even remission, it is clear that management of RA should include systematic and regular evaluation of rheumatoid inflammation (35). Monitoring of long-term effects, especially disability and joint damage, also may be useful in practice.

For assessment of rheumatoid inflammation in daily clinical practice, it is an advantage that the DAS and DAS28 are measures that are used in clinical studies, especially clinical trials. This facilitates knowledge transfer, or *evidence based practice*, because it is easier to translate study results to the practice of an individual rheumatologist (36). Furthermore, as the DAS and DAS28 are absolute measures, suited to determine and evaluate the status and course of disease activity in individual RA patients. Relative measures, as the ACR improvement criteria, are not suited for this purpose (Fig. 7) (37).

In practice, the DAS28 may appear to be more feasible than the DAS because of the reduced joint counts. At the same time, it must be clear that the DAS and DAS28 can support clinical decision-making, but they do not replace careful patient examination and inquiry. For instance further investigations should be done in case of discrepancies between the acute phase response and the joint scores. Infections or a *fibromyalgia-like* behaviour can cause discrepant elevations in the acute phase response

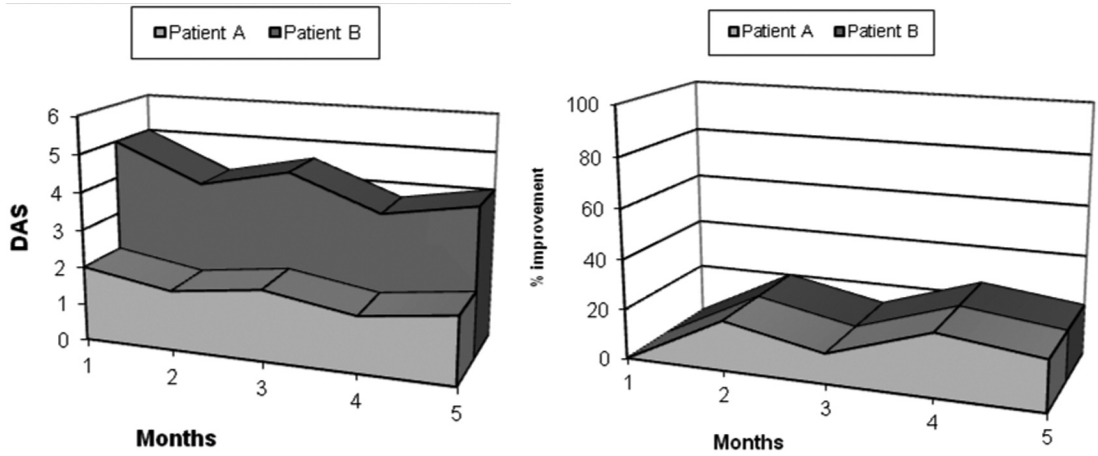


Fig. 7. Both fictitious patients A and B show equal (20%) improvement, but have highly different levels of disease activity.
VAN RIEL PLCM, VAN GESTEL AM. *Arthritis Rheum* 2001; 44(7): 1719-22.

or tender joint count (and patient global), respectively.
In daily clinical practice, regular and systematic monitoring of inflammatory activity has several practical uses (38, 39). The most important practical uses may be:

- Understand if the therapy chosen is needed and effective.
- Assure that rheumatoid inflammation is still under control.
- Reduce the likelihood of over treatment.
- Identify rapidly advancing disease, where *aggressive* treatment may be needed.
- Support the choice of specific DMARDs.
- Adjust DMARD dosage in the titration of disease activity.
- Support treatment expectations. For example, a full response may take longer than expected, and it may be appropriate to continue the therapy if an adequate response may be achieved by additional treatment time.

DMARD dose titration
A good example of dose titration involves therapy with anti-TNF-α agents. Dose titration with these expensive therapies may prevent overtreatment as well as undertreatment. A study was undertaken in 21 patients with low disease activity in an open extension study of anti-TNF-α, lasting 40 weeks (40). The dose of anti-TNF-α was reduced stepwise and dosing intervals were kept stable (Fig. 8).
Dose reduction was accomplished in 15 patients, and the total amount of anti-TNF-α given was reduced by 67%. At the end of the study, the mean DAS28 had not changed. This type of approach may not only save costs but also redue the likelihood of long-term side effects. Several studies to taper and discontinue therapies in patients with RA have been reported in recent years primarily anti TNF agents. Patients who had a DAS28 less than 2.6 had a lower chance to experience an exacerbation of disease activity after stopping TNF treatment (41). Flare criteria based on the DAS28 have been developed for this purpose (42).

DMARD strategy
Analysis of the effectiveness of adaptation of treatment strategy is even more complex than DMARD titration, due in large part to the non-homogeneous treatment approach in RA and the clustered nature (*i.e.* the dependence of patients on their rheumatologist) of such a study (43). A randomised controlled trial was performed (n=110) to test whether tight control of early rheumatoid arthritis can be achieved using standard DMARDs within an intensive treatment protocol, and whether this tight control will result in significantly better outcomes (44). Tight control included monthly objective assessments of disease activity, and the targeting of persistent disease activity using a protocol to escalate DMARD

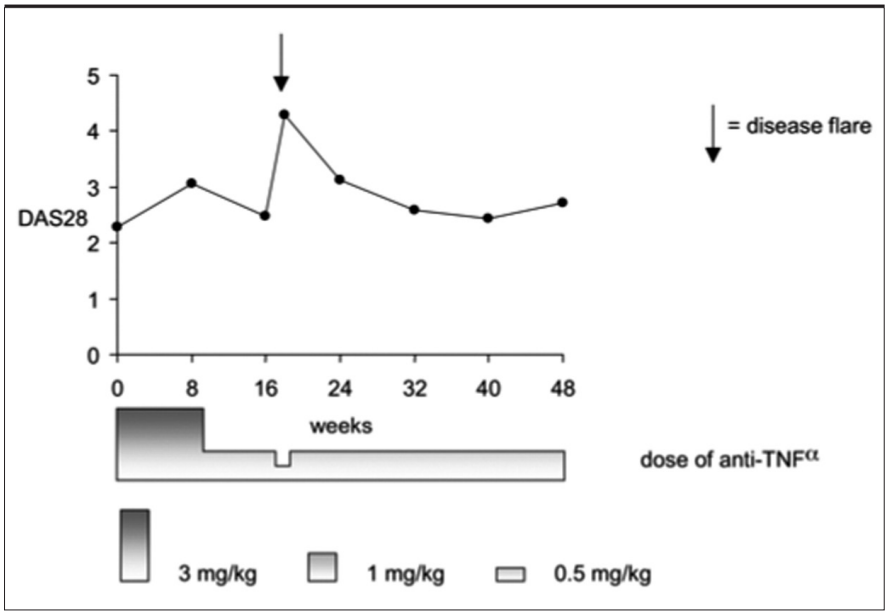


Fig. 8. DAS28 course and anti-TNF-α dose titration in one patient. After a decrease in dose of anti-TNF-α from 3.0 to 1.0 and subsequently to 0.5 mg/kg a flare of the disease occurs, reflected in an increase of the DAS28. After increasing the dose of anti-TNF-α to 1.0 mg/kg the DAS28 returns to the previous low level. DEN BROEDER *et al*. *Rheumatology* (Oxford) 2002; 41: 638-42.

Table VI. DAS values, *$p<0.001$. GRIGOR *et al*.

Month	0	3	6	9	12	15	18
Usual care	4.6	3.7	3.4	3.1	2.8	2.7	2.7
Intensive	4.9	2.7*	2.3*	2.1*	1.8*	1.5*	1.4*

therapy in patients with a DAS>2.4. (Table VI). Many other strategy studies following the Tight control or Treat-to-Target principle have been published since then (45).

Use of DAS and EULAR criteria in clinical trials

Composite measures

Indices like the DAS, the EULAR response criteria and the ACR improvement criteria, are developed because the underlying rheumatoid inflammation is difficult to measure. The main advantages of indices over a set of single measures are the avoidance of duplicationity and increased sensitivity to change. The main advantage of the DAS and DAS28 for clinical trials is that these are absolute measures of rheumatoid inflammation.

Measures of change

In contrast, the ACR improvement criteria provide a measure of change. Although the ACR improvement criteria and the EULAR response criteria use a different approach, both perform quite well in discriminating placebo from active treatment and discriminating between two active treatments. However, experiencing sufficient reduction in rheumatoid inflammation to fulfil the ACR criteria for response does not indicatesay whether rheumatoid inflammation is reduced to amounts leading to sufficient symptom relief or prevention of progression of joint damage. But relative measures as the ACR criteria can still be used when the objective is to discriminate a drug from placebo, especially in phase II trials or in absence of very effective drugs.

The problem becomes apparent when drugs become more effective. When a new, very effective drug is tested in a clinical trial using the ACR 20% criteria as endpoint, it is imaginable that 100% of new drug treated patients achieve response, which underestimates the real properties of the drug.

Future use

Another advantage of using continuous and absolute endpoints like the DAS in clinical trials is, that dependent on the trial objectives, cut-off points may be chosen when the thus created categories have prognostic value and are clinical meaningful. An example is the categorisation of the DAS to indicate low disease activity or remission in RA. When even more effective new drugs become available, measures like *time-to-remission* or *time-to-low-disease activity* may become interesting for use as endpoints in clinical trials, which can already be measured using the DAS and DAS28.

References

1. VAN RIEL PLCM, VAN DE PUTTE LBA: Clinical assessment and clinical trials in rheumatoid arthritis. *Curr Opin Rheumatol* 1994; 6: 132-9.
2. WOOLEY PH, GRIFFIN J, PANAYI GS, BATCHELOR JR, WELSH KI, GIBSON TJ: HLA-DR antigens and toxic reactions to sodium aurothiomalate and D-penicillamine in patients with rheumatoid arthritis. *N Engl J Med* 1980; 303: 300.
3. MALLYA RK, MACE BE: The assessment of disease activity in rheumatoid arthritis using a multivariate analysis. *Rheumatol Rehabil* 1981; 20: 14-7.
4. VAN RIEL PLCM, REEKERS P, VAN DE PUTTE LBA, GRIBNAU FWJ: Association of HLA antigens, toxic reactions and therapeutic response to auranofin and aurothioglucose in patients with rheumatoid arthritis. *Tissue Antigens* 1983; 22: 194-9.
5. VAN DER HEIJDE DMFM, VAN 'T HOF MA, VAN RIEL PLCM *et al*.: Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990; 49: 916-20.
6. VAN DER HEIJDE DMFM, VAN 'T HOF MA, VAN RIEL PLCM, VAN LEEUWEN MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA: Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 177-81.
7. FELSON DT, ANDERSON JJ, BOERS M *et al*.: The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993; 36: 729-40.
8. VAN GESTEL AM, PREVOO MLL, VAN 'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA, VAN RIEL PLCM: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. *Arthritis Rheum* 1996; 39: 34-40.
9. FELSON DT, ANDERSON JJ, BOERS M *et al*.: American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
10. VAN DER HEIJDE DMFM, VAN 'T HOF MA, VAN RIEL PLCM, VAN DE PUTTE LBA: Validity of single variables and indices to measure disease activity in rheumatoid arthritis. *J Rheumatol* 1993; 20: 538-41.
11. VAN DER HEIJDE DMFM, VAN RIEL PLCM, VAN LEEUWEN MA, VAN 'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA: Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br J Rheumatol* 1992; 31: 519-25.
12. WELSING PMJ, VAN GESTEL AM, SWINKELS HL, KIEMENEY LALM, VAN RIEL PLCM: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2009-17.
13. WELSING PMJ, LANDEWÉ RB, VAN RIEL PLCM *et al*.: The relationship between disease activity and radiological progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum* 2004; 50: 2082-93.
14. PREVOO MLL, VAN 'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LBA, VAN RIEL PLCM: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
15. FUCHS HA, BROOKS RH, CALLAHAN LF, PINCUS T: A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheum* 1989; 32: 531.
16. VAN GESTEL AM, HAAGSMA CJ, VAN RIEL PLCM: Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998; 41: 1845-50.
17. VAN GESTEL AM, ANDERSON JJ, VAN RIEL PLCM *et al*.: ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. *J Rheumatol* 1999; 26: 705-11.
18. SALAFFI F, PERONI M, FERRACCIOLI GF: Discriminating ability of composite indices for measuring disease activity in rheumatoid arthritis: a comparison of the Chronic Arthritis Systemic Index, Disease Activity Score and Thompson's Articular Index. *Rheumatology* 2000; 39: 90-6.
19. VILLAVERDE V, BALSA A, CANTALEJO M *et al*.: Activity indices in rheumatoid arthritis. *J Rheumatol* 2000; 27: 2576-81.
20. DROSSAERS-BAKKER KW, DE BUCK M, VAN ZEBEN D, ZWINDEMAN AH, BREEDVELD FC, HAZES JMW: Long-term course and outcome of functional capacity in rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1854-60.
21. FRANSEN J, UEBELHART D, STUCKI G, LANGENEGGER T, SEITZ M, MICHEL BA: The ICIDH-2 as a framework for the assessment of functioning and disability in rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 225-31.
22. VERHOEVEN AC, BOERS M, VAN DER LINDEN

S: Responsiveness of the core set, response criteria, and utilities in early rheumatoid arthritis. *Ann Rheum Dis* 2000; 39: 966-74.

23. FRANSEN J, HÄUSELMANN H, MICHEL B, CARAVATTI M, STUCKI G: Responsiveness of the self-assessed rheumatoid arthritis disease activity index to a flare of disease activity. *Arthritis Rheum* 2001; 44: 53-60.
24. SVENSSON B, SCHAUFELBERGER C, TELEMAN A, THEANDER J: Remission and response to early treatment of RA assessed by the disease activity score. *Rheumatology* 2000; 39: 1031-6.
25. BOERS M: Demonstration of response in rheumatoid arthritis patients who are nonresponders according to the American College of Rheumatology 20% criteria: the paradox of beneficial treatment effects in nonresponders in the ATTRACT trial. *Arthritis Rheum* 2001; 44: 2703-4.
26. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63: 573-86.
27. PUNDER YMR, FRANSEN J, KIEVIT W *et al*.: The prevalence of clinical remission in RA patients treated with anti –TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Rheumatology* 2012; 51: 1610-7.
28. PREVOO MLL, VAN GESTEL AM, VAN 'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA, VAN RIEL PLCM: Remission in a prospective study of patients with rheumatoid arthritis. *Br J Rheumatol* 1996; 35: 1101-5.
29. FRANSEN J, WELSING PMJ, VAN RIEL PLCM: Remission in RA: Agreement of the Disease Activity Score (DAS28) with the ARA preliminary remission criteria. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 68.
30. VAN RIEL PLCM, VAN GESTEL AM: Clinical outcome measures in rheumatoid arthritis. *Ann Rheum Dis* 2000; 59 (Suppl. I): i28-i31.
31. FRANSEN J, WELSING PMJ, DE KEIJZER RMH, VAN RIEL PLCM: Development and validation of the DAS28 using CRP. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 10.
32. VAN RIEL PLCM, FRANSEN J, SCOTT DL: EULAR handbook of clinical assessments in rheumatoid arthritis. Alphen aan den Rijn: van Zuiden Communications 2004
33. SIEMONS L, VONKEMAN HE, TEN KLOOSTER PM, VAN RIEL PLCM, VAN DE LAAR MAFJ: Interchangeability of 28-joint disease activity scores using the erythrocyte sedimentation rate or the C-reactive protein as inflammatory marker. *Clin Rheumatol* 2014; 33: 783-9.
34. MORELAND LW, RUSSELL AS, PAULUS HE: Management of rheumatoid arthritis: the historical context. *J Rheumatol* 2001; 28: 1431-52.
35. VAN RIEL PLCM, SCHUMACHER HR: How does one assess early rheumatoid arthritis in daily clinical practice? *Best Pract Res Clin Rheumatol* 2001; 15: 67-76.
36. PINCUS T, SOKKA T: Evidence-based practice and practice-based evidence. *Nature Rheumatology* 2006; 2: 114-5.
37. VAN RIEL PLCM, VAN GESTEL AM: Area under the curve for the American College of Rheumatology improvement criteria: a valid addition to existing criteria in rheumatoid arthritis? *Arthritis Rheum* 2001; 44: 1719-22.
38. FRANSEN J, STUCKI G, VAN RIEL PLCM: The merits of monitoring: should we follow all our rheumatoid arthritis patients in daily practice? *Rheumatology* (Oxford) 2002; 41: 601-4.
39. WOLFE F, CUSH JJ, O'DELL JR *et al*.: Consensus recommendations for the assessment and treatment of rheumatoid arthritis. *J Rheumatol* 2001; 28:1413-30.
40. DEN BROEDER AA, CREEMERS MCW, VAN GESTEL AM, VAN RIEL PLCM: Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-α. *Rheumatology* (Oxford) 2002; 41: 638-42.
41. TANAKA Y, TAKEUCHI T, MIMORI T *et al*.: Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR study. *Ann Rheum Dis* 2010; 69: 1286-91.
42. VAN DER MAAS A, LIE E, CHRISTENSEN R *et al*.: Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. *Ann Rheum Dis* 2013; 72: 1800-5.
43. FRANSEN J, TWISK J, CREEMERS MCW, VAN RIEL PLCM: Design and analysis of a randomized controlled trial testing the effects of clinical decision support on the management of rheumatoid arthritis. *Arthritis Rheum* 2004; 51: 124-7.
44. GRIGOR C, CAPELL HA, STIRLING A *et al*.: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single blind randomised controlled trial. *Lancet* 2004; 364: 263-9.
45. PINCUS T, CASTREJON I: Evidence that the strategy is more important than the agent to treat rheumatoid arthritis. Data from clinical trials of combinations of non-biologic DMARDs, with a protocol-driven intensification of therapy for tight control or treat-to-target. *Bull Hosp Jt Dis* 2013; 71 (Suppl. 1): S33-40.