# Disease activity measures for rheumatoid arthritis

M. Dougados[1], D. Aletaha[2], P. van Riel[3]

*[1]Hopital Cochin, Descartes University, Paris, France; [2]Medical University Vienna, Vienna, Austria; [3]University Hospital Nijimegen, Nijmegen, The Netherlands.*

*Maxime Dougados, MD;*
*Daniel Aletaha, MD;*
*P. van Riel MD, PhD.*

*Please address correspondence and reprint requests to: Prof. M. Dougados, Hopital Cochin, Descartes University, Service de Rhumatologie B, 27 Rue du Faubourg Saint Jacques, Paris 75014, France.*
*E-mail: maxime.dougados@cch.ap-hop-paris.fr* or *Maxime.dougados@cch.aphp.fr*

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**ABSTRACT**

*Rheumatoid arthritis (RA) is an inflammatory autoimmune and progressive disease. In patients with RA, persistent disease activity ultimately results in irreversible radiographic damage of the joints with persistent functional loss as a consequence. Disease activity measures assess a disease state at a particular time point. In order to evaluate the course of the disease in daily clinical practice or to judge the efficacy of a treatment in a clinical trial, a measure should also comprise the dimension of time.*

*Composite indices provide a comprehensive view of disease activity and include the Disease Activity Score 28, the American College of Rheumatology criteria and newer indices such as the Clinical Disease Activity Index, the Rheumatoid Arthritis Disease Activity Index, and the Simplified Disease Activity Index. The target of RA treatment is to suppress disease activity as completely as possible, with remission being the ultimate goal. The composite index chosen should, therefore, be applicable to the circumstance in which it will be used, with different requirements in clinical practice versus clinical trials. In addition to the choice of an assessment index, novel disease monitoring strategies have been used to optimize treatment and disease control, as in the TICORA and BeST studies. It is clear that the best benefit for the patient can be obtained by combining the optimal treatment strategy and the most appropriate outcome measure. Low disease activity, intensive monitoring, and rapid adjustments in treatment seem to promise the greatest benefit. Further studies are required to better evaluate the clinical relevance of methods for assessing disease activity in patients with RA.*

## Introduction

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory autoimmune disease with multiple clinical manifestations. Although RA primarily impacts the peripheral joints, leading to tenderness, swelling, pain and loss of physical function, other symptoms include weight loss and fatigue. Persistent disease activity will ultimately result in irreversible radiographic damage of the joints, with persistent functional loss as a consequence (1, 2). With the recent arrival of new therapeutic options in RA, remission is now considered to be the ultimate goal of treatment. Remission is the absence of, or a state of very low, disease activity over a specific period of time. In any given individual, however, disease activity may fluctuate. It is therefore important to monitor disease activity regularly using appropriate and validated assessment tools. Many variables can be used to assess disease activity; however, as the presentation of RA may vary substantially between individuals, composite indices comprising multiple variables are often the used to monitor the disease process (3).

Composite indices provide a comprehensive view of disease activity. Their advantages include: (a) the unambiguous interpretation of disease activity, (b) the comparability of trial results, and (c) increased power in clinical trials (4). Disadvantages are that they are complicated to calculate and difficult to break down into their individual components (5). Many composite indices exist; the most commonly used are the Disease Activity Score 28 (DAS28) (6-8) and the American College of Rheumatology (ACR) criteria (9, 10), although the latter was designed for use in clinical trials. Newer, more practical indices have since been developed for use in both clinical practice and clinical trials, including the Clinical Disease Activity Index (CDAI) (11), the Rheumatoid Arthritis Disease Activity Index (RADAI) (12), and the Simplified Disease Activity Index (SDAI) (13).

Composite indices fall into different categories, depending on the scales they use (continuous or ordinal) and

**Table I.** Summary of composite measures used to assess response to treatment and disease activity in rheumatoid arthritis.

| Tool | Status or response measure? | Ordinal or continuous? | Definition | Thresholds |
|---|---|---|---|---|
| ACR criteria | Response | Ordinal | Based on a set of seven core measures: SJC; TJC; physician global assessment; patient-reported physical function; patient-reported pain; patient-reported global status; ESR or CRP | ACR20 = improvement of at least 20% in swollen and tender joint counts and at least three of the five additional measures<br>ACR50/70 = as above, but based on 50% or 70% improvements |
| Hybrid ACR | Response | Ordinal | (1) Calculate the mean percentage change in core set measures<br>(2) For each measure, subtract the score after treatment from the baseline score and obtain the percentage improvement in each measure. If a core measure worsened by more than 100%, limit the change to 100%<br>(3) Average the percentage changes for all core measures<br>(4) Determine whether ACR20, 50 or 70 has been achieved<br>(5) Utilize a scoring methods table to obtain the Hybrid ACR response measure | See Table 4 in (39) |
| DAS | Status | Continuous | Continuous scale (range 0–10), comprising: Ritchie articular index (range 0–78); 44 SJC (range 0–44); ESR or CRP;<br>Optional general health assessment on 100 mm VAS | DAS < 1.6 = remission;<br>DAS ≤ 2.4 = low disease activity;<br>2.4 < DAS ≤ 3.7 = moderate disease activity;<br>DAS > 3.7 = high disease activity |
| DAS28 | Status | Continuous | Continuous scale (range 0–9.4), comprising: 28 TJC (range 0–28); 28 SJC (range 0–28); ESR or CRP;<br>Optional general health assessment on VAS (range 1–100)<br>DAS28 (ESR) = 0.56 x √TJC + 0.28 √SJC + 0.70 x Ln (ESR) + 0.014 x PGA<br>DAS28 (CRP) = 0.56 x √TJC + 0.28 √0.36 x Ln (CRP+1) + 0.014 x PGA | Δ DAS28 of 1.2 = significant change;<br>DAS28 ≤ 2.6 = remission (or, more recently, ≤ 2.4 (11));<br>DAS28 ≤ 3.2 = low disease activity (or, more recently, ≤ 3.6 (11));<br>3.2 < DAS28 ≤ 5.1 = moderate disease activity (or, more recently, ≤ 5.5 (11));<br>DAS28 > 5.1 = high disease activity (or, more recently, > 5.5 (11))<br>EULAR response criteria classify patients as good, moderate or non-responders according to change in DAS or DAS28, and the DAS or DAS28 value achieved (6, 10, 19, 29, 30) |
| RADAI | Status | Continuous | Five-item questionnaire about:<br>1. Global past disease activity<br>2. Current disease activity<br>3. Arthritis pain<br>4. Morning stiffness<br>5. Tender joints | Range 0–10 |
| SDAI | Status | Continuous | 28 SJC; 28 TJC; PGA (100 mm VAS); EGA (100 mm VAS); CRP level (mg/dL);<br>SDAI = SJC + TJC + PGA + EGA + CRP (scores can potentially range from 0.1–86.0) | Δ SDAI of ≥ 7 = significant change;<br>SDAI > 26 = high disease activity;<br>SDAI ≤ 26 = moderate disease activity;<br>SDAI ≤ 11 = low disease activity;<br>SDAI ≤ 3.3 = remission<br>(11) |
| CDAI | Status | Continuous | 28 SJC; 28 TJC; PGA (100 mm VAS); physician global assessment (100 mm VAS);<br>CDAI = SJC + TJC + PGA + EGA (scores can potentially range from 0–76.0) | Δ CDAI of ≥ 6.5 = significant change;<br>CDAI > 22 = high disease activity;<br>CDAI ≤ 22 = moderate disease activity;<br>CDAI ≤ 10 = low disease activity;<br>CDAI ≤ 2.8 = remission<br>(11) |

ACR: American College of Rheumatology; SJC: swollen joint count; TJC: tender joint count; EGA: evaluator global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: Visual Analog Scale; PGA: patient global assessment; DAS: Disease Activity Score; SDAI: Simpified Disease Activity Index; CDAI: Clinical Disease Activity Index.

whether they measure disease status or change (Table I). When using a disease activity index, it is important to focus on the disease process (level of inflammation), rather than on the consequences of disease (*i.e.*, outcome such as joint damage resulting in irreversible function loss). These features should be considered and assessed independently. Disease activity measures can include morning stiffness, night pain, synovitis, pain, and the patient's global assessment, but not structural damage (x-rays). Depending on the phase of the disease, functional impairment measures disease activity (early in the disease course), a combination of disease activity and structural damage (late in the disease course), or damage exclusively (absence of disease activity late in the course of the disease (1, 2). By accurately monitoring disease activity during treatment, it should be possible to optimize treatment management to achieve the desired outcomes for both the patient and the clinician.

This review will overview the different approaches used to evaluate disease activity in clinical trials and clinical practice, and the advantages and disadvantages of each, with a focus on composite indices.

**Assessment of disease activity**

Disease activity measures assess a disease state at a particular point in time. However, to evaluate the course of the disease in daily clinical practice or to judge the efficacy of a given treatment in a clinical trial, the measure should include the dimension of time. This can be done by measuring disease activity at regular intervals during the course of the disease, by calculating the mean disease activity or the area under the curve (AUC), or by calculating the change in disease activity over time. In daily practice these measures are important, because they allow rheumatologists to assess treatment options for individual patients. The ultimate goal of RA treatment is to suppress disease activity completely, so that (progression of) radiographic damage does not occur. The main response measures used to evaluate treatments are based on the ACR and European League Against Rheumatism (EULAR) criteria, which are discussed in detail below. Response measures are, by definition, expressed on ordinal scales, as they are designed to provide results such as 'responder versus non-responder', or 'good, moderate and non-responder'. On the other hand, continuous measures do not categorize data, but provide a value along a continuum, and hence have greater sensitivity in detecting more subtle differences between treatments. However, when cut-points for response levels are applied to continuous measures, these instruments can also be used to assess treatment response.

Considered alone, individual measures are not able to reflect the entire spectrum of disease activity, which means that improvements assessed using only one measure can mask deterioration in other aspects of the disease. The consideration of multiple individual measures therefore provides a more comprehensive understanding of both disease status and response to therapy. These measures can be combined into composite indices, which allow clinical trials to be compared and provide them with more statistical power (5). A number of composite indices have been developed that measure response to treatment, disease status or both; these are discussed below.

**Composite indices: status measures**

Status measures assess disease activity at a particular point in time. Examples of status measures are discussed in the following sections.

*Disease Activity Score*

The original Disease Activity Score (DAS) combines four different continuous measures – the Ritchie Articular Index performed on 53 joints (14), a 44-joint swollen joint count, the erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP), and a general health assessment (Table I) – to create an overall measure of disease activity (15, 16). Calculation of the DAS involves the weighting of the individual variables in a complex calculation, to obtain a result on a scale of 1–10 (17). Disease activity can then be expressed as a mean or mean change, or as low, moderate or high disease activity (Table I) based on a set of pre-defined cut-off values. In addition, a DAS value of $< 1.6$ corresponds to disease remission according to the American Rheumatism Association (ARA) (18).

A derivative of DAS, the DAS28, utilizes reduced and ungraded joint counts, has a continuous scale ranging from 0–9.4, and is easier to perform than the original DAS (8). It was developed using the same cohort of patients as the original DAS, but with a longer follow up and including more patients (8). A formula can be used to convert DAS28 to DAS when necessary, since the derived values are not directly comparable (6). While the DAS and DAS28 have been shown to be highly effective indices of disease activity, they are somewhat complicated to use in clinical practice because of the weighting and transformation required (19), although this hurdle can easily be overcome using a calculator or computer.

Both the original DAS (19) and the DAS28 (8) have been extensively validated. The DAS28 has a high correlation with both physician and patient global assessments of disease activity (20). As for the original DAS, the DAS28 results can be used to classify disease activity as low, moderate or high (Table I), or to indicate disease remission (DAS28 $< 2.6$) (7). This was confirmed by a recent study that found an optimal cutoff value of $< 2.4$, which is only negligibly smaller than $< 2.6$ (27).

The DAS and DAS28 therefore are easily calculated and can be used in both trials and clinical practice to evaluate the level of current disease activity and its course over time. This information can be valuable in discussions with the patient as it may help guide informed treatment decisions. In several trials the DAS has been used to guide treatment, with the aim of achieving low disease activity (21, 22).

Despite the increase in the frequency of clinical remission, it is still a relatively rare event in RA. Instead, patients can realistically aim for a state of very low disease activity. One definition of minimal disease activity (MDA) is a DAS28 $\leq 2.85$ (23).

*Simplified and Clinical Disease Activity Indices*

The SDAI was designed to provide a simple measure of disease activity at a given time point. It involves the direct summing of individual measures (Table I), with no complex weighting or transformations required. Moreover, by including both the patient and the physician global assessment of disease activity, the SDAI integrates the differences commonly observed between these two perspectives. The index includes the parameter of CRP levels, and therefore requires a blood sample to be taken in advance of its calculation. However, since the CRP test is not always done in clinical practice, a modification of the SDAI – the CDAI – was developed (24).

The CDAI is a composite index that does not incorporate the parameter of acute phase reactants (CRP or ESR) (Table I). The elimination of the blood test means that the CDAI can be used to evaluate disease activity quickly in almost any setting, allowing for the frequent monitoring of patients. The rationale behind the development of CDAI includes the fact that acute phase reactants tend to correlate with the other core set values, meaning that the amount of information they add may be limited. In support of the view that acute phase reactant measures are not always essential, the ACR criteria do not necessarily require an improvement in acute phase reactants to define a response. Both the SDAI and the CDAI have been validated in a number of clinical trials and the results can be expressed as mean values or mean changes (11). The simplicity of these scales means that physicians can monitor disease activity more easily and patients may gain a better understanding of their disease, allowing them to monitor their condition more effectively and seek medical advice when necessary.

*Rheumatoid Arthritis Disease Activity Index*

The RADAI is a patient-assessed measure of disease activity and requires no laboratory tests. The RADAI may complement or replace the physician's assessment of disease activity, especially in health service or epidemiological research, and can be used for patient management (12). The RADAI is a five-item questionnaire that asks the patient to assess: (i) global disease activity in the past 6 months; (ii) current disease activity in terms of swollen and tender joints; (iii) arthritic pain; (iv) duration of morning stiffness; and (v) joint tenderness (by rating a list of joints). The RADAI score is calculated as the mean of the non-missing items and ranges from 0 (no disease activity) to 10 (high disease activity). The RADAI is short, easy to understand for the patient, collects information on RA signs and symptoms that are of clinical value, and has been validated in several studies (25-27).

*ACR criteria for clinical remission*

In an effort to define clinical remission of RA, the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the ARA Committee on Diagnostic and Therapeutic Criteria performed a statistical study based on the ACR criteria. They analyzed data provided by 35 practicing rheumatologists on RA patients who were either in remission (complete or partial) or had active disease (28). The investigators assessed the relative strength of a range of variables in distinguishing between remission and active disease. The result of this study was the ACR definition of complete clinical remission – a patient must satisfy 5 of 6 criteria for at least 2 consecutive months: ≤ 15 minutes of morning stiffness; no fatigue, no joint pain (based on the patient's history), no swollen and tender joints, and an ESR < 30 mm/hr for females and < 20 mm/hr for males.

**Composite indices: response measures**

Response measures allow the assessment of changes in disease activity over time, particularly in response to treatment in clinical trials. Their use greatly facilitates the interpretation of data and the comparison of trials. Response measures currently in use are discussed below.

*European League Against Rheumatism criteria*

One set of criteria that takes into account a patient's actual disease status, as well as his/her response to treatment compared with baseline evaluations, are the EULAR criteria (6, 10, 19, 29, 30). These classify a patient as a 'good, moderate or non-responder' based on the magnitude of improvement in the DAS (or DAS28), as well as the absolute DAS (or DAS28) score achieved (Table I) (29). For example, to be classified as a good responder, patients must show a significant amount of improvement (>1.2) and achieve low disease activity (DAS28 ≤3.2). Like the ACR criteria, the EULAR criteria are effective in distinguishing between active and placebo treatments in clinical trials. The validity of the EULAR criteria has been evaluated (6, 29, 31) and shown to be comparable to that of the ACR criteria (31). However, while the ACR criteria provide an ordinal measure of change, the EULAR criteria evaluate both the absolute level of disease activity reached and the change from basline.

*American College of Rheumatology criteria*

The American College of Rheumatology proposed a core set of seven standard measures (the ACR Core Data Set; Table I) that can be used to calculate a composite index of disease response. The ACR20 response is defined as a 20% improvement in the tender and swollen joint counts, as well as in 3 of the 5 additional criteria (Table I) (10). In addition, ACR50 and ACR70 responses can be calculated based on 50% and 70% improvement, respectively, in the above components. The ACR improvement criteria can effectively distinguish between placebo and active treatment in clinical trials, and are now required by the Food and Drug Administration (FDA) to evaluate new RA therapies (32).

One limitation of the ACR response criteria, however, is that they do not incorporate a measure of actual disease status at the time of evaluation, but rather a measure of improvement compared with a baseline. Thus, while the ACR criteria for a response may be met, there is no information on the level of inflammation at the endpoint, which may not be sufficiently low to result in

symptom improvement or the interruption of radiographic damage. In addition, although the ACR20 is commonly viewed as the gold standard for assessments in clinical trials, the criteria are not always applied consistently. For example, ACR20 response rates may be assessed at the endpoint or at *ad hoc* endpoints at any time during a trial, or the ACR criteria may be applied using an AUC methodology (33).

While the ACR20 is certainly useful for measuring the efficacy of new agents in comparison with a placebo, there are situations where it may not be applicable. These include head-to-head comparisons between two active treatments, risk/benefit assessments, and dose optimization studies, in which more subtle differences in response may need to be detected than ACR20 can achieve (34).

*Numeric American College of Rheumatology response*

In order to evaluate actual improvement in the ACR criteria over time, a numerical ACR index (ACR-N) was developed (34). This continuous measure expresses disease activity as the lowest percentage change in: (1) the number of tender joints; (2) the number of swollen joints; and (3) the median percentage improvement in the pain assessment, physician global assessment, patient global assessment, physical function, and acute phase reactant value at each visit to the clinic. Unlike the well-established continuous DAS measure, ACR-N assesses improvement rather than the actual level of disease activity, and includes more patient-reported outcome measures (Health Assessment Questionnaire [HAQ] and a 100 mm visual analog scale [VAS] pain assessment). The mean or median ACR-N value can therefore be used to demonstrate improvement at a specific time point. Thus, if a patient has a median ACR-N of 60, this indicates improvement greater than an ACR50 and halfway towards an ACR70 response, and provides more information than the ordinal ACR50 outcome measured using the traditional ACR scoring system (34).

In order to increase the sensitivity of the measure, a series of ACR-N assessments can be used to generate an AUC that shows the change in disease activity over time. However, there may be difficulties associated with this methodology, in that patients can theoretically have similar ACR-N AUC values but very different disease outcomes depending on their levels of disease activity (35). There is a question as to the relevance of measuring the lowest percentage change in the above core set variables, and whether this is a valid method of assessing disease activity. That the ACR-N AUC may not be the best means of assessing disease outcomes was demonstrated in a study of patients with early RA that compared ACR-N AUC with DAS AUC, in which the latter correlated well with the disease outcome whereas the former did not (35, 36). The use of the ACR-N AUC has also been criticised by others (37, 38).

Another variation on the ACR criteria considers the number that improve by at least 20% and has been denoted the nACR (34), but this approach is not yet widely used.

*Hybrid American College of Rheumatology*

Following a recent evaluation of their improvement criteria, the ACR Committee proposed a possible alternative method of measuring response. Their study was aimed at redefining RA responses so that they: (i) correspond to the clinical impression of response (*i.e.*, are clinically valid); (ii) maximize sensitivity to change; and (iii) maintain the ACR 20 measure to conserve the standardization of reporting clinical trial data (39). Of all the measures assessed (standard measures and their variations), continuous measures proved to be the most sensitive to change, as was to be expected. One of the most effective was a hybrid measure that retained information from the ACR20, 50 and 70 and combined it with the mean percentage improvement in core set measures (Table I). It was posited that this hybrid measure successfully captures slight differences in treatment response while conserving the use of the standardized ACR20, and that it would allow the enrolment of a smaller number of patients in clinical trials. However, it is still unclear how this (somewhat complicated) tool for assessing response will be accepted by trialists and regulatory agencies.

**Choosing the most appropriate tool for assessing disease activity**

As discussed above, a wide range of composite indices are currently available. However, not all of these instruments are suitable for use in both clinical trials and daily clinical practice. In clinical studies patients are followed for a restricted period of time and the main goal is to answer the question: 'Is treatment A superior to treatment B?' In daily clinical practice it is important to know whether a patient is responding to an intervention (*i.e.*, whether there is a significant or relevant change in disease activity), but we are less concerned with the exact degree or percentage of response than in clinical trials. The aim is not to achieve the highest possible percentage of improvement, but to suppress disease activity as completely as possible. The composite index chosen should therefore be appropriate to its purpose. For example, certain measures may be more useful in a clinical trial setting than they would be in the clinic, or *vice versa*. This may relate to the scales used: ordinal versus continuous or whether it measures disease status or response to treatment over time. Below we compare the merits of status criteria versus response criteria in the assessment of disease activity. We also discuss the advantages and disadvantages of ordinal versus continuous scales, and consider the settings in which one might be more applicable than another.

*Benefits of status versus response criteria*

For the assessment of disease activity and prognosis in real-life clinical practice, it is generally considered more useful to have a measure of disease status rather than of change in disease over time. For example, the DAS provides information on the disease state, and therefore the underlying disease activity, at any point in time and therefore whenever this information is required.

The development of cut-off points for the parameters has allowed the categorization of disease activity states – typically as low, moderate or high, and remission (Table I). DAS-defined remission is not remission in the strictest sense (*i.e.*, the complete absence of signs and symptoms of disease), but can be considered as 'near remission'. Definitions of remission based on the SDAI and CDAI have also been published and validated (40, 41),

By contrast, the ACR and EULAR criteria measure the response rate, *i.e.*, the change in disease activity between two assessment points. As explained above, the ACR remission criteria and response measures were designed for clinical trials and cannot be used to make individual treatment decisions in the clinic. The EULAR response criteria evaluate both the status of the disease and the response versus baseline, which some consider preferable to relying on response or status measures alone. The EULAR criteria include cut-off points that provide additional outcomes for evaluation in clinical trials, allow clinicians to interpret continuous measures (19), and can be useful in defining the point at which changes in dosage or type of treatment should be made.

When evaluating the merits of response versus status measures, the question arises as to whether the clinician's aim should be to improve a patient's disease status or achieve low disease activity, as discussed in a recent editorial (42). Is a strong response (such as ACR 70) reflective of greater benefit than the induction of an improved disease status (such as remission) (42)? It can be argued that an ACR70 is as good a measure of a strong response as a low DAS (LDAS), based on the figures obtained in clinical trials, with on average 15–25% of patients achieving ACR70 or a LDAS score, respectively, with active treatment (43-47). However, it is clear that ACR70 will be easier to achieve in those patients with high baseline disease activity. Likewise, a LDAS is easier to achieve in patients with low baseline disease activity. Therefore, in clinical trials both improvement and condition must be examined. In clinical practice, where the baseline of disease activity may be more variable, studies have suggested that a LDAS is more clinically relevant than assessments of improvement. In this respect, when analyzing patients with a similar degree of clinical response, it is striking that functional and radiographic outcomes are much better in those who have achieved a better clinical state (M. Dougados, unpublished observation, as supported by refs. 35 and 48).

*Ordinal versus continuous measures of disease activity*

As described above, measures based on ordinal scales provide a single value using a pre-established cut-off (*e.g.*, 'responder versus non-responder' as defined by the ACR20, or 'good, moderate and non-responders' by the EULAR criteria). A key advantage of these measures is that they do allow one to evaluate improvement versus baseline. Thus, measuring the percentage of patients who have reached ACR 20 by the end of a study is useful to evaluate group level improvements, and to compare placebo and active treatment groups. The same applies to the proportion of patients achieving a LDAS or DAS28-defined remission at study endpoints.

While ordinal measures have definite advantages, they also have limitations that must be taken into account before they are used. First of all, they can only measure changes up to the pre-defined cut-off point. Thus, when using the ACR 20, responses exceeding 20% improvement are not measured. Secondly, an ordinal scale cannot measure the mean response; it only records the percentage of patients who have reached the predefined cut-off. For example, ordinal measures do not provide a concept of actual disease activity along a continuum at baseline or endpoint. Thus a patient may have demonstrated a 20% improvement in dusease activity, but this does not give an idea of their actual disease activity. This is crucial, because the level of disease activity can influence the actual significance of an improvement in disease activity measured according to an ordinal measure. For example, a patient with a LDAS at baseline who achieves a 20% improvement in disease activity would have lower actual disease activity than a patient with high disease activity who achieved a 20% improvement. In addition, a very small improvement/worsening of disease activity may result in a patient being re-classified into a different responder category.

An additional limitation of ordinal assessments is that they do not allow the disease course to be tracked in daily clinical practice. That is, while ACR response rates can differentiate between the benefits seen in groups of patients (treatment vs. placebo), they are not very useful for assessing the response to treatment of an individual patient and do not measure actual activity at the time of assessment. In other words, ordinal assessments are carried out at single time points and provide 'snapshots' of disease activity, but do not measure the variability of the disease course.

For this reason, continuous measures of activity such as the mean DAS28 or CDAI or SDAI scores, may be more applicable in clinical practice as they allow the disease status to be monitored easily. Because less information is lost using a continuous measure than when data are categorized for ordinal measures, continuous measures may detect relatively small differences between groups. In addition, continuous measures can detect worsening disease.

## How can disease assessment influence treatment strategies?

Some clinical trials on patients with RA have suggested that the regular monitoring of DAS, combined with a pre-defined protocol for the escalation of therapy when a particular level of disease activity is not achieved, can be effective in improving outcomes. One such trial, the TIght COntrol for Rheumatoid Arthritis (TICORA) study, evaluated the efficacy of an intensive outpatient management strategy versus routine outpatient care in RA patients with a disease duration of less than 5 years (22). This comprised the continuous monitoring of disease activity (every 3 months) with the escalation of disease-modifying antirheumatic drug (DMARD) therapy in cases of persisting disease activity (a DAS score > 2.4). Patients treated in this intensive

manner experienced a significantly greater mean decrease in DAS than the routine treatment group. They were also significantly more likely to show a good EULAR or ACR 70 response, or to achieve remission. In addition, reduced radiographic progression of erosion and reduced total Sharp scores were seen in patients in the aggressive therapy group versus those treated with routine therapy.

The Dutch BeST (Behandel-Strategieën or "treatment strategies") trial also evaluated the efficacy of regular DAS monitoring (every 3 months), combined with therapy adjustments to achieve and maintain a DAS of ≤ 2.4. The BeST trial enrolled patients who had had RA for more than 2 years, and randomized them to receive either: (i) sequential monotherapy; (ii) step-up to combination therapy [both (i) and (ii) began with methotrexate (MTX) treatment]; (iii) initial combination therapy with non-biologic DMARDs plus corticosteroids; or (iv) initial combination therapy with MTX and infliximab. Following 2 years of treatment, 80% of patients had reached a DAS of ≤ 2.4, while 42% had achieved clinical remission (DAS < 1.6), thus suggesting that frequent monitoring and treatment adjustments can lead to significant clinical improvement (21). In addition, the combination therapy options were found to be more effective than the sequential or step-up treatment strategies.

The BeST and TICORA trials therefore indicate that more stringent control of disease activity based on the regular monitoring of DAS can lead to improved outcomes. With this in mind, regular assessments to maintain low disease activity should be one of the primary goals of treatment. The current challenge for the rheumatology community is to press for the routine use of measures of disease activity such as the DAS by rheumatologists in their daily practice. Clinicians must be encouraged to base therapeutic decisions not only on their personal judgement but also on the level of disease activity, as assessed by a composite disease activity index. Continued evaluation will then allow rheumatologists to better manage changes in their patients' treatment regimens.

## Conclusions

Disease activity can be evaluated in patients with RA by assessing one or more aspects of the disease using either single component variables or composite indices. Although it has yet to be defined which measures and reporting techniques are most relevant for use in clinical practice and in clinical trials, remains to be defined, there is consensus that composite indices, combining multiple variables, provide the most comprehensive view of disease activity. The utility of a particular index is also influenced by the setting for use , with response measures more suitable for the assessment of clinical benefit in clinical trials; while continuous or status measures are appropriate for disease monitoring in both clinical trials and practice. Recently, novel disease monitoring strategies to optimize treatment and disease control have been tested in the TICORA and BeST trials. However, the best benefit for the patient cannot be arrived at solely on the basis of the treatment strategy or the outcome measure used. A combination of the two – *i.e.*, an ambitious treatment goal (*e.g.* remission) and intensive monitoring with timely treatment modifications – will likely achieve the best result. Further studies will be required to better evaluate the clinical relevance of the available methods for assessing disease activity in patients with RA.

## Key points box

- Disease activity manifestation in rheumatoid arthritis (RA) is complex, and outcome measures need to address this complexity by combining measures into composite indices
- Any single attribute of disease activity will fail to reliably represent the overall level of disease activity
- The DAS, DAS28, SDAI, CDAI, RADAI, ACR response and EULAR response measures are validated scores to be used in disease activity assessment in RA
- The choice of instrument used will solely depend on the needs of specific trials or the infrastructure in clinical practice
- The greatest success in the management of RA can be achieved if treatment is aimed at remission, if assessments are done frequently, and if therapy is modified rapidly in individual patients

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