Scores for all seasons: SDAI and CDAI

J.S. Smolen[1,2], D. Aletaha[1]

[1]*Division of Rheumatology, Department of Medicine 3, Medical University of Vienna;* [2]*2nd Department of Medicine-Center for Rheumatic Diseases, Hietzing Hospital Vienna, Austria.*

Josef S. Smolen, MD
Daniel Aletaha, MD

Please address correspondence to:
Josef S. Smolen,
Division of Rheumatology,
Department of Medicine 3,
Medical University of Vienna,
Waehringer Guertel 18–20,
A-1090 Vienna, Austria.
E-mail: josef.smolen@wienkav.at

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ABSTRACT

Disease activity assessment is one of the most pivotal aspects in the care of RA patients. Composite measures of disease activity are superior to individual measures, since they capture the multiple facets of the disease. Since swollen joint counts correlate with joint damage progression and tender joint counts with physical function, composite scores that include joint counts are preferable. The simplified and clinical disease activity indices (SDAI, CDAI) are easy to calculate and correlate well with joint damage and physical function. Cutpoints for disease activity states have been established and improvement criteria likewise. The SDAI and CDAI remission criteria (ACR-EULAR index-based remission) are stringent, usually associated with a halt of progression of damage and optimisation of physical function and can still be achieved in 1 of 4 clinic patients and up to one third of patients in trials of early arthritis.

Assessing disease activity has become the single most important approach to reach optimal outcomes in rheumatoid arthritis (RA). While this statement sounds unrealistic at first, because we would tend to believe that drugs – and particularly the recent introduction of biologic agents into the therapeutic arena – are the most important source of clinical success, this success can only be defined once we appreciate how to measure it, since, as Verna Wright was quoted: "Clinicians may all too easily spend years writing 'doing well' in the notes of a patient who has become progressively crippled before their eyes…" (1). Hence, appreciation of therapeutic achievements results only secondarily to the definition and measurement of disease activity (and its change) in general and disease activity states in particular. In other words, once treatment decisions have been made, their appropriateness must be tested against the change of disease activity within short and – with its desired complete reversal – for the longer term. Thus, while we can achieve optimal outcomes only with appropriate therapy, the decision to treat and the subsequent treatment adaptations are all a consequence of the most important instrument used in RA patient care: disease activity assessment.

Indeed, the majority, if not, all of our recent advances in and insights from clinical studies are related to disease assessment. There would be no new drug on the market if it were not able to reduce or halt disease activity (2-6) and its likewise measurable consequences, damage and disability. There would be no strategic approach to the treatment of RA, as it has ultimately optimised patient care, without disease activity assessment (7-9): we would not be able to define clear and reproducible outcome targets for therapeutic interventions in our patients without feasible definitions of disease activity states. While often the term remission is used in a rather colloquial way, it is obviously related to the restitution to normal of disease activity (9-13), and not some informal mindset of one or another rheumatologist. And it can be achieved quite frequently (14).

Disease activity may be assessed by employing single instruments or composite scores (15). A heterogeneous disease, such as RA, has multiple facets, and consequently multiple domains should be assessed to determine its disease activity. No single valuation allows one to call one domain more important than another. There are, however, domains that differ regarding their sensitivity to change, their specificity for disease activity (or in other words: their proneness for being influenced by factors outside RA, *e.g.* comorbidities), their construct validity (their relevance regarding long-term outcomes of RA), their stakeholder perspective (Patient? Physician?) and so forth (16, 17). For

example, some variables, such as swollen joint counts (SJC) and C-reactive protein (CRP), are highly related to future joint damage (18-21), while others such as patient reported outcomes and tender joint counts (TJC) relate to physical function (18, 22).

Since all this creates a considerable heterogeneity of measurement across different patients (and sometimes also within a patient over time) for each of the single measures, there is strong evidence to support the use of composite measures, which have the advantage of overcoming shortcomings of each individual measure by combining multiple measures into composite scores and indices. These scores must not, however, miss important domains of the disease to correctly reflect disease activity. The most important one of these measures are swollen joint counts, since they have recurrently been shown to correlate with progression of joint damage, which again leads to irreversible disability (23, 24), and composite measure should comprise formal joint counts, as it is also stated in the treat-to-target recommendations (9).

Among the many individual measures used to assess RA, such as pain levels, global assessments by patient (PATGA) or evaluator (EGA), joint counts, morning stiffness, acute phase reactants, physical function, quality of life, etc., a core set has been selected more than 20 years ago and has withstood the test of time (25, 26). However, some of these variables are quite redundant, like CRP and ESR or patient pain assessment and patient global assessment, and, therefore, it is not necessary to use all of them in a composite score.

In many studies composite measures were investigated (27, 28), but the most pivotal work has been performed by van der Heijde et al who developed the disease activity score (DAS) based on actual data of individual variables thoroughly obtained in their patients when rheumatologists changed DMARDs, informing a statistical program to select the best variables and the best weights for these variables to account for a continuous index of disease activity in regards to the observed treatment decision (adaptation or not) by the physician; this led to weights, square roots, and logarithmic transformations in the ensuing formula (3). Since the DAS used the graded Ritchie index to assess joint tenderness and an extended 44 joint count for joint swelling, a modification was performed for which a reduced joint count, the well validated 28 joint count (29, 30) was used, leading to the DAS28 (11) and its subsequent modifications (15); while the grading of joint tenderness was shown to not be necessary, the statistical program still maintained weighting, logarithmic transformation and square rooting of the measures obtained. Thus, in the early days, a calculator was needed to assess the DAS28, making disease activity assessment in clinical practice cumbersome. Therefore we wondered, if all these transformations of the actual data were truly necessary.

Since we had already developed a simple composite measure to assess disease activity in reactive arthritis, the DAREA, by just summing 5 variables without any transformation (31), which much later turned out to also be a valid and valuable tool for assessment of disease activity in psoriatic arthritis, the DAPSA (32, 33), we tested if one could apply a similar principle of simplicity to assess RA. These deliberations led to the development of the simplified and the clinical disease activity index (SDAI, CDAI) (4, 34, 35). The SDAI is the arithmetic sum of SJC+TJC+PATGA+EGA+CRP, whereby the 28 joint count is used for joint assessment, the global evaluations are employed in cm rather than mm, and CRP as mg/dl. Consequently, the SDAI can range between 0 and 100 (roughly, depending on the maximum reasonably assumable CRP level in RA). The CDAI uses the same arithmetic approach but without CRP, and thus constitutes a purely clinical score that uses neither an acute phase reactant nor physical function, which we regard as an outcome measure rather than a process or activity measure (although in early stages of the disease it may obviously reflect disease activity as well); the CDAI ranges from 0 to 76. Both scores correlate highly with the ACR response and the DAS28 (4, 34).

Since the SDAI Includes SJC and CRP and CDAI includes SJC (Fig. 1), they both correlate well with progression of joint damage, and by comprising PATGA and TJC, they also are highly related to the HAQ (4, 34). We regard composite scores that account for formal joint counts (at least the SJC) as extremely important, because only these unequivocally mirror all future outcomes of RA. Scores that are solely based on patient reported outcomes (PROs) (36, 37) may have difficulties in reflecting disease activity and joint damage appropriately, since as stated previously progression

Score/Characteristic	SJC	TJC	PGA	EGA	APR	Pain	HAQ	Weighted
DAS28/DAS	■	■	■	■	■			+
SDAI	■	■	■	■	■			-
CDAI	■	■	■	■				-
RAPID3			■			■	■	-
Correlation with damage	+				+			n.a.
Correlation with function		+	+	+		+	n.a.	n.a.

Fig. 1. Variables contained in the different scores employed for disease activity assessment DAS: disease activity score; SDAI: simplified disease activity index; CDAI: clinical disease activity index; RAPID: routine assessment of patient index data; SJC: swollen joint count; TJC: tender joint count; PGA: patient's global assessment; EGA: evaluator's (physician's) global assessment; APR: acute phase reactant (CRP or ESR); HAQ: health assessment questionnaire; grey: included; white: not included; n.a. not applicable. For references see text.

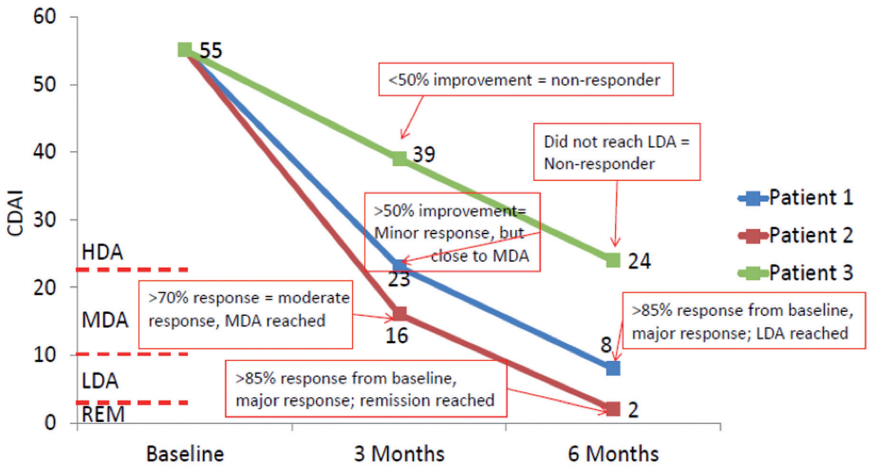

Fig. 2. Changes of CDAI and what they mean. Three hypothetical patients are presented who initially have no CDAI response, a minor (≥50% reduction), or a moderate (≥70% reduction) response; two, after 6 months, have a major (≥85% reduction) CDAI response. Treatment targets are usually remission or low disease activity. No response at the 3-month timepoint will usually not be followed by a moderate or major overall response. A major CDAI response is usually associated with reaching at last a state of low disease activity (57). Dotted lines indicate cutpoints between the different disease activity states: REM: remission; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; CDAI: clinical disease activity index. Similar data would pertain also to the simplified disease activity index (SDAI).

of damage is related to joint swelling which is not contained in composite measures that are comprised only of PROs. From a clinician's perspective, it is obviously not sufficient to claim that a single "How are you today?" question to the patient is sufficient, because on the group level the quantitatively rated answers to that question correlate to RA outcomes, maybe even similarly to more complex composite measures. Clinicians want to be correct in the individual patient, and not on the group level. This has some analogy to classification criteria and diagnostic criteria. The use of the former is not recommended, because they are meant to work for groups, and, in fact, accept to be wrong in quite some patients.

Moreover, in long-standing disease with significant joint destruction physical function will be limited by a high floor, so that even in remission of disease activity this irreversible nature of functional measures (accrued joint damage and similar) will not allow to show the presence of remission (23, 24); indeed, this can also be deducted from a recent study in which patients with long-standing disease achieved remission much more frequently when using CDAI than a PRO-based score (38) and also from a recent analysis of all clinical and functional variables comparing early and established disease (39). None of these comments is supposed to downgrade the importance and value of physical function assessment since – at least historically – it relates to work disability and mortality (40) and irrespective of this aspect is an extremely important outcome that is governed by both disease activity and damage. But in our view it should not be included in, or as a major portion of, disease activity measures and should be addressed separately to inform the rheumatologist on the functional consequences of the disease in its totality.

Of note, since (next to tender joint counts) the weight of ESR and CRP is quite high in the DAS28 formula (41, 42), therapies that interfere with the acute phase response, such as inhibitors of the IL-6 pathway, will convey an exaggerated reduction in DAS28 with DAS28-"remission" rates that exceed ACR70 and sometimes even ACR50 response rates (43-46), a finding that has no face validity and thus places doubts on the usefulness of the DAS28 for the more profound outcomes, as also discussed when deriving the ACR-EULAR remission criteria (12).

SDAI and CDAI can also be used for assessment of disease activity states. The cutpoints are shown in Table I and the remission cutpoints (SDAI≤3.3 and CDAI≤2.8) have recently been adopted as the index-based provisional definition of remission by ACR and EULAR (12). Indeed, it has been consistently shown that joint damage does not progress in SDAI/CDAI remission irrespective of the type of therapy (20, 34, 47, 48), while it can still progress significantly in patients who have a DAS28<2.6 (47, 48), since "remission" according to DAS28 is afflicted with the potential of having a large number of residual swollen joints which, as discussed above, is related to damage progression (47, 49, 50).

SDAI and CDAI remission (but not DAS28<2.6) have been consistently shown to be associated with no or minimal joint involvement even by sonography (51-53). Moreover, SDAI and CDAI remission states have also been shown as best reflecting quality of life and reduction of cardiovascular risk scores (54, 55), and the quality of life and working capacity is close to normal in CDAI remission (56).

One of the most important aspects in relation to disease activity assess-

Table I. Borders of disease activity states and improvement criteria for the simplified and clinical disease activity index (SDAI, CDAI).

Score	Remission	Low disease activity	Moderate disease activity	High disease activity	Minor response*	Moderate response*	Major response*
SDAI	≤3.3	>3.3 to ≤11	>11 to ≤26	>26	≥50%	≥70%	≥85%
CDAI	≤2.8	>2.8 to ≤10	>10 to ≤22	>22	≥50%	≥70%	≥85%

*Improvement from baseline value.

ment is the evaluation of a change or improvement in disease activity. The ACR improvement criteria are a bit complex (reduction by a certain percentage of SJC and TJC *plus* reduction by the same percentage of 3 out of 5 other variables); the DAS28 improvement criteria are also not free of complexity, as they require a certain extent of an absolute change (1.2) plus a shift from one disease activity category to a better one. In contrast, the SDAI and CDAI improvement criteria are quite straightforward: minor improvement relates to a reduction of the score by 50%, moderate improvement by 70% and major improvement by 85% (57). This is simple enough to be easily used in clinical practice but also in clinical trials, and these categories are related to the ACR20, 50 and 70 responses, respectively.

Despite the fact that SDAI and CDAI remission criteria are quite stringent, they allow a considerable proportion of patients to reach this desired state: about 25% of our clinic patients are in SDAI/CDAI remission (14) and even in clinical trials the proportions of patients attaining SDAI remission may be quite high and even exceed 30% among early arthritis patients (58).

In summary, SDAI and CDAI are easy to apply; are sensitive to change; correlate with the two main outcomes of RA: disability and damage; can be used to define disease activity states, the ACR/EULAR index-based remission definition employs SDAI and CDAI; response criteria have been defined; and early improvement correlates with good outcomes. Thus, SDAI and CDAI are two scores that can be used "for all seasons", *i.e.* for all purposes in the assessment of RA.

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