Editorial

Can We Combine Patient's and Doctor's Perspective When Assessing Rheumatoid Arthritis Disease Activity?

RHEUMATOID ARTHRITIS TREATMENT OBJECTIVES

The single main objective for the treatment of rheumatoid arthritis (RA) is to improve/maintain the quality of life of patients. Quality of life is impaired mainly due to joint abnormalities (as well as systemic inflammation, which can be considered to impair quality of life because of resulting fatigue and generally feeling sick). The joint abnormalities of RA include joint inflammation (hydrarthrodial effusion, synovitis, subchondral bone edema) and joint destruction (cartilage breakdown and subchondral bone erosions). Most researchers consider that joint destruction is driven mainly by joint inflammation. Moreover, most physicians consider that both inflammation and structural deterioration are the most important domains to assess for monitoring RA. Usually, the concept "disease activity" is thought to refer to the domain of inflammation and the concept "disease severity" to the domain of structural deterioration.

THE DOCTOR'S PERSPECTIVE WHEN ASSESSING RA DISEASE ACTIVITY

From a doctor's perspective, the tools for monitoring disease activity are quite easy to define. Inflammation is easily assessed by biological markers (e.g., acute phase reactants) and synovitis by joint count. Structural deterioration is easily assessed in daily practice by plain radiographs. Because of the importance of such variables, one could consider that currently available tools do not perform adequately. For example, persistent synovitis in 4 to 6 joints in a patient with early arthritis may be considered unacceptable despite a dramatic improvement in his/her level of pain and functional disability after 12 weeks of methotrexate therapy; moreover, addition of tumor necrosis factor blockers would need to be considered. Before making such an important therapeutical decision, a more objective and effective tool to assess synovitis might be preferable. This is one of the reasons for increased interest in ultrasonographic evaluation of synovitis in RA.

PATIENT'S PERSPECTIVE

Symptoms perceived by patients may be related to inflammation and/or structural deterioration. And there is debate whether we can differentiate the symptoms related to inflammation from those related to structural deterioration. For example, night pain, pain at rest, and morning stiffness are thought to reflect the inflammatory process, while pain occurring after physical activities is thought to reflect structural deterioration. However, it is difficult to clearly differentiate inflammation and structural deterioration based only on symptoms. For example, the level of global pain and/or functional disability may be related to both inflammation *and* structural deterioration.

Because of these difficulties, there is a current trend to consider the patient's perspective without trying to refer to the 2 main aspects of the disease (inflammation versus structural deterioration). In this case, the concept "impact" of the disease is referred to more frequently than "activity" or "severity."

Concerning development of tools to assess the impact of disease, the patient's opinion is increasingly being taken into account. Thus, the OMERACT Patient's Perspective Group has dramatically improved our knowledge in this area; in particular, the OMERACT group has emphasized that besides pain and functional disability (the 2 main domains considered by doctors as most important for patients) there are other domains to be considered, such as fatigue and sleep disturbances[1].

CURRENTLY AVAILABLE COMPOSITE INDICES

Despite the above comments, the need for a single tool permitting us to define a primary outcome measure in clinical trials and/or a single method to describe a patient in daily practice has prompted rheumatologists to use composite indices. Two well known composite indices are the American College of Rheumatology Responder Criteria (Table 1)[2] and an instrument developed by a Dutch team, the Disease Activity Score (Table 2)[3]. Both composite indices include domains from both

See DAS to measure disease activity in patients with early RA, *page 1987*

Table 1. American College of Rheumatology rheumatoid arthritis responder criteria[2].

A patient is considered a responder if he/she fulfills the following:

- Improvement in swollen joint count of at least 20%

AND

- Improvement in tender joint count of at least 20%

AND

- Improvement of at least 20% in at least 3 of the following:
  1. Pain assessed by the patient
  2. Patient's global assessment
  3. Doctor's global assessment
  4. Functional impairment assessed by the patient
  5. Acute phase reactants

Table 2. Current available rheumatoid arthritis disease activity scores (DAS)[2-4].

	Formula
DAS[4]	0.54 *√ Ritchie articular index* + 0.065* (44 swollen joint count) + 0.33*Ln (ESR) + 0.0072* (Patient's global)
DAS[3]	0.54 *√ Ritchie articular index* + 0.065* (44 swollen joint count) + 0.33*Ln (ESR) + 0.0022
DAS-4 (CRP)	0.54 *√ Ritchie articular index* + 0.065* (44 swollen joint count) + 0.17*Ln (CRP+1) + 0.0072* (Patient's global) + 0.45
DAS-3 (CRP)	0.54*√ Ritchie articular index* + 0.065* (44 swollen joint count) + 0.17* Ln (CRP+1) + 0.65
DAS 28[4]	0.56*√ 28 tender joint count + 0.28* √ 28 swollen joint count + 0.70*Ln (ESR) + 0.014* (Patient's global)
DAS 28[3]	0.56 *√ 28 tender joint count + 0.28* √ 28 swollen joint count + 0.70*Ln (VS)]*1.08 + 0.16
DAS 28 – CRP[4]	0.56* √ 28 tender joint count + 0.28* √ 28 swollen joint count + 0.36*Ln (CRP+1) + 0.014* (Patient's global) + 0.96
DAS 28 – CRP[3]	0.56 *√ 28 tender joint count + 0.28* √ 28 swollen joint count + 0.36*Ln (CRP+1)* 1.10 + 1.15
SDAI	28 swollen joint count + 28 tender joint count + patient's global (0–10) + doctor's global (0–10) + CRP (mg/dl)
CDAI	28 swollen joint count + 28 tender joint count + patient's global (0–10) + doctor's global (0–10)

CRP: C-reactive protein; ESR: erythrocyte sedimenation rate; CDAI: Clinical Disease Activity Index.

the patient's and doctor's perspective. The patient's global assessment and functional impairment instruments are obviously patient-reported outcomes. Moreover, some physicians consider that the score of tender joint count (related to the level of pain at physical examination) should also be considered a patient-reported outcome.

The main difference between the 2 composite indices is that, conceptually, the ACR criteria are used only in patient monitoring, while the DAS is used for both patient assessment and patient monitoring. Patient monitoring is defined by the capacity to describe changes in the patient's condition between 2 visits (e.g., no response, moderate response, good response, high response). Concerning the DAS, EULAR has endorsed a responder criteria set based both on changes in absolute values of the DAS between 2 visits and on an absolute value of the DAS at the final visit[4] (Table 3). Patient assessment is defined by the capacity to describe the patient's condition at a single point in time (e.g., remission, moderate activity, high activity). Table 4 summarizes the different proposed cutoffs with regard to the different available Disease Activity Scores[5-7].

USE OF COMPOSITE INDICES IN DAILY PRACTICE

Both composite indices (ACR and DAS) have been shown to be very useful for conducting, analyzing, and reporting clinical trials. The main remaining question is whether such composite indices could be useful in daily practice. Their usefulness has been discussed with the 3 following possible answers:

(1) The patient's global satisfaction is the most important outcome (the objective to reach in the future) and outcome measure/tool to evaluate the current condition; therefore, there is no obvious advantage to systematically collecting components of the composite indices.

(2) It would be useful in daily practice to collect most components included in the composite indices, but calculation of the score of the composite index is not useful. Such lack of usefulness was attributed to the fact that rheumatologists themselves can easily combine the information from different domains, e.g., data collected during the patient's interview, at physical examination, and via specific investigations such as laboratory tests or radiological investigations.

(3) There is an advantage to systematically collecting the score of a specific composite index.

Concerning the ACR criteria, its complicated format limits its general use in daily practice. Concerning the DAS, obtaining a value at a single timepoint is of greatest interest since currently the target is no longer to reach an improvement (to feel better/be a responder), but to reach a status (to feel good/be in remission/be in a low disease activity state/be in an acceptable state).

The calculation of the score of such composite indices in daily practice can be considered useful if a therapeutic decision can be made based on the observed value. A strategy trial

Table 3. EULAR rheumatoid arthritis response criteria[5,6].

Absolute DAS at Final Visit		Changes in DAS Baseline vs Final Visit		
DAS	DAS 28	≥ 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 2.4	≤ 3.2	Good response	Moderate response	No response
> 2.4, ≤ 3.7	> 3.2, ≤ 5.1	Moderate response	Moderate response	No response
> 3.7	> 5.1	No response	No response	No response

Table 4. Proposed thresholds of available rheumatoid arthritis disease activity scores[4-7].

Tool	Relevant Changes	Remission	Threshold Low Disease Activity State	High Disease Activity State
DAS	≥ 1.2	< 1.6	≤ 2.4	> 3.7
DAS 28	≥ 1.2	< 2.6	≤ 3.2	> 5.1
SDAI	≥ 7	≤ 3.3	≤ 11	> 26
CDAI	≥ 6.5	≤ 2.8	≤ 10	> 22

SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.

has demonstrated that at a group level, the therapeutical decision based on such a cutoff (e.g., to treat the patient as soon as the DAS score is above the proposed "acceptable" threshold: 3.2 for DAS) is resulting in a better outcome for patients than a therapeutical decision based only on the rheumatologist's opinion[8]. Such results have been confirmed in other studies[9,10].

Despite the high level of evidence for the usefulness of such an approach, debate continues on the use of DAS in daily practice. Such debate is based on the potential discrepancies existing between a specific DAS score and the doctor's opinion. Because of the format of the DAS, it is possible for a patient without any sign of inflammation (i.e., no synovitis, normal erythrocyte sedimentation rate) to be considered in a "nonacceptable" condition only because of "high" patient reported-outcomes (e.g., tender joint count and patient global assessment). In contrast, it is also possible for a patient with obvious signs of inflammation (synovitis and increased ESR) to be considered in an "acceptable" condition only because of "low" patient-reported outcomes (e.g., no pain at physical examination and excellent patient global assessment).

The quantitative evaluation of such discrepancies is the main objective of the study by Mäkinen, *et al* in this issue of *The Journal*[11]. The main conclusion of the report (see their Figure 2) is a that non-negligible number of joints with synovitis (up to 12) can be observed in patients considered in a low disease activity state.

Another instrument, the Simplified Disease Activity Index (SDAI), has been proposed; the SDAI takes into account the same components as the DAS but with a different formula (see Table 2)[6,7]. The SDAI was originally proposed to simplify calculation of the score. However, it appeared that the change in formula also resulted in a change in the total number of swollen joints in an individual patient considered in low disease activity. Using this composite index the maximum number of joints with synovitis in an individual patient considered in low disease activity cannot be more than 3.

CONCLUSION

The rheumatological community faces the dilemma of whether to:

- conclude that currently available tools (e.g., DAS) demonstrate usefulness both at the group level, i.e., for conducting/analyzing/reporting of clinical trials, and at the individual level
- conclude that it is necessary, because of our current treatment objectives, to further investigate the tools evaluating patient symptoms, inflammation, and structural deterioration.

In the first scenario, a huge amount of effort has been put into disseminating and implementing such a recommendation (e.g., systematically collecting DAS scores at each visit). It has to be emphasized that in addition to this educational process, strategy trials are also under way. During such strategy trials, the treatment is not fixed from baseline to the final visit but can be changed with regard to the patient condition during the trial. Usually the patient condition is defined by the DAS score.

In the second scenario, one could also conclude that besides the improvement in tools used in both clinical trials and/or daily practice (e.g., ultrasonographic evaluation of synovitis), we should be in a position in the near future to propose

new composite indices taking into account both patient and physician perspectives including the new tools and with "relevant" cutoffs.

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