New remission criteria for RA: 'modern times' in rheumatology—not a silent film, rather a 3D movie

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Response levels in clinical trials of rheumatoid arthritis (RA), such as ACR20, may be useful for evaluating the efficacy of new treatments but are inappropriate in clinical practice where the goals should be set higher. Much higher. We 'operate in the window of opportunity'[1] with early aggressive intervention, 'aim at remission' for our patients[2] and apply 'tight control' and 'treat to target' strategies[3 4] backed by research data that support these concepts of early therapeutic interventions.[2 3 5]

With modern treatment ambitions it has become increasingly clear that 'old time' definitions do not fit modern treatment opportunities and goals. New ACR-EULAR classification criteria for RA have therefore been developed which were published earlier this year,[6 7] with the new criteria focusing on patients with short disease duration with unspecified inflammatory arthritis. The goal is to prevent chronic and erosive disease by identifying patients who are at high risk and should receive disease-modifying treatment.

With the new classification criteria and ambitious treatment strategies leading to improved clinical and radiographic outcomes, long-term and drug-free remission has become a realistic goal in many patients and a great need has emerged for consensus on how to (re) define remission.

In this issue of *Annals of the Rheumatic Diseases*, preliminary new criteria for remission in patients with RA—another merit of the new times—are published by Felson *et al*. [8] This paper is also the result of an ACR-EULAR collaboration, underlining globalisation of the world of rheumatology.

The old remission criteria were like silent films—with disease potentially progressing silently under a cover of remission that allowed substantial disease activity to be present. The new criteria are more like a 3D movie—requiring no or minimal activity based on three dimensions: clinician's (swollen and tender joint counts) and patient's (global health score) judgements together with laboratory data (C reactive protein (CRP)) (figure 1).

REMISSION IN RA

Historically, several definitions for remission in RA have been developed (table 1). The first published definition for remission in RA was developed by Pinals and co-workers and published as the 'preliminary criteria for clinical remission in rheumatoid arthritis' in 1981.[9] These criteria required the presence over two consecutive months of at least five out of six elements (table 1). The criteria were rarely met and were therefore only of limited clinical use, especially in the prebiological era when such remission was indeed rare. Even by today's treatment standards, complete absence of, for example, fatigue and joint pain is rare.

When the disease activity score (DAS), developed in the Netherlands, came into use in the 1990s,[10 11] it was an important step forward because it allowed for comparison of studies and centres. Various cut-off points for remission were computed, having the criteria by Pinals *et al* as a reference, both for the original DAS[12] and later for the DAS28.[13] The most widely used definition in randomised controlled trials (RCTs) during the last decade has been DAS28 remission (a value of <2.6). In addition, in RCTs the ACR70 and ACR90 response levels have sometimes been reported, both of which define smaller groups of patients with less residual disease activity compared with DAS28 remission.[3 14 15] The DAS instrument has been very useful over the last two decades in the development of treatment strategies such as 'treat to target', but it has not been widely used in clinical practice because of the complicated formula for calculation and because the value does not intuitively make sense in the individual treatment situation. Furthermore, there may be substantial clinical residual disease activity, even in the form of obvious synovitis in multiple joints, in patients

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Table 1 Various definitions developed for remission in rheumatoid arthritis over time

	ARA[9] (1981)	DAS[12] (1996)*	DAS28[13] (2004)†	SDAI[16] (2005)‡	CDAI[16] (2005)§	ACR/EULAR[8] (2010)
Cut-off for remission	5/6 for 2 consecutive months	<1.6	<2.4	≤3.3	≤2.6	4/4 at one time point
Elements included						
Morning stiffness	≤15 min	–	–	–	–	–
Fatigue	None	–	–	–	–	–
Joint pain	None	–	–	–	–	–
Tender joint count	0	Ritchie articular index	28 joints	28 joints	28 joints	28 joints
Swollen joint count	0	44 joints	28 joints	28 joints	28 joints	28 joints
ESR/CRP	ESR<20 (men) ESR<30 (women)	ESR (mm/h)	ESR (mm/h)	CRP (mg/dl)	Not included	CRP (mg/dl)
Patient's GH	–	0–100 scale	0–100 scale	0–10 scale	0–10 scale	0–10 scale
Physician's GH	–	–	–	0–10 scale	0–10 scale	–

*DAS = $0.53938 \times \sqrt{(\text{Ritchie})} + 0.06465 \times (\text{Swollen joints}) + 0.330 \times \ln(\text{ESR}) + 0.00722 \times (\text{GH})$.
†DAS28 = $0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times (\text{GH})$.
‡SDAI, the sum of the five elements.
§CDAI, the sum of the four elements.
ACR, American College of Rheumatology; ARA, American Rheumatism Association; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; EULAR, European League Against. Rheumatism; GH, global assessment; SDAI, Simple Disease Activity Index; SJC28, 28 joint count for swollenness; TJC28, 28 joint count for tenderness.

who are by definition in DAS28 remission. In line with this, many clinicians have experienced that patients in DAS28 remission who are asked to participate in studies of controlled discontinuation of tumour necrosis factor inhibitors often feel that they are not 'healthy' enough to participate.

To overcome these problems, the Simple Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) (table 1) were later developed and both have been shown to perform so well that they were included in the present effort.[16] A state of remission with these instruments, just as with the DAS28, may entail some residual disease activity. In the case of SDAI and CDAI this is, however, more transparent owing to the simplicity of the formula.

THE NEW REMISSION CRITERIA

In the present work the Committee, together with patient experts, evaluated the eight core set criteria elements and defined the highest level of residual disease activity that, in their opinion, was compatible with remission. Using data from large RCTs, they examined in a stepwise fashion the added contribution of patient-reported outcomes and the ability of the candidate measures to predict subsequent good radiographic and functional outcomes. The definition of x-ray remission was a complete halt of progression in the second year of the included RCTs.

Two preliminary definitions of remission in RA are presented: (1) a maximum value of 1 for each of the following: 28 joint count for swollenness (SJC28) and tenderness (TJC28), CRP (mg/dl) and patient's global assessment (0–10 scale) and (2) SDAI remission (simple sum of TJC28, SJC28, patient global (0–10 scale), physician global (0–10 scale) and CRP (mg/dl)) ≤3.3.

In addition, CDAI ≤2.8 (similar to SDAI but without CRP) performed as well as SDAI ≤3.3 in predicting good radiological and functional outcome, and both SDAI and CDAI may be used in clinical practice. In clinical trials, CRP should be included because it is an important predictor of long-term radiographic damage. Although not formally stated, it makes sense not to use the criteria interchangeably on an individual patient level.

Patient-reported outcomes contributed significantly in the remission models. The additional effect of scoring 66/68 joints instead of 28 in the evaluation was found to be minimal because the loss of information was mitigated by the requirement of a low patient global score.

A STEP FORWARD

The presented definitions represent several major steps forward.

First, the remission criteria are feasible to calculate even in routine care, and they can easily be applied to, for example, observational registries, thereby improving the monitoring of patients treated in clinical practice.

Second, we know that high disease activity has a detrimental impact on patient-reported health-related quality of life and that patients who fulfil more stringent remission criteria score higher on utility indexes such as the EQ-5D.[17] The new criteria will therefore also support the strive to improve quality of life in more patients.

Third, they represent another successful ACR-EULAR collaboration. With 'treat to target' as the modern treatment principle, permanent remission is the ultimate goal—although not a realistic one in all patients. Nevertheless, aiming at remission will also improve outcome in those patients who do not reach remission. Even if not always a realistic goal on an individual level, treatment goals such as these may be very useful on a group level to ensure that outcome overall is improving.

Fourth, the generalisability of the criteria is likely to be improved by the use of contemporary data from clinical trials published during the last decade in which modern biological therapy has been represented in one of the treatment arms. The DAS cut-off points for remission were, for example, developed in the prebiological area and were based on treatment decisions by physicians rather than the patient's opinion. In this sense the new criteria will need to be further validated in larger patient groups against the level of disease activity that patients find acceptable (and not only the patient experts participating in the present study).

FURTHER CHALLENGES

Some possible weaknesses and potential future challenges should also be considered. As the title of the paper states, these criteria are preliminary, should be subject to further validation and may need adjustment as we move along.

First, imaging was not included in the criteria. It has been documented over the last years that, although patients with RA may be clinically in remission, residual inflammation may be seen by

imaging techniques such as ultrasound and MRI which predict further joint destruction.[18–21]

Second (and related to the issue of residual inflammation not detected clinically), the sensitivities and likelihood ratios for predicting very good outcome in terms of x-rays and function were relatively modest for all evaluated sets of criteria tested in the present study. For example, the proportion having good outcomes on x-ray with the two proposed criteria sets were 77%, meaning that a substantial proportion (23%) still progressed radiologically, indicating that there is room for further improvement in the definition of remission.

Third, the use of data from clinical trials enables relatively complete and long-term follow-up of large groups of patients treated according to protocols. One drawback from this approach is that only very selected subgroups of patients were included, who had not only met the inclusion criteria but also been compliant in the studies. The remission criteria will therefore need further validation in the setting of observational studies and especially in early disease.

Fourth, only the core set of criteria elements[22] were evaluated. The only patient-derived element was the patient global assessment. Although it is possible that this variable captures much of what is relevant for inflammatory disease, there might be additional precision to be gained by including more specific items measuring, for example, fatigue. Furthermore, the patient global scale is difficult to interpret by many patients and some may include poor well-being caused by unrelated or related comorbidities. This may hamper the proposed criteria.

CONCLUSION

The new remission criteria are feasible and easy to use and give a contemporary definition of a relatively healthy state for a patient with RA. Despite this, we are not at the end of the road. The current criteria may not define definite and true remission enabling patients to participate in all wanted activities. Furthermore, as the data indicate, they do not completely predict the end of radiological progression. There will therefore be a future need to develop additional response criteria, entailing more components such as imaging techniques. Such criteria will probably lose simplicity and be less suitable for use in clinical practice. The new preliminary ACR/EULAR criteria are therefore likely to be used for a long time.

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