

# To be in remission or not: is that the question?

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## Monitoring disease activity regularly is preferable to classification as remission at one point in time

The goal of the management of rheumatoid arthritis (RA) is to suppress disease activity as much as possible, to prevent loss of function, and to prevent or control joint damage.<sup>1</sup> As for most chronic diseases, cure—meaning complete disappearance of all signs and symptoms which persist after stopping treatment—occurs only seldomly. Therefore often the term “remission” is used to define a state which approaches cure as closely as possible. However, remission in RA is not clearly defined, and might, alternatively, be understood to be absence of disease activity, absence of measurable disease activity, or very low disease activity, probably without clinical consequences like progressive damage to the joints or functional loss.<sup>2</sup> For the assessment of remission of disease activity in RA, disease activity is probably best regarded as a continuum, and remission can be seen as a state at the very end of it.

“Disease activity is a continuum with remission a state at the end of it”

As no “gold standard” exists for the measurement of disease activity, the Disease Activity Score (DAS) and DAS28 (28 joint count) were developed and validated in the 1990s.<sup>3,4</sup> These composite scores express disease activity, ranging from 0 to 9. To facilitate the interpretation of these scores cut off points of high, moderate, and low disease activity have been defined and used to develop the EULAR response criteria.<sup>5</sup> Additionally, it has been shown that a DAS28 <2.6 corresponds with fulfilment of modified American Rheumatism Association (ARA) criteria for clinical remission.<sup>2</sup> This cut off point may be regarded as a refinement of the above mentioned criteria that helps in the interpretation of low DAS28 scores.

In several clinical studies this cut off point was used, and described as “DAS28 remission”, “near remission”, or “remission-like low disease activity”. Figure 1 shows that DAS28 values are indeed appreciably low when the ARA

remission criteria are fulfilled, but it can also be seen that there is considerable overlap in DAS28 values between both distributions. Therefore, rather than being identical to the ARA remission criteria, the DAS28 <2.6 describes a state of low disease activity that includes nearly all patients who fulfil the ARA remission criteria, while scarcely anyone with a higher DAS28 fulfils the ARA remission criteria. At the same time, as can be seen in fig 1, patients with a DAS28 <2.6 are a mix of cases in which the ARA remission criteria are fulfilled and not fulfilled, and non-fulfilment is even more common than fulfilment of the ARA remission criteria.

“Patients classified as in remission may still have swollen or tender joints”

Mäkinen *et al* found in their study that 11% and 19% of the patients with a DAS28 score under their cut off point for remission of 2.32 still had swollen or tender joints (68 joint count), respectively.<sup>6</sup> The reason for this apparent discrepancy lies in the different construction of the DAS28 and the ARA criteria. The DAS28 can be calculated using the formula<sup>4</sup>:  $0.56 \times \sqrt{(28TJC)} + 0.28 \times \sqrt{(28SJC)} + 0.70 \times \ln(ESR) + 0.014 \times GH$ , where TJC = tender joint count; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; GH = general health.

A patient is classified as in remission according to the preliminary ARA remission criteria if five out of six criteria are fulfilled: no tender joints, no swollen joints, ESR <20 mm/1st h for men or <30 mm/1st h for women, no joint pain, duration of morning stiffness ≤ 15 minutes, no fatigue.<sup>7</sup>

It follows that different combinations of disease activity indicators are possible to obtain low DAS28 values, but not for fulfilment of the ARA remission criteria. For example, a patient with RA with two tender joints, no swollen joints, ESR 10 mm/1st h, and 10 mm GH has a DAS28 of 2.54, and may well be in

clinical remission according to the ARA criteria. When the same patient has one tender joint, one swollen joint, ESR 10 mm/1st h, and 10 mm GH he/she has a DAS28 of 2.54, appears to have low disease activity, but will not fulfil the ARA remission criteria. In the paper of Mäkinen *et al* a modification of the ARA remission criteria was used. Patients had to fulfil five out of five criteria (fatigue was not measured) in order to be classified as being in remission. It is therefore not surprising that with these more stringent criteria the cut off point of the DAS28 was lower than in earlier reports.

Another problem with a dichotomous variable like the remission criteria is that small changes in disease activity have a great impact as this changes the state of the patient from remission into no remission (fig 2). In daily clinical practice as well as in clinical trials better insight into the total amount of disease activity is obtained by measuring the cumulative amount of disease activity over a certain period of time. Recently, it was shown that not only the mean disease activity measured with the DAS28 but also fluctuations in disease activity are related to radiological progression.<sup>8</sup>

Finally, the authors also discussed whether the fact that the DAS28 uses reduced joint counts is valid to measure “remission”. It seems logical that if one is interested in very low disease activity, the use of more comprehensive joint counts to assess patients would make it more likely that swollen or tender joints were found. We described this in our paper in 2004, where we showed that the sensitivity for the DAS is slightly greater than for the DAS28.<sup>2</sup> However, assessing more joints does not automatically means a greater validity as, recently, others have shown that including ankle and feet joints did not significantly influence the cut off point for remission.<sup>9</sup> An explanation for this might be the difficulty in validly assessing joints of the feet.<sup>10</sup>

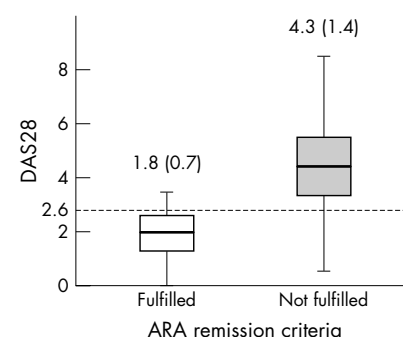
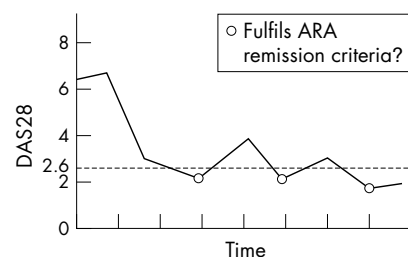


Figure 1 Relationship between the DAS28 and the ARA preliminary remission criteria.



**Figure 2** Course of disease activity over time.

In conclusion, disease activity is a continuum, cut off points are used to categorise patients at a certain time point and in addition they help us in the interpretation of scores. Using the same criteria for remission is more important than arguing about the levels of a cut off point. A better way of expressing the disease status of a patient would be to follow the disease activity regularly and calculate the mean disease activity and standard deviation of the mean over a certain period, instead of classifying a patient as being in remission at one point in time.

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