Concise Report

Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria

J. Fransen, M. C. W. Creemers and P. L. C. M. Van Riel

Objective. To determine which cut-off point in the RA disease activity score (DAS28) corresponds to fulfilment of the ARA criteria for clinical remission.

Methods. The disease activity of patients included in the Nijmegen RA inception cohort was systematically assessed every 3 months. For all visits, a modification of the ARA preliminary criteria for clinical remission was applied and the DAS28 was calculated. Receiver operating characteristic analysis was used to determine the cut-off point with maximum sensitivity and specificity in DAS28 corresponding with fulfilment of the modified ARA criteria.

Results. Three hundred and seventy-eight patients contributed 4378 visits. In 6.5% of the visits four of the five items and in 1.5% all five items of the modified ARA criteria were fulfilled. The optimal cut-off point for the DAS28 that corresponds to fulfilment of the modified ARA criteria was determined to be 2.66.

Conclusion. DAS28 < 2.6 corresponds to fulfilment of the preliminary ARA criteria for clinical remission in RA.

KEY WORDS: Rheumatoid arthritis, Disease activity, Disease activity score, Remission, Criteria.

The ultimate goal of medical treatment in RA may be formulated as being to reach a state of remission. In practice, clinical remission may occur infrequently, may only be temporary and may require ongoing therapy with DMARDs or biological agents. Remission in RA is not clearly defined, and could alternatively be understood as the absence of disease activity, the absence of measurable disease activity, or very low disease activity, probably without clinical consequences. As long as the definition of remission in RA is unclear, it is probably better not to speak of remission without defining it. 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 [1]. The difficulty lies in deciding when disease activity is likely to be absent, and how to measure this absence.

Remission can be assessed clinically using the preliminary criteria of the American Rheumatology Association (ARA) or the disease activity score (DAS) [2, 3]. The DAS is a continuous measure including the Ritchie articular index (RAI), a 44 swollen joint count, ESR and general health. The DAS is continuous, with a theoretical range from 0 to 10. A DAS <1.6 corresponds to fulfilment of the ARA remission criteria [4]. For assessment of disease activity in daily clinical practice, a disease activity score with reduced joint count (DAS28) can be used [5]. A cut-off point of DAS28 <2.6 has been proposed but has not been tested in a clinical sample [1].

The objective of this study was to determine which cut-off point in a disease activity score (DAS28) for RA corresponds to fulfilment of the ARA criteria for clinical remission.

Patients and methods

Sample

Data were used from the Nijmegen RA inception cohort [6], in which the DAS and DAS28 were developed and the cut-off point for remission of the DAS was also determined. RA patients were included in the cohort immediately upon diagnosis according to the ACR criteria [7], but only when duration of RA symptoms was less than 1 yr. Cohort patients were evaluated every 3 months using standardized assessments. We included all visits of all patients enrolled from the start of the cohort in 1985 to mid-1992 and from mid-1994 to 2002, for a maximum of 6 yr of individual follow-up time. The reason for this gap was that most patients were followed annually instead of every 3 months in the period from mid-1992 to mid-1994, due to reduced funding. Follow-up was censored for one of three reasons: (i) end of the observation period; (ii) more than one consecutive visit missing; (iii) lost to follow-up.

Treatment strategy for RA patients followed guidelines published recently [8]. With few exceptions, all patients were treated with DMARDs and/or biologicals and whenever appropriate NSAIDs and/or corticosteroids were added.

The Nijmegen RA inception cohort was approved by the responsible ethics committee. Informed consent was supplied by the patients before enrolment in the cohort.

Assessments

Specially trained research nurses performed the standardized joint counts and collected all other data, which included determination...
of ESR (Westergren) by the laboratory, patient ratings of general health and pain on 100 mm visual analogue scales, and duration of morning stiffness in minutes.

According to the preliminary ARA criteria for clinical remission in RA, a state of clinical remission is reached when five of the following six criteria are fulfilled for at least two consecutive months: morning stiffness ≤15 min; no fatigue; no joint pain (by history); no joint tenderness or pain on motion; no soft tissue swelling in joints or tendon sheaths; ESR <30 mm/h for females or <20 mm/h for males [2].

In our cohort, patients were followed every 3 months, and fatigue was not assessed. Therefore, a modification of the ARA remission criteria was used [4]. A patient was categorized as fulfilling remission criteria when four of the following five criteria were fulfilled: morning stiffness ≤15 min; VAS pain ≤10 mm; 53 tender joint count = 0; 44 swollen joint count = 0; ESR <30 for females or <20 for males.

The DAS28 is a validated index of RA disease activity [5]. The DAS28 is continuous, has a Gaussian distribution with a theoretical range from 0 to 10. DAS28 values ≤3.2 are regarded as representing low disease activity and DAS28 values >5.1 as representing high disease activity [9]. The DAS28 is calculated using the results of the 28 tender joint count (TJC 28) and the 28 swollen joint count (SJC 28), ESR and general health (GH) using:

\[
\text{DAS28-4} = 0.56\sqrt{(\text{TJC}28) + 0.28(\text{SJC}28) + 0.70\ln(\text{ESR}) + 0.014(\text{GH})}.
\]

In cases where GH is not measured, the DAS28 can be calculated using:

\[
\text{DAS28-3} = \left[0.56\sqrt{(\text{tJC}28) + 0.28(\text{SJC}28) + 0.70\ln(\text{ESR})}\right]^{1.08} + 0.16
\]

Statistical analysis

For every visit of every patient, the DAS and DAS28 (using the notation DAS28-4 and DAS28-3 to discriminate between the formulas with four and three variables) were calculated and fulfilment of the modified ARA criteria for clinical remission was determined [3–5]. Receiver operating characteristic (ROC) analysis was used to determine the cut-off point with maximum sensitivity and specificity in DAS28 that corresponds to clinical remission may be 2.65, conservatively rounded off at 2.6 [1, 4].

### Table 1. ARA clinical remission

<table>
<thead>
<tr>
<th>Year*</th>
<th>N</th>
<th>Total: n</th>
<th>Per patient: median (range)</th>
<th>Patients with ≥1 ARA remission visit n (%)</th>
<th>Patients with remission visits in a previous year n</th>
<th>Patients with ≥2 ARA consecutive remission visits n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>378</td>
<td>67</td>
<td>1 (1–4)</td>
<td>42 (11%)</td>
<td>–</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>2</td>
<td>287</td>
<td>91</td>
<td>2 (1–4)</td>
<td>50 (17%)</td>
<td>24</td>
<td>25 (9%)</td>
</tr>
<tr>
<td>3</td>
<td>218</td>
<td>78</td>
<td>1 (1–4)</td>
<td>48 (22%)</td>
<td>22</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>50</td>
<td>1 (1–4)</td>
<td>28 (19%)</td>
<td>17</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>37</td>
<td>2 (1–4)</td>
<td>18 (19%)</td>
<td>11</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>33</td>
<td>2 (1–4)</td>
<td>14 (18%)</td>
<td>12</td>
<td>9 (12%)</td>
</tr>
</tbody>
</table>

Occurrence of ARA clinical remission in the Nijmegen RA cohort by years of follow-up. Fulfilment of the modified ARA criteria for remission at a single visit is noted as ‘remission visit’.

*Follow-up year.

N, number of patients; n, number of visits.
The table shows the AUC with 95% confidence intervals (95% CI) of the three ROC curves of the graph in Fig. 1. Several possible cut-off points are shown with their associated sensitivity and specificity to predict fulfillment of modified ARA criteria. Optimal cut-off points are shown in bold type.

Table 2. Sensitivity and specificity for different cut-off points in disease activity scores

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Cut-off point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-4</td>
<td>0.93 (0.92–0.94)</td>
<td>2.60</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.65</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.70</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>DAS28-3</td>
<td>0.90 (0.89–0.91)</td>
<td>2.60</td>
<td>76</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.65</td>
<td>79</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.70</td>
<td>80</td>
<td>84</td>
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<td></td>
<td></td>
<td>2.80</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.90</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>DAS</td>
<td>0.96 (0.95–0.97)</td>
<td>1.60</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

The results of this study show that DAS28 <2.6 corresponds to fulfillment of the ARA criteria for clinical remission in RA, in a single visit. The optimal cut-off point found by this study, as well as by transformation of the DAS, was somewhere between 2.6 and 2.7, but a cut-off point of 2.6 may be preferred because of its higher specificity. This cut-off point may be regarded as a refinement that gives meaning to low DAS28 scores. But in our opinion it does not replace the cut-off point of DAS28 ≤3.2 that is regarded as representing low disease activity, based on decisions of rheumatologists considering DMARD treatment in a clinical cohort [9]. The prognostic value of cut-off points in disease activity, such as DAS28 <2.6 and ARA criteria for clinical remission, needs to be determined in further longitudinal studies. Often, cut-off points in continuous measures seem biologically arbitrary. If they do not possess prognostic or clinical meaning, the use of cut-off points is perhaps a bad habit, and their use should be avoided as far as possible. Furthermore, a cut-off point may change as knowledge about the disease increases or as changes occur in attitudes to appropriate treatment. The availability of more effective treatments in RA will raise further interest in the definition and assessment of absence of disease activity or criteria for sufficiently low disease activity. As for the treatment of RA, it would be very useful to know how long a period of remission or very low disease activity should be in order to make progression of disability and joint damage unlikely. However, disease activity may not be regarded as an on–off phenomenon, and disease activity of a patient may fluctuate around a level of no or minimal disease activity. Accordingly, a better way of expressing the disease status of a patient would be the cumulative amount of disease activity over a certain period of time or the mean disease activity in a certain period, instead of classifying a patient as being in remission [1]. Likewise, it has been shown that patients with constant 'low' disease activity (DAS28 ≤3.2) over time have significantly less progression of joint damage than patients who have 'high' disease activity (DAS28 >5.1) over time [10].

In our cohort, a modification of the ARA remission criteria was used, notably by omitting fatigue and using 3 months of follow-up instead of 2 months. This modification was also used in other studies [11, 12], but it limits generalizability to the original ARA criteria. However, the original ARA remission criteria still performed well when the criterion was changed to four out of six instead of five out of six [2]. Fatigue was not assessed in our cohort, because it is difficult to measure and to interpret. Using 3 months of follow-up instead of 2 months may not have led to important underestimation of the occurrence of remission. In our sample, the occurrence of ARA clinical remission was lowest in the first year after inclusion (4%), and remained fairly constant (∼10%) over the following years. Also, there was no difference in occurrence of remission over time between the two different subcohorts, one starting between 1985 and 1992 and another starting between 1995 and 2002 (not shown). Thus, there appeared to be no influence of time (change of treatment habits) on the occurrence of remission. The remission rates found in our cohort were comparable to the rates found in the other cohorts using (modified) ARA criteria [11, 12]. Accordingly, it appears that ARA clinical remission can be reached in early RA as well as later in the disease. However, remission according to the ARA criteria still seems a rare event and difficult to reach in a majority of patients [13].

In conclusion, DAS28 <2.6 corresponds to fulfillment of the preliminary ARA criteria for clinical remission. The prognostic value of cut-off points in disease activity such as DAS28 <2.6 and ARA criteria for clinical remission needs to be determined in further longitudinal studies. As this study used the same cohort in which the DAS28 was developed, it would also be informative if the performance of the DAS28 were to be tested in another cohort.

### Key messages

- DAS28 <2.6 corresponds to fulfillment of the ARA criteria for clinical remission in RA.
- More important than remission is the length of the period with low disease activity.

The authors have declared no conflicts of interest.
References