REMISSION IN A PROSPECTIVE STUDY OF PATIENTS WITH RHEUMATOID ARTHRITIS. AMERICAN RHEUMATISM ASSOCIATION PRELIMINARY REMISSION CRITERIA IN RELATION TO THE DISEASE ACTIVITY SCORE

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SUMMARY

In a prospective follow-up study of patients with early-onset rheumatoid arthritis, the prevalence of remission according to the 1981 American Rheumatism Association (ARA) preliminary criteria was evaluated. A total of 227 patients with a median follow-up of 3.9 yr and a total of 2832 follow-up visits were studied. The ARA remission criteria were fulfilled in 9.5% of these visits. The percentage of patients with at least one visit fulfilling the ARA criteria was for years 2 6 ~ 25%. Each year, ~15% of the patients were in remission for at least two consecutive visits. A comparison was made between the ARA remission criteria and the Disease Activity Score (DAS). DAS <1.6 corresponded with being in remission according to the ARA criteria. The DAS is being proposed as a tool to define remission because absence of disease activity should be measured using the same method as for higher levels of disease activity, preferably on a continuous scale.

Key words: Rheumatoid arthritis, Disease Activity Score, Remission.

Rheumatoid arthritis (RA) is a chronic systemic disease of unknown aetiology with as its main feature polyarthritis leading to joint damage and functional impairment. The treatment of RA aims at a reduction of disease activity and thereby prevention of joint damage and functional impairment. The ultimate goal of treatment is remission, i.e. complete suppression of disease activity [1, 2]. The American Rheumatism Association (ARA) defined preliminary remission criteria [3]. For the development of these criteria, the opinion of 35 rheumatologists about the disease state of 344 patients (remission during treatment, remission no treatment, partial remission, active disease) was chosen as standard. The criteria had to be fulfilled for a period of two consecutive months because permanent remission cannot be measured in trials, and resulted in a dichotomous scale: remission yes/no. These ARA criteria have been evaluated [4, 5] in two studies. In both studies, the patients had an established disease; one study was done cross-sectional [5], while in the other no standardized follow-up was defined [4].

The concept of how to measure disease activity has changed rather over the last few years. Core sets of variables have been selected which were based on consensus of several rheumatologists and on the validity to measure disease activity [2, 6, 7]. It has been advised to assess disease activity by these almost identical, core sets, to gain uniformity in the evaluations of clinical studies. Two out of the six variables mentioned in the ARA criteria of remission are not included in these core sets, which limits the use of these criteria.

Remission, being absence of disease activity, should be defined with the same measures as used to assess disease activity. We propose the Disease Activity Score (DAS), a validated index including only core set variables, to assess absence of disease activity [8, 9]. An advantage of defining remission by a continuous variable like the DAS is that remission can be placed on a spectrum of disease activity, which gives the opportunity to adjust cut-off values of DAS with respect to new insights.

The goal of this study is to evaluate the prevalence of remission according to the ARA preliminary criteria in a standardized follow-up study of patients with a recent onset of RA. A secondary goal was to investigate the relationship of the ARA remission criteria with the DAS.

PATIENTS AND METHODS

Patients with recent-onset RA visiting the outpatient department of the University Hospital of Nijmegen were eligible for this study if they fulfilled the following criteria: RA according to the American College of Rheumatism criteria (ACR) [11], a disease duration (since diagnosis) of < 1 yr, and not previously treated with disease-modifying anti-rheumatic drugs (DMARDs). Since 1985 until now, 237 patients took part in this study. For different reasons, 10 patients were not included: refused participation (n = 6) or had serious co-morbidities at the time of diagnosis which hindered follow-up (n = 4, anemia, malignancy, lung fibrosis). During the follow-up, 15 patients died and 16...
patients withdrew alive [refusal of follow-up ($n = 14$) or moving far away ($n = 2$)].

The patients were seen by research nurses and by one of the rheumatologists at least every 3 months. The following assessments were made: morning stiffness (min); pain on a visual analogue scale of 100 mm (pain; 0 = no pain, 100 = worst pain possible); general health on a visual analogue scale (GH; 0 = best possible, 100 = worst possible); erythrocyte sedimentation rate (ESR) according to Westergren. Also, a complete joint examination took place, from which the following joint counts (JCs) [12] were calculated: Ritchie Articular Index (RAI; 53 joints graded for tenderness); total number of tender joints (TOTT; 53 joints); total number of swollen joints (TOTS; 44 joints).

Data concerning medication, whether patients had stopped, changed or started with DMARDs, or non-steroidal anti-inflammatory drugs (NSAIDs), were also collected. Although the treatment schedule of the DMARDs has changed during the past few years (1985-1993), the following sequence was used in most patients: the first step included sulphasalazine or hydroxychloroquine, the second step methotrexate or i.m. gold, thereafter d-penicillamine or azathioprine. Almost all patients were concomitantly treated with NSAIDs, and restricted use of low-dose corticosteroids as adjuvants was allowed in a small number of patients.

The preliminary remission criteria of the ARA [3] are described in Table I. The description of the variables, however, is not sufficiently detailed. Therefore, the following assumptions were made in this study: the criterion no joint pain (by history) was replaced by the variable pain on a visual analogue scale. To compensate for patients' inaccuracy, a value of $\leq 10$ mm was chosen to represent no pain; the criterion no joint tenderness or pain on motion was fulfilled if no joint was scored painful out of 53 joints (TOTT = 0); no soft tissue swelling in joints or tendon sheaths was fulfilled if no joint was scored swollen out of 44 joints (TOTS = 0); the criteria for ESR and morning stiffness were applied as mentioned. Fatigue was not measured in this study, for this reason we decided that 4/5 criteria (instead of 5/6) had to be present to qualify for a remission (similar to a part in the study of Wolfe and Hawley [4]). Instead of a time period of 2 months, we used 3 months in this study.

For each patient, the DAS [8] was calculated by the following formula:

$$
\text{DAS} = 0.54 \sqrt{\text{RAI}} + 0.065 \text{TOTS} + 0.33 \ln \text{ESR} + 0.0072 \text{GH}
$$

The range of the DAS varies from 0 to 10.

In the analyses, only 3-monthly visits were included. However, four patients, known by the rheumatologists to have low disease activity, refused to visit the out-patient department every 3 months. For these patients, another follow-up schedule (a minimum of one visit a year) was applied. It was assumed that the disease activity was low during the period with no visits, since it was agreed with the patients that in the case that complaints recurred they should call for an appointment. For these patients, 3-monthly visits were added for the period being in remission. For all other patients, an interruption of 6 months (one visit missed) was allowed. If the interruption was longer, the follow-up was ended at that point.

For each patient at each visit, it was calculated how many ARA remission criteria were fulfilled. Also, the prevalences of the fulfillment of single criteria were computed. For each follow-up year (first to sixth), both the number of patients in remission and the number of visits fulfilling the ARA remission criteria were computed. As a measure of dispersion, medians and interquartile ranges (P25-P75) are presented. The distribution of DAS values for patients in remission and not in remission according to the ARA criteria is presented.

**RESULTS**

Of the 227 patients included in this study, 63% were female; the median age was 55 yr (P25-P75: 43-65 yr), 78% were IgM rheumatoid factor positive (> 10 IU) and 53% were HLA-DR4 positive. The median number of visits of the patients was 13 (P25-P75: 5-22) and the median duration of follow-up (since diagnosis) was 3.9 yr (P25-P75: 1.1-5.6 yr).

Of all visits of patients ($n = 2832$), the number in which five and four of the ARA remission criteria were fulfilled were, respectively, 72 visits (2.5%) and 198 visits (7%). According to this, at 9.5% of all visits patients had no disease activity. These visits concern 69 patients (37%) who fulfilled the criteria at least once during follow-up (Table II). The median number of 'remission visits' per patient was three and ranged from 1 to 22. Thirty-nine patients had at least two consecutive visits fulfilling the remission criteria. Because of the difference in follow-up duration, patients with more visits have more chance of meeting the remission criteria. Therefore, the number of patients fulfilling the remission criteria per follow-up year was calculated. For year 1, the percentage of patients with at least one remission visit was 10% (6% for two consecutive visits), and for years 2-6 the percentage was ~25% (15% for two consecutive visits). The relative number of patients who fulfilled the remission criteria in a previous year increases with the duration of follow-up. However, even at year 6 there were patients reaching remission for the first time.

The percentages of all visits ($n = 2832$) in which a...
single criterion of the ARA set was fulfilled was 62% for morning stiffness, 22% for pain, 19% for tender joints, 6% for swollen joints and 65% for ESR. Swollen joints seems to be the "rate limiter" for reaching remission according to the ARA criteria. Therefore, we studied the probability of being in remission according to the ARA if a single criterion is fulfilled or not (Table III). The criterion swollen joints most strongly determined whether a patient was in remission or not. In contrast, the criteria morning stiffness and ESR have almost no influence on being in remission or not.

The distribution of DAS for visits that patients did or did not fulfil the ARA remission criteria is shown in Fig. 1. At a cut-off value for the DAS of 1.6, the percentages of misclassification were equal for both groups of patients, namely 10%. In Fig. 2, the course of the DAS in relation to the ARA criteria is presented for four patients. As can be seen in this figure, low DAS values correspond with being in remission according to the ARA criteria and high DAS values with not being in remission. Apart from this, these figures show that visits in which patients fulfil the remission criteria are not always consecutive or, if consecutive, only last temporarily.

**DISCUSSION**

As the ultimate goal of treatment of patients with RA is achieving a status of complete suppression of disease activity, a definition of remission was proposed by the ARA preliminary criteria in 1981 [3]. However, these criteria were only evaluated in two studies [4, 5]. Both studies included selected patients with established disease and did not have a standardized follow-up. In the present study, the prevalence of remission according to the ARA preliminary criteria in a cohort of patients who were followed from the start of the disease in a standardized way is described. In addition, a comparison was made between these criteria and the DAS values as a first attempt to define new remission criteria consistent with the current views of assessing disease activity.

In our study, ~25% of the patients fulfilled at least once the ARA remission criteria, and ~15% of the patients fulfilled the criteria on two consecutive visits. In the study of Wolfe and Hawley [4], out of 458 patients with an established disease with at least three clinic visits, 18.1% fulfilled the ARA criteria once. The results of the study of Alarcon et al. [5], which were based on only one visit in two populations of different countries, showed prevalences of remission of 1 and 30%, respectively, of the patients according to the ARA criteria. In both the last mentioned studies, patients were selected during a visit at the clinic; this is in contrast with the present study in which patients were followed from the start of the disease in a standardized way. Owing to these different selection strategies and to methodological differences, it is difficult to compare the different studies.

We had to deal with several problems when applying the ARA remission criteria in our study. In the first place, the criteria are not sufficiently described. As a
result, several assumptions had to be made to use these criteria, also in this study, which will have consequences for the prevalences of remission found. For example, the criteria no joint pain and no joint swelling were measured by joint counts including 53 and 44 joints, respectively. If joint counts measuring more joints are included in the criteria, a lower prevalence could be expected. Secondly, in the definition of remission according to the ARA, a time period is also included. This aspect, however, could not be investigated in the original study [3] and in the studies of Wolfe and Hawley [4] and Alarcon et al. [5] because their follow-up was not standardized. As the frequency of follow-up in our study, once in 3 months, did not deviate much from the frequency included in the definition, we were able to overcome this problem. The variable fatigue was not included in our study because clinical practice and trial experience showed that ‘time until fatigue’ is difficult to assess and, by international consensus, fatigue is not included in the core set of disease activity variables [2, 7]. Also, no recommendations on how fatigue is to be measured are given by the ARA. Therefore, we modified the criteria so that 4/5 of the remaining variables had to be fulfilled.

In the original study of the ARA criteria [3], the variable morning stiffness discriminated best. Recently, morning stiffness has been evaluated by Hazes et al. [13]. It appeared that this variable was a poor discriminator between RA and non-inflammatory joint disease, and between active and inactive RA. In the present study, this was confirmed because the influence of this variable on remission could be neglected: many patients fulfilling this criterion were not in remission. In contrast with the variable swollen joints which had the largest influence: if it is fulfilled it is, in most cases (68%), accompanied by the absence of pain and tender joints, low ESR and a short duration of morning stiffness (≥3/4).

The assessment of disease activity in RA has undergone quite a change since the proposal of the ARA preliminary remission criteria in 1981. At this moment, several variables included in the ARA remission criteria are judged to be less valid and were therefore not included in the ACR and EULAR core set [6, 7]. The DAS is an extensively validated composite index which can be calculated with three or four variables from the core sets [8–10, 12, 14, 15]. Including more variables in the DAS did not increase its validity [9]. The DAS, which has a continuous scale, corresponds strongly with the ARA preliminary remission criteria. This is not surprising as the most important elements of the ARA criteria (swollen joints, tender joints; Table II) are included in the DAS. At a cut-off value of 1.6, the percentages of misclassification
for patients' visits in remission or not in remission were 10%. The problem with a dichotomous variable, however, is that a small change in disease activity may have a great impact on whether a patient fulfills the remission criteria or not. As can be seen in Fig. 2, during a 'remission period' (most of the visits in a certain time period fulfilled the criteria) at one time point a patient does not completely meet the criteria, e.g. the follow-up of Patients 1 and 4 in Fig. 2.

This study of patients with recent-onset RA shows that remission according to the ARA criteria seldom occurs: the criteria were fulfilled in 9.5% of all visits in patients with a median follow-up of 3.9 yr. During each follow-up year wherein the patients were assessed 3 monthly, ~25% of the patients fulfilled the ARA remission criteria once and ~15% fulfilled the criteria for two consecutive visits. Because complete remission cannot easily be assessed, it might be better to use the term 'no disease activity' instead. No disease activity should be measured with the same tools as used to assess higher levels of disease activity. The DAS would be preferable because it is a continuous validated index using core set variables. DAS levels are in agreement with the ARA remission classification. If remission should be a dichotomous outcome, this study suggests a cut-off point of the DAS of 1.6. For comparison, a patient without any swollen or tender joints and an ESR of 10 mm in 1 h has a DAS of 1.0. Further validation of these provisional DAS remission criteria is needed. It has to be investigated, for instance, whether patients in remission do have less radiographic progression and functional loss than patients not in remission. In addition, the importance of the duration of remission should be elaborated further.

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References