Value of Disease Activity Score 28 (DAS28) and DAS28-3 Compared to American College of Rheumatology-Defined Remission in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To assess the criteria for remission based on Disease Activity Score 28 (DAS28) and DAS28-3 (excluding patients' evaluation of disease activity) compared to American College of Rheumatology (ACR) preliminary criteria in established rheumatoid arthritis (RA), and to examine the value of each ACR criterion individually.

Methods. The EMECAR study was designed to assess the burden of comorbidity and inflammatory activity for RA in Spain. A random sample of 788 patients with RA from 34 Spanish centers was selected. Remission was defined by preliminary ACR criteria applied specifically and the clinical activity assessed by the DAS28 and the DAS28-3. A receiver operating characteristics curve analysis was performed to identify cutoff values with the highest usefulness in defining remission on both DAS indices.

Results. Thirty-two patients (4.1%) were in ACR-defined remission, 62 (7.9%) if fatigue was excluded from the criteria. The frequency of any single criterion that patients in remission fulfilled: no fatigue and joint pain by anamnesis in 31 patients (96.9%); morning stiffness < 15 min in 26 (81.3%); no swelling in joints in 21 (65.6%); normal erythrocyte sedimentation rate (ESR) in 29 (90.6%); and no joint tenderness in 21 (65.6%) patients. The positive predictive value for remission of each criterion: normal ESR 6.5%; morning stiffness < 15 min 8.4%; no fatigue 8.7%; no joint tenderness 13%; no swelling in joints 15.8%; and no joint pain by anamnesis 27.7%. The DAS28 cutoff values with higher discriminatory power for remission were 3.14 (sensitivity 87%; specificity 67%) when all the ACR criteria were used, and 2.81 (sensitivity 84%; specificity 81%) when fatigue was omitted. The equivalent cutoffs for the DAS28-3 were 3.52 (sensitivity 84%; specificity 66%) and 2.95 (sensitivity 82%; specificity 83%), respectively.

Conclusion. DAS28 and DAS28-3 are good tools to define remission in established RA. No joint pain by anamnesis is the criterion with the highest value in defining remission, while normal ESR, an absence of morning stiffness, and fatigue are the least effective. (J Rheumatol 2004;31:40–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS REMISSION DISEASE ACTIVITY SCORE 28
AMERICAN COLLEGE OF RHEUMATOLOGY-REMISSION CRITERIA
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The primary objective when treating rheumatoid arthritis (RA) is to control the inflammatory activity of the disease and, if possible, to achieve remission. It is essential to establish an appropriate definition of remission in order to determine when it has been attained. In 1981, Pinals, *et al*[1] proposed a definition based on clinical assessments performed by 35 rheumatologists, and from these evaluations 6 criteria were found to correlate with the rheumatologists' perception of clinical remission (Table 1). These criteria have been evaluated in 2 studies, one cross-sectional

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Table 1. Proposed criteria for clinical remission in RA.

Five or more of the following criteria must be fulfilled for at least 2 consecutive months
1. Duration of morning stiffness not exceeding 15 minutes
2. No fatigue
3. No joint pain by anamnesis
4. No joint tenderness or pain on motion
5. No soft tissue swelling in joints or tendon sheaths
6. ESR < 30 mm/h for a female or < 20 mm/h for a male

and one retrospective; the results showed good specificity and different degrees of sensitivity[2,3]. Other definitions of remission, either spontaneous or treatment-induced, have been used in different studies[4-7], and this variability of definition makes comparisons of remission rates difficult.

All these definitions consider remission as a dichotomous variable, but an alternative is to consider remission as a disease state at the lower end of a continuum[8]. This ensures that remission is defined with the same tools used to assess disease activity in standard clinical practice. The Disease Activity Score (DAS) is a composite index that includes variables such as the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and, as an option, the patient's assessment of disease activity. This index facilitates the quantification of disease activity and provides a more reliable overall estimate than would each individual measurement[9].

In 1996, Prevoo, *et al*[10], in a cohort of patients with early RA and based upon a definition of remission as the presence of at least 4 of 5 criteria of the American College of Rheumatology (ACR), defined a state of very low disease activity as a DAS score < 1.6. This cutoff was accepted as indicating remission and has been used in other studies, with good results[11]. Prevoo's study was conducted in patients with recent-onset RA, with extended joint counts on examination, excluding fatigue from the definition of remission, replacing the "joint pain by anamnesis" criterion with pain measured on a visual analog scale (VAS), and with a cutoff value at which the misclassification was 10% for both patient groups. As the authors emphasized, further studies were needed to validate these provisional DAS remission criteria.

In assessing patients with RA, reduced joint counts are as valid as the more comprehensive graded ones, since this preferentially includes joints that change with therapy[12]. Using 28 tender and swollen joint counts, a modification of the original DAS index, DAS28, was developed and validated[13] and, for reasons of simplicity, it is preferred in clinical practice. Using a formula to transform DAS values into DAS28 scores, the cutoff value for remission with DAS28 was extrapolated to 2.6. However, no validation in real patients had been performed and no remission point for DAS28-3 (excluding patients' assessment of disease activity) has been proposed.

The purpose of our study was to determine, using DAS28 and DAS28-3, the cutoff point for remission that showed the best sensitivity and specificity in a sample of RA patients with well established disease. The ACR preliminary criteria for remission were used for comparison and we examined the value of each individual ACR criterion as well.

MATERIALS AND METHODS

Patient sampling and selection. The EMECAR cohort (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide) comprises a sample of patients with RA randomly selected from the clinical databases of 34 centers throughout Spain (new and old patients). The selection complied with the Spanish regulations for data protection. Initially, the participating rheumatologists were instructed to confirm, based on the clinical records, that the selected patients fulfilled the ACR criteria for the classification of RA[14]. The rheumatologist then had to follow a contacting protocol that included 3 telephone calls at different times of the day, a search in mortality registries, and postage of a letter to the address of the patient recorded in the database. If a patient could not be reached with this procedure, the name was removed from the list and replaced by another randomly selected from the same center's database. If a contacted patient chose not to enter the study, a short questionnaire was applied to document the reasons for refusal together with basic sociodemographic and clinical characteristics. The patient would not, however, be replaced in the proposed study sample. All patients who entered the cohort provided written informed consent after the details of the study had been explained. The study protocol was reviewed and approved by the institutional research ethics committees.

Design. Data were obtained from a cross-section of the baseline year (November 1999–November 2000) of the EMECAR cohort. The attending rheumatologists were instructed to collect the data following standard definitions and procedures and to conduct the 28-joint counts and other measurements. All patients were examined and had radiographs of hands and wrists and the relevant laboratory tests were conducted. Data on current and previous treatments with disease modifying antirheumatic drugs (DMARD) were collected from the medical records and confirmed by the patient during the clinical visit. Also, data on treatments, comorbidity, and signs and symptoms of extraarticular involvement were collected retrospectively from the clinical records and compared with data obtained from the patient at the initial clinical (baseline) visit.

The Disease Activity Score was obtained from 28-joint counts, applying the formula with 4 (DAS28) and 3 variables (DAS28-3), respectively[13]. At the time of the baseline visit, patients were asked to complete a questionnaire that evaluated the duration of morning stiffness, the presence or absence of fatigue, joint pain in the previous 2 months, and patient global assessment of disease activity on a VAS. Joint tenderness and swelling were assessed during examination. ESR and C-reactive protein (CRP) tests were performed and the results obtained within 15 days of the visit. Remission was defined with the preliminary criteria developed by Pinals, *et al*[1] (Table 1), although there were no 2 month periods of followup. Since fatigue is not included within the core set of variables used to assess RA[15] and is not routinely measured in clinical practice, as it was by Prevoo, *et al*[10], the DAS cutoff value for remission was determined with and without fatigue in the criteria list. For the ACR criteria, 4 out of 5 needed to be present to define remission.

Statistical considerations. The number of remission-defining ACR criteria was recorded for each patient at the baseline visit. Frequencies were obtained by direct counting and sensitivity, predictive values, accuracy, and confidence intervals were calculated as a cross-product ratio in a 2×2 contingency table. For continuous variables, the mean differences between groups were analyzed using the Student t test, and for discontinuous variables with the Mann-Whitney U test. Correlations between variables were assessed with Pearson correlation test.

To determine the cutoff value for remission using DAS28 and DAS28-3, receiver operating characteristics (ROC) curves were constructed. ROC curves plot relationships between sensitivity and specificity for the different cutoff levels of test and are constructed using DAS values of each patient. The area under the curve (AUC) provides a measure of the overall discriminative capacity of a model, from which it is possible to calculate the cutoff value with higher sensitivity and specificity. To calculate this value we obtained the sum of sensitivity and specificity of all possible cutoff points and chose the highest one.

Data analyses were performed with the SPSS package, version 9.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

For this study, data were available on 788 patients randomly selected from a total eligible population of 13,260 (all patients with RA registered in the 34 participating centers). Only patients with no missing data in the main variables (remission criteria and DAS components) were selected for evaluation (735 patients). Sex distribution was 72.1% female, 73.7% had a positive rheumatoid factor, and the average age at the time of diagnosis was 48 ± 15 years. The mean disease duration at baseline was 10 ± 8 years, with 36.2% of patients having extraarticular involvement and > 70% having some comorbidity. The clinical and demographic characteristics of this population are shown in Table 2.

Of the 735 patients, 32 (4.1%, 95% CI 3.05 ± 6.02) were in remission according to Pinals' criteria[1] — 62 patients (7.9%, 95% CI 6.58 ± 10.61) if the fatigue criterion was excluded. The number of patients fulfilling each criterion in the overall cohort and of those in remission are presented in Tables 3 and 4. The positive predictive value of each criterion was as follows: normal ESR 6.5%, morning stiffness < 15 min 8.4%, no fatigue 8.7%, no joint tenderness 13%, no swelling in joints 15.8%, and no history of joint pain 27.7%. The accuracy for each criterion for the 2 situations (with and without fatigue) is also shown. The criterion of no joint pain by anamnesis showed the highest accuracy, while fatigue, morning stiffness, and ESR had the lowest.

Table 2. Clinical and demographic characteristics of patients in EMECAR cohort.

Variable	
Women, %	72.1
Rheumatoid factor +, %	73.7
Mean age, yrs	61 ± 13
Mean age at onset of RA, yrs	48 ± 15
Mean disease duration, yrs	10.1 ± 7.9
With early arthritis (< 2 yrs), %	14.4
Mean HAQ score (range 0–3)	1.6 ± 0.4
Mean Larsen score (hands)	54.68 ± 26.37
Median number of painful joints (interquartile range)	4 (1–8)
Median number of swollen joints (interquartile range)	3 (0–7)
Mean pain VAS (10 cm)	4.46 ± 2.17
Mean ESR, mm/h	27.9 ± 22.3
Mean CRP, mg/dl	1.64 ± 2.66

HAQ: Stanford Health Assessment Questionnaire.

There was a high degree of correlation between the 2 indices (DAS28 and DAS28-3) with respect to disease activity ($r = 0.95$, $p < 0.0001$). No differences in age or disease duration between remission groups were found. Patients in ACR-defined remission had lower DAS28, DAS28-3, tender joint count, swollen joint count, ESR, and CRP, but there were no differences in patient global assessment of disease activity by VAS (Table 5). No statistically significant correlation between DAS28-3 and patient global assessment of disease activity was found ($r = 0.40$, $p = 0.12$).

The ROC curves to discriminate between remission and nonremission in the 2 models with the DAS indices were similar. The discriminatory power of the full remission criteria with both DAS types was good, with an AUC of 0.82 (95% CI 0.75 ± 0.86) for the DAS28, and 0.81 (95% CI 0.75 ± 0.87) for the DAS28-3 (Figure 1). When fatigue was omitted from the criteria, the discriminative power was slightly better, with an AUC value of 0.88 (95% CI 0.85 ± 0.92) for the DAS28 and 0.88 (95% CI 0.85 ± 0.92) for the DAS28-3 (Figure 1). From these data we calculated the cutoff value for remission with the highest combination of sensitivity and specificity. The resulting value for DAS28 was 3.14 (sensitivity 87%; specificity 67%) when all the ACR criteria were used, and 2.81 (sensitivity 84%; specificity 81%) when fatigue was omitted. The cutoff values for the DAS28-3 were 3.52 (sensitivity 84%; specificity 66%) and 2.95 (sensitivity 82%; specificity 83%) with and without fatigue, respectively.

With these data, remission would be present in 170 patients with a DAS28 < 2.81, but with the previously proposed value of 2.6, only 149 patients would have been in remission, showing a sensitivity of 81% and a specificity of 82% (with the ACR criteria excluding fatigue).

Table 3. Distribution of remission criteria in EMECAR patients.

	Present, n (%)	Not Present, n (%)	Sensitivity, n (%)	Positive Predictive Values, %	Accuracy (95% CI)
Morning stiffness < 15 min	308 (42)	427 (58)	26 (81)	8.4	60.8 (64.3–57.3)
No fatigue	355 (48)	380 (52)	31 (97)	8.7	55.7 (59.5–52.1)
No joint pain (by anamnesis) in the previous 2 months	112 (15)	623 (85)	31 (97)	28	88.8 (91.1–86.5)
No tender joints	161 (22)	574 (78)	21 (66)	13	79.4 (82.3–76.5)
No swollen joints	183 (25)	552 (75)	29 (91)	16	78.6 (81.5–75.7)
Normal ESR	444 (60)	291 (40)	29 (91)	7	43.1 (48.7–39.5)

Table 4. Distribution of remission criteria in EMECAR patients when fatigue is excluded as a criterion of remission.

	Present, n (%)	Not Present, n (%)	Sensitivity, n (%)	Positive Predictive Values, %	Accuracy (95% CI)
Morning stiffness < 15 min	308 (42)	427 (58)	29 (47)	9	57.5 (61.1–53.9)
No joint pain (by anamnesis) in the previous 2 months	112 (15)	623 (85)	61 (98)	54	92.9 (94.7–91.1)
No tender joints	161 (22)	574 (78)	51 (82)	31	83.5 (86.2–80.8)
No swollen joints	183 (25)	552 (75)	56 (90)	31	81.9 (84.7–79.1)
Normal ESR	444 (60)	291 (40)	59 (95)	13	47.7 (50.6–43.6)

Table 5. Clinical variables defining the state of remission.

	ACR Criteria			ACR Criteria Without Fatigue		
	Remission	No Remission	p	Remission	No Remission	p
DAS28	2.39 ± 0.81	3.76 ± 1.27	< 0.0001	2.13 ± 0.72	3.84 ± 1.22	< 0.0001
DAS28-3	2.71 ± 0.89	4.16 ± 1.37	< 0.0001	2.40 ± 0.78	4.25 ± 1.32	< 0.0001
Number of tender joints	0 (0–5)	4 (0–28)	< 0.0001	0 (0–5)	4 (0–28)	< 0.0001
Number of swollen joints	0 (0–9)	3 (0–24)	< 0.0001	0 (0–9)	3 (0–24)	< 0.0001
ESR	12 (3–85)	22 (1–140)	< 0.001	12 (3–85)	22 (1–140)	< 0.0001
CRP, mg/l	4.2 (0–11.9)	8.4 (0–21.1)	< 0.02	4.3 (0–11.9)	9 (0–21.1)	< 0.0001
Patient global assessment (VAS)	46 ± 27	56 ± 21	0.11	43 ± 23	53 ± 28	0.31

VAS: Visual analog scale (0–100). Results are expressed as mean ± SD or median (range).

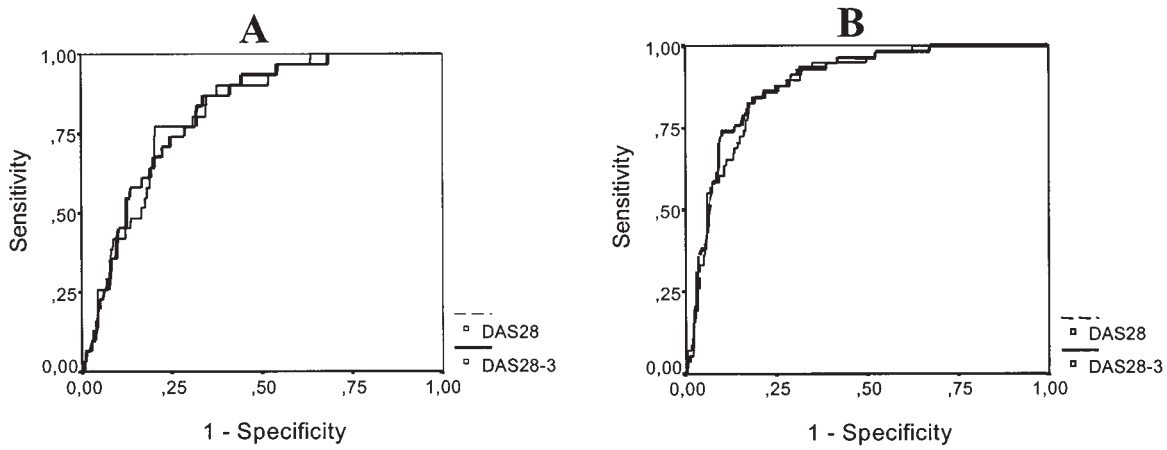

Figure 1. ROC curve of the DAS28 and DAS28-3 when used to discriminate the presence or absence of remission using the original ACR criteria (A) and the ACR criteria excluding fatigue (B). The curves plot the relationship between the sensitivity and 1–specificity of DAS28 and DAS28-3 for different cutoff levels of test positivity.

DISCUSSION

We evaluated the performance of ACR remission criteria in patients with established RA (mean disease duration 10 years) and compared this to DAS28 and DAS28-3 cutoff values calculated with the highest sensitivity and specificity to define remission.

Remission in RA is a state of very low, or absence of, disease activity over a defined period of time. However, there is no consensus on how to assess the state of disease activity and how long this period needs to be. The ACR preliminary criteria for remission have several shortcomings that hamper their clinical usefulness. The descriptions of the criteria are not sufficiently detailed and there are no specifications on how they are to be measured. Two of the 6 items, "little morning stiffness" and "absence of fatigue," may duplicate each other, are hard to determine reliably, and are not included in the core set of measures of RA[15]. Three of the 6 criteria ("little morning stiffness," "absence of fatigue," and "no pain by anamnesis") are patient-derived perspectives that sometimes, and mainly in established disease, may truly reflect not disease activity but, instead, disease damage and comorbidity. ESR is influenced by

many unrelated disease processes. The remission definition obtained using ACR criteria is a dichotomous variable, which implies that small changes in disease activity may cause a change in the patient's classification[16], and finally, these criteria have problems of face validity when 5 of the criteria are fulfilled but the 6th is not because the patient has swollen joints[17].

In our study, 4.1% of patients were in remission according to the ACR criteria, and almost 8% when fatigue was excluded from the list. These results are clearly lower than those reported from initial cohorts of patients with early RA in which remission rates were reported to vary between 7% and 37%[18], but similar to those in the study by Alarcon, *et al* in patients with long-established RA, using a similar study design[3]. As we did not follow these patients for the 2 months required by ACR preliminary criteria, the real percentage could be smaller. It is claimed that remission in RA tends to occur early in the disease[19], if at all. However, owing to selection strategies and to methodological differences, it is difficult to compare the different studies, and due to the small percentage of patients in remission the results may not be applicable to the entire RA population.

In our study, the variable "no joint pain by anamnesis" showed the largest influence on defining remission. In early disease, the absence of joint pain for at least 2 months is highly sensitive and specific for remission. However, this is not necessarily the same in established disease, in which "no joint pain" can be sensitive, but not specific. This is because patients with advanced disease may have joint involvement secondary to mechanical derangement without evidence of active inflammation. Also, recording "no joint pain" as a dichotomous variable (i.e., present or absent) can be misleading. We concur with Prevoo, *et al*[10] that it is better to measure joint pain on a 0–100 VAS and to consider any value < 11 as "no pain." This compensates not only for patients' inaccuracies in describing pain, but it also enables the attending physician to discriminate better between low pain levels that could be secondary to minimal disease activity, or to permanent articular damage.

The criteria "no joint pain" and "no joint swelling" upon examination were measured in 28 joints. Using extended joint counts it is possible that a lower prevalence would have been observed. However, it has been demonstrated that reduced joint counts are as valid as the more comprehensive ones[12,20]. A DAS index using a low number of joint counts (DAS28) has been developed and validated[13] and the response criteria appear to be as valid as the ones with larger numbers of joint counts[21]. Hence, for simplicity, the reduced number of joint counts is preferred in standard clinical practice.

We observed that the "fatigue" variable had not much weight in the definition of remission. Because there are several problems with its use, fatigue is not included in the core set of disease activity variables[15]. It is not usually employed in clinical practice because there is no consensus on how to assess it, and because this variable can be influenced by other comorbidities that are invariably present in established RA. In our study, as with others[7], the exclusion of fatigue from the ACR criteria led to a significant increase in specificity while maintaining sensitivity. As expected, patients in ACR remission had lower DAS28, DAS28-3, number of tender joint counts, number of swollen joint counts, ESR, and CRP, but the size of the difference in these variables between patients with and without remission was consistently greater when fatigue was excluded from the list of criteria. Certainly, patients with advanced disease may have joint symptoms secondary to mechanical distortion and various comorbidities that may influence the symptom of fatigue, even in the absence of joint inflammation.

ESR is used extensively to assess disease activity in RA. However, it is only an indirect measure of joint inflammation and it is influenced by age, gender anemia, fibrinogen levels, immunoglobulins, and rheumatoid factor. Although extensively used because of its simplicity and low cost, it is not as accurate a measure of inflammation as CRP[22]. Occasionally, there are discrepancies between the 2 measurements that may be explained on the basis of a variety of preexisting factors. In ACR-defined remission criteria, ESR values are corrected for sex, and replacing ESR with CRP may improve the definition of remission.

As with Prevoo, *et al*[10], we observed that the morning stiffness variable had little statistical weight in the definition of remission, and only when all ACR criteria are included. It would seem that this variable is a poor discriminator between RA and noninflammatory joint disease and between active and inactive RA[23], and is relatively insensitive to change[24], and as such is not included in the core set of variables of RA[15]. However, morning stiffness is included in the classification criteria for RA[14] and is also useful in the diagnosis of early RA[25].

In evaluating disease activity in established RA, it is important to distinguish between the effects of active inflammation and the effects of irreversible damage. This is what makes the evaluation somewhat different from that of early disease. It has been proposed that in established RA it is better to use the DAS index with only 3 variables (tender joints, swollen joints, and ESR), as global health or patient global assessment of disease activity can be considered mixed variables that combine the effects of the disease process and damage[26]. In our patients, there were no differences in patient global assessment of disease activity between groups, as evaluated in long-established disease. Nevertheless, the low weight given to patient global assessment in the DAS28 formula causes a high correlation between DAS28 and DAS28-3, since patient global assessment adds very little to the final score of the DAS28. Since the evaluations using DAS28 and DAS28-3 compared to ACR-defined remission criteria were good and equivalent, this would suggest that both schemes could be used to assess

disease activity in established RA with the same degree of effectiveness.

We found a remission cutoff value of 2.81 on the DAS28, which is slightly different from the 2.6 that had been established originally. There could be several reasons that explain this difference. Our value was derived from original data (not extrapolated) from patients with long-standing disease (not early arthritis); Pinal's criteria were used in our study as proposed (except the 2 month followup) and not modified as Prevoo, *et al* did; we used reduced joint counts instead as the more comprehensive ones; and finally our cutoff value reflected the highest sensitivity and specificity. In case of patient global assessment not being determined, we have also proposed a remission cutoff value using DAS28-3 that has a performance level similar to that of DAS28.

Of further interest is how to define remission in standard clinical practice (in contrast to clinical trials) and how to do so in patients with well established RA. The ACR criteria are very rigorous, since they take into account patients' as well as the physicians' perspectives. Several variables that are included in this definition have been judged to be less valid, and therefore have not been included in the core set measurements of RA[15]. Besides, DAS cutoff values may differ depending on the RA population studied, the methods used to assess them, and the "gold standard" used to define remission. We consider it clinically useful to set a therapeutic goal of < 3.1 on the DAS28 scale. This was found to be related to low disease activity as well as low disability progression and radiological damage[21].

Defining remission in RA is not a simple task and, given its low prevalence, can be of limited value as an outcome in established RA. In patients with long-established RA, DAS28 and DAS28-3 cutoff values for remission show good sensitivity and specificity in detecting patients who are considered to be in remission by the ACR criteria.

APPENDIX

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