Editorial

Defining Remission in Rheumatoid Arthritis: What Is It? Does It Matter?

When the American College of Rheumatology (ACR) preliminary criteria for remission[1] were developed in 1981, patients with established rheumatoid arthritis (RA) rarely experienced remission, although a number of patients with recent onset of polyarthritis had periods when their RA temporarily regressed or remitted and a few had prolonged remission or even permanent recovery from the disease. This was more frequent in children with oligoarthritis, and was generally considered to be a gift from God. The guiding principle for treatment of RA was "primum non nocere," exemplified by the therapeutic pyramid. Because RA was expected to persist for the lifetime of the patient, available drugs were used cautiously so one would not run out of therapeutic options too rapidly. For most patients therapy had little effect on continued disease progression.

Today, the pyramid has been replaced with early aggressive therapy, and if major improvement does not occur within 3 months or so, the treatment is replaced or combined with other aggressive therapies[2]. "ACR 20" responses are expected, but are not sufficient; "ACR 50" responses are acceptable, but we really want "ACR 70" or greater responses[3]. These goals are being approached with methotrexate, leflunomide, and the anti-tumor necrosis factor biologic agents and have been incorporated into searches for new drugs for RA, e.g., autologous stem cell rescue following intensive cytotoxic marrow ablation[4], or combination of rituximab anti-B cell therapy with megadoses of corticosteroids and cyclophosphamide[5]. Still, relatively few patients satisfy the rigorous requirements of the ACR definition of remission for at least 2 months. Are the ACR criteria too rigorous? Would more attainable definition(s) hasten the development of new and better drugs and biological agents?

The consequences of RA are measurable in 3 distinct domains: signs and symptoms of inflammation, functional impairment, and structural damage to joints; ideally one would like to restore each to normal, and each should be considered in a definition of remission (Table 1). The ACR criteria for remission include 6 signs and symptoms: fatigue, joint pain, morning stiffness, joint tenderness, joint swelling, and erythrocyte sedimentation rate (ESR); physical function and structural damage to joints are ignored. The DAS (Disease Activity Score) index uses a mathematical formula to arrive at a single composite quantitative score representing tender joints (Ritchie index), swollen joints (44-joint count), Westergren ESR and patient's global assessment (0–100 visual analog scale) of disease activity[6]. It is a useful continuous quantitative summary measure of signs and symptoms of RA inflammation, similar to the signs and symptoms included in the dichotomous ACR remission criteria, but also ignores physical function and structural damage. The DAS-28 uses the abbreviated 28-joint counts for tender and swollen joints, omitting the feet[7]. The DAS-28-3 omits the patient global assessment. The Health Assessment Questionnaire disability index (HAQ-DI) is a generally accepted and extensively validated continuous quantitative measure of functional impairment that is sensitive to improvement as well as deterioration of RA[8]. Structural damage to the joints of the hands, wrists, and forefeet has been quantitated on continuous scales using the Sharp[9], Larsen[10], or other validated methods. Prevention of progressive joint damage, the structural equivalent of improvement, usually requires one year or longer to document in controlled clinical trials.

In this issue, Balsa and associates[11] evaluate 735 patients with RA who had complete data for each of the 6 components of the ACR remission criteria and the 4 components of the DAS-28; the patients were randomly selected as a representative cross-sectional sample from 13,260 RA patients seen in 34 rheumatology centers in Spain. At least 5 of the 6 ACR remission criteria were satisfied, at the single timepoint of the study, by 4.1% (32 patients) of the 735 patients. If absence of fatigue was not required, 7.9% satisfied at least 4 of the remaining 5 criteria. Fewer patients would have satisfied the ACR remission criteria for the required 2 consecutive months. Among the 32 patients in ACR remis-

See Value of DAS28 and DAS28-3 as compared to ACR defined remission in RA, *page 40*

Table 1. Defining "remission" in rheumatoid arthritis.

Criteria	ACR Preliminary Criteria for Remission[1]			Disease Activity Scores[6,7,11,12]			ACR-70[3]	Guidance for Industry. US Food and Drug Administration[25]		
	Complete	Except Fatigue	Modified	DAS Remission[12] EULAR "good" response[6]	DAS 28	DAS 28-3		Complete Clinical Response	Remission	Major Clinical Response
I. Signs and symptoms A 1. No fatigue 2. No joint pain by history 3. AM stiffness < 15 min 4. Tender joints = 0 5. Swollen joints = 0 6. ESR normal 7. Patient global opinion B Duration required for remission II. Physical function III. Structural damage	5 of A 1 to A6 for ≥ 2 mo	4 of A 2 to A 6 for ≥ 2 mo	4 of A 2 to A 6 for a single point in time (no duration requirement)	A 4 to A 7 DAS remission = DAS < 1.6 EULAR "good" response = DAS ≤ 2.4, with ≥ 1.2 improvement since baseline Note: With DAS ≤ 2.4, mean: Tender jt = 1; swollen jt = 4; ESR = 13; general health (VAS) = 16	A 4 to A 7 DAS 28 ≤ 2.81	A 4–6 DAS 28-3 ≤ 2.95	70% improvement of: tender and swollen joint counts, and ≥ 3 of: pain, patient global, physician global, ESR (or CRP), and disability (e.g., HAQ)	1988 ACR remission criteria (5 of A1–6) plus radiographic arrest (Larsen or Sharp) for ≥ 6 mo with continuing drug therapy	1988 ACR remission criteria (5 of A1–6) plus radio-graphic arrest for ≥ 6 mo with no drug therapy	ACR 70(?) (specific criteria to be determined) plus radio-graphic arrest for ≥ 6 mo with continuing drug therapy

DAS: 0.54 $\sqrt{\text{Ritchie Articular Index}}$ + 0.65 (0–44 swollen joints) + 0.33 ($\log_n$ ESR) + 0.0072 (general health status 0–100). DAS 28: 0.56 $\sqrt{\text{0–28 tender joints}}$ + 0.28 $\sqrt{\text{0–28 swollen joints}}$ + 0.70 ($\log_n$ ESR) + 0.014 (general health status 0–100). [DAS 28 = 1.072 × DAS+ 0.938]. DAS 28-3: DAS 28, omitting general health status. VAS: visual analogue scale. CRP: C-reactive protein. HAQ: Health Assessment Questionnaire.

sion, 97% had no joint pain by history, 97% no fatigue, 81% less than 15 minutes of morning stiffness, 91% normal ESR, 66% no swollen joints, and 68% no joint tenderness or pain on motion. In these patients the DAS-28 value that was equivalent to satisfying the full ACR remission criteria and had the highest sensitivity and specificity was 3.14; if fatigue was omitted from the ACR criteria, the equivalent DAS-28 value was 2.81. For the DAS-28-3, the equivalent cutoff values were 3.52 and 2.95. These cutoff values substantially increase the number of patients who would be classified in remission. With a DAS-28 cutoff of 2.81, 23% of the 735 patients would be in remission, compared to 7.9% with the ACR criteria excluding fatigue. For use in clinical practice, the authors suggest that a DAS-28 value < 3.1 is a reasonable therapeutic equivalent of remission.

A similar study observed 189 patients with early RA for 3.9 years and found that ACR remission excluding fatigue was present in 9.5% of 2832 visits (37% of patients). DAS values during ACR remission visits ranged from 0 to 2.6, and 95% of remission visits were included if the DAS cutoff value was 1.6; conversely, DAS < 1.6 was present in about 5% of visits when ACR remission excluding fatigue was not present. DAS < 1.6, therefore, was proposed as the cutoff value for remission[12].

REMISSION WITHOUT DISEASE MODIFYING ANTIRHEUMATIC DRUGS

In a classic observational study, Short, *et al*[13] enrolled 293 consecutive patients with "rheumatoid arthritis" who were admitted to Massachusetts General Hospital between 1930 and 1936 and reassessed in 1937, 1947, and 1954. The series included 14% with "rheumatoid spondylitis," half of whom had peripheral joint symptoms at onset, and 8% with an onset younger than age 16 years. In 1937, remissions, defined as "periods of complete or near complete freedom from articular symptoms" as determined by direct history from the patients, were noted in 17% of 239 patients, who had an intermittent course compared to the remainder with a progressive course. The average duration of remission was 21 months. Intermittent courses were more frequent in patients with an onset before age 40, those with an acute onset, those with less than one year duration of arthritis, and those with a monoarticular onset. Treatment consisted of 2 to 3 week hospitalizations for rest, aspirin, and physical therapies, followed by conservative therapy at home with bed rest, heat applications, aspirin or analgesics, vitamins, corrective exercises, and non-operative orthopedic procedures. When 225 of the patients were re-evaluated in 1947, 17% were in remission, 38% were moderately or slightly improved, 34% were worse, and 13% were unchanged. Half

of the patients in remission in 1947 had been in remission in 1937. In 1954, only 174 patients remained because 59 had died and 17 were lost to followup; 13% were in remission and 22% were improved, but 63% were worse 20 to 24 years after starting the study. Only one of the 102 patients considered stable or worse in 1947 had attained partial improvement by 1954.

A 3-year, randomized clinical trial done between 1984 and 1989 compared the nonsteroidal antiinflammatory drugs etodolac and ibuprofen, and did not permit disease modifying antirheumatic drugs (DMARD)[14]. At entry, disease duration averaged 3.5 years (range 1–7), 67% had positive rheumatoid factor (RF), ESR averaged 49 mm/h, and tender and swollen joint counts averaged 29 and 22. Among the 1433 patients who were enrolled, there were only 33 (2.3%) remissions by the complete ACR criteria. The average followup was 48 weeks (maximum 3 years); the patients' drug treatment was not much different than that used by Short, *et al* 50 years earlier, but the patients in the etodolac study probably had more severe RA and the followup was much shorter.

REMISSIONS DURING STANDARD DMARD TREATMENT OF ESTABLISHED RA

How frequent were remissions during clinical trials of standard DMARD? During the 1980s and 1990s, the CSSRD (Cooperative Systematic Study of Rheumatic Diseases) cooperating clinics coordinated by the University of Utah Division of Rheumatology studied 1334 patients with active established RA of 6–10 years' duration in 6 controlled clinical trials of 18 to 48 weeks' duration. The trials included 4 placebo arms, 3 D-penicillamine arms, 2 methotrexate arms, 2 auranofin arms, 2 aurothiomalate arms, and one arm each of azathioprine, sulfasalazine and combined auranofin/methotrexate. Complete ACR remission criteria were met in only 2 of 1109 of these patients, one treated with placebo and one with sulfasalazine. Different remission criteria (no swollen joints and no more than 2 tender joints) were used in the D-penicillamine study; 4 of 175 patients met those less rigorous criteria[15].

REMISSIONS IN EARLY RA

The CSSRD also studied inception cohorts (enrolled within one year of symptom onset) of patients with classical or definite RA or unexplained polyarthritis (UPA) and followed them for 10 years with no restrictions on treatment[16]. Among the 57 patients with RA, complete ACR remission criteria were present in 39% of those remaining after one year, 22% after 3 years, 26% after 5 years, and 16% after 10 years of followup. Among 67 patients initially classified as UPA, 12 were reclassified as RA during followup; 3 of the 12 were in remission at year 5, but not at year 10. Among the remaining 55 UPA patients, 13 (24%) were in remission at 10 years.

Wolfe, *et al* (1993) found that when 503 patients enrolled within 2 years of RA onset were evaluated an average of 6.9 years later, 7.6% were "symptom free"[17]. Earlier (1985) the same authors had reported that 18% of 450 RA patients had at least one remission during 2 years of observation; the average length of remission was 10 months[18].

The Western Consortium of Practicing Rheumatologists enrolled patients with active RF positive RA and symptom duration of less than 12 months. The patients had no previous DMARD therapy but DMARD were started after entering the study. At routine office visits the 6 components of the ACR remission criteria were listed and the rheumatologists were asked to indicate whether the RA was "controlled" or not. Among 129 patients, RA "controlled" was indicated at least once in 17.8%, 2 or more times in 7%, and at 2 or more consecutive visits in 4.7%. Detailed data were recorded at formal rheumatology evaluations 6 months and one year after entry and included all of the 6 ACR remission criteria. Five or more of the 6 criteria were met by only 0.6% of patients at the 6 month examination, and by 11.1% at the one year evaluation[19]. Sokka and Pincus[20] reported that when 232 patients with mean duration of 1.8 years were evaluated, none met remission criteria. When 183 Swedish patients with RA duration less than 2 years were monitored annually for 10 years, 79% had a relapsing remitting course and 18% were in ACR remission[21].

REMISSIONS IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

A review of 683 Italian patients with juvenile rheumatoid arthritis (JRA) followed for a mean of 10 years found that at their last assessment 33% had been symptom-free with no antirheumatic therapy for at least 6 months[22]. A similar evaluation of 268 Norwegian JRA patients 15 years (range 12 to 25) after onset found that 50% were in remission[23]. Among 392 patients with JRA studied in Winnipeg, Canada, remission (no active disease while off treatment for at least 2 years) after 10 years of followup had occurred in 37% with systemic, 47% with pauciarticular, and 23% with RF negative polyarticular JRA, but in only 6% with RF positive polyarticular JRA[24].

WHAT IS REMISSION? DOES IT MATTER?

To a considerable extent, defining remission in RA is like defining pornography; we have great difficulty agreeing on a definition, but we recognize it when we see it. This subjective definition is probably sufficient for clinical practice, provided the 3 domains of RA are carefully considered for each patient, i.e., signs and symptoms of inflammation, functional impairment, and structural damage to joints. Clearly, remissions can be independent of treatment, although controlled clinical trials are beginning to indicate that major improvement or "near remission" is more frequent with certain DMARD and/or biologic agents than with control treatments, even in long-standing RA.

Varying proportions of patients with RA are classified "in remission" depending on the definition chosen. The ACR definition[1] is quite restrictive and few patients qualify. Variations of the ACR definition and different cutoff values for DAS, DAS-28, and DAS-28-3 are less restrictive and in some studies up to 23% of patients were in "remission"[11]. The major benefit of the precise definitions proposed by the US Food and Drug Administration[25], e.g., complete clinical response, remission, and major clinical response, and those proposed in this issue by Balsa, *et al*[11], is to provide everyone with a common vocabulary to describe the same clinical condition. In addition, these definitions provide tangible targets for drug developers who may gain commercial advantage when they can claim that their product produces more or better remissions than their competitors' products. Therapeutic progress evolves from this disorderly competitive process, but one must carefully assess the precise definitions of the claimed "remissions."

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