We want remission, but what is it?



"It is clear that the rheumatologic and medical community needs to vigorously pursue a full understanding and validation of a definition of remission."

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The treatment of rheumatoid arthritis has undergone marked changes in the last 50 years. Organic gold therapy, first tested in a controlled trial in the 1960s, was a major step towards effective treatment of rheumatoid arthritis [1]. Methotrexate therapy and NSAIDs increased the armamentarium of useful drugs for the treatment of this condition [2,3]. More recently, biologic therapy has resulted in another major step forward (see below).

In the late 1980s and 1990s, two closely related events further advanced the therapy of rheumatoid arthritis:

- The development and validation of combined measures of response for rheumatoid arthritis, among the first of these being that published by Paulus *et al.* [4]. This was followed by the publication of the ACR preliminary definition of improvement [5] and the development of the Disease Activity Score (DAS) in Europe [6]. These measures have been accepted by regulatory agencies and pharmaceutical sponsors as valid measures of response to therapies. This, in turn, has led to numerous studies with compatible (if not directly comparable) results, and the approval of a number of useful medications for the treatment of rheumatoid arthritis.
- The development of the technology to produce targeted biologic therapies for the treatment of rheumatoid arthritis, such as abatacept, adalimumab, etanercept, infliximab, anakinra and rituximab. These medications represent a very significant step towards highly effective therapy.

It is in the context of the aforementioned events that trying to attain remission has become possible. It is true that one of the first descriptions of remission in rheumatoid arthritis was in 1948, when remission was defined as 'if the disease was inactive, the patients were asymptomatic, an examination of the joints was negative except for residual deformity' [7]. However, it was not really until the availability of the TNF inhibitors that remission was considered as an achievable goal in well-controlled treatment trials of rheumatoid arthritis.

Thus, in the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO), comparing methotrexate, etanercept and their combination, remission was one of the outcome measures [8]. This was among the first well-controlled studies to do so. Remission was obtained in 37% of the combination-treated group compared with 14% of those on methotrexate at 1 year.

However, as soon as the word remission is used, one must ask its precise meaning. Should objective criteria (e.g., imaging and/or acute phase reactants) be included? Is it represented at a single point in time or must there be a duration of time during which remission exists? Can remission occur in the presence of ongoing therapy? What is the goal of remission?

In 1980, a subcommittee of the American Rheumatism Association (now the American College of Rheumatology) defined remission as 'total absence of all articular and extra articular inflammation and immunological activities related to RA' [9]. Since that time, a number of definitions of 'remission', based on various combined measures of response, have been promulgated (Table 1). A recent article examines these preliminary definitions in an early seropositive rheumatoid arthritis cohort [10]. Using a single point in time, but measuring the occurrence of remission at 6, 12 and 24 months and a 200-patient observational cohort, remission occurred at very different rates, depending on the definition used. For example, at 6 months, 0.7% of the patients achieved an ACR remission, 3% achieved the WHO/International League of Associations for Rheumatology (ILAR) remission, and 11, 12, 13 and 15% achieved remission by four other definitions (Simplified Disease Activity Index [SDAI], Clinical Disease Activity Index [CDAI], DAS28 <2.4 and DAS28 <2.6,

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Table 1. Definitions of remission.

Measure	Remission
ACR remission: Morning stiffness ≤15 min; fatigue = 0; TJC = 0; SJC = 0; joint pain = 0; ESR <30 mm/h (F); <20 mm/h (M)	5 of 6
Modified ACR remission: TJC = 0; SJC = 0; ESR ≤10 mm/h	All
DAS28, ESR, 4-item: 0.56 • √(t28) + 0.28 • √(sw28) + 0.70 • Ln(ESR) + 0.014 • GH	<2.6
SDAI: TJC28 + SJC28 + PtGH (10 cm) + MDGH (10 cm) + CRP	≤3.3
CDAI: TJC28 + SJC28 + PtGH (10 cm) + MDGH (10 cm)	≤2.8

Modified from [10].
CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease activity score; ESR: Erythrocyte sedimentation rate; F: Female; GH: Global Health using a visual analogue scale; Ln(ESR): Natural logarithm of the erythrocyte sedimentation rate; M: Male; MDGH: Physician-derived estimation of global patient disease activity; PtGH: Patient-derived visual analogue scale of global disease activity (global or overall health); SDAI: Simplified Disease Activity Index; SJC: Swollen joint count; sw28: Swollen joint count using 28 joints; t28: Tender joint count using 28 joints; TJC: Total joint count.

respectively [Table 1]). Furthermore, over time the number of patients achieving remission by any of these definitions varied. While the remission rate for the most stringent criteria (ACR remission) was only 0–0.7%, it varied between 15 and 33% for the DAS28 <2.6 definition of remission, and between 12 and 17% for the CDAI remission. Finally, the degree of agreement between the different definitions of remission was generally poor to moderate (κ-values between 0.07 and 0.52), indicating the possibility that these definitions are actually measuring different aspects of disease.

While these definitions of remission were generally at a single point in time, others have attempted to examine a more rigorous definition, requiring remission over a sustained period. Leirisalo-Repo *et al.* completed a double-blind, double-dummy study comparing combination therapy with and without infliximab [11]. In this study, sustained remission (lasting from 6–24 months) was achieved in 31% of the patients in a DMARD-combination-plus-placebo-infliximab arm, versus 40% in a DMARD-combination-plus-infliximab arm ($p = 0.40$).

Further complicating the picture is recent data suggesting that radiographic progression may continue despite achieving 'remission' [12]. Brown *et al.* demonstrated that most patients in ACR or DAS clinical remission had synovitis on magnetic resonance imaging of the wrists and/or metacarpophalangeal joints [13]. These findings indicate that remission, if the goal is to prevent structural progression, may need to include imaging studies as well as clinical response.

What, in fact, is the goal of remission? If the goal is patient comfort and present function, then a clinical definition would be most appropriate. If the goal is long-term productivity in society and in the family, a very prolonged duration of remission and a definition requiring imaging techniques might be most appropriate.

> "These findings indicate that remission, if the goal is to prevent structural progression, may need to include imaging studies as well as clinical response."

In response to the question 'We want remission, but what is it?', it is clear that the rheumatologic and medical community needs to vigorously pursue a full understanding and validation of a definition of remission suited to specific(and possibly different) purposes. Meanwhile, studies that aim to use remission as an outcome variable must clearly state which of the various definitions of remission they are using, and describe in detail how they calculate it. We have made a good start, but there is a long way to go.

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