Progress Toward the Development of a New Definition of Remission in Rheumatoid Arthritis


Abstract

The first definition of remission in rheumatoid arthritis was proposed by Pinals and colleagues in 1981. Although its development process was of high quality, the definition proved unfeasible and was not often applied. Subsequently many other definitions appeared, either as variations or as cutpoints of disease activity indices. The American College of Rheumatology, together with the European League Against Rheumatism and the Initiative for Outcome Measures in Rheumatology (OMERACT) decided to develop a new definition that would meet the OMERACT Filter of Truth, discrimination and Feasibility. This article summarizes the development process to date. The new definition is expected to be launched in 2010.

The concept of remission can be usefully defined as “The state of absence of disease activity in patients with a chronic illness, with the possibility of a return of disease activity.” The first definition of remission in rheumatoid arthritis (RA) was formulated by Pinals and colleagues in 1981. This “preliminary” definition has remained in force until today. In the authors’ view “complete remission” implies the total absence of all articular and extra-articular inflammation and immunologic activity related to RA. However, detecting such a state “could entail documentation by ‘extraordinary measures,’” so they developed the concept of “complete clinical remission,” which could be detected with generally acceptable and convenient measures. The approach to derive a definition for this concept was exemplary even by today’s standards.

Unfortunately, the definition was never widely used in its original form, as it included measures such as morning stiffness and joint sheath swelling that were later excluded from the RA core set. Additionally, it contained a duration requirement of 2 months that did not fit well with routine measurement intervals. In many different modifications, component measures were deleted and the duration was varied or deleted as well. Other definitions were formulated using cut points from composite indices, such as the disease activity score (DAS) and its 28-joint form (DAS28), as well as the more recent simplified and clinical disease activity indices (SDAI and CDAI, respectively). None of these definitions (including the original definition by Pinals and coworkers) were fully validated (e.g., against long-term outcome), and the proportion of patients classified as in remission varied substantially between definitions. The more stringent definitions are rarely met, whereas the less stringent definitions resemble that of the recently formulated “state of minimal disease activity.”

Treatment efficacy is improving and the need for a new, congruent definition of remission has become more pressing. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) together with the initiative for Outcome Measures in Rheumatology (OMERACT) jointly constituted a committee to redefine remission in RA. This article summarizes the choices, and the methodology followed.
by the committee, in the expectation that a new definition will be presented in 2010.

Initial Steps
A core committee was formed comprising the current authors as members. The full committee was composed of leading international experts, RA clinical researchers, trialists, clinical epidemiologists, and two patients. This group met in November 2007, June 2009, and October 2009. During the intervening periods and continuing to date, the core committee has been working on the analyses following recommendations from the larger committee. At the first meeting, issues on concepts, measurement, and application were introduced and subsequently discussed in breakout groups. This resulted in recommendations on the format of the new definition and the research agenda.⁷

The committee followed the framework of the OMER- ACT (Outcome Measures in Rheumatology) Filter that requires all measures to be truthful, discriminative, and feasible in their intended setting.⁸ On concepts, the committee decided that any definition should be strict, corresponding with “no clinical disease” to differentiate remission from the concept of minimal disease activity. Treatment would not be part of the definition, and long-term outcome measures, such as physical function and damage, would be used to validate the definition, thus excluding them from the definition itself.

On measurement, the committee decided that any definition should include a tender and swollen joint count, as well as an acute phase reactant, and result in a minimum of physical disability and a halt in the progression of joint damage. Other measures could be considered when appropriate. At this time, the validity of newer imaging measures to detect disease activity, such as magnetic resonance imaging (MRI) and ultrasound, was found insufficient to consider them for inclusion. No duration requirement would be included in the definition. Setting applicability for clinical practice was deemed important, and if necessary, a separate definition for practice would be developed.

Analyses of Predictive and Face Validity
The core committee decided to focus first on predictive validity. Lilian van Tuyl took the lead in performing a systematic literature review to see how well current remission definitions had been validated against long-term outcome.⁹ For this review, outcome was defined as good physical function and low (or lack of) evidence of radiographic damage progression. Her search identified 1138 records, of which only 14 were relevant to the research question. All 14 studies showed a relationship between remission and long-term structural damage or disability, regardless of the definition that was used. Patients that achieved a state of remission, defined in various ways, showed less deterioration of function and radiographic progression, compared to patients who did not reach a state of remission.

As this review did not help in preselecting promising candidates among existing definitions, in the next step, the core committee searched for data sets of clinical trials to study the same question. Several data sets were identified that contained information on disease activity, where patients were followed long enough to study subsequent changes in physical function and radiographic damage. Unfortunately, none of these contained information on the features of disease recently identified by patients as being important, including fatigue and sleep quality. The committee decided to move ahead and formulate a new definition in view of the urgency and the knowledge that it would take several more years for such data sets, including these measures, to become available.

Over 50 candidate definitions were formulated from various combinations of core set measures and the available indices. A survey among the larger committee indicated a preference for strict cut points for each of the measures, e.g., a swollen joint count not exceeding 1. These definitions were then tested for their ability to select patients in the data sets that would not show damage progression and would maintain a good physical function. This analysis showed two things. First, the results of the systematic review were confirmed in that patients meeting any of the definitions would by and large have a better long-term prognosis than patients not meeting a definition. Second, it turned out that this exercise, when run in different permutations, did not produce a consistent “winner.” A candidate definition could be good at predicting a good physical function, but not do so well in predicting damage stability and vice versa. The order of definitions in their predictive validity differed from one data set to the next, and so on.

The committee then turned to face validity as a potential selection tool. It was felt that the new definition of remission should not allow unacceptable residual disease activity in any of the measures not included in the definition. For example, if “physician global assessment” were not part of a definition, patients in remission should not have a high value on their physician global assessment. This proved to be a good way to move forward, allowing many definitions to be deleted from further consideration.

Meetings of the Larger Committee
Interim results of the above analyses were presented in June 2009, resulting in suggestions for further analyses. The full results were presented in October 2009 and discussed in plenary and small group sessions. As a result, a short list of five definitions is now undergoing final evaluation. The final definition will be presented in 2010.

Patient Perspective
As stated above, it was not possible to include fully all aspects of the patient perspective in the definition. However, in the RA core set measures considered for inclusion, three are patient-reported: pain and patient global assessment, and patient function (usually assessed using the Health Assess-
ment Questionnaire). Nevertheless, it is important that the patient perspective is explored further. As a consequence, at OMERACT 10 a focused research program will be developed. This program will 1. investigate the need among patients to determine absence of disease (or no impact of disease) or absence of disease activity (remission); 2. investigate the concept of the absence of disease activity according to the patient perspective; and 3. if appropriate, develop a patient-based definition for remission.

Conclusion
The development of a new definition of remission for RA is almost complete. It is a product of evidence-based consensus and meets the OMERACT filter of truth, discrimination, and feasibility.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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