Published in final edited form as:
Arthritis Rheum. 2011 March ; 63(3): 573–586. doi:10.1002/art.30129.

American College of Rheumatology/European League against Rheumatism Preliminary Definition of Remission in Rheumatoid Arthritis for Clinical Trials

David T. Felson[1,34,*], **Josef S. Smolen**[2,*], **George Wells**[3], **Bin Zhang**[1], **Lilian H. D. van Tuyl**[4], **Julia Funovits**[5], **Daniel Aletaha**[5], **Renée Allaart**[6], **Joan Bathon**[7], **Stefano Bombardieri**[8], **Peter Brooks**[9], **Andrew Brown**[10], **Marco Matucci-Cerinic**[11], **Hyon Choi**[1], **Bernard Combe**[12], **Maarten de Wit**[13], **Maxime Dougados**[14], **Paul Emery**[15], **Dan Furst**[16], **Juan Gomez-Reino**[17], **Gillian Hawker** [18], **Edward Keystone**[19], **Dinesh Khanna**[16], **John Kirwan**[20], **Tore Kvien**[21], **Robert Landewé**[22], **Joachim Listing**[23], **Kaleb Michaud**[24], **Emilio Martin Mola**[25], **Pam Montie**[26], **Ted Pincus**[27], **Pam Richards**[20], **Jeff Siegel**[28], **Lee Simon**[29], **Tuulikki Sokka**[30], **Vibeke Strand**[31], **Peter Tugwell**[32], **Alan Tyndall**[33], **Desirée van der Heijde**[6], **Suzan Verstappen**[34], **Barbara White**[35], **Fred Wolfe**[36], **Angela Zink**[37], and **Maarten Boers**[4]

[1] Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, USA. [2] Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, and 2nd Department of Medicine, Center of Rheumatic Diseases, Hietzing Hospital, Vienna, Austria. [3] Department of Epidemiology and Community Medicine, University of Ottawa, Canada. [4] The Department of Epidemiology and Biostatistics and the Department of Rheumatology, VU University Medical Center, Amsterdam, Netherlands [5] Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria. [6] Leiden University Medical Center, Netherlands. [7] Johns Hopkins University School of Medicine, Baltimore, USA. [8] University of Pisa, Italy. [9] University of Melbourne, Melbourne, Australia. [10] Hull York Medical School, University of York, UK. [11] University of Florence, Italy. [12] Division Hopital Lapeyronie, Montpellier University Hospital Montpellier, France. [13] Department of Medical Humanities, VU University Medical Center, Amsterdam, Netherlands. [14] Paris-Descartes University, Medicine Faculty; UPRES-EA ; AP-HP, Cochin Hospital, Rheumatology B Department, Paris, France. [15] University of Leeds and Leeds Teaching Hospitals NHS Trust, UK. [16] David Geffen School of Medicine at the University of California in Los Angeles, USA. [17] Hospital Clinico Universitario at the Universidad de Santiago de Compostela, Santiago, Spain. [18] Women's College Hospital, Toronto, Canada. [19] University of Toronto, Canada. [20] University of Bristol, Bristol, UK. [21] Diakonhjemmet Hospital, Oslo, Norway. [22] Department of Internal Medicine/Rheumatology, University Hospital Maastricht, Netherlands. [23] Deutsches Rheuma-Forschungszentrum, Berlin, Germany. [24] University of Nebraska, Omaha, USA. [25] Hospital Universitario La Paz, Madrid, Spain. [26] Arthritis Research Centre of Canada, Vancouver, Canada. [27] New York University School of Medicine, New York, USA. [28] Food and Drug Administration, Center for Drug Evaluation and Research, Washington DC, USA. [29] SDG

Corresponding author: Maarten Boers, MSc, MD, PhD Professor of Clinical Epidemiology Department of Epidemiology and Biostatistics VU University Medical Center, PK 6Z 165 PO Box 7057 1007 MB Amsterdam, Netherlands ph: +3120 444 4474 fx: +3120 444 4475 mboers56@xs4all.nl.

*These two authors contributed equally to this work.

The views presented in this manuscript do not necessarily reflect those of the Food and Drug Administration.

*Boolean measures:

This is the logic that computers use to determine if a statement is true or false. There are 4 main Boolean operators: AND, NOT, OR, and XOR. Below is an example from defining remission of how one operator works:

Assume x and y are both core set variables for RA whose values are in the range of remission. x AND y returns True if both x and y are true, otherwise the expression returns False. False means that patient is NOT in remission.

LLC, Cambridge, USA. [30] Jyväskylä Central Hospital, Jyväskylä, Finland. [31] Stanford University School of Medicine, Palo Alto, USA. [32] University of Ottawa, Canada. [33] University of Basel, Switzerland [34] Arthritis Research UK Epidemiology Unit, The University of Manchester, UK. [35] MedImmune, Gaithersburg, USA. [36] National Data Bank for Rheumatic Diseases, Wichita, USA. [37] German Rheumatism Research Center, Berlin, Germany.

Abstract

Background—With remission in rheumatoid arthritis (RA) an increasingly attainable goal, there is no widely used definition of remission that is stringent but achievable and could be applied uniformly as an outcome in clinical trials.

Methods—A committee consisting of members of the American College of Rheumatology, the European League Against Rheumatism and the Outcome Measures in Rheumatology Initiative (OMERACT) met to guide the process and review prespecified analyses from clinical trials of patients with RA. The committee requested a stringent definition (little, if any, active disease) and decided to use core set measures to define remission including at least joint counts and an acute phase reactant. Members were surveyed to select the level of each core set measure consistent with remission. Candidate definitions of remission were tested including those that constituted a number of individual measures in remission (Boolean approach) as well as definitions using disease activity indexes. To select a definition of remission, trial data were analyzed to examine the added contribution of patient reported outcomes and the ability of candidate measures to predict later good x-ray and functional outcomes.

Results—Survey results for the definition of remission pointed to indexes at published thresholds and to a count of core set measures with each measure scored as 1 or less (e.g. tender and swollen joint counts, CRP and global assessments on 0-10 scale). Analyses suggested the need to include a patient reported measure. Examination of 2 year follow-up data suggested that many candidate definitions performed comparably in terms of predicting later good x-ray and functional outcomes, although DAS28 based measures of remission did not predict good radiographic outcomes as well as did the other candidate definitions. Given these and other considerations, we propose that a patient be defined as in remission based on one of two definitions : 1: When their scores on the following measures are all $\leq$1: tender joint count, swollen joint count, CRP (in mg/dL) and patient global assessment (0-10 scale), OR 2: when their score on the SDAI is $\leq$ 3.3.

Conclusion—We propose two new definitions of remission both of which can be uniformly applied and widely used in RA clinical trials. We recommend that one of these be selected in each trial as an outcome and that the results on both be reported in each trial.

With the advent of new therapies and therapeutic strategies for rheumatoid arthritis (RA), remission has become a realistic goal (1-3) and has recently become a secondary or even primary endpoint for clinical studies and trials(4-8). Remission is also regarded as a major therapeutic target in clinical practice(9-12) and can be achieved in a significant proportion of patients followed in routine care(13-15). However, the formal definition of remission differs between studies.

The current American College of Rheumatology (ACR) definition of remission in RA(16) was developed in 1981 prior to the introduction of the core set measures(17). In this classic paper, Pinals et al. stated: '…"complete remission" implies the total absence of all articular and extraarticular inflammation and immunologic activity related to rheumatoid arthritis (RA).' Recognizing that detecting such a state could entail documentation by 'extraordinary measures', they settled on the concept of 'complete clinical remission' aiming to achieve 'uniformity in clinical application using generally acceptable and convenient measures.'

Even though this concept is of considerable value for trials and clinical practice as a therapeutic target, the 1981 ACR definition has not been widely used in clinical trials in RA because it contains some elements not in the core set (morning stiffness, swelling in tendon sheaths) and a time requirement. Also, this original version was so stringent that few patients met the criteria. Subsequently many modifications of the ACR criteria were developed, usually omitting one or more of the measures as well as the time requirement.

The development of composite indices of disease activity allowed the definition of cutpoint values representing remission(18-20), but their validation was often limited to comparisons with such modified ACR criteria. For instance, we now know that the widely used definition of remission based on the Disease Activity Score (DAS28) of less than 2.6(18) better represents minimal disease activity than remission as multiple joints can remain swollen or tender at that score(19;21-23). This is further exemplified by the fact that in many recent clinical trials the proportion of patients with ACR70 response is around, or even lower than, the proportion of patients attaining DAS28 remission(5;24-26). Thus, the 1981 statement by Pinals et al. remains relevant today: “Substantial variation appears to exist in the concept of remission within the group of participating rheumatologists”(16).

In the meantime, effective treatments for rheumatoid arthritis have led to more exacting criteria for improvement (e.g. ACR 50, 70 and even 90 percent improvement) and have led to recently proposed definitions of minimal disease activity(27). In light of the heterogeneity of definitions of remission , the time has come for consensus on a new definition, a uniform definition of remission. Therefore, the ACR and European League Against Rheumatism (EULAR) together with the Outcome Measures in Rheumatology Initiative (OMERACT) jointly constituted a committee to redefine remission in rheumatoid arthritis. This committee subsequently published a systematic review of prognostic validity of current remission definitions(28) as well as an outline of the goals of redefining remission and the methods by which we would attain them (2).

In this outline of our goals already published, the committee decided by consensus to create a stringent definition for remission; and that any definition should include as a minimum tender and swollen joint counts and an acute phase reactant. Excluded were treatment, duration of remission (the committee felt that this should be specified in each trial), and measures of physical function and damage. The latter two were to be used to validate candidate remission definitions: the chosen definition should predict absence of X-ray damage progression and good functional outcomes in the future. Remission should also predict future remission and minimal disease activity, i.e. show stability. Finally, the requirement for full or 28-joint counts had to be studied.

The committee suggested that core set measures should be used to define remission and that any definition of remission in clinical trials should look toward and make possible a similar definition in clinical practice.

The selection of the optimal definition of remission was guided by the research agenda as put forward by the committee at the beginning of our deliberations. In general, the evidence-based consensus method adhered to was in line with similar activities previously performed by OMERACT and ACR and EULAR(29-31) with the intent of deriving a definition that would pass the OMERACT filter of Truth, Discrimination and Feasibility(32). In this paper we present the results of analyses addressing this research agenda, report on later meetings of the committee in which these results were evaluated and present a consensus definition of remission.

METHODS

General aspects

The initial committee was formed by inviting members of the ACR committee who had previously formulated the new ACR response criteria, principal investigators of recent clinical trials, methodologists and patient experts from the OMERACT community, and ACR, EULAR and OMERACT executives with a view to be inclusive and geographically representative. All members present at one of the committee meetings were asked to consider authorship of the present paper. A patient expert (or research partner) can be described as a patient involved in research based on personal experience of disease that is not available to most researchers, but that complements researchers' analytical skills and scientific perspective(33). During the development of the remission definition, 6 patient experts were involved, of whom 3 are co-authors. Following the specifications provided by the committee, a steering group (DTF, JS, GW, BZ, LvT, JF, MB) designed and performed the necessary investigations; this included a survey as well as analyses of clinical trial data. Clinical trial databanks with slightly different total patient numbers and data composition were created at different centers. Because these have been the largest RA trials carried out and data collected allowed us to test remission definitions hypothesized, we solicited industry funded RA clinical trials data with their approval. Industry had no role in data analysis, criteria development, testing or evaluating the process or final choices made by the committee. Nor were they consulted or involved in manuscript development. These data were analyzed by the steering group according to the committee's specifications and methodological discussions in the steering group.

Survey

Our first goal in selecting candidate criteria for remission was to define for the core set measures what cut points might constitute remission. In a survey we asked committee members (experienced RA clinical researchers and patient experts) what level of residual activity in individual core set measures would constitute remission. For all measures except joint counts, we used a 0-10 scale. For CRP we used a scale in milligrams per deciliter (mg/dL). For initial analyses of joint counts, we used a 28-joint count and then examined its validity for remission (see below). We asked for the highest level of each core set measure that would be compatible with remission if it were the only measure assessed and also asked for the highest level of a particular core set measure compatible with remission if all other measures pointed to remission.

Value of patient reported outcomes

The committee raised the question as to whether patient reported outcomes should be included in the definition of remission. We addressed this issue by asking whether patient reported outcomes at the level of remission discriminated between active versus control treatment in trials. In a subset of our databank which comprised core set data from four clinical trials(34-37) we performed two sets of analyses in each trial. In both analyses the dependent variable was treatment assignment. First, we carried out a logistic regression with each of the core set measures as predictors (recoded as remission level, e.g. swollen joint count ≤ 1, yes or no). Second we performed recursive partitioning by Classification and Regression Tree (CART) analysis on data from four clinical trials(34-37) in which we ranked core set measures at remission level based on the tree created from a series of binary splits. Recursive partitioning is a statistical method for multivariable analysis creating a tree with branches that strives to correctly classify members of the population based on a dichotomous dependent variable. If the patient reported outcomes helped differentiate active treatment from control (either by being a significant predictor in the regression analysis or having a high rank in the classification tree) then these outcomes would be said to contribute

importantly to defining remission. Patient reported outcomes tested in this analysis were patient global assessment and patient pain. Functional status measurement was not included for reasons outlined earlier.

Assessment of predictive validity

Once we had decided that patient reported outcomes were to be included and had determined the cut points to be used to define remission, we embarked on the analysis of predictive validity. To this end we evaluated various two year datasets from randomized clinical trials (RCTs; 80-90% random patient level data) kindly provided by the sponsors of these studies(34;37-41) and obtained permission to use these data for the present analysis. The data are described in more detail in those publications. For the present analyses, only patients with all pertinent data over two years were evaluated.

We initially defined a good outcome for x-ray damage and physical function separately. For x-ray it comprised stable x-ray scores over 1 year (defined as change ≤ 0 in Sharp or van der Heijde modified Sharp scores during the 2nd year of respective trials). For physical function, it comprised stable and low scores on the Health Assessment Questionnaire (HAQ change ≤ 0 and HAQ score consistently ≤ 0.5 during the 2nd year of respective trials). We then tested whether those who met a particular definition of remission at six months or twelve months were more likely to have a good outcome in the subsequent period, i.e. between one and two years after trial onset. Likelihood ratios compared the proportion of patients in remission having the good outcome to the proportion of patients *not* in remission having the good outcome. To rank candidate definitions of remission, we used the *p* value from the logistic regression chi square test. As has been reported, most patients in trials followed long term do not show radiographic progression(42). This limited our capacity to discriminate between candidate definitions of remission. Moreover, intensive therapy with TNF-inhibitors plus MTX dissociates clinical disease activity from progression of joint damage, since - unlike patients treated with MTX alone – those on aggressive treatments have no or minimal radiographic progression irrespective of their disease activity(43-45). Therefore, we primarily performed the analyses in patients treated with MTX monotherapy, but we also evaluated TNF inhibitor monotherapy and combination therapy in sensitivity analyses. To assess the robustness of the results, we also did the analyses in a subset of trial patients with an especially poor prognosis in terms of radiographic disease as follows: presence of rheumatoid factor AND presence of damage at baseline. Finally, we tested an additional definition of a good outcome, namely stability of both x-ray damage and HAQ.

Selection of Candidate Definitions

Candidate definitions of remission were selected from two general categories: first, indices that have been widely used including the DAS28, the Simplified Disease Activity Index (SDAI) and the Clinical Disease Actvitiy index (CDAI)(18;19;30;31;46-48); and second, definitions including one or more core set measures at cutpoints previously defined by the survey, but requiring all included measures to be at or below that cutpoint. For example, to meet remission defined as low scores on tender and swollen joint count and physician and patient global assessment, the patient must have had low scores on all four measures. We shall label these the Boolean measures based on their approach which is to define each core set measure as in remission or not (values of 0 and 1) and use possible combinations of the patient's core set measure remission status to determine the patient's overall remission status (also 0 or 1)*.

Further Evaluations of Candidate Definitions including Face Validity

After completing the analysis of predictive validity, we tested our candidate definitions for face validity. Since we had decided that any definition of remission must be stringent with

respect to not allowing much disease activity, we studied whether patients could meet a definition of remission yet still have moderate to high levels of disease activity in any core set measure. To do this, in the group of patients meeting a certain definition of remission, we studied the 90th percentile and maximum level of disease activity observed in each core set measure. Lastly, we looked at recent trial data to determine what proportion of patients met each remission definition. It was our goal not to have an undetectably low percentage of patients meet remission, or one so high as to be unreasonable given clinical experience with these treatments.

We also examined two related issues for our candidate definitions. First, we wished to select a definition(s) that was reliable and we defined this by analyzing in one trial with monthly visits whether a person in remission at one visit attained the same state at adjacent visits <=1 month from the first; if not in remission at the adjacent visit, we tested whether these patients in remission attained a state of minimal disease activity(27). Second, we were concerned that a 28-joint count might not capture active joints outside these 28; to this end, we reviewed literature and analyzed trial data to determine whether we should define remission differently when using 28 versus, for example, 66 joints. For the latter, we evaluated data from a set of trials that included tenderness and swelling counts of individual joints. In these we assessed residual disease activity in ankles and feet in patients with 28-joint counts of 1 or less and determined what proportion of such patients would satisfy the other requirements of our candidate definitions. These patients would represent real misclassification (‘false positive remissions’). In the same dataset we subsequently investigated whether such misclassification could materially affect the predictive validity of the remission definitions. For this purpose we compared the prevalence of good outcome (damage or function) in ‘true remission’ patients (i.e., based on full joint counts at 1 or less) with that of all patients with remission based on 28 joint counts (i.e. ‘true’ plus ‘false positive’ remissions).

RESULTS

Survey

Twenty seven committee members including two patients completed the survey on threshold levels for remission (see Table 1). In the scenario where only one variable was available, the responses clustered around core set disease activity levels of 1 such that, for example, the swollen or tender joint count ought to be 1 or less; CRP level ought to be 1 mg/dl, and patient and physician global assessments and pain ought to be 1 or less on a ten point scale. The question as to which was the highest level of a particular core set measure compatible with remission if all other measures pointed to remission yielded more varied answers, with thresholds ranging from 2 for swollen joint counts and CRP to 4 for tender joint counts. Since they did not provide us with a single threshold value that was uniform across core set measures, we focused on the more stringent cutpoints.

Patient reported outcomes

We then proceeded with an analysis of clinical trial data of active treatment versus control to help determine whether patient reported outcomes, namely patient global assessment or patient pain, should be incorporated into our definition of remission. In an analysis of 4 clinical trials, both logistic regression and CART analysis demonstrated that these measures added important information to physician-linked measures. In other words, in these trials, these measures were statistically significant predictors discriminating between treatments after controlling for physician reported measures (TJC and SJC) and a lab measure (CRP). For example in the CART analysis, among the 4 trials, patient global assessment was the best predictor of treatment assignment among all outcomes in one trial and 4th best of core

set measures in another. Patient pain was the second best predictor (SJC was the best) in a 3rd trial. .

Based on these preliminary analyses, we came up with a list of candidate remission definitions to test for predictive validity. When presented with the more stringent definitions versus the more relaxed definitions, our committee selected those in the more stringent category and as a consequence, we present results only for these. In line with the charge by the committee and the assessment of the contribution of patient reported outcomes, we mainly focused on measures that comprised tender joint count (TJC), swollen joint count (SJC), C Reactive Protein (CRP) and patient global assessment (PtG). We tried combinations of these and and other core set measures to determine if any group of measures would have important advantages.

Predictive validity

We then tested whether patients in remission according to one of these definitions had a higher likelihood of a good outcome. We focused on patients with methotrexate monotherapy, although we obtained similar results when we analyzed data from all patients (not shown). We found that patients in a state of remission by several of the Boolean candidate definitions, as well as by traditional SDAI (≤3.3) and CDAI (≤2.8) definitions had an increased likelihood of x-ray stability during the subsequent year (see Table 2a) as well as an increased likelihood of both x-ray and HAQ stability (see Table 2b). Similar data were also obtained in an additional dataset from the COBRA study(40) (data not shown). However, reaching remission according to DAS28, both at the traditional (<2.6) and a more stringent cut point (<2.0), was associated only with the likelihood of HAQ stability but not x-ray stability. Candidate definitions of remission did not differ in their prediction of HAQ stability (data not shown). Additional definitions were tested including incorporating either remission level pain or patient global and other variations, and results were similar. Apart from the DAS28 result, the analyses did not help to distinguish between definitions. This was also true in the analysis with a more strict definition of good outcome, and when we studied only patients with a poor prognosis (data not shown).

Face validity of the different candidate definitions, expressed as residual disease activity in the presence of remission, is shown in Table 3. For the Boolean definitions, the high values, as expected, tended to be for core set measures that were not pre-specified by the rule. For example, if we used the definition of tender joint count, swollen joint count, CRP and pain all ≤ 1, we found 10% of patients (90th percentile) had levels of physician and patient global assessment compatible with active disease. If we used tender joint count, swollen joint count and CRP all ≤ 1, then the patient reported outcomes often suggested high levels of symptoms. For the traditional DAS28 definition (<2.6) we found that many of the core set measures remained at levels that would be incompatible with remission. This was even true for DAS28 <2.0 which was a threshold few patients reached. This was not true for other index measures that defined remission such as SDAI or CDAI where results were closely aligned with the Boolean definitions and the results of our survey.

When we examined the proportion of patients in trials that met candidate definitions of remission (Table 4), we found that 18-26% of patients on combination therapy with TNF inhibitors and methotrexate met most of these definitions compared to only 6-10% of those on either monotherapy, percentages that we felt had face validity.

Consensus activity

Our committee met prior to the ACR meeting in October 2009 to discuss the analyses described above. As noted earlier, the committee did not select in any case a more relaxed

definition of remission, consistent with their earlier directive. During the committee meeting two subgroups were formed to discuss the tabular results presented, especially including results regarding predictive validity. Both groups voted that there ought to be both a Boolean approach and an index based definition. One group voted among individual definitions of remission, and in doing so, the highest vote was received by the Boolean definition which included tender joint count, swollen joint count, CRP and patient global assessment, all at levels less than or equal to 1. The index definition with the highest vote count was SDAI ≤ 3.3. In the other subgroup, after a discussion involving all study group members, the same conclusion was reached without a formal vote. Members of the subgroup noted that in the clinic an acute phase response measure was often not available at every visit and the subgroup suggested that a definition of remission be developed for clinic based practice that would not require an acute phase reactant, as long as it would capture remission as stringently as the measure employed for clinical trials. Indeed, a Boolean measure comprising tender joint count, swollen joint count and patient global assessment provided similar statistical results as the same measures encompassing CRP, and the CDAI, which does not contain CRP, did likewise (bottom of Table 2a). Thus, these definitions of remission may be used in clinical practice until better measures for that purpose become available.

In a trial with monthly visits we found that our selected definitions of remission showed good reliability. Specifically, of patients in remission at one time point, 66% remained in remission one month later and all the rest met criteria for minimal disease activity(27).

Joint counts

We consulted published literature and our own data analysis to determine if remission thresholds for 28-joint counts should be the same as threshold for counts with more joints counted (such as 66 or 68 joints). One study(49) examined whether adding ankles and metatarsophalangeal joints to the 28-joint count affected remission and found that less than 10% of patients with no tender or swollen joints using a 28-joint count had tender or swollen ankles or metatarsophalangeal joints and that the average patient global assessment score in these latter patients was significantly higher, suggesting they would not meet proposed definitions of remission. Landewé and colleagues(23) also noted that a 28-joint count in remission often concealed active joints elsewhere, especially in the feet and ankles. However, they also reported that global assessments for those with 28 joints in remission but active joints elsewhere resembled those of patients not in 28-joint count remission, suggesting that requiring a low patient global assessment will, to some extent, mitigate the limitation of using a 28-joint count.

In the 2 trials in our dataset that included tenderness and swelling counts of individual joints, remission prevalence using 66 or 68 joints was 4% and 9%, respectively. As in the studies quoted above, we found that patients with 28-joint counts at or below 1 often had residual tenderness or swelling in the ankles or feet. However, most of these patients did not satisfy the other requirements of our candidate definitions of remission. Nevertheless, the estimate of remission prevalence increased to 6% and 14% of the total population when 28-joint counts were used. In another data set of two trials with 2-year follow up data, we compared patients in remission according to full (66/68) joint counts vs. patients in remission only according to 28-joint counts (i.e., with residual disease activity in joints not assessed). In the patients with a ‘full joint count remission’, 80% had good X-ray damage outcomes (no change in Sharp score); this number decreased by 1% in the patients with only a ’28-joint count remission. Likewise, in the patients with a ‘full joint count remission’, 90% had good HAQ outcomes; this number decreased by 1 and 4% in the two trials in the patients with only a ‘28-joint count remission’. Based on these analyses we concluded that the overall impact on misclassification due to reduced joint counts is small.

The final definitions of remission recommended are described in Table 5 with specific suggestions on how to measure them.

DISCUSSION

Based on considerations of face and predictive validity and the need to include both stringency and patient reported outcomes, the ACR/EULAR committee charged with defining remission in RA has produced two definitions for evaluating remission in clinical trials, one a Boolean based definition, more categorical in structure than the traditional definition from Pinals et al, and the other based on a composite index of RA activity, the SDAI(19;47).

Ideally, we would have liked to select a candidate definition which clearly differentiated those whose long-term course was without disease progression versus those whose disease continued to progress. Our analysis of long term data confirmed the findings of our systematic review(28) that most definitions of remission did well—i.e., that patients in remission at any point during a clinical trial, based on any of the definitions we used, were likely to have long term courses that were better than those who did not meet the definition of remission. One exception was the DAS28 which has been shown previously to allow for significant residual disease activity (19;21;22;50;51). Thus, except for DAS28 based definitions, differences in predictive validity between candidate definitions were small (see Tables 2a and 2b), and it was difficult to differentiate the course of patients meeting any of these definitions of remission. Among the many tested definitions, none importantly exceeded the ability of the ultimately selected criteria to predict favorable long-term effects on x-ray progression and physical function. Although we can confirm the predictive validity of remission, the goal of our work was to define remission, not to develop a predictive marker.

In our datasets we assessed definitions of remission by 28-joint counts. When we examined more comprehensive counts among those with 28 joint counts in remission, we found that residual disease activity was frequently present in ankles and feet. However, most of these patients failed to meet other criteria in the remission definition (e.g. their patient global assessments were often high). In other words, even when joints outside the 28 joints counted were active, other measures of disease activity often prevented misclassification of these patients as being in remission. In addition, the impact of misclassification on long-term outcome proved to be small. We should also bear in mind that the assessment of ankles and forefeet is particularly limited and poorly reproducible(52). In line with this, the discordance between tenderness and swelling has proved to be larger in the joints of the feet than other joints(53). Therefore we do not *require* inclusion of ankles and forefeet in the assessment of remission but recommend that these joints are also included in the examination. Investigators should always report which joints were examined.

In 2008 EULAR and ACR recommended that each RA trial should report the percentage of patients achieving a low disease activity state and remission(30;31). On the basis of the present analyses and consensus, we recommend that one of the definitions of remission recommended here be reported as a preselected outcome in trials and that results for both be reported in trials. Of the approaches to defining low disease activity, the OMERACT definitions of ‘minimal disease activity’ (MDA), designed to reflect the ‘next best’ option apart from remission, have been the best vetted and were consensually developed (27).

There are a few limitations to our approach and possibly of the definitions produced as a consequence. First, we used a HAQ ≤ 0.5 as evidence for stability of the remission criteria; while this is a disability score which is essentially above values obtained in the general

population(54), many of the studies evaluated were of patients with longstanding disease who are known to accumulate significant irreversible disability(55). However, we accounted for this potential contrast to the normal situation by also requiring that HAQ scores did not deteriorate at all over a full one-year period (HAQ change ≤0 during the 2nd year of observation). Second, we have not yet validated the recommended definitions of remission in observational data sets. This is the next step in our work. In developing definitions, we anticipated clinic based evaluations, trying to choose definitions of remission which would be easy to apply in an observational context and take advantage of variables that are probably already being measured. In clinical practice, acute phase reactants are frequently not immediately available and, therefore, an additional set of a Boolean and an index based definition not requiring acute phase reactants are provided for that setting. Nevertheless, our preliminary suggestions for defining remission in practice are still incomplete, as we did not test them in a clinic based setting. While the remission definitions not requiring an acute phase reactant performed comparably to those requiring it, our committee felt that including an acute phase reactant for reporting remission in clinical trials was preferable because acute phase reactants are important predictors of later radiographic damage (56-58).

Another limitation of the proposed definition is that the patient experience of remission may not have been adequately captured with only one element, the patient's global assessment of their disease activity. Indeed an index based on patient measures alone may clinically discriminate active from control treatment as well as some of the indexes tested in this effort(59;60). However, the committee had stipulated that joint counts should be part of the remission criteria; moreover, joints are the “organ” involved in RA and in the context of assessing remission it was deemed advisable to assess that organ. Further, fatigue was not evaluated(61). However, fatigue was not assessed in most trials published over the last decade or used here for the derivation of the remission criteria; we were also unable to procure datasets that contained information on other non-core set measures. As these datasets are likely to become available only over the course of several years, we decided not to postpone the development of the new remission definition. Indeed, we felt it was important to spend more time developing the concept of patient-assessed ‘absence of disease’. This will require qualitative research involving focus groups, as well as quantitative research e.g. collection of patient related outcomes in clinical trials, a task that will be taken forward within the OMERACT framework. Once a working definition of this concept is available, it can be compared with the proposed definition of remission.

Yet another theoretical limitation is that we are not using imaging in our definition of remission. Our goal was to use clinical parameters that are widely used and convenient to assess, but we recognize that residual synovitis may exist in many patients whose disease appears inactive based on conventional clinical evaluation(51;62;63). Importantly, however, our definitions of remission were associated with a retardation of x-ray progression, suggesting that the clinical definition has biological meaning. Moreover, a recent sonographic analysis on patients in remission defined by different means was in line with the present results(51). Thus, while our definitions permit a tender or swollen joint to be present, we require multiple pieces of evidence of inactive disease (one or no tender and swollen joints and low acute phase reactant score and assessment by the patient that the disease is inactive) before a patient meets remission criteria. Since inactive disease may be accompanied by one residual swollen or tender joint and since the reliability of the exam diminishes with the number of active joints, this procedure enhances the sensitivity of our definition of remission.

We should note that our tested trial data sets included CRP more frequently than ESR, explaining why our definitions present thresholds for CRP. A similar ESR threshold for inactive disease might be <20mm/hour for men and <30mm/hour for women, or even lower,

but this may require further testing(64). Our preference for CRP is, in part, because it can be standardized across centers, making it the preferred acute phase reactant measure in multicenter trials. Also, while CRP levels may have different upper limits of normal in different laboratories, this test is widely standardized today and a value of 1mg/dl covers all these upper limits; at 1mg/dl or less the progression of joint damage is minimized(56;57). Given these findings, the practicality of using the same value (1) for all measures was deemed more important than searching for potential minimal differences between cutpoints of 1mg/dl or slightly less.

A 'treat to target' approach may yield better outcomes than a conventional approach to treatment in RA, and remission can serve as that target for some patients. However, remission according to the stringent definition presented here may not yet be a realistic goal for most patients. (10)

In conclusion, we present new definitions of remission for use as outcome measures in clinical trials, either the compilation of 4 individual measures or an index based alternative.. We hope that these new definitions will be adopted widely and can provide a uniform approach to assessing this increasingly important outcome.

Acknowledgments

We are grateful to several colleagues who participated in the committee discussions but declined to be named as co-author on this paper; and to Abbott, Amgen and Wyeth for sharing clinical trial data.

This work was supported by ACR, EULAR and by NIH AR47785

REFERENCE LIST

1. Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis. 1995; 54:944–7. [PubMed: 8546524]
2. van Tuyl LH, Vlad SC, Felson DT, Wells G, Boers M. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum. 2009; 61(5):704–10. [PubMed: 19405006]
3. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? Clin Exp Rheumatol. 2006; 24(6 Suppl 43):S–13.
4. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999; 353(9164):1568–73.
5. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008; 372(9636):375–82. [PubMed: 18635256]
6. Burmester GR, Ferraccioli G, Flipo RM, Monteagudo-Saez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2007; 59(1):32–41. [PubMed: 18163417]
7. Verstappen SMM, Jacobs JWG, van der Venn MJ, Heurkens AHM, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis. 2007; 66(11):1443–9. [PubMed: 17519278]
8. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005; 52(1):27–35. [PubMed: 15641102]

9. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld FC, Dougados M, et al. Eular recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006; 66:34–45. [PubMed: 16396980]
10. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010; 69:631–7. [PubMed: 20215140]
11. Khanna D, Oh M, Furst DE, Ranganath V, Gold RH, Sharp JT, et al. Evaluation of the preliminary definitions of minimal disease activity and remission in an early seropositive rheumatoid arthritis cohort. Arthritis Rheum. 2007; 57(3):440–7. [PubMed: 17394230]
12. Listing J, Strangfeld A, Rau R, Kekow J, Gromnica-Ihle E, Klopsch T, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther. 2006; 8(3):R66. [PubMed: 16600016]
13. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology. 2007; 46:975–9. Epub 2007 Mar 6. [PubMed: 17341506]
14. Sokka T, Hetland ML, Makinen H, Kautiainen H, Horslev-Petersen K, Luukkainen RK, et al. Remission and rheumatoid arthritis: Data on patients receiving usual care in twenty-four countries. Arthritis Rheum. 2008; 58(9):2642–51. [PubMed: 18759292]
15. Gossec L, Dougados M, Goupille P, Cantagrel A, Sibilia J, Meyer O, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann Rheum Dis. 2004; 63:675–80. [PubMed: 15140774]
16. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum. 1981; 24(1308):1315.
17. Boers M, Tugwell P, Felson DT, van Riel PL, Kirwan JR, Edmonds JP, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. J Rheumatol. 1994; 41(Suppl):86–9. J Rheumatol 1994; 41 (Suppl):86-9.
18. Fransen J, Creemers MC, van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology (Oxford). 2004; 43(10):1252–5. [PubMed: 15238643]
19. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. Arthritis Rheum. 2005; 52:2625–36. [PubMed: 16142705]
20. Prevoo ML, van Gestel AM, Van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996; 35(11):1101–5. [PubMed: 8948296]
21. van der Heijde D, Klareskog L, Boers M, Landewe R, Codreanu C, Bolosiu HD, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis. 2005; 64:1582–7. [PubMed: 15860509]
22. Makinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis. 2005; 64:1410–3. originally published online 7 Jun 2005; doi:10.1136/ard.2005.037333. [PubMed: 15941836]
23. Landewe R, van der Heijde D, n der Linden S, ers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006; 65(5):637–41. [PubMed: 16219709]
24. Emery P, Keystone E, Tony HP, Cantagrel A, van VR, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008; 67(11):1516–23. [PubMed: 18625622]
25. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha

inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009; 374(9685):210–21. [PubMed: 19560810]

26. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008; 371:987–97. [PubMed: 18358926]
27. Wells G, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol. 2005; 32:2016–24. [PubMed: 16206362]
28. van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M. Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: A systematic review. Arthritis Care Res (Hoboken). 2010; 62(1):108–17. [PubMed: 20191498]
29. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials. 2007; 8:38. [PubMed: 18039364]
30. Aletaha D, Landewe R, Karonitsch T, Bathon J, Boers M, Bombardier C, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Arthritis Rheum. 2008; 59(10):1371–7. [PubMed: 18821648]
31. Aletaha D, Landewe R, Karonitsch T, Bathon J, Boers M, Bombardier C, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Ann Rheum Dis. 2008; 67(10):1360–4. [PubMed: 18791055]
32. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol. 1998; 25(2):198–9. [PubMed: 9489805]
33. Hewlett S, Wit M, Richards P, Quest E, Hughes R, Heiberg T, et al. Patients and professionals as research partners: challenges, practicalities, and benefits. Arthritis Rheum. 2006; 55(4):676–80. [PubMed: 16874772]
34. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000; 343(22):1586–93. [PubMed: 11096165]
35. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004; 50:1400–11. [PubMed: 15146409]
36. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003; 48(1):35–45. [PubMed: 12528101]
37. Klareskog L, van der Heijde D, de Jager JP, Gough AKJ, Malaise M, Martin-Mola E, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004; 363:675–81. [PubMed: 15001324]
38. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study - A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006; 54:26–37. [PubMed: 16385520]
39. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum. 2007; 57(2):193–202. [PubMed: 17330293]
40. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002; 46:347–56. [PubMed: 11840436]

41. Smolen JS, Aletaha D, Grisar JC, Stamm TA, Sharp JT. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. Ann Rheum Dis. 2009

42. Landewe R, van der Heijde D. Radiographic progression depicted by probability plots: presenting data with optimal use of individual values. Arthritis Rheum. 2004; 50(3):699–706. [PubMed: 15022307]

43. Smolen JS, Han C, Bala M, Maini R, Kalden J, van der Heijde D, et al. Evidence of Radiographic Benefit of Infliximab Plus Methotrexate in Rheumatoid Arthritis Patients Who Had No Clinical Improvement: A Detailed Subanalysis of the ATTRACT Trial. Arthritis Rheum. 2005; 52:1020–30. [PubMed: 15818697]

44. Smolen JS, Han C, Van der Heijde DM, Emery P, Bathon JM, Keystone E, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and TNF-blockade. Ann Rheum Dis. 2009; 68:823–7. Epub 2008 Jul 1. [PubMed: 18593759]

45. Landewe R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis Rheum. 2006; 54(10):3119–25. [PubMed: 17009230]

46. Prevoo MLL, van't Hof MA, Kuper HH, van de Putte LBA, van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995; 38:44–8. [PubMed: 7818570]

47. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A Simplified Disease Activity Index for Rheumatoid Arthritis For Use In Clinical Practice. Rheumatology. 2003; 42:244–57. [PubMed: 12595618]

48. Aletaha D, Smolen JS. The Definition and Measurement of Disease Modification in Inflammatory Rheumatic Diseases. Rheum Dis Clin North Am. 2006; 32:9–44. [PubMed: 16504819]

49. Kapral T, Dernoschnig F, Machold KP, Stamm T, Schoels M, Smolen JS, et al. Remission by composite scores in rheumatoid arthritis: are ankles and feet important? Arthritis Res Ther. 2007; 9(4):R72. [PubMed: 17662115]

50. Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Hetland ML. Does clinical remission lead to normalization of EQ-5D in patients with rheumatoid arthritis and is selection of remission criteria important? J Rheumatol. 2010; 37(2):285–90. [PubMed: 20080905]

51. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology (Oxford). 2010; 49(4):683–90. [PubMed: 20047979]

52. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum. 1994; 37(4):470–5. [PubMed: 8147923]

53. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995; 38(1):38–43. [PubMed: 7818569]

54. Vita AJ, Terry RB, Hubert HB, Fries JF. Aging, health risks, and cumulative disability. N Engl J Med. 1998; 338(15):1035–41. [PubMed: 9535669]

55. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. Ann Rheum Dis. 2008; 67(2):238–43. [PubMed: 17644550]

56. Dawes PT, Fowler PD, Clarke S, Fisher J, Lawton A, Shadforth MF. Rheumatoid arthritis: treatment which controls the C-reactive protein and erythrocyte sedimentation rate reduces radiological progression. Br J Rheumatol. 1986; 25:44–9. [PubMed: 3942847]

57. van Leeuwen MA, Van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Rheumatol. 1994; 21(3):425–9. [PubMed: 7516430]

58. Van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. Prognostic factors for radiographic damage and physical disability in early rheumatoid

arthritis. A prospective follow-up study of 147 patients. Br J Rheumatol. 1992; 31(8):519–25. [PubMed: 1386548]

59. Pincus T, Yazici Y, Bergman M, Maclean R, Harrington T. A proposed continuous quality improvement approach to assessment and management of patients with rheumatoid arthritis without formal joint counts, based on quantitative routine assessment of patient index data (RAPID) scores on a multidimensional health assessment questionnaire (MDHAQ). Best Pract Res Clin Rheumatol. 2007; 21(4):789–804. [PubMed: 17678835]
60. Pincus T, Amara I, Segurado O, Koch G. An index based on only patient reported outcome (PRO) measures, routine assessment of patient index data (RAPID3), distinguishes adalimumab from control at levels similar to disease activity score (DAS28) and clinical disease activity index (CDAI). Ann Rheum Dis. 2007; 66:184. [PubMed: 16760255]
61. Kirwan JR, Hewlett S. Patient perspective: reasons and methods for measuring fatigue in rheumatoid arthritis. J Rheumatol. 2007; 34(5):1171–3. [PubMed: 17477481]
62. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006; 54(12):3761–73. [PubMed: 17133543]
63. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008; 58(10):2958–67. [PubMed: 18821687]
64. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. J Rheumatol. 1997; 24(8):1477–85. [PubMed: 9263138]

Table 1

Threshold levels of the core set measures for remission according to the survey of committee members.*

	Highest level of the core set measure that would be compatible with remission:									
	If it were the only measure assessed					If all other measures pointed to remission				
Core set measure†	**mean (SD)**	**min**	**med**	**80%**	**max**	**mean (SD)**	**min**	**med**	**80%**	**max**
TJC28	1.1 (1.3)	0	1	2	6	2.6 (2.0)	1	2	4	10
Full TJC (68 joints)	1.6 (1.5)	0	2	2	6	2.6 (2.0)	1	2	4	10
SJC28	0.5 (0.9)	0	0	1	4	1.3 (1.3)	0	1	2	6
Full SJC (66 joints)	0.6 (0.9)	0	0	1	4	1.4 (1.2)	0	1	2	6
ESR (mm/h)	21 (6)	10	20	25	30	25 (6)	20	25	30	40
CRP (mg/dL)	0.9 (0.4)	0	1	1	2	1.1 (0.6)	0	1	1.5	2
Pain (0-10 scale)	1.3 (0.7)	0	1	2	3	2.4 (1.3)	1	2	3	6
PhGA (0-10 scale)	1.0 (0.9)	0	1	1	4	1.6 (1.0)	0	2	2	4
PtGA (0-10 scale)	1.2 (0.8)	0	1	2	3	2.2 (1.3)	0	2	3	6
HAQ (0-3 scale)	0.7 (0.7)	0	0.5	0.5	3	0.9 (0.8)	0.2	0.6	1	3

*27 committee members responded to the survey: 25 experienced RA clinical researchers and two patients. The columns following the mean report minimum, median, 80th percentile and maximum.

†TJC, tender joint count, SJC, swollen joint count (For example, TJC28 means tender joint count of 28 joints). ESR, Erythrocyte sedimentation rate. CRP, C-reactive protein. PhGA, physician/observer global assessment. PtGA, patient global assessment. HAQ, Health Assessment Questionnaire.

Table 2A

Predictive validity of candidate remission definitions for a good outcome in x-ray damage.*

Candidate remission definition	Prevalence of good outcome in patients: *in* remission	*not in* remission	Positive likelihood ratio (95% CI)	P-value†
TJC28, SJC28, CRP ≤ 1	69% (34/49)	50% (154/306)	2.0 (1.1, 3.6)	0.01
TJC28, SJC28, CRP, PhGA ≤1	76% (26/34)	51% (162/320)	2.9 (1.3, 6.2)	0.004
TJC28, SJC28, CRP, PtGA ≤1	77% (23/30)	51% (165/325)	2.9 (1.3, 6.6)	0.006
TJC28, SJC28, CRP, Pain ≤1	74% (23/31)	51% (165/324)	2.6 (1.2, 5.6)	0.01
TJC28, SJC28, CRP, PhGA, PtGA ≤	77% (20/26)	51% (168/328)	2.9 (1.2, 7.2)	0.01
TJC28, SJC28, CRP, PhGA, Pain ≤1	77% (20/26)	51% (168/328)	2.9 (1.2, 7.2)	0.01
TJC28, SJC28, CRP, PtGA, Pain ≤1	76% (22/29)	51% (166/326)	2.8 (1.2, 6.4)	0.001
TJC28, SJC28, CRP, PhGA, PtGA, Pain ≤1	76% (19/25)	51% (169/329)	2.8 (1.1, 6.8)	0.02
DAS28<2.6	60% (21/35)	59% (93/157)	1.0 (0.6, 1.9)	0.93
DAS28<2.0	70% (7/10)	59% (107/182)	1.6 (0.4, 6.0)	0.48
SDAI≤3.3§	77% (27/35)	50% (161/319)	3.0 (1.4, 6.4)	0.003
Definitions without CRP (for clinical practice)				
TJC28, SJC28, PhGA, PtGA ≤ 1	75% (24/32)	51% (167/326)	2.6 (1.2, 5.7)	0.01
TJC28, SJC28, PtGA ≤ 1	75% (27/36)	51% (164/323)	2.6 (1.3, 5.4)	0.007
CDAI≤2.8**	75% (27/36)	51% (164/322)	2.6 (1.3, 5.4)	0.006

* Presence or absence of remission measured at 6 months after baseline.

Good X-ray outcome defined as change ≤ 0 in Sharp-van der Heijde scores between 12 and 24 months after baseline.

Based on combined data from methotrexate alone groups from 3 trials (34, 37, 38), limited to patients with complete data over 2 years.

Abbreviations as defined in Table 1.

† P value from Chi-square from logistic regression analysis in which independent variable is remission (based on candidate tested) and dependent is x-ray stability.

§ SDAI, Simplified Disease Activity Index the simple sum of the tender joint count (28), swollen joint count (28), patient global assessment (on a 0-10 scale), physician global assessment (on a 0-10 scale) and CRP (mg/dL).

** CDAI, Clinical Disease Activity Index, same as SDAI but without CRP.

¥ Remission and not in remission were defined according to the candidate remission definition in that row.

Table 2B

Predictive validity of candidate remission definitions for a good outcome in both x-ray and health assessment questionnaire.*

Candidate remission definition	Prevalence of good outcome in patients: *in* remission	*not in* remission	Positive likelihood ratio (95% CI)	P-value†
TJC28, SJC28, CRP ≤ 1	46% (22/48)	17% (51/301)	3.2 (1.9, 5.3)	<.0001
TJC28, SJC28, CRP, PhGA ≤1	55% (18/33)	17% (55/315)	4.5 (2.4, 8.5)	<.0001
TJC28, SJC28, CRP, PtGA ≤1	66% (19/29)	17% (54/320)	7.2 (3.5, 14.8)	<.0001
TJC28, SJC28, CRP, Pain ≤1	60% (18/30)	17% (55/319)	5.7 (2.9, 11.2)	<.0001
TJC28, SJC28, CRP, PhGA, PtGA ≤	68% (17/25)	17% (56/323)	8.0 (3.6, 17.8)	<.0001
TJC28, SJC28, CRP, PhGA, Pain ≤1	64% (16/25)	18% (57/323)	6.7 (3.1, 14.5)	<.0001
TJC28, SJC28, CRP, PtGA, Pain ≤1	64% (18/28)	17% (55/321)	6.8 (3.3, 14.1)	<.0001
TJC28, SJC28, CRP, PhGA, PtGA, Pain ≤1	67% (16/24)	18% (57/324)	7.5 (3.4, 16.9)	<.0001
DAS28<2.6	38% (13/34)	18% (28/154)	2.2 (1.2, 4.0)	0.01
DAS28<2.0	56% (5/9)	20% (36/179)	4.5 (1.3, 15.9)	0.01
SDAI≤3.3	56% (19/34)	17% (54/314)	4.8 (2.6, 8.9)	<.0001
Definitions without CRP (for clinical practice)				
TJC28, SJC28, PhGA, PtGA ≤ 1	68% (21/31)	17% (53/321)	7.9 (3.9,16.0)	<.0001
TJC28, SJC28, PtGA ≤ 1	66% (23/35)	16% (51/318)	7.2 (3.8,13.9)	<.0001
CDAI≤2.8	63% (22/35)	16% (52/317)	6.36 (3.4,12.0)	<.0001

*Presence or absence of remission measured at 6 months after baseline.

Simultaneous good outcome in both:

- X-ray: defined as change ≤ 0 in Sharp-van der Heijde scores between 12 and 24 months after baseline.
- Health Assessment Questionnaire (HAQ): defined as change ≤ 0 and HAQ ≤ 0.5 at both the 12 and 24 month time points.

Based on combined data from methotrexate alone groups from 3 trials (34, 37, 38), limited to patients with complete data over 2 years.

Abbreviations as defined in Tables 1 and 3A.

†P value from Chi-square from logistic regression analysis in which the independent variable is remission (based on candidate tested) and the dependent variable is x-ray stability.

¥Remission and not in remission were defined according to the candidate remission definition in that row.

Table 3

Face validity. Upper limits of residual disease activity in the core set measures for candidate definitions of remission observed in trial datasets using all trial arms (methotrexate monotherapy, TNF-inhibitor monotherapy and combination therapy of TNF inhibitors plus methotrexate).*

Candidate remission definition	TJC28		SJC28		CRP		PhGA		PtGA		Pain	
	90%	max*	90%	max	90%	max	90%	max	90%	max	90%	max
TJC28, SJC28, CRP ≤1	1	1	1	1	0.6	1	2	6	4	8	4	8
TJC28, SJC28, CRP, PhGA ≤1	1	1	1	1	0.6	1	1	1	2	7	2	8
TJC28, SJC28, CRP, PtGA ≤1	1	1	1	1	0.6	1	2	2	1	1	2	3
TJC28, SJC28, CRP, Pain ≤1	1	1	1	1	0.6	1	2	4	2	6	1	1
TJC28, SJC28, CRP, PhGA, PtGA ≤1	1	1	1	1	0.7	1	1	1	1	1	1	3
TJC28, SJC28, CRP, PhGA, Pain ≤1	1	1	1	1	0.7	1	1	1	1	5	1	1
TJC28, SJC28, CRP, PtGA, Pain ≤1	1	1	1	1	0.7	1	1	2	1	1	1	1
TJC28, SJC28, CRP, PhGA, PtGA, Pain ≤1	1	1	1	1	0.7	1	1	1	1	1	1	1
DAS28<2.6	2	7	4	21	0.7	2.5	2	5	3	8	2	10
DAS28<2.0	0	3	2	6	0.7	2.5	2	3	2	4	2	4
SDAI≤3.3	1	2	1	2	0.7	2.7	2	2	1	2	1	3

*90%: 90th percentile; max, maximum observed value.

Abbreviations as defined in Tables 1 and 2A.

Table 4

Face Validity. Prevalence of remission (%) in recent trials of patients with rheumatoid arthritis.*

Remission definition	DMARD monotherapy (n=380)	Biological monotherapy (n=520)	Combination Therapy (n=330)	Total (n=1230)
TJC,SJC,CRP,PtGA	9	7	22	12
TJC,SJC,CRP,PtGA,pain	8	6	20	12
TJC,SJC,CRP,PhGA,PtGA	8	7	20	10
TJC,SJC,CRP,PhGA,pain	8	6	20	10
TJC,SJC,CRP,PhGA,PtGA,pain	7	6	18	9
DAS28 <2.6	19	17	35	21
DAS28<2.0	5	8	24	10
SDAI ≤ 3.3	10	8	26	14

*Abbreviations as defined in Tables 1 and 3A.

Pooled data from ERA, PREMIER and TEMPO trials.[34,37,38]

Table 5

ACR/EULAR definitions of remission in rheumatoid arthritis clinical trials.*

Boolean Based Definition:
At any time point, patient must satisfy all of the following:
Tender Joint Count ≤1†
Swollen Joint Count ≤1†
CRP ≤1 mg/dL
Patient Global Assessment ≤1 (on a 0-10 scale)§
Index Based Definition
At any time point, patient must have SDAI ≤3.3**

*For recommendations regarding remission in clinical practice settings, see Tables 2 A, B and text of the results and discussion sections.

†For tender and swollen joint counts, a 28 joint count may miss active joints especially in the feet and ankles and it is preferable to include feet and ankles also when evaluating remission.

§The following wording and response categories should be used for global assessment: Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today? Verbal anchors for the response can range from ‘asymptomatic’ to ‘severe symptoms’.

**SDAI, Simplified Disease Activity Index is defined as the simple sum of the tender joint count (28), swollen joint count (28), patient global assessment (on a 0-10 scale), physician global assessment (on a 0-10 scale) and CRP (mg/dL).