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Defining Remission in Rheumatoid Arthritis: Results of an Initial ACR Consensus Conference

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Abstract

Due to advances in therapies for rheumatoid arthritis (RA) over the last years, an increasing proportion of patients are able to achieve a state of 'remission'. But what exactly is remission? At the moment, randomized controlled trials around the world use different remission definitions and consequently measure different aspects of a patient's disease state. For research findings to be correctly interpreted, the need for a uniform definition of remission is vital. The ACR constituted a committee to redefine remission in RA that included international clinical researchers, trialists and clinical epidemiologists. This group was asked to study current definitions of remission, explore the theoretical underpinning of the concept of 'remission', and develop a research agenda that would inform future work in the development of an ACR definition of remission.

In its first meeting, the committee preferred to develop a 'strict' definition, implying no or very low disease activity. Such a definition would need to be validated against long-term outcome e.g. physical function and damage. The committee decided to consider both a definition for trials and a modified version for clinical practice.

INTRODUCTION

The current ACR definition of clinical remission for rheumatoid arthritis (RA)(Preliminary ARA Criteria for Clinical Remission), was published in 1981 (Table 1) (1).

At the time of this development relatively few patients achieved remission, in part because there were few highly effective treatments for disease. Since this time, randomized controlled trials have focused on whether drugs could be shown to improve disease, prompting the development and widespread use of a single core set of endpoints for trials (WHO-ILAR core set) (2), and validated measures of disease improvement (ACR20, EULAR criteria). At the time of its development, showing a significant ACR20 improvement compared to placebo represented a significant advance in improving disease outcomes (3;4).

With the evolution of more effective treatments for RA, these improvement measures have been stretched. RA trials now routinely use ACR50, ACR70 and sometimes even ACR90 responses as secondary outcomes, and increasing numbers of trial subjects achieve these endpoints (5–7). Within the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative, the importance of achieving an acceptable state of low disease

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activity has resulted in a preliminary definition of what is termed ‘minimal disease activity’ (8). With emerging new treatment strategies, developments are rapid, and trials where remission is the primary outcome are becoming more and more prevalent (7;9–11).

However, there are problems with the current definitions of remission. While the ACR remission criteria might be used to characterize persons attaining remission, they are problematic, since they are so restrictive that few patients, even in current trials attain this state (12). Further, they include measures not in the core set (fatigue, morning stiffness; tendon sheath swelling) and others that are not always routinely assessed in trials (ESR). To account for some of these issues, modified ACR criteria (mACR) have been employed where fatigue is omitted and the presence of 4 of the remaining 5 items is required (13;14).

Amongst all disease activity scoring systems that are available today, the most commonly used measures for remission are based on the Disease Activity Score (DAS). A (full joint count) DAS < 1.6 correlates well with the ACR remission criteria (15), but it is the 28-joint count DAS (DAS28) that is currently most commonly used. A DAS28 with a cut-off point of 2.6 corresponded best to the fulfilment of the modified ACR criteria for clinical remission, which means that patients who meet the modified ACR remission criteria will meet the DAS28 cut-off (although because the DAS cut-off is less stringent, those who meet DAS cut-off will not necessarily meet modified ACR remission criteria) (13). However, a DAS < 1.6 may constitute a more stringent measure of remission than DAS28 < 2.6 (16). Indeed it has been reported that up to 20% of patients in DAS28 remission have 2 or more residual swollen joints, and the number of swollen joints can reach more than a dozen (17–20). These findings suggest that patients in DAS28 remission may actually be in a ‘minimal disease activity state’ rather than in a true remission (8). However, also in DAS remission there can be a considerable number of swollen joints (20). Further, in recent clinical trials DAS28 remission rates exceeded those of ACR70 response rates (7;9;21;22), meaning that more patients achieved a state of DAS28 remission than the proportion of patients reaching a 70% or higher decrease in tender and swollen joints.

Since neither the ACR remission criteria nor the full DAS definition is often used and the DAS28 may not be stringent enough to define true remission, there appears to be a need for an easy to use definition that is suitable as either a secondary or primary outcome in clinical trials. Given these concerns, the ACR constituted a committee joint by EULAR representation, to redefine remission in RA. This group met initially in November 2007, and consisted of an international group of rheumatoid arthritis (RA) clinical researchers, trialists and clinical epidemiologists. Their charge was to study current definitions of remission, explore the theoretical underpinning of the concept of ‘remission’, and develop a research agenda that would inform future work in the development of an ‘authorized’ ACR clinical trial definition. This document summarizes their considerations, conclusions and research agenda for the coming period and aims to give readers insight into the complexity of the process by raising many questions that have to be taken into account.

METHODS

Meeting Format

The format of the meeting is shown in Table 2. Three presentations were given by the committee chairpersons to clarify the issues involved. The whole group was then divided into three breakout groups, each charged with exploring a series of questions concerning remission: (1) conceptual issues, (2) measurement issues or (3) potential setting and uses (Table 2). Members of each group were encouraged to develop additional questions in their areas.

Presentations

Basic Concepts of Remission and Current Definitions (Maarten Boers)—Dr. Boers began the meeting by reminding the group of the "OMERACT filter", that requires that measures used should be truthful, discriminative, and feasible in their intended setting (23). He expanded on this core definition, suggesting that being truthful implied that the definition was free from bias and relevant, that discriminative implied that the definition could distinguish between states reliably and reproducibly at multiple time points and was sensitive to change, and that feasibility applied to time for implementation of the definition, cost of use, and ease of interpretability.

He then presented the concept that remission could be defined as absence of disease activity, but with the possibility that disease could return in time. In this way it was to be distinguished from a 'cure' or 'arrest' of the disease. In this concept, remission is a state, not a change or a transition between states. In his opinion, the concept of remission is independent of the time spent in the state, although time may be of use in defining a sustained state of remission. He asked the group to consider how one could be sure that RA disease activity was absent and suggested that the definition of remission could change depending on the setting (trial vs. clinic).

Turning to current definitions of remission, he reviewed Pinals' 1981 definition of remission (Table 1) and other definitions including:

1. DAS < 1.6 or DAS28 < 2.6. These are commonly used definitions (esp. the DAS28) and researchers in Nijmegen, The Netherlands have validated these against a less stringent version of preliminary ARA criteria for clinical remission (also called the mACR criteria defined as 4 out of 5 criteria from which fatigue was omitted and for a period of 3 months) (13).
2. The simplified disease activity index (SDAI) ≤ 3.3 and the clinical disease activity index (CDAI) ≤2.8. These two definitions use almost the same variables as the DAS28 (i.e. swollen and tender joint counts and the patient global assessment) but in addition they include physician global assessment which is not included in the DAS28, and CRP (in SDAI but not in CDAI) which is used in a modified DAS28 (otherwise ESR is used). For the SDAI and CDAI, these variables are summed into one total score (17). By virtue of their formula, in a state of remission 2 swollen or 2 tender joints, or 1 of each, cannot be exceeded.
3. The patient activity score (PAS) ≤ 1.25 and the routine assessment of patient index data version 3 (RAPID3) score ≤ 1. These are similar, patient-derived measures consisting of different weighted combinations of function, pain, and patient global assessment. They were not designed for trials, but rather are meant for clinical use (24).

Evaluation of these definitions in large cross-sectional studies (14;25;26) suggest that they can roughly be categorised as either 'strict' (ACR, CDAI/SDAI, PAS/RAPID3) or 'lax' (the mACR criteria and the DAS28 definition), with the latter being very similar to the OMERACT definition for minimal disease activity (MDA) (8); MDA is a different, though related concept than that of remission because by definition, everyone in remission will also be in MDA. During the OMERACT 6 and 7 meetings, participants agreed to a preliminary MDA definition: a decision node places all patients without tender and swollen joints and an ESR <10 in MDA; furthermore, patients with either a DAS28≤2.85 or meeting 5 out of 7 core set criteria were placed in MDA (27;28).

Besides the unfavourable situation that different proportions of patients are classified as MDA or remission depending on the definition that is used (29;30), there are also aspects of

feasibility and acceptability to patients and health professionals that should be taken into account (25;31); How much time/effort does it take to obtain a complete measure of remission? What is an acceptable burden for patients in obtaining a measure of remission?

Issue of Validity in Defining Remission in RA (David Felson)—Dr. Felson suggested that a definition or measurement should have 'content validity'; i.e. it should represent all facets of a concept. With content validity in mind, he challenged the group to consider what elements would be required for a definition of remission by presenting the following questions:

1. Is a definition based on a 28 joint count (such as the DAS28 and SDAI/CDAI) sufficient to define remission? Would this be acceptable if joints in the feet (not assessed in the 28 joint count) were active?
2. Should a definition use only measures from the ACR core set (tender and swollen joint counts, patient and physician global assessment, function, pain, and ESR/CRP), or would additional measurements (e.g. fatigue) be needed?
3. What role does morning stiffness and or/ fatigue play in defining remission?
4. What role does imaging play? Should 'remission' imply a lack of radiographic or MRI progression over time? What if measures of 'clinical' and 'radiographic' remission do not agree in a single subject?
5. How should changes due to chronic disease be incorporated (or not incorporated) into a remission definition?
6. Does time play a role in a definition of remission?
    a. Should remission at one time predict remission at all future times?
    b. What if a patient is in 'remission' at one clinic visit but not the following one? Has that subject achieved remission?
7. Should remission have predictive validity? That is, should it predict outcomes such as joint damage, disability, and death?

Issues of Discrimination in Definitions of Remission in RA (George Wells)—Discrimination implies that a measurement is able to distinguish between different states that are of interest at a certain time point and on different time points, in a reliable, reproducibly and sensitive way. Using actual data from a group of randomized controlled trials, Dr Wells conducted preliminary studies to determine how current definitions of remission discriminate between placebo and active treatment (either DMARD's or biologic agents) in trials. A number of definitions did this well, including the DAS, physician global, and PAS II. Also of note, remission rates varied markedly depending on the remission definition, with the DAS28 and PAS II giving the highest rates of remission and the SDAI, CDAI and ACR criteria giving the lowest.

These factors will be important for the issue of feasibility. The sample size necessary in a trial depends on the discriminative ability of a measure. At a given level of alpha (probability of a type I error) and beta (probability of a type II error) the better the discrimination of a measure then the smaller the number of subjects needed to show a significant difference between control and active medication.

RESULTS FROM BREAKOUT GROUPS

The following results (Table 3) are based on the feedback from the three breakout groups and the subsequent plenary session.

Topic 1: Conceptual issues related to the definition of remission

Should remission be defined as an absence of disease activity or as minimal disease activity?—There was unanimous agreement on the need for a strict definition of remission with stringent criteria (to differentiate remission from low disease activity). These criteria should include: (1) no clinical disease (although the participants acknowledged that an absence of disease activity and of / pain may not always be possible); and (2) lack of progression over time. It would be wise to create a separate remission definition with a similar structure as used for the minimal disease activity definition. The group also felt it was important to continue to work separately on the validation of a minimal disease activity definition in relation to the new remission definition.

Should long term outcomes be included?—It was felt that the definition of remission should be independent of long term outcomes such as radiographic damage, but that the validity of the definition should be tested using x-ray/ultrasonography/MRI damage indices and HAQ function. Those in remission should have no/reduced progression of joint damage and should have less deterioration or more improvement in functional status (using HAQ) over time (remission definition should have predictive validity). However, the definition of remission should be based largely on clinical and biochemical parameters at this stage, and not include definitions that require imaging. It was felt that at present there is not enough data on the use of imaging such as ultrasonography and MRI in this field to formulate a precise imaging based definition of remission but that this is an important area for future research.

Should treatment be part of the definition?—All agreed that therapy should not be a part of the definition of remission.

Other conceptual issues—One question concerned the best cut-off points for each current definition that predicts lack of damage progression. Can we explore existing data to find the best cut-off points?

Topic 2: Measurement issues

What variables should be included?—The three most important variables were felt to be: (1) tender joint count, (2) swollen joint count and (3) an acute phase reactant. For all other possible variables it was felt that more data are needed; first with a focus on pain (for example, how should one deal with non-RA pain?), and then focusing on fatigue, physician global assessment (utility of continuous vs dichotomous scale), patient global assessment, sleep, and the HAQ.

Should we use limited joint counts or full joint counts?—It was felt that while a 28 joint count may be sufficient to assess disease activity, more joints should be included if a stringent remission definition is desirable. Further data were felt to be needed about how many patients in a DAS28 remission state still have activity in non DAS28 joints. Based on these data, it should then be decided whether this is an important issue (in trials the issue may be less important than in clinical practice). With current knowledge, most attendants felt that a 28-joint count was not sufficient for the purpose of developing a stringent definition of remission.

Should duration of state be incorporated?—The group felt that sustained remission was a critical outcome but that time was not necessarily a part of the trial definition of remission (although it might be a secondary outcome). Some felt that it would be valuable to ask patients about their perception of the importance of 'time in remission'. The patient-attendee stressed the importance of time for her in the definition of remission: she saw it as a permanent state, from which there should be no recurrence of disease, especially not within a limited time. The relevance of time was also discussed in the light of damage progression: Can we calculate what period of time in remission is needed so as not to see any future damage progression?

Should we focus on particular remission definitions currently proposed or variations on them?—No conclusion was reached on this topic. There is a need to collect prospective data including a wide range of variables to make sure we are not locked into previous decisions about what variables to include.

Topic 3: Potential setting and uses

Do we also need to define remission for practice settings?—All participants agreed that there should also be a remission definition for clinical practice. Trials differ from clinical practice in aspects such as restricted time, measures that lead to additional health care cost, patient characteristics that differ from those in clinical trials, and physicians' needs. These differences may result in different definitions of remission in trial versus practice settings. A patient based measure could be developed for this environment.

Should trial and practice based definitions be related?—The trial definition should be closely linked with the practice definition, taking into account clinical trials' need for accuracy, and the need for feasibility and cost in clinical practice. A trial definition should maximize the efficiency of the trial while a modified or lower efficiency version might be used in clinical practice.

Should remission be used as a primary or secondary outcome in trials?—The needs of a trial should determine whether remission is the primary or a secondary outcome in a study.

What other not yet validated measures of disease activity should be considered for inclusion in future definitions of remission?—No conclusion was reached.

DISCUSSION/CONCLUSION

The first ACR remission workshop concluded that a new remission definition should be strict, based on no or very low disease activity and should be validated against long-term outcome, specifically physical function and radiographic progression. Treatment should not be part of the remission definition, nor should long term absence of disease activity, although the latter could be used for validation purposes. The definition should at least include the tender and swollen joint counts, probably include non-DAS28 joints, and an acute phase reactant. Besides an efficient trial remission definition, there is also a need for a modified version for use in clinical practice.

Similar work has been done by experts in the field of Juvenile Inflammatory Arthritis (JIA), who using consensus approaches, formulated preliminary remission definitions in JIA. Similarities between the JIA definition and the RA definition are the need for stringency: the JIA criteria for a patient to qualify for inactive disease are: no joints with active arthritis; no

fever, rash, serositis, spenomegaly, or generalized lymphadenopathy attributable to JIA; normal ESR or CRP; and physician's global assessment of 0. Important differences with the RA definition of remission are the incorporation of drug use and duration in JIA: in JIA, a patient is in remission if criteria for inactive disease are met for 6 continuous months for a patient on medication, and for 12 continuous months off medication. Unlike JIA, the construction of the RA remission definition started with expert consensus on the main elements of a new definition, but will be guided by analysis of data from clinical trials (32).

This initial workshop has raised many important research questions that will be addressed by a research agenda and subsequent meetings of the committee to evaluate findings from the data analysis that is part of the research agenda. ACR and EULAR have decided to sponsor this initiative as an official ACR-EULAR collaboration.

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REFERENCES

1. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum. 1981; 24(10):1308–1315. [PubMed: 7306232]
2. 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 Suppl. 1994; 41:86–89. [PubMed: 7799394]
3. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995; 38(6):727–735. [PubMed: 7779114]
4. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. J Rheumatol. 1999; 26(3):705–711. [PubMed: 10090187]
5. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van VR, 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(1):26–37. [PubMed: 16385520]
6. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008; 47(4): 495–499. [PubMed: 18316338]
7. van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA, et al. Tight control and intensified COBRA combination therapy in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis. 2008
8. Wells GA, 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(10):2016–2024. [PubMed: 16206362]
9. 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):375–382. [PubMed: 18635256]
10. Makinen H, Hannonen P, Sokka T. Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. Clin Exp Rheumatol. 2006; 24(6 Suppl 43):S-8.

11. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä 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):1568–1573. [PubMed: 10334255]
12. Sokka T, Makinen H, Hannonen P, Pincus T. Most people over age 50 in the general population do not meet ACR remission criteria or OMERACT minimal disease activity criteria for rheumatoid arthritis. Rheumatology (Oxford). 2007; 46(6):1020–1023. [PubMed: 17405761]
13. 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):1252–1255. [PubMed: 15238643]
14. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology (Oxford). 2007; 46(6):975–979. [PubMed: 17341506]
15. Prevoo ML, van Gestel AM, van 't Hof M, 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):1101–1105. [PubMed: 8948296]
16. Landewé R, van der HD, van der LS, Boers 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):637–641. [PubMed: 16219709]
17. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum. 2005; 52(9): 2625–2636. [PubMed: 16142705]
18. 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]
19. Makinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis. 2005; 64(10):1410–1413. [PubMed: 15941836]
20. 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(11):1582–1587. [PubMed: 15860509]
21. 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-TNF biologics: results from a 24-week multicentre Randomised Placebo Controlled Trial. Ann Rheum Dis. 2008
22. 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(9617):987–997. [PubMed: 18358926]
23. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol. 1998; 25(2):198–199. [PubMed: 9489805]
24. Pincus T, Amara I, Segurado OG, Bergman M, Koch GG. Relative efficiencies of physician/assessor global estimates and patient questionnaire measures are similar to or greater than joint counts to distinguish adalimumab from control treatments in rheumatoid arthritis clinical trials. J Rheumatol. 2008; 35(2):201–205. [PubMed: 18050378]
25. Shaver TS, Anderson JD, Weidensaul DN, Shahouri SS, Busch RE, Mikuls TR, et al. The problem of rheumatoid arthritis disease activity and remission in clinical practice. J Rheumatol. 2008; 35(6):1015–1022. [PubMed: 18412311]
26. 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):2642–2651. [PubMed: 18759292]
27. Wells G, Boers M, Shea B, Anderson J, Felson D, Johnson K, et al. MCID/Low Disease Activity State Workshop: low disease activity state in rheumatoid arthritis. J Rheumatol. 2003; 30(5):1110–1111. [PubMed: 12734918]

28. Wells G, Anderson J, Boers M, Felson D, Heiberg T, Hewlett S, et al. MCID/Low Disease Activity State Workshop: summary, recommendations, and research agenda. J Rheumatol. 2003; 30(5): 1115–1118. [PubMed: 12734920]

29. 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):440–447. [PubMed: 17394230]

30. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006; 54(4):1063–1074. [PubMed: 16572441]

31. Yazici Y, Bergman M, Pincus T. Time to score quantitative rheumatoid arthritis measures: 28-Joint Count, Disease Activity Score, Health Assessment Questionnaire (HAQ), Multidimensional HAQ (MDHAQ), and Routine Assessment of Patient Index Data (RAPID) scores. J Rheumatol. 2008; 35(4):603–609. [PubMed: 18322993]

32. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol. 2004; 31(11):2290–2294. [PubMed: 15517647]

APPENDIX

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Table 1

ACR Preliminary Criteria for Remission of Rheumatoid Arthritis

A minimum of five of the following for at least 2 consecutive months:
1. Morning stiffness not to exceed 15 minutes
2. No fatigue
3. No joint pain
4. No joint tenderness or pain on motion
5. No soft tissue swelling in joints or tendon sheaths
6. ESR (Westergren method) less than 30mm/h (females) or 20mm/hr (males)

Exclusions prohibiting a designation for complete clinic remission: clinical manifestations of vasculitis, pericarditis, pleuritis, myositis, unexplained recent weight loss or fever secondary to RA

Table 2

Structure of the ACR remission Workshop

Session type	Content
Presentations	- Basic Concepts of Remission and Current Definitions (Maarten Boers) - Issue of Validity in Defining Remission (David Felson) - Issues of Discrimination in Definitions of Remission (George Wells)
Breakout groups	1. Conceptual issues - *Should remission be defined as an absence of disease activity or as minimal disease activity?* - *Should long term outcomes be included?* - *Should remission be defined only as remission off anti-rheumatic treatment or regardless of anti-rheumatic treatment?* 2. Measurement issues - *What variables should be included?* - *Should we use limited joint counts or only full joint counts?* - *Should duration of state be incorporated?* - *Should we focus on particular remission definitions currently proposed or variations on them?* 3. Potential setting and uses - *Do we also need to define remission for practice settings?* - *Should trial and practice based definitions be related?* - *Should remission be used as a primary or secondary outcome in trials?* - *What other not yet validated measures of disease activity should be considered for inclusion in future definitions of remission?*
Presentations of results and discussion	
Plenary	Summary Overview of research agenda

Table 3

ACR remission committee research agenda

Research agenda
Conceptual issues
- Assessment of reliability/reproducibility of the remission definition: consistency of remission over visits in a trial on constant treatment (or for a patient in remission at one visit some assurance that their adjacent visits show very low disease activity at most).
- Predictive validity of candidate definition against X-rays and physical function.
- Relationship between remission and MDA and longer term outcome (function, disability)
- The role of imaging (ultrasonography and MRI) in the definition, measurement, assessment and monitoring of the remission state
Measurement issues
- What disease activity measures should be included? Consider data sets where there is an independent measure of remission to test the relation of remission to disease activity measures.
- What is the exact question in physician and patient globals?
- What about reliability: between physician variability?
- Do we need 28 joints or more? Review of literature on the likelihood of joint activity when 28 joints are 0. And when 28 joint count is zero, how many other joints are active?
- Should we give priority to specific joints?
- Should we ask patients if they feel they are in remission?
- Duration of remission: for patients in remission at one time point, are they likely to be in remission at adjacent time points? If not, is their disease very inactive at adjacent time points? If adjacent time points show very low disease activity, then remission at one time is valid and remission probably does not need to be defined at more than one time point.
- Role of imaging (ultrasonography and MRI)
Potential setting and uses
- Are there equivalent measures, easier to use in practice, which give the same information?
- Could we reduce the number of measures for the practical setting, but still resemble the same remission criterion?