

Patient Perspective on Remission in Rheumatoid Arthritis

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ABSTRACT. Absence of disease activity, or remission, is the most important treatment goal for patients with rheumatoid arthritis (RA). Since a new preliminary definition of remission in RA for clinical trials has been proposed, we investigated what determinants of disease activity patients associate with a state of remission and whether dimensions of impact of disease on daily life are involved. Our report summarizes progress of a workshop at OMERACT 10 on the patient perspective on remission in RA, including the results of a short pre-conference survey among patients, the discussions among the participants and a research agenda resulting from these discussions. This initial OMERACT workshop on remission from the patient perspective showed that there is a great interest among patients, physicians, and researchers to study the concept of remission, taking into account measures that patients indicate as important, but that there is a lack of data on appropriate measures, resulting in a considerable research agenda. *J Rheumatol* 2011;38:1735–8; doi:10.3899/jrheum.110394

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REMISSION

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As treatment efficacy improves, patients with rheumatoid arthritis (RA) increasingly reach a state of remission. Remission is defined in various ways and the proportion of patients classified as in remission varies substantially between definitions. The more stringent definitions are rarely met, whereas the less stringent definitions resemble a state of minimal disease activity. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) together with the initiative for Outcome Measures in Rheumatology Clinical Trials (OMERACT) jointly constituted a committee to redefine remission in RA¹.

This committee was tasked to develop a strict definition of remission at a minimum, including tender and swollen joint count and an acute-phase reactant. Following the framework of the OMERACT Filter, which requires all measures to be truthful, discriminative, and feasible in their intended setting, 50 candidate definitions were evaluated based on the RA core set and tested for their ability to select patients in the datasets that would not show damage progression and would maintain a good physical function. In addition, remission definitions were tested for their likelihood to show residual disease activity in any of the measures not included in the definition. This resulted in 2 definitions of remission: (1) When a patient's scores on the following measures are all ≤ 1 : tender joint count, swollen

joint count, C-reactive protein (mg/dl), and patient global assessment (PtGA, 0–10 scale); OR (2) When a patient's score on the Simplified Disease Activity Index is $\leq 3.3^{1a}$.

These new definitions of remission focus on core set measures and are derived mostly from clinical trial data. While these data had information on patient pain, functional status, and the patient's overall assessment of disease activity, some patient measures, such as fatigue or sleep, were unavailable in these trial data sets and therefore could not be evaluated for potential inclusion. Although patient research partners were present at the committee meetings, the development of the definition of remission may not have been sufficiently informed by patients.

From the literature we know that the physician perspective on disease and the patient perspective on disease are often rather different^{2,3,4}. Differences between assessments of physician global and patient global are well known^{5,6,7}. The rheumatologist might observe a large improvement in joint count and erythrocyte sedimentation rate, whereas the patient fails to experience improvement in pain or global well-being. The importance of the patient's perspective is increasingly recognized, as can be seen in the success of the patient perspective program in the OMERACT initiative. As an example, the OMERACT community has accepted that fatigue is a relevant and important symptom in RA and should be measured in all trials^{8,9}.

It is currently unknown what determinants of disease activity patients associate with a state of remission and whether other dimensions of impact of disease on daily living are involved or deemed more important than disease activity measures. Meanwhile, a new tool to measure "RA patient's impact of disease" has been developed, the Rheumatoid

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Arthritis Impact of Disease (RAID) instrument¹⁰. In this development, domains of impact of disease have been researched extensively, and patients have given weights to mark the importance of the different domains.

The purpose of our remission workshop at OMERACT 10 was to investigate the interest and ideas among OMERACT participants in a research agenda on the patient perspective on remission.

METHODS

Survey. One month before OMERACT 10 we circulated a survey among 87 patients to get a general idea of the patient perspective on remission, and to investigate the patient perspective on the distinction between disease activity and impact of disease. Patients were contacted using 3 networks: the OMERACT patient network (n = 32), the RAID network (n = 5), and the Dutch patient research partner network (n = 50). Patients within the international networks of OMERACT and RAID received a survey in English; the Dutch research partners received a Dutch version. All surveys were sent by E-mail. The survey included an introduction to the topic, and an explanation on the difference between impact of disease and disease activity, and consisted of 5 questions — 4 questions using a 5-point Likert scale and one open-ended question (Table 1). Answers to the closed questions were summarized by means, medians, and range. Answers to the open-ended question were grouped into topics and summarized as such (Table 2).

Program at OMERACT 10. Pre-reading material consisted of a summary of the development of the new trial definition of remission¹¹. The plenary ses-

sion of the workshop started with a brief presentation on the development of the new trial definition of remission (J. Smolen), followed by a presentation on evidence for the value of patient-reported outcomes (PRO; G. Wells), and a presentation on development and domains of RAID (M. Scholte-Voshaar), and concluded with a presentation on results of the survey among patients, as reported here (L. van Tuyt). After the plenary session, participants convened in 8 discussion groups of about 20 participants, including 2 or more patients, of which at least one had RA.

For each discussion group a session leader (senior researcher) and reporter (RA patient) were appointed. All 8 groups discussed the same questions:

1. Is there anything missing in the current trial definition of remission from the patients' perspective? Think in terms of disease activity (PRO), impact of disease on daily life, or "other."
2. Depending on the discussion regarding question 1, what would be a good way to gain information on the parts that are missing? Think of developing a cutoff point for remission within RAID, a bottom-up approach investigating domains that reflect remission to patients, validating the current trial definition using PRO, etc.
3. Discuss how to get there and prioritize what needs to be done.

It was made clear that the form and content of the "new" ACR/EULAR definition was not for discussion at this time, that the concept of remission underlying this definition is "absence of disease, with the possibility of its return" (or: remission is *NOT* equal to cure), and that the currently recommended formulation of the PtGA question is as follows: "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?"

A summary of the discussion in the groups was given by the reporters dur-

Table 1. Survey results, response to the closed questions.

Question	Mean	SD	Median	IQR
Anchors: 1 = not important at all, 5 = very important				
1. Do you think it is important that we develop a definition of remission based on the experience of patients with the impact of the disease, alongside the clinical definition of remission used by rheumatologists?	4.0	1.1	4.0	1
2. Do you think it is important that a patient definition of remission measures "disease activity"?	3.7	1.0	4.0	1
3. Do you think it is important that a patient definition of remission measures "impact of the disease on daily life"?	4.0	1.2	4.0	1
Anchors: 1 = disease activity most important, 5 = impact on daily life most important				
4. Which component (disease activity or impact on daily life) is most important to you?	3.5	1.3	4.0	2

IQR: interquartile range.

Table 2. Survey results, response to the open-ended question.

5. How did remission feel? Or: How do you think it should feel?

"Remission has been experienced when pain and fatigue have been minimal and blood results have shown no active disease. Pain is a constant during remission, due to the damage caused by the disease when it was active. This is quite different to the pain of active disease. Mainly because the pain of active disease is always combined with debilitating fatigue that causes a psychological strain that has consequences through all daily life activities and that of your families."

"Taking into consideration any damage to joints, functional ability and cognitive ability would return to "my" normal before RA. Fatigue would improve because disease is no longer active and because I wouldn't be working so hard to retain information, read, perform ADL, etc. However, with drug induced remission, fatigue from certain meds may happen and would be totally acceptable to me. Joint damage would cease. No swollen joints. Assessing these 2 areas is more important to me than ESR. ESR does not accurately reflect my disease activity and my response to treatment."

"For years now, there is a big difference between the "objective data" of my rheumatologist and how I experience the disease. That made me insecure in the beginning. I am still curious to hear the data from my rheumatologist (on blood results, x-rays, etc.), but when we discuss my meds I trust my own "subjective experience" more."

"I think remission should be absence of pain and fatigue for a period of at least 6 months."

ADL: activities of daily living.

ing the final plenary session, followed by a voting on the questions presented in Table 3.

RESULTS

Survey. Of 87 patients, 47 (54%) returned the survey. Twenty-nine respondents were Dutch, 38 had RA, and 35 had ever experienced a state of remission. Questions and answers to the closed questions of the survey are displayed in Table 1, which shows that in general, patients felt that impact of the disease on daily life was important, perhaps even more important than disease activity (question 4, see Table 1).

Responses to the open-ended question, "How does remission feel?" (Table 2) were diverse and included (but were not limited to) less pain; more energy/more active/more fit; less fatigue; no inflammation; move without restriction/liberating; better night rest; better mood. Patients did not uniformly agree if the feeling of pain due to damage should be allowed while in remission, and if the use and side effects of medication could/should be present while in remission. Additionally, duration of state was deemed important.

Discussion groups. Discussions were lively and, despite the same discussion topics for each group, the ideas and suggestions were diverse. However, when discussing whether the new remission definition was missing anything, a large majority of participants felt that the wording and anchoring of the PtGA needed to be further investigated. Despite its widespread use (in different formulations and using different anchors!) little is known about the domains or concepts that are measured by the PtGA; in addition, it is unknown how patients interpret the scale or to what extent they incorporate their current status of fatigue, pain, or even disease-unrelated matters when ticking a box on the scale. Discussion groups reported back that we need to get a better understanding of what the PtGA measures exactly, which domains are covered, and how patients interpret the question.

Similarly, it was felt that the RAID as a tool to measure

remission should be further investigated, to understand its domains and their respective weights in the context of remission. As the RAID is a very new tool, no prospective data are currently available on its performance in either active disease or absence of disease¹⁰. It was felt that RAID at a certain cut-point might play a role as an add-on to the current definition of remission or that the PtGA might be substituted by the RAID.

Many participants noted that the concept of remission is different for patients with early versus longstanding disease, is dependent on age and life circumstances, and is influenced by comorbid conditions. Participants wondered to what extent longterm damage to joints and disease duration would be incorporated in RAID and whether remission should be a sliding scale depending on age and disease duration. With regard to irreversible damage, it was suggested to include a measure of damaged joints in a remission definition. Some participants struggled with the word "remission," by nature implying "cure," and suggested using another term to avoid great expectations from inexperienced patients. Patients were worried about the implications of a remission definition for reimbursement of costly medication.

To evaluate the new remission definition from the patient perspective, it was suggested to undertake qualitative research asking patients for their perspective on remission, thus investigating the face validity of the current remission definitions for patients and/or defining remission from the patient perspective. In general it was felt that the new ACR/EULAR definition for remission in RA was acceptable for now, but that additional research on PRO should be put on the agenda, so that the definition can be reevaluated in about 5 years.

Final plenary session. A summary of the findings from the workshop, including the research agenda, was presented in the final plenary session. A total of 120 participants voted on the questions presented in Table 4. The large majority (> 90%) was in favor of investigating the PtGA scale, as well as a

Table 3. Research agenda.

Remission and expectations of reaching this state is different for patients that are newly diagnosed versus patients with longstanding disease, as it is for other demographic factors (age, sex, culture, etc.)
Consider splitting PtGA into a physical and emotional domain
Duration/sustainability of remission is very important to patients as well as to clinicians
How to distinguish between inflammatory vs mechanical pain?
Impact vs activity, the importance for the patient
Explore imaging/MRI as an additional measure
Consider separate definitions for clinical trials, clinical practice and patients
The word remission could imply "cure", and could be misused by health insurance providers
Think of measuring patient-reported remission and its correlation to the current definition
How do we avoid misclassification of patients that might be in remission but have other sources of swelling or pain
Investigate the role of different PRO such as pain and fatigue, but also RAID as a tool to measure impact, and their relation to remission
Gather normative data on PRO based on age and gender
Take into account that there could be different states of remission, depending on demographic factors, disease duration, and irreversible damage
Think of qualitative research among patients to investigate face validity of the current definition (e.g., relating to 28 joint count), acceptability of the stringency and sustainability; and to develop a remission definition from the patient perspective

PtGA: patient global assessment; PRO: patient-reported outcome; RAID: Rheumatoid Arthritis Impact of Disease

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Table 4. Results (%) of plenary voting session.

Question	n	Yes	No	Don't Know
1. Do you agree that the formulation and scope of the patient global needs further research, such as its relationship to RAID, disease specificity, the possibility to split it into multiple questions such as an emotional and physical domain, etc.?	120	93	4	3
2. Do you agree that the current ACR/EULAR definition needs to be reassessed with the possibility of revision no later than 5 years from now, based on new information, such as patient-related outcomes currently being collected in clinical trials?	115	90	5	5
3. Do you agree that the remission and flare group should examine common ground?	117	74	10	15

RAID: Rheumatoid Arthritis Impact of Disease.

reevaluation of the remission definition in 5 years, to see if PRO can improve the definition.

As the OMERACT flare group has done a lot of work in the area of PRO and patient perspective on flare, and since flare could be regarded as the opposite of remission, a majority of participants (74%) voted for cooperation between the 2 groups.

CONCLUSION

This initial OMERACT workshop on remission from the patient's perspective showed that there is a great interest among patients, physicians, and researchers to study the concept of remission, taking into account measures that patients indicate as important, but for which there is a lack of data on appropriate measures, resulting in a considerable research agenda. Focus for the next few years will be on understanding the patient perspective on remission in RA, identifying domains that patients associate with remission, and investigating how these domains can best be measured.

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REFERENCES

- 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;61:704-10.
- Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404-13.
- Ahlmen M, Nordenskiöld U, Archenholtz B, Thyberg I, Ronnqvist R, Linden L, et al. Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients. *Rheumatology* 2005;44:105-10.
- van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Kerstens PJ, Dijkmans BA et al. Discordant perspectives of rheumatologists and patients on COBRA combination therapy in rheumatoid arthritis. *Rheumatology* 2008;47:1571-6.
- Varekamp I, Haafkens JA, Detaille SI, Tak PP, van Dijk FJ. Preventing work disability among employees with rheumatoid arthritis: what medical professionals can learn from the patients' perspective. *Arthritis Rheum* 2005;53:965-72.
- Leeb BF, Sautner J, Leeb BA, Fassl C, Rintelen B. Lack of agreement between patients' and physicians' perspectives of rheumatoid arthritis disease activity changes. *Scand J Rheumatol* 2006;35:441-6.
- Spoorenberg A, van Tubergen A, Landewe R, Dougados M, van der Linden S, Mielants H, et al. Measuring disease activity in ankylosing spondylitis: patient and physician have different perspectives. *Rheumatology* 2005;44:789-95.
- Aletaha D, Smolen JS. Remission of rheumatoid arthritis: should we care about definitions? *Clin Exp Rheumatol* 2006;24 Suppl 43:S45-51.
- Kirwan JR, Hewlett SE, Heiberg T, Hughes RA, Carr M, Hehir M, et al. Incorporating the patient perspective into outcome assessment in rheumatoid arthritis — progress at OMERACT 7. *J Rheumatol* 2005;32:2250-6.
- Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, de Wit M, et al. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol* 2007;34:1174-7.
- Gossec L, Dougados M, Rincheval N, Balanescu A, Boumpas DT, Canadello S, et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. *Ann Rheum Dis* 2009;68:1680-5.
- Boers M, Felson D, Wells G, van Tuyl LH, Zhang B, Funovits J, et al. Progress towards the development of a new definition of remission in rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2010;68:140-2.