Remission in Rheumatoid Arthritis: Working Toward Incorporation of the Patient Perspective at OMERACT 12

Lilian H. van Tuyl, Martina Sadlonova, Bev Davis, Caroline Flurey, Niti Goel, Sarah E. Hewlett, Catherine L. Hill, Wijnanda Hoogland, John R. Kirwan, Dirkjan van Schaardenburg, Marieke Scholte-Voshaar, Josef S. Smolen, Tanja Stamm, George A. Wells, and Maarten Boers

ABSTRACT. Objective. The treatment of rheumatoid arthritis (RA) should target patient-relevant outcomes, making patient perspective on remission essential. In 2010, patients, physicians, health professionals, and researchers at the Outcome Measures in Rheumatology (OMERACT) conference developed an ambitious research agenda to study the concept of remission. Qualitative research has since helped us understand the concept of remission from the patient perspective.

Methods. During OMERACT 12, the OMERACT working group on patient perspective on remission in RA elaborated on data generated to date and discussed the methodological challenges ahead. Challenges included (1) selection of domains, (2) choice of a patient remission definition or a single domain to add to the current remission definition, and (3) the importance of pain in defining remission from a patient perspective.

Results. Focus in the coming years will be on increasing our understanding by identifying the most important domains from the patient perspective regarding remission and investigating how these domains can be measured. Investigation into the Rheumatoid Arthritis Impact of Disease questionnaire, disease flare, as well as the concordance of domains from our ongoing remission survey is appropriate. More data and further discussions are needed to decide on the next steps.

Conclusion. Progress summarized over 4 years highlights the main methodological challenges discussed within the working group on patient perspective on remission in RA during OMERACT 12. (J Rheumatol First Release Feb 15 2015; doi:10.3899/jrheum.141113)

Key Indexing Terms:
OMERACT RHEUMATOID ARTHRITIS REMISSION
PATIENT-REPORTED OUTCOME PATIENT PERSPECTIVE

Developments in the treatment of rheumatoid arthritis (RA) have improved the control of joint inflammation and pain[1,2], and a goal of minimal disease activity or even remission is now realistic[3,4,5]. Work on defining stronger criteria for remission[6,7] reviewed outcome measures available from clinical trial data. These included only the 3

From the Department of Rheumatology, and the Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; Division of Rheumatology, Department of Medicine, Medical University of Vienna, Vienna, Austria; University of Bristol, and the University of the West of England, Academic Rheumatology Unit, Bristol Royal Infirmary; Bristol, UK; Quintiles Inc., Morrisville; Division of Rheumatology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA; Queen Elizabeth Hospital Department of Rheumatology, Woodville, South Australia; University of Adelaide, The Health Observatory Woodville, South Australia, Australia; Reade/Jan van Breemen Research Institute, Amsterdam, the Netherlands; Department of Epidemiology and Community Medicine, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

Supported by a research grant from the European League Against Rheumatism.

L.H. van Tuyl, Postdoctoral Researcher, PhD, Department of Rheumatology, VU University Medical Center; M. Sadlonova, Occupational Therapist, MSc, Division of Rheumatology, Department of Medicine, Medical University of Vienna; B. Davis, Patient Research Partner, University of Bristol, Academic Rheumatology Unit, Bristol Royal Infirmary; C. Flurey, Research Fellow, PhD, University of the West of England, Academic Rheumatology Unit, Bristol Royal Infirmary; N. Goel, MD, Senior Medical Director and Adjunct Assistant Professor of Medicine, Quintiles Inc., and Division of Rheumatology, Department of Medicine, Duke University School of Medicine; S.E. Hewlett, Professor of Rheumatology Nursing, PhD, University of the West of England, Academic Rheumatology Unit, Bristol Royal Infirmary; Queen Elizabeth Hospital, Department of Rheumatology, Woodville; C.L. Hill, MD, Rheumatologist, Queen Elizabeth Hospital Department of Rheumatology, Woodville, University of Adelaide, Health Observatory Woodville; W. Hoogland, MD, Patient Research Partner, Department of Rheumatology, VU University Medical Center; J.R. Kirwan, Professor of Rheumatic Diseases, MD, PhD, University of Bristol, Academic Rheumatology Unit, Bristol Royal Infirmary; D. van Schaardenburg, MD, PhD, Rheumatologist, Department of Rheumatology, VU University Medical Center, Reade/Jan van Breemen Research Institute; M. Scholte-Voshaar, Patient Research Partner, MSc, Department of Rheumatology, VU University Medical Center; J.S. Smolen, MD, PhD, Professor of Rheumatic Diseases; T. Stamm, Associate Professor, PhD, Medical University of Vienna, Department of Medicine III, Division of Rheumatology; G.A. Wells, PhD, Professor of Clinical Epidemiology, Department of Epidemiology and Community Medicine, University of Ottawa Heart Institute; M. Boers, MD, MSc, PhD, Professor of Clinical Epidemiology, Department of Rheumatology, and Department of Epidemiology and Biostatistics, VU University Medical Center.

Address correspondence to Dr. L.H. van Tuyl, Boelelaan 1118, 1053 MB Amsterdam, the Netherlands. E-mail: L.vantuyl@vumc.nl

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2015. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

patient-reported outcomes (PRO) incorporated in the initial RA core outcome measurement set: patient global, pain, and physical function[8,9]. Data were not consistently available on other potentially important aspects of remission from the patient perspective, including fatigue, which had since been recognized as an important outcome to include in clinical trials[10]. At the Outcome Measures in Rheumatology meeting in 2010 (OMERACT 10), both participating patients and professionals endorsed the need to study the concept of remission in RA from the patient perspective, to identify new potential PRO to optimize targeted therapy and possibly improve the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) definition of remission[11].

Progress since OMERACT 10

Qualitative exploration. To understand the patient perspective on periods of remission, we undertook a qualitative study[12]. In 3 European countries (Austria, United Kingdom, and the Netherlands), focus group discussions were organized with patients with RA. From these discussions, 26 aspects of remission were identified and grouped into 3 major themes of patient-perceived remission (Figure 1). For elaboration on the different items and grouping into themes, we refer to this work[12].

Rating for importance. To determine the relative importance of the many aspects of remission identified in our qualitative work, a large group of patients with RA is currently completing a ranking exercise. The goal of this exercise is to determine a short list of aspects related to remission that can then be further researched. The survey contains all 26 aspects of remission identified in focus group discussions. First, respondents are asked to rate each item as either "not important," "important," or "essential" for characterizing a period of remission. Second, respondents are then asked to determine their personal top 3 most important/essential items that characterize remission. A copy of the survey is available from the corresponding author.

Patients from the 3 aforementioned European countries are participating. In addition, all RA patient research partners (PRP) who took part in OMERACT 12 were invited to participate by e-mail. We aim to collect data from at least 100 patients.

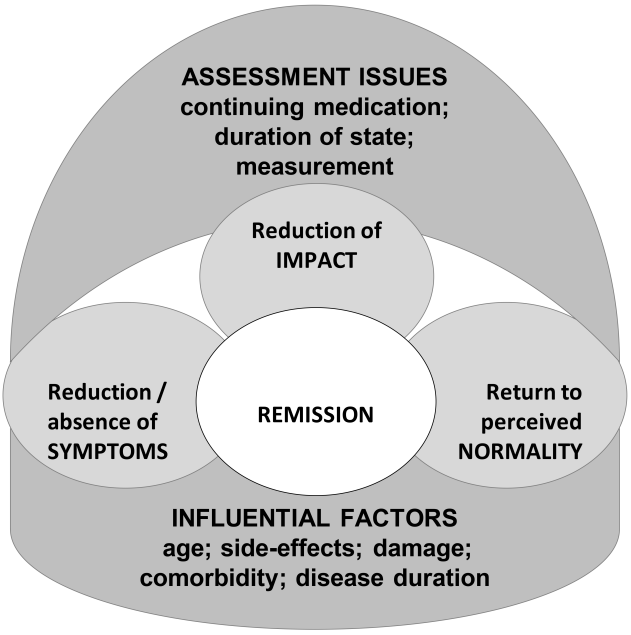

Figure 1. Main themes of rheumatoid arthritis remission. The 3 main themes (symptoms, impact, and normality) are underpinned by a theme of influential factors, with an overarching theme of assessment issues.

Data Presented at OMERACT 12

During the Patient Perspective on Remission in RA special interest group (SIG) session at OMERACT 12, results of the focus group discussions[12] as described above were presented. Additionally, preliminary results of the survey were presented. These data were limited to those from the first 49 respondents obtained prior to the conference, comprising patients with RA from Austria (n = 28), the Netherlands (n = 16), and OMERACT PRP (n = 5; Table 1).

There are several ways to reduce the number of domains from 26 to a manageable number, while taking into account the importance of the different features of periods of remission. For presentation during our SIG, we approached the preliminary data in 2 ways:

1. We calculated the frequency that a particular domain was mentioned in the top 3, irrespective of its position (1, 2, or 3). Table 2 provides the 12 most-mentioned domains in the top 3 for 49 respondents. While pain was by far the most-mentioned feature, differences between other features were small. It was confirmed that a larger number of patients would be needed to identify other domains that play a key role in the patient perception of remission.
2. Of the 26 domains that were each rated as either "not important," "important," or "essential," we removed domains that > 30% of patients identified as "not important." The remaining domains were sorted by the percentage of patients that evaluated a particular domain as "essential." This resulted in the removal of domains "Unpredictability of the disease;" "use of DMARD" (disease-modifying antirheumatic drugs); "use of pain-killers;" "mood;" and "the way other people see me." Table 3 presents the 12 domains that are most frequently rated as "essential" to characterize a period of remission.

Approaching the data in these 2 ways resulted in agreement regarding the top 3 and essential features; however, there was discrepancy between the top 3 items and items rated "not important" by > 30%. Two items from the top 3 were also ranked as "not important" (use of DMARD, mood). Because these are preliminary findings based on

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2015. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

Table 1. Preliminary survey results: respondent demographics.

	Total	Amsterdam	Vienna	OMERACT PRP
N	49	16	28	5
Age, yrs, mean (SD)	56.4 (12.7)	63.8 (8.3)	52.2 (13.9)	55 (0.6)
Female, %	78	75	75	100
At least 1 comorbidity (%)	57	69	54	40
Disease duration, yrs, mean (SD)	12.4 (10)	11.8 (7)	9.8 (10)	29.0 (3)
Currently in remission, self-perceived, %	47	69	43	100

PRP: patient research partners.

Table 2. Top 3 features by frequency (%), irrespective of the first, second, or third position (preliminary data).

Domain	Frequency in Top 3, n = 46*	Amsterdam, n = 14	Vienna, n = 27	PRP, n = 5
Pain	28 (61)	5 (36)	19 (70)	4 (80)
Independence	11 (24)	2 (14)	7 (26)	2 (40)
Fatigue	10 (22)	2 (14)	6 (22)	2 (40)
Leisure/sports	9 (20)	4 (29)	5 (19)	0 (0)
Physical functioning	7 (15)	2 (14)	4 (15)	1 (20)
Being mobile	6 (13)	1 (7)	5 (19)	0 (0)
Social life	6 (13)	5 (36)	1 (4)	0 (0)
Ability to work	6 (13)	3 (21)	3 (11)	0 (0)
Swelling	5 (11)	1 (7)	3 (11)	1 (20)
Mood	5 (11)	0 (0)	5 (19)	0 (0)
Use of DMARD	5 (11)	2 (14)	3 (11)	0 (0)
Daily activities	5 (11)	1 (7)	3 (11)	1 (20)

* Three respondents did not provide the top 3 features. DMARD: disease-modifying antirheumatic drugs; PRP: patient research partners.

Table 3. Frequency of features ranked as essential (%) for 49 respondents (preliminary data).

Feature	Not Important	Ranking Important	Essential
Physical functioning	1 (2.1)	15 (31.3)	32 (66.7)
Mobility	2 (4.2)	18 (37.5)	28 (58.3)
Independence	4 (8.3)	17 (35.4)	27 (56.3)
Pain	5 (10.4)	17 (35.4)	26 (54.2)
Daily activities	2 (4.2)	24 (50.0)	22 (45.8)
Mental power	8 (16.7)	18 (37.5)	22 (45.8)
Fine motor skills	4 (8.3)	24 (50.0)	20 (41.7)
Flares	8 (16.7)	21 (43.8)	19 (39.6)
Swelling	5 (10.4)	26 (54.2)	17 (35.4)
Grip	5 (10.4)	26 (54.2)	17 (35.4)
Family role	5 (10.4)	26 (54.2)	17 (35.4)
Leisure	1 (2.1)	31 (64.6)	16 (33.3)

limited data, final datasets will show whether the originally planned analysis method needs to be reevaluated.

Discussion at OMERACT 12

An estimated 60 to 80 OMERACT participants joined our SIG, including more than 6 PRP. About 15% of the participants actively contributed to the discussion.

Following the presentation of results as summarized above, 3 points for discussion were prepared:

Survey. How do we select the most important domains from a list of items rated as important and essential, in combination with a top 3 list?

Outcome. Do we need to work toward a patient remission definition, or should we determine the added value of including one of the PRO in the current ACR/EULAR remission definition?

Pain. What is the value of pain when included in the ACR/EULAR remission definition in addition to, or in place of, the patient global assessment of disease activity?

Survey: No specific methodological preference was evident for selecting the most important domains for patient-perceived remission from the survey. Several methodologies were discussed, including use of the Rheumatoid Arthritis Impact of Disease (RAID) methodology for ranking domains and distributing points[13]; use of principal component analysis to group domains, assuming that some of the items are not independent of each other and might represent the same underlying construct; use of computer assisted methodology; and use of a Venn diagram.

The issue was raised that, by asking patients to rank domains for importance, some will rank everything as either

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2015. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

important or essential. It was suggested that the discrepancy between the methods of "top 3" and "ranking of essential items" might be solved by checking for and removing survey responses where all items are ranked as either important or essential.

Outcome: Preliminary data of 49 respondents as presented during the SIG were insufficient to make concrete plans about the next steps, i.e., whether to revise the ACR/EULAR criteria or draft a patient-reported core set of remission/absence of effect scale. More data are needed before deciding whether changing the criteria is necessary: Altering the criteria is not a trivial decision, with implications for researchers and funding bodies.

It was discussed in the context of the OMERACT filter 2.0[15] that it may be useful for the ACR/EULAR remission criteria to be retained as a pathophysiological definition, in addition to separate effect or functional remission criteria that might allow for identification of patients needing treatment beyond current targeted therapy models.

Overall, there seemed to be a preference for a separate patient remission definition. However, worries were also expressed: If not incorporated into the ACR/EULAR remission definition, the patient perspective of remission might not be used; as well, policy-maker viewpoints need to be taken into account before deciding the outcome of this project.

It was suggested that the anticipated patient sample (n = 100) for rating domains for importance is not large enough to enable the data to be divided according to disease and contextual factors. Several participants offered help in collecting more data, from different countries in and outside Europe, e.g., France and Australia. The centers in Amsterdam, Bristol, and Vienna agreed to expand their sample from the original 30 patients per country to at least 50 (excluding previous focus group participants and OMERACT patient delegates). It was discussed that we need to ensure inclusion of patients with both early and late disease, as well as erosive and nonerosive disease.

Pain: Although currently the highest ranked domain, pain is already reflected in the core set, albeit not in the remission criteria. The idea of taking this measure forward in additional research was discussed.

A discussion on the value of the patient global assessment of disease activity versus a measure of pain followed. Despite literature that questions the validity of the patient global assessment of disease activity in the remission criteria[16,17], it was deemed an appropriate outcome because it would measure several important aspects of the effect of the disease on a patient (pain, fatigue, and physical functioning), rather than one aspect such as pain[17]. Stressing the importance of having multiple aspects of effect in the remission definition, patients expressed their preference for the patient global assessment above a measure of pain as a single component of the remission criteria.

Table 4. Research agenda for the patient perspective on remission in rheumatoid arthritis.

- Survey: Increase sample of respondents to rate domains for importance by:
  - — involving countries outside the current scope
  - — including respondents with both early and late disease
  - — including respondents with both erosive and nonerosive disease
- Seek collaboration with the RA flare and RAID groups
- Compare RAID domains with remission domains
- Consider collecting additional identified domains alongside the RAID
- Investigate overlap between patient global assessment of disease activity and other important PRO, specifically pain and fatigue

RA: rheumatoid arthritis; RAID: RA Impact of Disease methodology; PRO: patient-reported outcomes.

We would need to know to what extent pain and other PRO are reflected in the patient global assessment.

General Discussion

During and after the SIG, similarities with the RAID and the disease flare group were further highlighted: As members of the remission group, we are studying the effect of RA disease activity from the perspective of its absence; the disease flare group is studying the effect of RA disease activity from the perspective of an acute and sustained increase; and the RAID is an instrument to assess the effect of RA, including disease activity. Rather than devise new tools to detect (the effect of) flare or remission, it was suggested to measure the additional identified domains not found in the RAID alongside the RAID; or to use a low cutoff RAID score to reflect remission in case the most frequently mentioned domains from the survey strongly resemble the 7 domains from the RAID.

Table 4 summarizes our research agenda.

Conclusion

The SIG on patient perspective on remission presented at OMERACT 12 elaborated on the data that have been generated to date and discussed the methodological challenges ahead. Focus in the coming years will be on increasing our understanding by identifying the most important domains from the patient perspective regarding remission and investigating how these domains can be measured. Investigation into the RAID and disease flare and their concordance with domains from our ongoing survey is appropriate. More data and further discussions are needed to decide whether this will lead to revision of the ACR/EULAR remission criteria or to establishing a patient core set of remission measures/an absence of effect scale.

REFERENCES

1. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2015. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

2. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.
3. van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis 2008;67:1574-7.
4. 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;32:2016-24.
5. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
6. 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.
7. Felson DT, Smolen J, Wells GA, 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.
8. Boers M, Tugwell P, Felson DT, van Riel PLCM, 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 Sept;41:86-9.
9. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729-40.
10. Kirwan J, Minnock P, Adebajo A, Bresnihan B, Choy E, De Witt M, et al. Patient Perspective Workshop: fatigue as a recommended patient-centred outcome measure in rheumatoid arthritis. J Rheumatol 2007;34:1174-7.
11. van Tuyl LH, Smolen JS, Wells GA, Scholte-Voshaar M, Hoogland W, Boers M. Patient perspective on remission in rheumatoid arthritis. J Rheumatol 2011;38:1735-8.
12. van Tuyl LH, Hewlett S, Stamm T, Davis B, Flurey C, Hoogland W, et al. "Back to being normal": the patient perspective on remission in rheumatoid arthritis. Ann Rheum Dis 2013;72 Suppl 3:562.
13. Gossec L, Dougados M, Rincheval N, Balanescu A, Boumpas DT, Canadelo S, et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. Ann Rheum Dis 2009;68:1680-5.
14. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
15. van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? Arthritis Rheum 2012;64:2811-3.
16. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702-5.
17. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139-45.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2015. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org