The Journal of Rheumatology Volume 44, no. 12

Validating Rheumatoid Arthritis Remission Using the Patients' Perspective: Results from a Special Interest Group at OMERACT 2016

Linda A. Rasch, Maarten Boers, Catherine L. Hill, Marieke Voshaar, Wijnanda Hoogland, Maarten de Wit, Caroline Flurey, Bev Davis, Merete Lund Hetland, Cecilie Heegaard Brahe, Laure Gossec, George A. Wells, Peter Tugwell, Bindee Kuriya, Niti Goel, Jasvinder A. Singh, Cátia Duarte, José Da Silva, Dirkjan van Schaardenburg, Susanna Proudman and Lilian H.D. van Tuyl, on behalf of the Working Group on the Patients Perspective on Remission in Rheumatoid Arthritis

J Rheumatol 2017;44;1889-1893
http://www.jrheum.org/content/44/12/1889

Validating Rheumatoid Arthritis Remission Using the Patients' Perspective: Results from a Special Interest Group at OMERACT 2016

Linda A. Rasch, Maarten Boers, Catherine L. Hill, Marieke Voshaar, Wijnanda Hoogland, Maarten de Wit, Caroline Flurey, Bev Davis, Merete Lund Hetland, Cecilie Heegaard Brahe, Laure Gossec, George A. Wells, Peter Tugwell, Bindee Kuriya, Niti Goel, Jasvinder A. Singh, Cátia Duarte, José Da Silva, Dirkjan van Schaardenburg, Susanna Proudman, and Lilian H.D. van Tuyl, on behalf of the Working Group on the Patients' Perspective on Remission in Rheumatoid Arthritis

ABSTRACT. ***Objective.*** The Outcome Measures in Rheumatology (OMERACT) working group on the patients' perspective on remission in rheumatoid arthritis (RA) has been working on this topic since 2010. At OMERACT 2016, progress and preliminary data on validity of measurement instruments for pain, fatigue, and independence in remission in RA were presented, and future directions were explored.

Methods. A special interest group was organized, in which the current data on the patients' perspective on remission were presented. The ongoing study that aimed to validate measurement instruments for pain, fatigue, and independence in a state of low disease activity or remission was presented, and preliminary data on construct validity and discriminative capacity were evaluated cross-sectionally.

Results. At OMERACT 2016, the progress of the working group and preliminary data from 142 of the anticipated 300 patients were presented. Selected instruments significantly correlated with the Disease Activity Score in 28 joints (construct validity) and all instruments except 1 discriminated between patients in and patients not in remission. The subsequent discussion mainly focused around 3 points: (1) the formulation of patient perceived remission, (2) the duration of remission, and (3) the measurement of the domain independence. An informal vote indicated a slight preference for working toward modifying the current remission criteria by adding patient-reported outcomes (PRO), or by substituting the patient's global assessment with 1 or more PRO.

Conclusion. More evidence on measuring patients' perspective on remission in RA is needed before an informed decision can be made regarding development or modification of remission definitions.

(First Release August 1 2017; J Rheumatol 2017;44:1889–93; doi:10.3899/jrheum.161111)

Key Indexing Terms:

OMERACT PATIENT PERSPECTIVE PATIENT-REPORTED OUTCOME
REMISSION RHEUMATOID ARTHRITIS

From the Amsterdam Rheumatology and Immunology Center | VU University Medical Center; Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands; Royal Adelaide Hospital and Discipline of Medicine, University of Adelaide, Adelaide, Australia; University of the West of England, Bristol, UK; Copenhagen Center for Arthritis Research and DANBIO, Center for Rheumatology and Spine Diseases, Righospitalet, Glostrup, Denmark; Sorbonne Universités, UPMC Univ Paris 06; AP-HP, Pitié Salpêtrière Hospital, Department of Rheumatology, Paris, France; Department of Medicine, University of Ottawa, Ottawa; University of Toronto, Toronto, Ontario, Canada; Quintiles and Duke University School of Medicine, Durham, North Carolina; University of Alabama at Birmingham, Birmingham, Alabama, USA; Faculty of Medicine and Academic Hospital, University of Coimbra, Coimbra, Portugal.

The validation study was funded by an unrestricted educational grant from Pfizer.

L.A. Rasch, MSc, Amsterdam Rheumatology and Immunology Center | VU University Medical Center; M. Boers, MD, MSc, PhD, Professor, Epidemiology and Biostatistics, VU University Medical Center, and Amsterdam Rheumatology and Immunology Center | Reade; C.L. Hill, MD, Professor, University of Adelaide; M. Voshaar, MSc, Patient Partner; W. Hoogland, MD, Patient Partner; M. de Wit, PhD, Patient Partner; C. Flurey, PhD, University of the West of England; B. Davis, Patient Partner; M.L. Hetland, MD, PhD, Professor, Copenhagen Center for Arthritis Research and DANBIO, Center for Rheumatology and Spine Diseases, Righospitalet; C.H. Brahe, MD, Copenhagen Center for Arthritis Research and DANBIO, Center for Rheumatology and Spine Diseases, Righospitalet; L. Gossec, MD, PhD, Professor, Sorbonne Universités, UPMC Univ Paris 06; AP-HP, Pitié Salpêtrière Hospital, Department of Rheumatology; G.A. Wells, MD, Professor, University of Ottawa; P. Tugwell, MD, Professor, Department of Medicine, University of Ottawa; B. Kuriya, MD, University of Toronto; N. Goel, MD, Assistant Professor, Quintiles and Duke University School of Medicine; J.A. Singh, MBBS, MPH, Professor, University of Alabama at Birmingham; C. Duarte, MD, Faculty of Medicine and Academic Hospital, University of Coimbra; J. Da Silva, MD, PhD, Professor, Faculty of Medicine and Academic Hospital, University of Coimbra; D. van Schaardenburg, MD, PhD, Professor, Amsterdam Rheumatology and Immunology Center | Reade; S. Proudman, MBBS, Royal Adelaide Hospital and Discipline of Medicine, University of Adelaide; L.H. van

Tuyl, PhD, MBA, Amsterdam Rheumatology and Immunology Center | VU University Medical Center.

Address correspondence to L.A. Rasch, VU University Medical Center, Department of Rheumatology, Room ZH3A-54, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail: l.rasch@vumc.nl

Accepted for publication June 1, 2017.

At the time of the development of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition of remission in rheumatoid arthritis (RA)[1], information on potentially important aspects of remission from the patients' perspective, apart from the 3 core set patient-reported outcomes (PRO), was not available[2]. This means that the current definition of remission, i.e., the target of treatment, may not include all relevant information.

The ACR/EULAR definition of remission in RA is 2-fold[1]:

1. Boolean-based definition: The tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP; mg/dl), and patient's global assessment (PtGA; 0–10 scale) are all ≤ 1;
2. Index-based definition: The score on the Simplified Disease Activity Index is ≤ 3.3, defined as the simple sum of the TJC, SJC, PtGA (0–10 scale), physician's global assessment (0–10 scale), and CRP (mg/dl).

At OMERACT 2010, both patients and professionals identified a lack of understanding regarding the patients' perspective on remission in RA and on appropriate measures[3,4]. Therefore, a qualitative study was undertaken in 3 European countries, involving 9 focus group discussions, which identified 26 domains that are involved in defining remission from a patients' perspective[5].

In the second phase of our study, the qualitative results were refined through means of a survey among Dutch, Austrian, British, French, Danish, and North American patients with RA to investigate the importance of domains in defining remission in RA from the patients' perspective. This provided a top 3 of the most important domains of remission as perceived by patients: pain, fatigue, and independence[6].

At OMERACT 2016, preliminary data on the third phase of this study assessing the validity of instruments to measure pain, fatigue, and independence in remission resulted in a slight preference for working toward modifying the current remission criteria, by adding PRO or by substituting the PtGA with 1 or more PRO.

Data Presented at OMERACT 2016: Instrument Validation

The aim of our ongoing validation study is to identify valid measurement instruments for the top 3 domains reflecting patient-perceived remission (pain, fatigue, and independence) and to investigate their added value in defining remission in RA.

In our validation study, approved by the medical ethics committees of the participating countries, a total of 300 patients will be assessed: half of them in patient-perceived remission ("Would you say that at this moment your disease activity is as good as gone, yes or no?") and the other half not in patient-perceived remission, but with low disease activity, i.e., Disease Activity Score at 28 joints (DAS28) < 3.2. At OMERACT 2016, preliminary data of 142 of the anticipated 300 patients was presented.

Because The OMERACT Handbook was not yet developed at the start of our study, the instruments for each of the 3 most important domains of remission as perceived by patients were selected with an eyeball test[7].

In the case of pain, the international reference standard was used as included in the RA core set. However, not as a visual analog scale, but as a numerical rating scale (NRS) as incorporated in the RA Impact of Disease questionnaire (RAID)[8,9].

In the case of fatigue, 2 instruments were selected: (1) The Bristol Rheumatoid Arthritis Fatigue questionnaire NRS (BRAF-NRS), consisting of 3 NRS that assess 3 different aspects of fatigue: level, effect, and coping[10]; and (2) the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue), composed of 13 items[11].

For the third domain of independence, the quotes from the focus group discussions[6] were studied to fully understand the meaning of this domain; it became clear that when discussing independence, patients referred to "doing things physically, without the help of others, managing yourself." Therefore, we selected the following instruments to measure this domain, all focusing on the physical component of independence:

1. the items on mobility, self-management, and daily activities of the EQ-5D;
2. the Health Assessment Questionnaire;
3. Functional impairment and physical well-being scales from the RAID;
4. the physical functioning component of the Medical Outcomes Study Short Form-36 questionnaire (SF-36 PCS);
5. a new independence NRS, formulated by the research team in close consultation with patient research partners and based on the focus group discussions, phrased as: "Over the last week, have you been able to do things as and when you want without needing any kind of assistance?", scoring 0 for no assistance to 10 for a lot of assistance.

For all instruments, construct validity was assessed by correlating the newly identified domain measures with the DAS28[12]. Discriminative capacity was evaluated by studying the difference in magnitude of the identified domain measures between patients in and patients not in remission.

General characteristics and demographics are shown in Table 1. All instruments significantly correlated with DAS28 scores, except for the BRAF-NRS coping, the EQ-5D self-management question, and the SF-36 PCS (Table 2). Further, all instruments of the 3 domains were able to discriminate between patients in and not in remission, except

Table 1. General characteristics and demographics.

Characteristics	Total, n = 142	The Netherlands, n = 56	Portugal, n = 54	Canada, n = 24	Australia, n = 8
Age, yrs, mean ± SD	55 ± 14	52 ± 15	56 ± 13	58 ± 14	60 ± 9
Female, %	70	63	78†	71	63
Disease duration, yrs, median (IQR)	5 (0–16)	0 (0–1)	11 (6–19)‡	21 (9–32)	10 (8–14)
Biological use, %	37	0	65	63	38
Comorbidities, %	34	32	32	42	38
DAS28, mean ± SD	1.8 ± 0.9	2.1 ± 0.8	1.6 ± 0.7	2.0 ± 1.2	0.7 ± 0.7
Patient perceived remission, %	54	66	39	46	88
ACR/EULAR Boolean remission, %	31	41	15	29†	75
PtGA, median (IQR)	2 (1–4)	1 (0–3)	3.5 (2–5)	2.5 (1–5)	1 (1–1)
PGA, median (IQR)	1 (0–2)	2 (1–2)*	0 (0–1)	0 (0–0)	0 (0–1)

†1 missing. ‡3 missing. *8 missing. IQR: interquartile range; DAS28: Disease Activity Score at 28 joints; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; PtGA: patient's global assessment; PGA: physician's global assessment.

Table 2. Construct validity of the instruments selected to measure the 3 most important domains for remission from a patient's perspective (pain, fatigue, and independence).

Instrument	DAS28, n = 140	
	Correlation	p
Pain		
RAID pain	0.473	< 0.001*
Fatigue		
BRAF level	0.321	< 0.001*
BRAF effect	0.309	< 0.001*
BRAF coping	0.099	0.243
FACIT-Fatigue†	0.369	0.001*
Independence		
EQ-5D mobility	0.348	0.001*
EQ-5D self-care	0.133	0.227
EQ-5D daily activities	0.300	0.006*
HAQ	0.230	0.007*
RAID functional impairment	0.372	< 0.001*
RAID physical well-being	0.364	< 0.001*
SF-36 PCS	0.122	0.161
Independence NRS	0.401	< 0.001*

*Statistically significant ($p < 0.05$). †n = 84. DAS28: Disease Activity Score at 28 joints; RAID: Rheumatoid Arthritis Impact of Disease; BRAF: Bristol Rheumatoid Arthritis Fatigue questionnaire; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue scale; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; NRS: numerical rating scale.

for the SF-36 PCS (Table 3). We did not discuss these findings in detail because these are only preliminary results, and the final results might be different. The following discussion aimed at clarifying the results and the future direction of the working group.

Discussion at OMERACT 2016

The discussion mainly focused on 3 points:

1. The formulation of patient-perceived remission was questioned. The use of the phrase "disease activity as good as gone" instead of "disease as good as gone" to describe remission to patients in different languages was deemed extremely important, because RA is never really gone, especially in the case of deformities.

2. There was a discussion on duration of remission. The group was reminded that the ACR/EULAR remission definition purposely does not include duration, proposing instead that further research should determine the minimum meaningful duration[1]. A wide variety of opinions existed on how long the disease had to be "as good as gone" before calling it remission. All 6 patients who were present gave a different answer, ranging from "at this moment" ("If I have a bad day, remission is over for me") to "a long period of time, for example a year" ("Remission does not change from moment to moment"). Moreover, the duration of remission for 1 domain may be different from that of other domains; for example, pain could be assessed within a shorter time frame than independence.

3. The measurement of the domain independence. Participants felt that independence was highly related to physical functioning and participation, and it was questioned which instrument was best to measure this domain. The NRS used in the validation study was discussed; some patients indicated that the feeling of independence can vary within a week, but for others a week was too short. There were differences in defining independence: some patients indicated they felt independent if they did not need help from other people, irrespective of tools or devices; others defined independence as doing things without the help of anything or anyone. The formulation of the anchors of the NRS ("highly able" and "not at all able") were discussed, which focused on assistance rather than independence of a patient. It was decided to leave this question unchanged and add an additional new question to cover the entire concept.

Finally, participants (n = 30) were asked for an informal vote for a preferred plan on how to combine the presented results with the existing ACR/EULAR RA remission criteria. Because it was pointed out that the current ACR/EULAR remission criteria are problematic with regard to specificity

Table 3. Discriminative capacity of the instruments selected to measure the 3 most important domains for remission from a patients' perspective (pain, fatigue, and independence). Remission defined based on patient-perceived remission versus Boolean remission. Values are median (interquartile range) unless otherwise specified.

Instrument	Patient-perceived Remission			Boolean Remission		
	No, n = 64	Yes, n = 75	p	No, n = 95	Yes, n = 44	p
Pain						
RAID pain	4 (2–6)	1 (1–3)	< 0.001*	4 (2–5)	1 (0–2)	< 0.001*
Fatigue						
BRAF level	5 (2–7)	3 (1–5)	0.001*	4 (2–6)	2 (1–6)	0.023*
BRAF effect	4 (2–7)	3 (0–5)	0.002*	4 (2–6)	2 (0–6)	0.019*
BRAF coping	5 (3–7)	8 (5–10)	< 0.001*	6 (4–8)	9 (5–10)	< 0.001*
FACIT-Fatigue§	36 (30–42)	44 (36–48)	< 0.001*	36 (31–44)	46 (44–50)	< 0.001*
Independence						
EQ-5D mobility†	1 (0–2)	0 (0–1)	< 0.001*	1 (0–2)	0 (0–0)	< 0.001*
EQ-5D self-care†	1 (0–2)	0 (0–0)	0.005*	0 (0–2)	0 (0–0)	0.002*
EQ-5D daily activities†	1 (1–2)	0 (0–1)	< 0.001*	1 (0–2)	0 (0–0)	< 0.001*
HAQ	0.7 (0.1–1.0)	0.1 (0.0–0.5)	< 0.001*	0.6 (0.0–1.0)	0.1 (0.0–0.3)	< 0.001*
RAID function impairment	4 (2–6)	1 (0–2)	< 0.001*	4 (2–5)	1 (0–1)	< 0.001*
RAID physical well-being	4 (2–6)	1 (0–3)	< 0.001*	3 (2–5)	1 (0–2)	< 0.001*
SF-36 PCS	36 (28–60)	51 (34–58)	0.058	41 (31–58)	53 (33–59)	0.104
Independence NRS‡	3 (1–5)	0 (0–2)	< 0.001*	3 (0–5)	0 (0–0)	< 0.001*

*Significant difference between remission and not in remission ($p < 0.05$). §Patient-perceived remission, n = 45/38, Boolean remission, n = 62/21. †Patient-perceived remission, n = 45/38, Boolean remission, n = 63/20. ‡Patient-perceived remission, n = 46/39, Boolean remission, n = 64/21. RAID: Rheumatoid Arthritis Impact of Disease; BRAF: Bristol Rheumatoid Arthritis Fatigue questionnaire; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue scale; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; NRS: numerical rating scale.

of the PtGA[13,14,15] and lack of inclusion of the patients' perspective[3,4], we formulated the following possibilities for the future direction:

1. Modify the ACR/EULAR remission criteria by adding or switching patient-reported domain(s): n = 16, 53%;
2. Modify the ACR/EULAR remission criteria by relaxing cutoff(s) of the existing patient-reported domain within the current criteria (n = 3, 10%);
3. Create a separate set of patient-perceived remission criteria (n = 11, 37%).

Naturally, any change in the current criteria, e.g., by adding pain, fatigue, and/or independence, substituting the PtGA with pain, fatigue, and/or independence, or relaxing the PtGA cutoff of 1, requires clinical evidence.

General Discussion

The working group on the Patients' Perspective on Remission in RA gathered at OMERACT 2016 to inform the group of the progress in this field. Preliminary data on validity of measurement instruments to measure pain, fatigue, and independence in remission were presented and discussed. There was a slight preference to work toward a modification of the current ACR/EULAR remission criteria by adding patient-reported domains or by using 1 or more patient-important outcomes instead of the PtGA. Naturally, this was only a first, uninformed examination of opinions, which needs further data, discussion, and a formalized international agreement procedure, e.g., through Delphi exercises.

Modification of the ACR/EULAR remission criteria would be a major undertaking and it can be questioned whether this is the best way forward. However, important patient representation in defining such an important endpoint of rheumatology clinical trials is essential in terms of face validity, and such representation is likely to become only more important in a future in which healthcare is primarily patient-centered.

Although the selection of questionnaires was done using an "eyeball" method, it is a limitation of our study that this was not such a structured and transparent process as the OMERACT eyeball test because our study started before publication of The OMERACT Handbook. However, most instruments are already validated extensively in RA, while in our study they are validated for defining remission in RA.

In the coming years, the focus will be on identifying the best instruments to measure remission from the patients' perspective according to the 3 most important domains for patients (pain, fatigue, and independence). It is anticipated that at OMERACT 2018, evidence will be presented that enables an informed decision on the added value of the PRO suggested, and the way to combine these with the current ACR/EULAR remission definition.

ACKNOWLEDGMENT

We thank all members of the OMERACT working group on the Patients' Perspective on Remission in Rheumatoid Arthritis for their contribution to the work reported in this manuscript: Professor S. Hewlett, Professor J. Kirwan, Dr. M. Sadlonova, Dr. V. Sloan, Professor J. Smolen, and Professor T. Stamm.

REFERENCES

1. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al; American College of Rheumatology; European League Against Rheumatism. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573-86.
2. van Tuyl LH, Boers M. Patient-reported outcomes in core domain sets for rheumatic diseases. Nat Rev Rheumatol 2015;11:705-12.
3. 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.
4. van Tuyl LH, Sadlonova M, Davis B, Flurey C, Goel N, Hewlett SE, et al. Remission in rheumatoid arthritis: working toward incorporation of the patient perspective at OMERACT 12. J Rheumatol 2016;43:203-7.
5. van Tuyl LH, Hewlett S, Sadlonova M, Davis B, Flurey C, Hoogland W, et al. The patient perspective on remission in rheumatoid arthritis: 'You've got limits, but you're back to being you again'. Ann Rheum Dis 2015;74:1004-10.
6. van Tuyl LH, Sadlonova M, Hewlett S, Davis B, Flurey C, Goel N, et al. The patient perspective on absence of disease activity in rheumatoid arthritis: a survey to identify key domains of patient-perceived remission. Ann Rheum Dis 2017;76:855-61.
7. Boers M, Kirwan JR, Tugwell P, Beaton D, Bingham CO III, Conaghan PG, et al. The OMERACT Handbook. [Internet. Accessed June 6, 2017.] Available from: www.omeract.org/pdf/OMERACT_Handbook.pdf
8. 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.
9. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70:935-42.
10. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S. Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. Arthritis Care Res 2010;62:1559-68.
11. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63-74.
12. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. 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.
13. 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.
14. Shahouri SH, Michaud K, Mikuls TR, Caplan L, Shaver TS, Anderson JD, et al. Remission of rheumatoid arthritis in clinical practice: application of the American College of Rheumatology/European League Against Rheumatism 2011 remission criteria. Arthritis Rheum 2011;63:3204-15.
15. van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? Arthritis Rheum 2012;64:2811-3.