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

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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.

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

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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), information on potentially important aspects of remission from the patients’ perspective, apart from the 3 core set patient-reported outcomes (PRO), was not available. This means that the current definition of remission, i.e., the target set patient-reported outcomes (PRO), was not available. This is why the current definition of remission, i.e., the target set patient-reported outcomes (PRO), was not available. This is 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.

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For the third domain of independence, the quotes from the focus group discussions 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 DAS2812. 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

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Table 1. General characteristics and demographics.

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

1 missing, 2 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).

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

*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. 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.
of the PtGA\textsuperscript{13,14,15} and lack of inclusion of the patients’ perspective\textsuperscript{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**

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REFERENCES