Assessing Remission in Rheumatoid Arthritis on the Basis of Patient Reported Outcomes
Advantages of Using RAPID3/MDHAQ in Routine Care

Isabel Castrejón, M.D., and Theodore Pincus, M.D.

Abstract
Advances in the management of rheumatoid arthritis (RA) have rendered remission an increasingly achievable goal. However, a single, universal definition of remission in RA does not exist. Remission criteria were developed in 1981 by a committee of the American College of Rheumatology (ACR) and have been described according to different composite indices. In 2011, a committee of the ACR and the European League against Rheumatism (EULAR) has proposed two remission criteria sets to be applied in clinical trials, a Boolean criteria set and a simplified disease activity index (SDAI), which are more stringent than disease activity score with 28 swollen joint count (DAS28) to identify remission. More recently, remission has been described based on routine assessment of patient index data (RAPID3), an index of only patient reported outcomes (PROs). Remission criteria of RAPID3 ≥ 3 and less than one swollen joint (RAPID3 SJ1) is comparable to Boolean criteria and can be implemented in busy clinical settings more easily than indices requiring a laboratory test or formal joint count.

Remission: No Single, Universal Criteria
In 1981, Pinals and colleagues presented a report of a committee of the ACR for preliminary remission criteria for RA. Remission was identified by “the total absence of all articular and extra-articular inflammation and immunologic activity related to RA.” Patients were required to meet 5 of 6 criteria during at least 2 consecutive months: morning stiffness of less than 15 minutes duration, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft-tissue swelling in joint or tendon sheaths, and a normal erythrocyte sedimentation rate (ESR) (Table 1). This criteria set has not been widely applied, as it was overly stringent and unattainable in the majority of patients. Multiple indices are available for criteria to identify remission in RA patients. Remission rates differ in RA studies depending on remission criteria selected. The rheumatology community has sought an optimal definition of remission in RA, since 1981, when the first report of a committee of the ACR was reported. Most reports over the last decade have described remission according to disease activity score (DAS) or DAS28. Remission also has been proposed according to a simplified disease activity index (SDAI) and clinical disease activity index (CDAI).

A committee of the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) has proposed two remission criteria sets, a Boolean Criteria set and SDAI, which are more stringent than DAS28 to identify remission. Recently, remission criteria sets have been described, based on routine assessment of patient index data (RAPID3), an index of only patient reported outcomes (PROs). This review will summarize evidence concerning the validity and advantages of using RAPID3 to recognize remission in RA and implementation in routine care to guide a treat to target strategy.

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tigue is considered a nonspecific symptom, as no significant association was found between fatigue and inflammation in RA, and a high percentage of patients with osteoarthritis (OA) and fibromyalgia also have fatigue. Morning stiffness and pain may also be common and have nonspecific symptoms. Duration of morning stiffness can be similar between patients with OA and RA, and chronic pain was reported by 35% of the Finnish population aged from 15 to 74 years. In addition, many people over 50 in the general population do not meet the ACR remission criteria. One attempt to make these criteria less stringent involved deletion of fatigue, in “modified Pinals criteria.”

The DAS was developed in the early 1990s to assess disease activity in RA. The DAS includes 4 measures, the Ritchie articular index of tender joints, a 44 swollen joint count, erythrocyte sedimentation rate (ESR), and a patient estimate of global status (PATGL) on a visual analogue scale (VAS). It is calculated according to a mathematical formula, developed from a discriminant analysis of when a doctor changed a patient’s disease modifying anti-rheumatic drug (DMARD). A modified version, including a 28 joint count, was subsequently described, which was shown to be as valid as the original DAS. A cut-point below 1.6 corresponds to remission for DAS compared to Pinals remission criteria. A cut-point below 1.6 corresponds to remission based on a formula to convert DAS to DAS28. However, patients classified as in remission according to DAS28 of 2.6 may have up to 8 swollen joints, leading to a search for more stringent remission criteria.

Two less complex composite indices include variables from the DAS but do not require a calculator. The simplified disease activity index (SDAI) constitutes a simple numerical summation of 5 measures, adding a physician estimate of global status (DOCGL), and includes a C-reactive protein (CRP) instead of ESR. A simpler version, the CDAI, does not include a laboratory test. Remission cut-points of 3.3 for the SDAI and 2.8 for the CDAI have been described, analyzing ratings of RA patients by expert rheumatologists.

In a combined effort to unify remission, a committee of the ACR and EULAR presented two criteria sets for remission to be used in clinical trials. One is the Boolean-based definition in which a patient must satisfy having no more than one swollen and tender joint, C reactive protein (CRP) level ≤ 1, and PATGL score ≤ 1 on a 0 to 10 scale. The second definition is based on the SDAI (value equal to or lower than 3.3). Both definitions include one patient-reported outcome, PATGL.

Application of these new criteria sets in routine care includes the same limitations as those of remission criteria based DAS28, SDAI, and CDAI. Laboratory measures often are not available when evaluating the patient, and ESR or CRP may be normal in the 40% of patients at presentation with RA. Furthermore, the two ACR/EULAR criteria sets include formal joint counts, which show high variability among observers and are not performed at most visits in usual care. Even when these new criteria sets were developed, the members of the committee pointed out that in routine care an acute-phase laboratory measure may not be available at every visit. Therefore, it was proposed to develop clinic-based practice criteria, which did not require laboratory variables, but are equally stringent as the two proposed criteria sets.

An index without formal joint counts, based on only PROs of physical function, pain, and patient global estimate, RAPID3 has been developed. RAPID3 alone appears insufficiently stringent as a remission criteria, although somewhat more stringent than DAS28. Therefore, additional simple criteria sets were analyzed in an early RA cohort, the ESPOIR cohort, as described in more detail below.

**Defining Remission Based on RAPID3**

RAPID3 is an index of the three patient self-report measures included in the RA Core Data Set: physical function, pain,
and patient global estimate of status. RAPID3 is correlated significantly with other composite indices, such as DAS28 and CDAI. Categories for high, moderate, and low activity and remission have been reported to be similar according to RAPID3, DAS28, and CDAI, suggesting that RAPID3 can be used as effectively as these composite indices.

Four RAPID3 based remission criteria sets have recently been described (Table 2). These criteria sets were compared to the previously described criteria sets based on the composite indices and the two newly proposed by the ACR-EULAR committee in an early arthritis population. The version most similar to the Boolean and SDAI criteria was RAPID3RSJ1, defined as $\text{RAPID3} \leq 3.0$ and fewer than a swollen joint on a careful examination (Table 3). Other proposed RAPID3-based criteria including DOCGL or no swollen joint appear more stringent than Boolean criteria. However, it seems reasonable to use a version which is similar to that proposed by the ACR/EULAR Committee but is more feasible in busy clinical settings.

As with the Boolean criteria, no patient had more than one swollen joint, by definition. The most frequently affected single joint in patients who were in remission was a wrist or MCP joint—not a knee, hip, or shoulder, which are more prognostic of severe outcomes.

### Advantages of Using PROs to Measure Disease Activity and Remission

According to the treat-to-target recommendations, treatment in RA should be targeted at remission (or low disease activity), in close consultation with the patient. PROs promote incorporation of a patient perspective in the physician’s assessment of RA. The three domains most frequently reported in clinical trials from the RA core set, physical function, pain, and PAMQOL, constitute RAPID3.

PROs present a number of advantages, which may be classified as pragmatic and scientific advantages. Pragmatic advantages include that the patient does almost all the work, completing a questionnaire helps prepare the patient for the encounter, and PROs promote patients as crucial partners in obtaining relevant clinical information. PROs improve patient-physician communication and facilitate patient involvement in shared treatment decisions. There is only one observer, the patient, so the data are more reproducible than with two observers; the same examiner at each visit.

### Table 2 RAPID3 Remission Criteria Sets

<table>
<thead>
<tr>
<th>Remission Criteria</th>
<th>RAPID3 ≤ 3</th>
<th>Careful Joint Examination</th>
<th>Physician Global ≤ 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPID3R</td>
<td>$\checkmark$</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RAPID3R SJ1</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>—</td>
</tr>
<tr>
<td>RAPID3R SJ1 DOC1</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>RAPID3R SJ0</td>
<td>$\checkmark$</td>
<td>—</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>RAPID3R SJ0 D1</td>
<td>$\checkmark$</td>
<td>—</td>
<td>$\checkmark$</td>
</tr>
</tbody>
</table>

### Table 3 Comparison between the Different Remission Criteria Using the ACR-EULAR Boolean Remission Criteria as Reference

<table>
<thead>
<tr>
<th>Indices</th>
<th>% Patients in Remission</th>
<th>ACR-EULAR Boolean (12.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agreement</td>
<td>Kappa (95% CI)</td>
</tr>
<tr>
<td>SDAI</td>
<td>17.1%</td>
<td>94.7% (0.73-0.86)</td>
</tr>
<tr>
<td>DAS28</td>
<td>32.5%</td>
<td>79.9% (0.39-0.52)</td>
</tr>
<tr>
<td>CDAI</td>
<td>17.9%</td>
<td>93.6% (0.69-0.82)</td>
</tr>
<tr>
<td>RAPID3R</td>
<td>25.1%</td>
<td>85.8% (0.48-0.62)</td>
</tr>
<tr>
<td>RAPID3R SJ1</td>
<td>18.2%</td>
<td>92.8% (0.66-0.80)</td>
</tr>
<tr>
<td>RAPID3R SJ1 D1</td>
<td>15.6%</td>
<td>93.7% (0.67-0.81)</td>
</tr>
<tr>
<td>RAPID3R SJ0</td>
<td>14.9%</td>
<td>92.2% (0.60-0.75)</td>
</tr>
<tr>
<td>RAPID3R SJ0 D1</td>
<td>12.8%</td>
<td>93.2% (0.61-0.78)</td>
</tr>
</tbody>
</table>

DAS28, disease activity score 28; SDAI, simplified disease activity index; CDAI, clinical activity index; RAPID3, routine assessment of patient index data; PPV, positive predictive value; NPV, negative predictive value.
for a joint count is not required; and measurement error and variation reported for joint counts\textsuperscript{9} are less with PROs.

PROs that are available before the visit save time for the doctor to direct the conversation. MDHAQ/RAPID3 may be informative in other rheumatic diseases,\textsuperscript{30} so it presents an additional advantage if the receptionist presents the same questionnaire to each patient, regardless of the diagnosis, to complete before seeing the doctor as part of the infrastructure of care. RAPID3 requires 5 seconds to score in contrast to almost 2 minutes for DAS28 or CDAI.\textsuperscript{31} A recent survey of ACR members indicated that RAPID3 is scored by 29% of respondents, similar to 27.8% for DAS28 and more frequent than 15.2% for CDAI.\textsuperscript{32}

PROs also present a number of scientific advantages. PROs distinguish active from control treatments at similar levels to DAS28 and CDAI in different clinical trials.\textsuperscript{33} Functional status is the most significant predictor of severe outcomes of RA, such as work disability, total joint replacement, and premature death,\textsuperscript{34} and predicts 5 year mortality even in the general population more significantly than smoking.\textsuperscript{35}

**Discussion**

The use of quantitative measures of disease activity facilitates clinical decision-making, including implementing a treat-to-target strategy to optimize outcomes in RA.\textsuperscript{36} The target of RA treatment is to suppress disease activity as completely as possible, with remission being the ultimate goal depending on patient characteristics. Quantitative measures allow comparison of patient status between visits in routine care, including possible remission status.

Estimation of remission from the patient and physician perspectives can differ. Physicians are more aware of disease features that could be harmful over long periods without necessarily causing pain or discomfort to the patient. For example, swollen joints and the acute phase response may be more associated with joint damage.\textsuperscript{37,38} Physicians tend to tolerate a higher number of tender joints compared to swollen joints to define similar levels of disease activity.\textsuperscript{39} By contrast, patients may not identify swelling accurately, tend to be ignorant of CRP or other laboratory data, and in general give higher priority to pain,\textsuperscript{40} even if pain is not related to RA activity.

Different remission rates have been described according to physician-derived or laboratory measures compared to those by patient-derived measures. Physician-patient discordance in global estimates has been reported, not only in RA,\textsuperscript{41} but also in other rheumatic diseases.\textsuperscript{42} Nonetheless, 79% full agreement between patient and physician estimates of remission has been found.\textsuperscript{43} In this study by Wolfe and colleagues, the prevalence of remission was 34.8% from the physician perspective and 30.9% from the patient perspective, less stringent than using DAS28 (28.5%) or CDAI (6.5%) in the same patients,\textsuperscript{44} probably representing more minimal disease activity than remission.

Limitations to patient self-report also are seen, including a need to translate questionnaires into different languages and cultural differences in interpretation of pain, fatigue, and other symptoms in different ethnic groups.\textsuperscript{45} Also, the capacity of HAQ physical function scores to document clinical improvement can be limited in part by irreversible joint damage.\textsuperscript{46}

Although the two remission criteria proposed by EULAR/ACR were developed for clinical trials, they have been tested in observational cohorts with similar results compared to trial data.\textsuperscript{47} Nonetheless, the need for laboratory tests and formal joint counts may present a limitation for implementation in routine care. MDHAQ/RAPID3 can provide a feasible basis for remission, with criteria that appear as scientifically valid as other remission criteria. Collection of MDHAQ/RAPID3 does not prevent collection of any additional remission criteria in clinical trials and clinical care for a treat-to-target strategy in RA patients.

**Disclosure Statement**

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

**References**


