RAPID3, An Index of Only 3 Patient Self-report Core Data Set Measures, but not ESR, Recognizes Incomplete Responses to Methotrexate in Usual Care of Patients with Rheumatoid Arthritis

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Abstract

Objective: To perform a longitudinal cohort study concerning the capacity of prospectively-collected erythrocyte sedimentation rates (ESR) and scores for physical function, pain, patient global estimate, and routine assessment of patient index data (RAPID3) on a multidimensional health assessment questionnaire (MDHAQ), to recognize incomplete versus adequate responses to methotrexate in rheumatoid arthritis (RA) in one usual care setting, prior to description of RAPID3.

Methods: All patients were seen in one academic setting, in which MDHAQ scores were collected in all patients at all visits in the infrastructure of care. ESR was collected in all RA patients. All 93 RA patients in whom methotrexate was initiated between 1996 and 2001 with available 5-year follow-up were analyzed. “Incomplete response” was defined as initiation of subsequent biological therapy and “adequate response” as no biological therapy over 5 years. Measures were analyzed at the baseline methotrexate visit and at a subsequent visit: in 30 “incomplete responders” when biological therapy was prescribed; and in 63 “adequate responders 2.6 years after methotrexate initiation (mean interval to biological therapy in “incomplete responders”).

Results: ESR fell similarly by 33% to 36% in both groups. MDHAQ scores fell by 56% to 79% over 2.6 years in adequate responders but increased by 0% to 31% in incomplete responders. Median RAPID3 fell from 10.6 to 3.6 (low severity = 3.1 to 6, remission ≤ 3) in adequate responders and rose from 14.9 to 16.2 (high severity > 12) in incomplete responders.

Conclusion: RAPID3, but not ESR, recognizes incomplete versus adequate methotrexate responses in usual clinical care, and may be useful in busy usual care settings.

A treat-to-target strategy, adjusting therapy to achieve low disease activity or remission according to an index, results in substantially better outcomes in patients with rheumatoid arthritis (RA) than traditional non-quantitative management.1-3 Most studies of treat-to-target involve the disease activity score with 28 joint count (DAS28),4 the most specific index for RA.5 However, DAS28 is limited in usual care by complex calculations (albeit available at an excellent web site: www.das-score.nl/das28/DAScalculators/dasculators.html) and need for a laboratory test, which often is not available or poorly informative.6 A clinical disease activity index (CDAI) eliminates these requirements.7 Nonetheless, both DAS28 and CDAI require a formal joint count, which is not performed at most rheumatology visits8 and is less reproducible than patient self-report scores for physical function and pain.9,10

An index of only the 3 RA Core Data Set patient self-report measures—physical function, pain, and patient global estimate—RAPID3 (routine assessment of patient index data 3), gives similar results to DAS28 and CDAI to distinguish active from control treatments in clinical trials of leflunomide,11 methotrexate,11 adalimumab,12 abatacept,13 and certolizumab,14 and is correlated significantly with DAS28 and CDAI in clinical trials11-14 and clinical care.15,16 RAPID3 is scored in about 5 seconds on a multidimensional health assessment questionnaire (MDHAQ), versus almost 2 minutes for DAS28 or CDAI.16 RAPID3 appears feasible in busy clinical care settings, and its potential capacity to implement a treat-to-target strategy in usual clinical care appeared of interest.17
Since 1980, the author has collected an MDHAQ from every patient at every visit. The individual measures were available to pursue a goal of tight control, described using a term from oncology—“no evidence of disease.”18 Formal RAPID3 scoring was introduced only in 2006,12,15 with categories of high (> 12), moderate (6.1 to 12), and low (3.1 to 6) severity, and remission (≤ 3),15,17 subsequent to all data analyzed in this report. The data provide an opportunity to analyze the capacity of RAPID3 to recognize adequate versus incomplete responses to methotrexate (MTX), prior to when RAPID3 became available to influence clinical decisions. RAPID3 scores could be analyzed retrospectively, on the basis prospectively-collected RAPID3 components on the MDHAQ, as presented in this report.

Methods

Patients

Patients in this study were seen by the author at a weekly academic clinical setting at Vanderbilt University between 1996 and 2006. Patients with RA have been described extensively in previous reports.19,20 Almost all patients were treated with MTX,20 unless there was a contraindication. After 1999, patients who had an inadequate response to MTX were treated with a biological agent. All 93 RA patients in whom MTX was initiated between 1996 and 2001 for whom MDHAQ scores were available 5 years later are included in analyses in this report.

Database

All patients completed a multidimensional health assessment questionnaire (MDHAQ),21 with three scores for physical function, pain, and patient global estimate, each scored 0-10. Each item in the physical function scale is scored 0-3 as in the traditional HAQ;22 the 10 physical function items of the MDHAQ (including 8 from the HAQ) have a total score range of 0-30, divided by 3 using a template on the MDHAQ to give a 0-10 score.21 Pain and patient global estimate each are assessed on a 0-10, 21 circle visual analog scale (VAS).21 All patients with RA had a careful joint examination, but not necessarily a formal joint count,18 and an erythrocyte sedimentation rate (ESR) recorded.

All visits were recorded in a database that included demographic, MDHAQ, laboratory, and medication data at each visit, organized electronically into paper flowsheets to monitor patients, which included individual measures of physical function, pain, and patient global estimate, but not RAPID3. “Abnormal values” were defined as: ESR ≥ 28 mm/hr, physical function, pain, patient estimate of global status > 2 of 10, and RAPID3 > 6 (moderate and high severity).15

Responses to Methotrexate

An “incomplete response” to MTX was defined as having treatment with a biological agent initiated by TP at a visit subsequent to MTX initiation. An “adequate response” to MTX was defined as not having any subsequent treatment with a biological agent over a period of 5 years. The mean interval from initiation of MTX to initiation of a biological agent in incomplete responders was 2.6 years (5.4 years in patients who initiated MTX pre-1999 when biological agents became available and 1.6 years post-1999).

Statistical Analyses

Mean and median ESR and MDHAQ scores were compared at baseline MTX initiation and at initiation of a biological agent in incomplete responders, and at MTX initiation and 2.6 years later in adequate responders. The proportions of patients who had an abnormal value, and mean changes in each clinical variable and RAPID3, as well as percent changes, were compared in the two groups at the baseline MTX visit versus the initiation of a biological agent in incomplete responders and 2.6 years later in adequate responders.

Results

Overall, 93 patients initiated MTX in 1996 to 2001 and had 5-year follow-up data, 63 (68%) with adequate responses (continued MTX and no biological agent) and 30 (32%) with incomplete responses (subsequent biological agent). Median age, disease duration, education level, and length of follow-up did not differ in the two groups (Table 1). As noted, the mean interval in incomplete responders from initiation of MTX to initiation of a biological agent was 2.6 years, 5.4 years in the 1990s prior to availability of biological agents (N = 13), and 1.6 years post-1999, when biological agents were initiated (N = 17) (data not shown).

In patients with subsequent adequate responses, baseline median ESR was 24 mm/hr, MDHAQ physical function 2.3, pain 4.1, patient global estimate 4.2 (all 0-10), and RAPID3 10.6 (0-30) (Table 2). By contrast, in subsequent incomplete responders, baseline median values were ESR 28 mm/hr, MDHAQ physical function 3.2, pain 5.2, patient global estimate 5.5, and RAPID3 14.9. An “abnormal value” in patients who would experience subsequent adequate versus incomplete responses to MTX was 46% vs. 50% for ESR, 53% vs. 63% for MDHAQ physical function, 73% vs. 90% for pain, 75% vs. 96% for patient global estimate, and 76% vs. 88% for RAPID3 (Table 2).

In the 63 patients with adequate MTX responses, median ESR fell by 33%, MDHAQ scores by 56% to 79%, and RAPID3 by 66% (Table 2). In the 30 patients with incomplete responses, only ESR was improved—by 36%. MDHAQ scores were unchanged or higher by 0% to 31% and RAPID3 higher by 9%. An abnormal value was seen in incomplete responders (at initiation of a biological agent) versus adequate responders to MTX (at 2.6 years after initiation of MTX) in 40% vs. 22% for ESR, 77% vs. 40% for MDHAQ physical function, 83% vs. 44% for pain, 87% vs. 35% for patient global estimate, and 87% vs. 39% for RAPID3 (Table 2).

Discussion

The data indicate that incomplete responses to MTX in patients RA, defined as being treated subsequently with a
biological agent, may be recognized in usual clinical care by RAPID3, and the three patient self-report RAPID3 component measures considerably more effectively than by ESR. Mean baseline RAPID3 scores at initiation of MTX were 10.6 in 63 subsequent adequate responders versus 14.9 in 30 subsequent incomplete responders, suggesting a higher likelihood of subsequent response associated with lower baseline scores. However, longitudinal differences between the two groups were considerably greater than those at baseline, as RAPID3 fell over 2.6 years from 10.6 to 3.6 in adequate MTX responders but rose from 14.9 to 16.2 at initiation of the biological agent in 30 incomplete responders. ESR, which is the most likely (often the only) quantitative measure found in the medical records of most RA patients, fell similarly in both groups.

Several limitations are seen in this study. Formal joint counts were available in only a minority of patients, and RAPID3 could not be compared to prospectively-collected DAS28 and CDAI for a treat-to-target strategy. The data were collected in a single setting by a single physician, who had a great interest in patient self-report scores over a period of decades. Therefore, rheumatologists who have limited or no experience with patient questionnaires may not be as responsive to MDHAQ data. Nonetheless, the data clearly document that a rheumatologist attuned to patient self-report data can use the information quite effectively to distinguish incomplete from adequate responses to methotrexate.

Ideally, data to compare DAS28, CDAI, or RAPID3 for a treat-to-target strategy might be studied in a clinical trial. However, such a trial might prove impossible at this time, as current emphasis on treat-to-target would likely result in “contamination of the control,” i.e., rheumatologists would inadvertently treat “control” patients “to target” according to any index. Furthermore, prospective computation of RAPID3 (or DAS28 or CDAI) at this time could influence a rheumatologist to decide that a patient has an “incomplete response” to MTX and initiate a biological agent. The decisions to initiate biological therapy (and MTX) in patients studied in this report were not guided by RAPID3, DAS28, or CDAI, or any formal criteria, although individual scores for physical function, pain, and patient global estimate were known to the treating physician.

### Table 1
Demographic Variables in 63 Adequate Methotrexate (MTX) Responders and 30 Incomplete MTX Responders (Data Are Expressed as Median, Interquartile Range)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adequate Response: No biological agent (N = 63)</th>
<th>Incomplete Response to MTX, with addition of biological agent (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.5 (19.7)</td>
<td>54.6 (20.9)</td>
</tr>
<tr>
<td>Duration of disease, years</td>
<td>3.5 (8.8)</td>
<td>2.9 (8.9)</td>
</tr>
<tr>
<td>Formal education, years</td>
<td>12.0 (3.0)</td>
<td>12.0 (2.0)</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td>2.6 (0.2)</td>
<td>2.7 (2.8)</td>
</tr>
</tbody>
</table>

### Table 2
Measures and Indices in 63 Adequate Methotrexate (MTX) Responders and 30 Incomplete MTX Responders, at MTX Initiation and at Follow-up or Initiation of Biological Agent, Respectively

#### Table 2a
63 patients who received MTX only: Adequate responses—no biological agent

<table>
<thead>
<tr>
<th>Measure (“Abnormal” Value)</th>
<th>At MTX Initiation</th>
<th>At Follow-up 2.6 Years Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR, mm/h (≥ 28)</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>Physical function, 0-10 scale (&gt; 2)</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>Pain, 0-10 scale (&gt; 2)</td>
<td>73%</td>
<td>44%</td>
</tr>
<tr>
<td>Patient global, 0-10 scale (&gt; 2)</td>
<td>75%</td>
<td>35%</td>
</tr>
<tr>
<td>RAPID3, 0-30 scale (&gt; 6)</td>
<td>78%</td>
<td>39%</td>
</tr>
</tbody>
</table>

#### Table 2b
30 patients who were treated with biological agents after incomplete response to MTX

<table>
<thead>
<tr>
<th>Measure (“Abnormal” Value)</th>
<th>At MTX Initiation</th>
<th>At Biologic Initiation (mean 2.6 years later)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR, mm/h (≥ 28)</td>
<td>28%</td>
<td>18%</td>
</tr>
<tr>
<td>Physical function, 0-10 scale (&gt; 2)</td>
<td>63%</td>
<td>77%</td>
</tr>
<tr>
<td>Pain, 0-10 scale (&gt; 2)</td>
<td>90%</td>
<td>83%</td>
</tr>
<tr>
<td>Patient global, 0-10 scale (&gt; 2)</td>
<td>96%</td>
<td>87%</td>
</tr>
<tr>
<td>RAPID3, 0-30 scale (&gt; 6)</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; RAPID3, routine assessment of patient index data.
The three components of RAPID3 were collected prospectively prior to a formal practice of “treat-to-target” and document that RAPID3 clearly recognizes incomplete versus adequate responses to MTX in patients with RA. The data provide a unique opportunity for such documentation, likely no longer available through randomized studies. RAPID3 is correlated significantly with DAS28 and CDAI\(^{15,16}\) and is similarly efficient to distinguish active from control treatment in clinical trials,\(^{11,13,14}\) suggesting that any of these three indices might be used effectively in a “treat-to-target” strategy. RAPID3 may be useful in busy usual care settings.

**Disclosure Statement**

The study was approved by the Institutional Review Board of Vanderbilt University, and all participants gave informed consent to participate. The author declares no competing interests. The work reported herein was supported in part by grants from the Arthritis Foundation, the Jack C. Massey Foundation, and Bristol-Myers Squibb (investigator-initiated study).

**References**


5. Pincus T. The DAS is the most specific measure, but a patient questionnaire is the most informative measure to assess rheumatoid arthritis. J Rheumatol. 2006 May;33(5):834-7.


