Agreement between Rheumatologist and Patient-reported Adherence to Methotrexate in a US Rheumatoid Arthritis Registry

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ABSTRACT. Objective. Rheumatologists have limited tools to assess medication adherence. The extent to which methotrexate (MTX) adherence is overestimated by rheumatologists is unknown.

Methods. We deployed an Internet survey to patients with rheumatoid arthritis (RA) participating in a US registry. Patient self-report was the gold standard compared to MTX recorded in the registry.

Results. Response rate to the survey was 44%. Of 228 patients whose rheumatologist reported current MTX at the time of the most recent registry visit, 45 (19.7%) had discontinued (n = 19, 8.3%) or missed ≥ 1 dose in the last month (n = 26, 11.4%). For the subgroup whose rheumatologist also confirmed at the next visit that they were still taking MTX (n = 149), only 2.6% reported not taking it, and 10.7% had missed at least 1 dose.

Conclusion. MTX use was misclassified for 13%–20% of patients, mainly because of 1 or more missed doses rather than overt discontinuation. Clinicians should be aware of suboptimal adherence when assessing MTX response. (First Release May 1 2016; J Rheumatol 2016;43:1027–9; doi:10.3899/jrheum.151136)

Key Indexing Terms: ADHERENCE PERSISTENCE RHEUMATOID ARTHRITIS METHOTREXATE

Physicians generally have a limited set of tools to assess patient’s adherence with their prescribed medications. A common practice to assess adherence clinically might be to ask patients at each office visit whether they are still taking each medication. This type of medication reconciliation is enjoined to meet Meaningful Use Stage 2 requirements as specified by the US Centers for Medicare & Medicaid Services Electronic Health Record Incentive Program1. Many rheumatoid arthritis (RA) registries identify information in a similar fashion, using data collected at the time of an office visit and recorded by the rheumatologist. Lower adherence to RA medications such as methotrexate (MTX) has been associated with higher disease activity and worse functional status2,3.

More sophisticated means might be used to identify additional detail about intentional or unintentional interruptions in medications. These methods might include the MEMSCap or drug metabolites3,4, or use of external data sources such as pharmacy databases5,6,7,8. However, these methods are usually expensive, cumbersome, or simply not available at the point of care. A more detailed clinical interview to assess patient’s medication adherence in the office setting might be useful but may be impractical because of time pressures in busy office settings. Moreover, it is possible that patients may be uncomfortable with admitting to their physicians that they are intentionally erratic in taking their prescribed medications or might even have discontinued. This phenomenon has been described as a “social desirability bias,” and it has been shown to be related to self-reported willingness to change behaviors and clinic attendance9.

Given these challenges in assessing medication use in the office setting, and because MTX is sometimes accompanied by a variety of symptoms that may be bothersome to patients and could affect persistence10, the focus of our study was on MTX adherence. We evaluated the validity of rheumatologist-reported MTX use compared to patients’ self-report when asked in an out-of-office setting.

MATERIALS AND METHODS

We used data from the Consortium of Rheumatology Researchers of North America (CORRONA) RA disease registry. In the first half of 2014, we conducted a cross-sectional, Internet-based survey of patients with RA participating in the CORRONA Effectiveness Registry to Study Therapies for Arthritis and Inflammatory coNditions (CERTAIN) substudy, which enrolled patients with RA with active disease (Clinical Disease Activity Index > 10)11. As part of CERTAIN participation, patients provided information and consent to allow direct-to-patient contact at home by e-mail, telephone, or other methods.
RESULTS
A total of 984 unique patients had a valid e-mail address and were eligible for the survey, and 430 (44%) responded. There were few systematic differences between survey responders and nonresponders, although survey respondents were slightly younger and with somewhat shorter RA disease duration (Appendix 1). Of 228 patients whose rheumatologist said at the most recent registry visit that they were taking MTX and therefore included in our analysis, the median (interquartile range) interval of time between the most recent registry visit and the Internet survey was 69 days (36–139). Overall, 45 patients (19.7%) said on the survey that they were either not taking MTX (n = 19, 8.3%) or had missed 1 or more doses in the last 4 weeks (n = 26, 11.4%). There were no strong risk factors when comparing patients fully adherent to MTX and those with imperfect adherence (Table 1), although higher physician’s and patient’s global assessments had a borderline statistical association with MTX adherence. There were no significant risk factors associated with adherence after multivariable adjustment, including the interval of time between the registry visit and the survey (data not shown). In the subgroup analysis of patients who had MTX use confirmed by the rheumatologist at the next registry visit within 6 months (n = 149), results were similar. Fewer patients (n = 4, 2.6%) said that they had discontinued MTX, and an additional 16 patients (10.7%) said that they had missed 1 or more doses in the last 4 weeks (13.3% in total).

DISCUSSION
In this large US registry, overall MTX use was generally ascertained accurately by rheumatologists as reported to the registry compared to the gold standard of patients asked about their actual MTX use in the last 4 weeks. The patients’ assess-
different results than we found in this patient population with largely established disease. We acknowledge that the e-mailed survey did not specifically probe for factors underlying the reasons for nonadherence to MTX and is a recognized limitation. We also note that the gold standard for our adherence assessment was patient self-report, a commonly used albeit admittedly imperfect measure of medication adherence that sometimes yields higher estimates of medication adherence compared with other measurement methods. We also asked about adherence only over the last 4 weeks, with concern that any time frame longer than this would yield potential recall bias and that patients could not accurately remember that far back. To our knowledge, there are no validated, drug-specific instruments to either detect or assess underlying reasons for nonadherence to specific medications. Moreover, we expect that mobile (e.g., smartphone-based) tools currently in development will make assessment of nonadherence easier for patients to report between office visits and for physicians to intervene, as warranted. Future evaluation is warranted of the downstream effects of MTX nonadherence in terms of higher disease activity, patient symptoms, immunogenicity, and safety events.

REFERENCES


**APPENDIX 1.** Characteristics of patients with RA treated with MTX by response versus nonresponse to the survey, and those not treated with MTX by response versus nonresponse to the survey. Values are mean (SD) unless otherwise specified.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treated with MTX, Responded to Survey</th>
<th>Treated with MTX, Not Responded to Survey</th>
<th>p</th>
<th>Not Treated with MTX, Responded to Survey</th>
<th>Treated with MTX, Not Treated with MTX, Not Responded</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>228</td>
<td>284</td>
<td>0.004</td>
<td>202</td>
<td>270</td>
<td>0.31</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>53.18 (12.42)</td>
<td>56.62 (12.43)</td>
<td></td>
<td>53.61 (12.51)</td>
<td>55.02 (13.15)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>184 (80.7)</td>
<td>213 (76.6)</td>
<td>0.26</td>
<td>163 (80.7)</td>
<td>225 (86.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>CDAI</td>
<td>17.46 (14.72)</td>
<td>16.59 (13.68)</td>
<td>0.67</td>
<td>17.28 (14.38)</td>
<td>17.90 (13.75)</td>
<td>0.52</td>
</tr>
<tr>
<td>mHAQ</td>
<td>0.42 (0.47)</td>
<td>0.43 (0.45)</td>
<td>0.59</td>
<td>0.46 (0.48)</td>
<td>0.48 (0.48)</td>
<td>0.60</td>
</tr>
<tr>
<td>PGA, 0–100</td>
<td>28.81 (24.08)</td>
<td>25.99 (21.93)</td>
<td>0.27</td>
<td>27.45 (22.23)</td>
<td>29.12 (23.08)</td>
<td>0.43</td>
</tr>
<tr>
<td>PtGA, 0–100</td>
<td>38.53 (26.87)</td>
<td>40.36 (27.95)</td>
<td>0.52</td>
<td>40.52 (27.37)</td>
<td>43.26 (27.14)</td>
<td>0.32</td>
</tr>
<tr>
<td>Patient pain, 0–100</td>
<td>39.15 (28.03)</td>
<td>43.72 (29.67)</td>
<td>0.61</td>
<td>43.53 (30.07)</td>
<td>46.32 (29.19)</td>
<td>0.36</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>7.31 (8.38)</td>
<td>9.14 (8.82)</td>
<td>0.0007</td>
<td>9.59 (8.44)</td>
<td>10.04 (9.27)</td>
<td>0.78</td>
</tr>
<tr>
<td>Glucocorticoid use, n (%)</td>
<td>59 (25.9)</td>
<td>76 (26.8)</td>
<td>0.82</td>
<td>56 (27.7)</td>
<td>63 (23.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Biologic use, n (%)</td>
<td>214 (93.9)</td>
<td>229 (80.6)</td>
<td>&lt;0.0001</td>
<td>167 (82.7)</td>
<td>201 (74.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; MTX: methotrexate; CDAI: Clinical Disease Activity Index; mHAQ: modified Health Assessment Questionnaire; PGA: physician’s global assessment; PtGA: patient’s global assessment.

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