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. (J Rheumatol First Release May 1 2016; 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 Program[1]. 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 status[2,3].

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 metabolites[3,4], or use of external data sources such as pharmacy databases[5,6,7,8]. 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 attendance[9].

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 persistence[10], 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.

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Patient survey. CERTAIN patients were eligible for our survey if they provided a valid e-mail address. They were contacted by e-mail and if they did not respond to the initial contact, were reminded again at 3 months. The survey asked patients, "Are you currently taking methotrexate for your rheumatoid arthritis? Methotrexate is usually taken once weekly" and "Many people find it sometimes difficult to take methotrexate because of side effects or other reasons. In the last 4 weeks, how many weekly doses of methotrexate do you think that you have taken?" Patient report from the survey was used as the gold standard for actual MTX use in the last 4 weeks. The analysis was restricted to patients with RA whose doctors recorded at the most recent registry visit that the patient was taking MTX at the time of the visit, as identified using the physician's usual practices of ascertaining medication initiation, use, and discontinuation. Covariates were measured at the time of this office visit. A subgroup analysis reevaluated the findings among the patients who also had a followup registry visit within 6 months where the rheumatologist again affirmed that the patient was still taking MTX.

Statistical analysis. Descriptive statistics including chi-square tests were used to compare characteristics of patients who were fully adherent (took all weekly doses expected in the preceding 4 weeks) compared with those who did not take all 4 doses. Multivariable logistic regression was used to identify independent factors associated with adherence, including all factors measured at the preceding registry visit as well as the number of days between the registry visit and the date of the survey. All analyses were conducted in SAS 9.3. The study and associated survey were governed by both a central institutional review board and relevant local institutional review boards.

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).

Table 1. Factors associated with patients with RA missing some or all MTX doses in the last 4 weeks whose rheumatologist reported MTX use at the most recent registry visit (n = 228 patients). Values are mean (SD) unless otherwise specified.

Variables	Missed 1 or More MTX Dose(s), n = 45	Took all MTX Doses, n = 183	p
Age, yrs	51.96 (11.70)	53.49 (12.61)	0.46
Female, n (%)	38 (84.4)	146 (79.8)	0.47
CDAI	20.05 (15.92)	16.82 (14.39)	0.21
mHAQ	0.47 (0.50)	0.40 (0.47)	0.64
PGA, 0–100	34.71 (26.31)	27.36 (23.35)	0.08
PtGA, 0–100	45.53 (29.94)	36.81 (25.86)	0.06
Patient pain, 0–100	43.82 (31.60)	38.01 (27.06)	0.29
Disease duration, yrs	9.05 (8.85)	6.88 (8.23)	0.22
Glucocorticoid use, n (%)	15 (33.3)	44 (24.0)	0.20
Biologics, n (%)	41 (91.1)	173 (94.5)	0.39
MTX use, n (%)			0.56
Oral	19 (73.1)	143 (78.1)	
SQ	7 (26.9)	40 (21.9)	

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; SQ: subcutaneous.

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' assessments were conducted online and at home, a setting where social desirability bias is expected to be lessened compared with in-office assessment. Of the patients whose rheumatologists said that they believed their patient was taking MTX at the past and next office visit, only 13% reported either not taking MTX at all or had missed some doses. A minority (3%) said that they had discontinued completely, and the remainder said that they had missed 1 or more doses in the last month. Given these findings, physicians should be aware that simply asking patients about whether they are still taking MTX (i.e., persistence or non-discontinuation) is perhaps overly simplistic, given that more patients in our analysis said that they were persistent with MTX yet had missed some doses.

Our study reflects an important design feature. Patients were asked about their adherence outside of the office setting, where social desirability bias may dissuade nonadherent patients from answering truthfully. Few past studies in rheumatology have been able to leverage orthogonal sources of information that bring together independent adherence assessments from both rheumatologists and patients. Moreover, while it is possible that rheumatologists may have instructed patients to discontinue MTX after the office visit, the subgroup analysis that restricted the analysis to people reported by the physician to be taking MTX at the next registry visit helped address this concern. While we acknowledge our modest sample size and note the response rate of 44% as a potential limitation, it is in the range commonly found in the medical literature[12,13,14]. Moreover, we found few systematic differences between responders and nonresponders to the survey.

It is notable that we did not find strong clinical risk factors for MTX nonadherence. It is possible that certain treatment settings (e.g., initiating MTX in very early RA) may yield

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[15]. 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 in rheumatology. For that reason, ongoing work is under way to develop a short paper-based instrument to allow rheumatologists to routinely assess MTX adherence and associated factors in an office setting in a time-efficient fashion[16]. 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.

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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.

Characteristics	Treated with MTX, Responded to Survey	Treated with MTX, Not Responded to Survey	p	Not Treated with MTX, Responded to Survey	Not Treated with MTX, Not Responded to Survey	p
n	228	284		202	270	
Age, yrs	53.18 (12.42)	56.62 (12.43)	0.004	53.61 (12.51)	55.02 (13.15)	0.31
Female, n (%)	184 (80.7)	213 (76.6)	0.26	163 (80.7)	225 (86.2)	0.11
CDAI	17.46 (14.72)	16.59 (13.68)	0.67	17.28 (14.38)	17.90 (13.75)	0.52
mHAQ	0.42 (0.47)	0.43 (0.45)	0.59	0.46 (0.48)	0.48 (0.48)	0.60
PGA, 0–100	28.81 (24.08)	25.99 (21.93)	0.27	27.45 (22.23)	29.12 (23.08)	0.43
PtGA, 0–100	38.53 (26.87)	40.36 (27.95)	0.52	40.52 (27.37)	43.26 (27.14)	0.32
Patient pain, 0–100	39.15 (28.03)	43.72 (29.67)	0.10	43.53 (30.07)	46.32 (29.19)	0.36
Disease duration, yrs	7.31 (8.38)	9.14 (8.82)	0.0007	9.59 (8.44)	10.04 (9.27)	0.78
Glucocorticoid use, n (%)	59 (25.9)	76 (26.8)	0.82	56 (27.7)	63 (23.3)	0.27
Biologic use, n (%)	214 (93.9)	229 (80.6)	< 0.0001	167 (82.7)	201 (74.4)	0.03

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.