ORIGINAL RESEARCH

Patient-Reported Nausea and Fatigue Related to Methotrexate: A Prospective, Self-Controlled Study in the ArthritisPower® Registry

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ABSTRACT

Introduction: The magnitude and frequency of temporally related methotrexate (MTX)-associated side effects in rheumatoid arthritis (RA) or psoriatic arthritis (PsA) patients are difficult to quantify using traditional research methods. As proof of concept designed in part to implement digital data collection for remote patient monitoring, we conducted a study implementing self-controlled case series analytic methods to understand MTX-related symptoms in RA or PsA.
Methods: In study phase 1, adults with RA or PsA from the ArthritisPower® Registry (past or current oral MTX users) participated in a cross-sectional survey. In phase 2, current MTX users participated in a longitudinal study and completed the Patient-Reported Outcomes Measurement Information System (PROMIS®) 1-day nausea/vomiting and fatigue measure. Within-person change in PROMIS scores between risk (6–36 h post-dose) and control (96–144 h post-dose) windows were compared using mixed models.
Results: The baseline survey was completed by 671 participants (mean age: 54 years, 88% female, 92% white, 79% with RA). Among current MTX users (353/671 [53%]), most reported MTX-associated side effects (216/353 [61%]), most frequently fatigue (161/353 [46%]). Among phase 2 participants with ($n = 39$) and without ($n = 84$) baseline nausea, mean increase in PROMIS nausea was 5.1 units ($P < 0.0001$) and 0.7 units ($P = 0.135$), respectively; among those with ($n = 51$) and without ($n = 72$) baseline fatigue, mean increase in PROMIS fatigue was 3.9 units ($P = 0.0003$) and 0.4 units ($P = 0.554$), respectively.
Conclusions: Digital remote patient monitoring presents an opportunity to detect and address medication tolerability in real time. Using a novel study design to control for between-person confounding, the magnitude of nausea and fatigue experienced by participants with RA and PsA temporally related to weekly MTX use was substantial.

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Key Summary Points

Why carry out this study?

Methotrexate is an important treatment option prescribed by physicians to optimize disease control in patients with RA or PsA; however, patients often experience bothersome side effects, notably fatigue and nausea, which are temporally related to weekly MTX dosing and may result in poor adherence and suboptimal disease management. Such data may be difficult to capture in routine care settings if symptoms fluctuate from day to day. Digital remote patient monitoring presents an opportunity to detect and address medication tolerability in real time.

What was learned from this study?

We used a self-controlled case series study design using electronic patient-reported outcome measures (e-PROMs) to generate real-world evidence regarding patients' experiences and perceptions of treatment side effects and found that the majority of current MTX users report side effects, such as fatigue and nausea, with mean changes exceeding a minimally important difference.

Gastrointestinal (GI) side effects, such as stomach upset and pain, may play a more substantial role in patients' decisions to discontinue MTX compared to other side effects.

Healthcare practitioners should consider the burden of MTX use in patients who may be bothered by side effects on a weekly basis but are not forthcoming in disclosing these symptoms to their clinician.

A smartphone-based strategy that implements remote patient monitoring to capture medication-related symptoms appears both feasible and acceptable to patients.

INTRODUCTION

Methotrexate (MTX) remains a frequently used therapy for patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) due to its cost-effectiveness and clinical benefits in both populations [1–5]. As the cornerstone of therapy for RA and PsA, its use is codified in recommendations to clinicians from the American College of Rheumatology about "Choosing Wisely" [6]. Other treatment options including biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic (ts)DMARDs are more effective when used in combination with MTX at a group level. Despite its well-known benefits, MTX use is associated with a number of adverse events (AEs), including nausea, fatigue, gastrointestinal (GI) toxicity, and mouth sores, as well as more serious, albeit rare, AEs such as liver toxicity and bone marrow suppression [5, 7, 8]. These rare AEs, as well as poor tolerability in some patients, may make the use of MTX burdensome for some individuals [9–11]. The impact of these safety and tolerability considerations may be appreciable. Indeed, past studies have shown that as many as 50% of RA and PsA patients discontinue MTX within 6 months to 2 years of treatment due to intolerance and GI symptoms [12–17], either with or without their physicians' knowledge [9–11]. A recent review of trials in RA found that non-serious medication-related AEs were not consistently reported [18].

Currently, a gap exists in patient-centric studies that focus on the patient experience with MTX, including beliefs regarding its benefits and behavioral distress and anxiety experienced by patients in anticipation of their upcoming dose. An important feature of MTX use is that some symptoms may be temporally related to its weekly administration [19]. For example, patients may experience nausea, fatigue, or malaise within a few days after MTX dosing, which may subsequently improve over time until the next weekly dose is given. This pattern is particularly difficult to study in clinical trials or with traditional study designs (e.g., a cohort study) because it would require multiple study visits within the same week, which is

something that may be infeasible from a participant burden perspective. A digital, app-based method for data collection from patients between office visits may improve accessibility and patient participation for a study or a clinical remote patient monitoring system that requires multiple data collection points within the same week.

Facilitating the implementation of such a digital data collection strategy, previous studies conducted in patients living with chronic conditions have indicated that the National Institutes of Health–developed Patient Reported Outcomes Measurement Information System (PROMIS®) can reliably capture important patient experiences across the domains of physical, mental, and social health. The PROMIS scales are available in both a fixed short form as well as a computer-adaptive testing format and have shown robust psychometric properties [13]. For example, the PROMIS fatigue instruments have been shown to be reliable, well correlated with, and responsive to change in RA disease activity [20, 21].

As a proof-of-concept study of a novel digital health strategy to capture medication-related symptoms and using a novel continuous self-controlled case series study design to control for between-person confounding, we collected data from a smartphone app at different time points before and after administration of MTX. This study aimed to assess the following outcomes: to characterize the frequency of various bothersome symptoms associated with MTX use; to examine patients' overall satisfaction with MTX; and to identify meaningful worsening in nausea or fatigue occurring shortly after weekly MTX administration using validated outcome measures.

METHODS

Study Population

Participants were recruited from within the ArthritisPower® Patient-Powered Research Network Registry. ArthritisPower is a collaboration between the nonprofit Global Healthy Living Foundation (the parent organization of the CreakyJoints® arthritis patient community) and academic researchers at the University of Alabama at Birmingham. It enrolls adult patients with RA, PsA, or other rheumatic, skin, and musculoskeletal conditions interested in participating in research studies and has grown to 34,164 patients to date. The current study was an ancillary study of the registry (Advarra IRB Protocol #00033156) during which eligible ArthritisPower members opted in for additional data collection. Because this was a sub-study that did not go beyond collection and analysis of patient-reported outcome or other observational data being routinely collected by the registry, no additional consent or addendum to consent was required. The study was conducted in accordance with ethical principles of the Declaration of Helsinki 1964, and its later amendments.

Eligibility for this ancillary study required ArthritisPower registry participation (US residents: aged ≥ 19 years; Puerto Rico residents: aged ≥ 21 years) with a self-reported physician diagnosis of RA or PsA and an invitation to participate in a cross-sectional survey (phase 1 of the study) via e-mail. Phase 1 participants were current or past users of oral MTX; current users were then invited to participate in the longitudinal phase of the study (phase 2), which required current MTX use, with at least 1 dose taken in the prior month, and use of MTX for < 10 years. In the absence of data indicating a tolerance threshold for duration of MTX therapy, the 10-year limit was chosen to strike a balance between possible adjustment to MTX tolerance over time and enabling adequate participation in the survey. MTX use was permitted either alone (i.e., monotherapy) or in combination with other DMARDs. Rolling recruitment of participants occurred from May 2019 to April 2020.

Survey Phases

The flow of the survey phases is shown in Fig. 1A. Phase 1 participants completed a cross-sectional survey online (see Supplementary Material, Phase 1 Survey Questions) using the health insurance portability and accountability
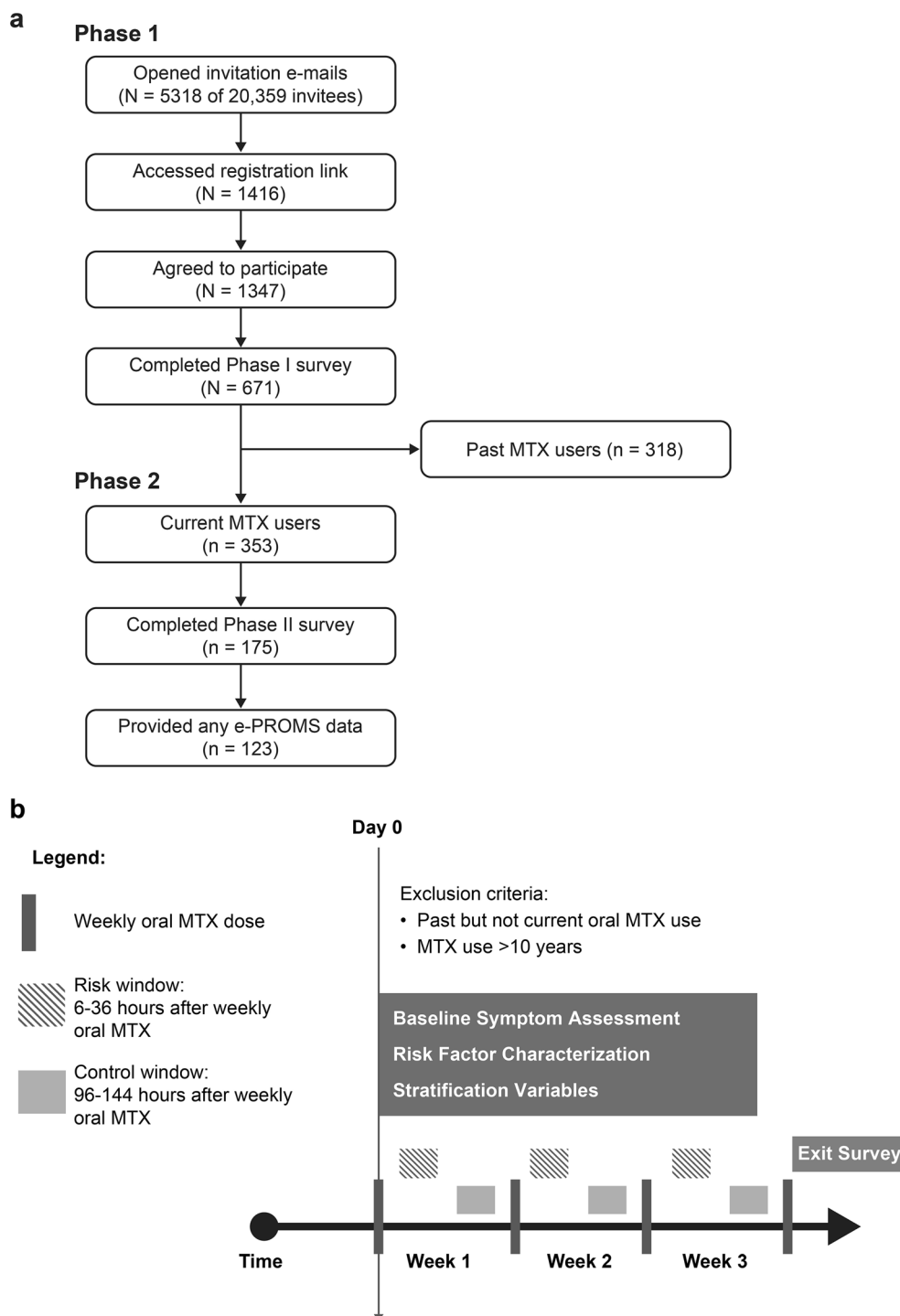
a

Phase 1

Opened invitation e-mails
(N = 5318 of 20,359 invitees)

↓

Accessed registration link
(N = 1416)

↓

Agreed to participate
(N = 1347)

↓

Completed Phase I survey
(N = 671)

→ Past MTX users (n = 318)

Phase 2

Current MTX users
(n = 353)

↓

Completed Phase II survey
(n = 175)

↓

Provided any e-PROMS data
(n = 123)

b

Day 0

Legend:

▌ Weekly oral MTX dose

▨ Risk window:
6-36 hours after weekly oral MTX

▨ Control window:
96-144 hours after weekly oral MTX

Exclusion criteria:
• Past but not current oral MTX use
• MTX use >10 years

Baseline Symptom Assessment

Risk Factor Characterization

Stratification Variables

Exit Survey

Time   Week 1   Week 2   Week 3

Fig. 1 A Flow of the participants in the phase 1 and phase 2 surveys and B study design for the self-controlled case series analysis over 3 weeks. *MTX* methotrexate

act-compliant SurveyMonkey platform, which included questions on what symptoms or side effects they have or had previously experienced while taking MTX, and the five-item specific-

necessity scale from the beliefs about medicine questionnaire [22].

Participants opting in for the phase 2 longitudinal study were asked to complete another brief baseline survey and patient-reported outcome assessments (Table S1). Phase 2 baseline survey assessments included questions pertaining to current MTX use such as dose and brand, timing of the RA or PsA diagnosis, and general physical and mental state associated with MTX dosing (Figure S1). During the 3-week observation period, participants were asked to record the exact date and time that they took MTX for each subsequent week, and then complete up to 6 (i.e., twice-weekly for 3 weeks) electronic patient-reported outcome measures (e-PROMs), both at 6–36 h after taking MTX (the "risk window") and 96–144 h after taking MTX (the "control window") (Fig. 1B). Risk and control windows were selected based on the expected temporal relationship between MTX use and peak onset of these symptoms. This study design is termed a continuous self-controlled case series (SCCS) [23] and compares participants' health state in the risk window with that in their control window. SCCS models are typically used with a binary outcome, but a continuous SCCS design was employed here, as done in other studies. Because participants serve as their own controls, this study design avoids typical between-person confounding because all-time invariant factors (e.g., age, sex, comorbidities, concomitant RA medications) are perfectly balanced within the same individual.

Four health domains were assessed in the phase 2 longitudinal survey: (1) physical health using a modified version of the PROMIS GI nausea and vomiting instrument; PROMIS Fatigue, PROMIS Physical Function, and PROMIS Pain Interference short forms; (2) mental health using the PROMIS Anxiety and Applied Cognition Abilities short forms; (3) social health using the PROMIS Ability to Participate in Social Roles and Activities short forms; and (4) MTX tolerance and satisfaction using the Methotrexate Intolerance Severity Score (i.e., MISS) questionnaire. Although PROMIS includes a four-item instrument for nausea (https://www.healthmeasures.net/index.php), the time referent for 1 of the questions ("In the past 7 days, how often did you throw up or vomit?") was unsuitable for a daily e-PROM. Thus, we removed that question and scored the remaining three items using the custom instrument scoring feature available for PROMIS instruments (https://www.assessmentcenter.net/ac_scoringservice) (Table S1). Although it may vary slightly across health domains and patient populations, the minimally important difference (MID) in PROMIS instruments for a group mean change is typically considered to be approximately 2–3 units, and a five-unit change for individual patients [24–26]. We conducted two analyses that considered either a within-person change of > 3 units as the MID for nausea and fatigue, and a within-person change of > 5 units.

Statistical Analysis

We conducted descriptive analysis using paired t tests, one-sided comparisons for continuous variables, and Chi-square tests for categorical variables. Within-person change in PROMIS scores between the risk and control windows were analyzed using mixed models for repeated measures and stratified by whether participants reported nausea or fatigue with MTX at baseline in their response to Yes/No questions: "Do you commonly feel fatigue within a day of taking methotrexate compared with other times?"; "Do you commonly have gastrointestinal symptoms, like nausea or vomiting, within a day of taking methotrexate compared with other times?". We also included an interaction term with the baseline score. Detecting a significant difference in the within-person change in the 1-day PROMIS GI nausea and vomiting score or the PROMIS fatigue score was determined at the 5% level ($P < 0.05$), with 95% confidence intervals. All analyses were performed using SAS 9.4 software (SAS Software, Cary, NC, USA).

RESULTS

Participant Characteristics: Phase 1

Invitations to participate were e-mailed to 17,981 eligible members in the ArthritisPower Registry and 2378 eligible members in the CreakyJoints community. Up to two e-mail reminders were sent to non-responders. E-mails were opened by 26.1% (5318/20,359) of members, and the registration link was accessed by 26.6% (1416/5318) of those who saw the e-mail. A total of 1347 members agreed to participate and 671 eligible members completed the phase 1 survey (Fig. 1A). Of the 671 respondents who completed the survey, 528 (78.7%) reported physician-diagnosed RA and 193 (28.8%) reported PsA; 50 (7.5%) respondents reported both RA and PsA. Among the eligible patients, 353 (52.6%) were taking oral MTX at the time of survey administration (i.e., current users) and 318 (47.4%) were prior users who had discontinued. Most respondents were female (88.4%), with a mean (standard deviation [SD]) age of 54.0 (11.6) years, and white (92.4%). Mean (SD) duration of MTX treatment among current users was 4.9 (6.2) years; nearly all users (96.6%) took folic acid concurrently. Among current MTX users ($N = 353$), about half (48.2%) agreed that their life would be impossible without MTX, 66.0% believed that MTX protects them against worsening disease, and 44.5% believed that they would be very sick without MTX (Fig. 2). However, among current MTX users, 79.6% agreed that they would stop taking MTX if their RA or PsA was well controlled and their doctors said it was okay to stop taking it.

A significantly higher percentage of past versus current MTX users reported experiencing at least one side effect that they related to the medication (78.9 vs. 61.2%; $P < 0.0001$) (Table 1), and among past users ($N = 318$), 65.1% said they stopped taking MTX because of unwanted side effects they thought were related to MTX. Fatigue was the most common side effect reported among both subgroups of patients and experienced by 45.6% of current and 44.7% of past users. Compared with current users of MTX, patients who discontinued MTX

(i.e., past users; asked to recall their symptoms based on prior use of MTX) reported a significantly higher incidence of GI side effects, including nausea (40.3 vs. 30.6%; $P = 0.009$) and abdominal pain (22.3 vs. 14.7%; $P = 0.011$). A significantly higher proportion of past versus current users also reported experiencing malaise related to their MTX dose (27.4 vs. 16.1%; $P < 0.001$). In addition, when current and past users of MTX were questioned on whether they believe that they experienced nausea/vomiting or fatigue within 1 day of MTX dosing, past users reported a higher incidence rate for both nausea/vomiting (50.0 vs. 38.2%) and fatigue (70.4 vs. 67.1%).

Participant Characteristics: Phase 2

Among the 353 individuals eligible for the phase 2 study, 198 (56.1%) participants signed up and completed the baseline characteristics form (Fig. 1B). A total of 175 (88.4%) participants joined the cohort and completed the phase 2 longitudinal survey (baseline characteristics), of which 136 (77.7%) provided the date of their next MTX dose.

Continuous Self-Controlled Case Series Analysis

In total, 123 participants provided any e-PROM data in the risk and control windows and were thus eligible for the SCCS analysis; within-week paired PROMIS nausea data were provided by 84 participants and within-week paired PROMIS fatigue data were provided by 85 participants. In terms of cohort characteristics, 77.2% were living with RA and 27.6% were living with PsA, with a mean (SD) baseline PROMIS Global score of 40.6 (7.0). Mean (SD) age was 51.7 (11.8) years, 87.0% of patients were female, and 93.5% were white. Mean (SD) duration of MTX treatment among current users was 2.6 (3.9) years. Among participants, 39.8% were on a biologic DMARD and 59.3% were on a non-biologic DMARD only (Table 2). At baseline, 58 (47.2%) reported nausea and/or fatigue in the phase 2 survey.
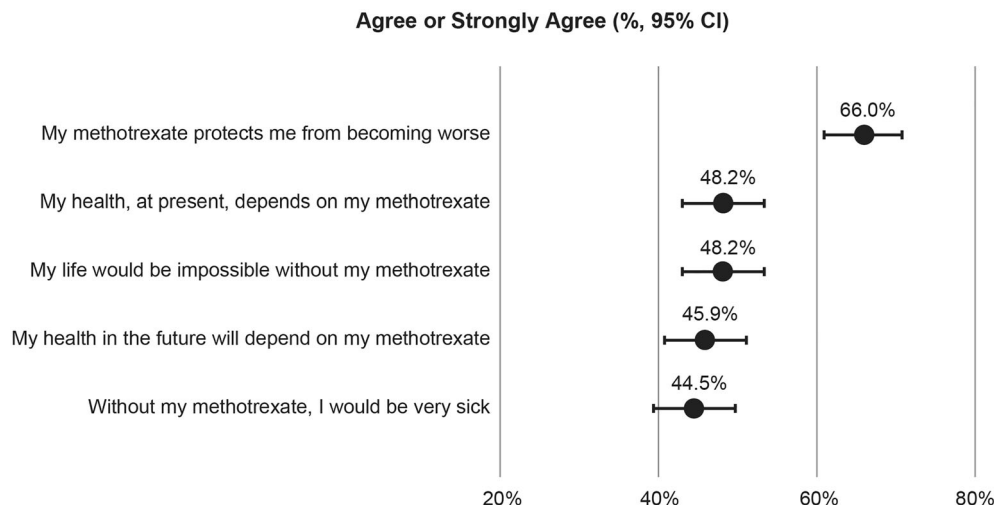
Agree or Strongly Agree (%, 95% CI)

Fig. 2 Patient beliefs: proportion of current users of MTX in agreement[†] (phase 1)[*]. [*]Items adapted from the five-item Specific-Necessity scale from the Beliefs about Medicine Questionnaire [22]; "methotrexate" substituted for "medicine". [†]Percentage and CI of current MTX users who indicated that they agree or strongly agree with each statement. *CI* confidence interval, *MTX* methotrexate

Among the 39 participants reporting MTX-associated nausea on their baseline survey, 25 contributed 43 paired sets of observations over the next 3 weeks; the mean increase in the PROMIS nausea score was 5.1 units (95% CI 3.1, 7.1; $P < 0.0001$) (Table 3; Fig. S2). Among the 84 participants without baseline nausea, 59 contributed 110 paired sets of observations; the mean increase in PROMIS nausea was 0.7 units (95% CI $-$ 0.2, 1.6; $P = 0.135$). Among the 51 participants reporting MTX-associated fatigue on their baseline survey, 35 contributed 62 paired sets of observations; the mean increase in PROMIS fatigue score was 3.9 units (95% CI 1.9, 6.0; $P = 0.0003$). Among the 72 participants without fatigue at baseline, 50 contributed 92 paired sets of observations; the mean increase in PROMIS fatigue was 0.4 units (95% CI $-$ 1.0, 1.8; $P = 0.554$). There was a small but significant interaction between baseline score and time (Fig. S3). Of the participants reporting MTX-associated nausea at baseline, 41% (16/39) experienced worsened nausea with an MID > 3 units compared with 24% (20/84) who did not report nausea at baseline. Of the participants reporting MTX-associated fatigue at baseline, 41% (21/51) experienced worsened fatigue with an MID > 3 units compared with 36% (26/72) who did not

report fatigue at baseline (Fig. 3). Using an alternative cutoff for MID of > 5 units, the corresponding proportions were 31% (12/39) and 17% (14/84) for nausea and 39% (20/51) and 29% (21/72) for fatigue.

DISCUSSION

The entirely virtual nature of this longitudinal study is promising for future research with RA and PsA patients adopting remote patient monitoring as an essential component of digital health, where out-of-office data capture from patients is critical. Participants were prompted to specify the date of their weekly MTX dose and received reminders to complete e-PROMs on the ArthritisPower smartphone app or web-based equivalent during the risk and control windows. This innovation in the way that clinical trials and real-world studies can be conducted shows that a study design with no involvement from clinical sites, and dependent only upon patients' use of smartphone technology, is feasible. Moreover, the within-person study design is novel and avoids all time-invariant confounding that would otherwise accompany a traditional cohort design [23, 27, 28]. Particularly in an era of widespread

Table 1 Participant demographics and perceived MTX-related side effects, by current or past MTX treatment

Characteristics	All participants, N = 671	Currently on MTX, n = 353	Previously on MTX, n = 318	P value*
Female, n (%)	593 (88.4)	313 (88.7)	280 (88.1)	0.803
Age, years, mean (SD)	54.0 (11.6)	53.4 (11.7)	54.7 (11.5)	0.130
White, n (%)	620 (92.4)	326 (92.4)	294 (92.5)	0.961
College graduate, n (%)	290 (43.2)	155 (43.9)	135 (42.5)	0.704
Employment status, n (%)				
Employed (full-time, part-time, or self-employed)	323 (48.1)	188 (53.3)	135 (42.5)	0.005
Current RA/PsA therapy, n (%)				
Non-biologic DMARDs only[a]	281 (41.9)	190 (53.8)	91 (28.6)	< 0.0001
Biologic DMARDs	383 (57.1)	163 (46.2)	220 (69.2)	< 0.0001
Corticosteroids only	7 (1.0)	0 (0.0)	7 (2.2)	0.005
Duration of current MTX use, years, mean (SD)	4.9 (6.2)	4.9 (6.2)	–	–
Current folic acid use, n (%)	341 (50.1)	341 (96.6)	–	–
BMI, kg/m^2, mean (SD)	31.9 (7.9)	32.2 (8.4)	31.5 (7.2)	0.251
Side effects[a], n (%)				
Any[b]	467 (69.6)	216 (61.2)	251 (78.9)	< 0.0001
Fatigue	303 (45.2)	161 (45.6)	142 (44.7)	0.804
Nausea	236 (35.2)	108 (30.6)	128 (40.3)	0.009
Hair thinning	225 (33.5)	121 (34.3)	104 (32.7)	0.667
Brain fog	197 (29.4)	111 (31.4)	86 (27.0)	0.211
Hair loss	163 (24.3)	83 (23.5)	80 (25.2)	0.620
Malaise	144 (21.5)	57 (16.1)	87 (27.4)	< 0.001
Mouth sores/ulcers	138 (20.6)	70 (19.8)	68 (21.4)	0.619
Difficulty sleeping	124 (18.5)	80 (22.7)	44 (13.8)	0.003
Abdominal pain	123 (18.3)	52 (14.7)	71 (22.3)	0.011
Diarrhea	112 (16.7)	56 (15.9)	56 (17.6)	0.545
Loss of appetite	84 (12.5)	37 (10.5)	47 (14.8)	0.093

Table 1 continued

Characteristics	All participants, $N = 671$	Currently on MTX, $n = 353$	Previously on MTX, $n = 318$	P value*
None of the above	2 (0.3)	0 (0.0)	2 (0.6)	0.136

Phase 1 study

BMI body mass index, *DMARD* disease-modifying anti-rheumatic drug, *MTX* methotrexate, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation

*Statistical significance between groups of participants who are currently on MTX and were on MTX in the past, $P < 0.05$; t tests were performed for continuous variables and Chi-square tests for categorical variables; P values are nominal in nature and should be interpreted in an exploratory manner

[a]Selection of side effects mentioned below were not mutually exclusive except for the "none of the above" option

[b]Experience of any side effect that participants believed was related to taking MTX (includes other related side effects not listed in Table 1)

technology availability and social distancing to mitigate the risk of a highly transmissible infection (e.g., COVID-19), this study demonstrates the capacity and willingness of patients (particularly those who may be susceptible to increased risk due to autoimmune conditions and associated immunomodulatory treatment) to use a digital platform for research that can easily be extended to remote patient monitoring as an essential component of telehealth and digital health care. In addition, as treatment paradigms shift towards an informed decision-making model, the incorporation of patients' views and experiences will be increasingly important [18], and remote approaches to collecting these data will be used more frequently. If these approaches were used routinely in clinical care settings, patient motivation to participate in efforts like this may increase as they become more familiar with the technology, particularly if encouraged to do so by their clinicians who may be able to provide improved care by having patient's data between office visits.

As has been observed previously [29], people taking MTX to manage RA or PsA commonly experience bothersome side effects, notably nausea and fatigue, which are temporally related to weekly MTX dosing. These AEs associated with chronic medication use are often combined with pre-existing fatigue, which is an important symptom experienced by patients with rheumatic diseases such as RA and PsA.

Based on this study's findings, only half to two-thirds of patients taking MTX acknowledge its role in achieving optimal disease control yet were nevertheless still taking it. While only patients with intolerable side effects with MTX should be switched to alternative csDMARDs or b/tsDMARDs, if their clinician is able to have insights into tolerability problems, it allows dose adjustments or alteration in the route of administration (e.g., to SQ injection) if needed.

Indeed, of the current MTX users (353/671 [53%]), most of the participants reported side effects associated with MTX (216/353 [61%]), of which fatigue was the most frequent (161/353 [46%]). Among participants in the phase 2 longitudinal study reporting baseline fatigue ($n = 35$ with 62 observations) or nausea ($n = 25$ with 43 observations), the mean increase in PROMIS nausea score was 5.1 units ($P < 0.0001$) and the mean increase in PROMIS fatigue score was 3.9 units ($P = 0.0003$), both exceeding the MID. Because 5 units represents a half SD change on PROMIS instruments, a 4- or 5-unit change would be noticeable and clinically relevant for most patients [24–26]. As expected, differences in PROMIS scores were not significant among participants without baseline symptoms. It is notable that only about one-third of patients in this sample experienced meaningful worsening of nausea or fatigue in the day following their weekly MTX dose, with a magnitude of that change exceeds the MID. Thus, stratifying by self-reported symptoms not

Table 2 Characteristics of participants reporting MTX-related fatigue or nausea (SCCS survey at baseline)

Characteristics	All participants, N = 123	No nausea or fatigue from MTX, n = 65	Report nausea and/or fatigue from MTX, n = 58	P value*
Female, n (%)	107 (87.0)	58 (89.2)	49 (84.5)	0.61
Age, years, mean (SD)	51.7 (11.8)	52.3 (12.6)	51.1 (10.9)	0.56
White, n (%)	115 (93.5)	63 (96.9)	52 (89.7)	0.21
Bachelor's degree or higher, n (%)	62 (50.4)	33 (50.8)	29 (50.0)	1.00
Employed (full-time, part-time, self-employed), n (%)	67 (54.5)	37 (56.9)	30 (51.7)	0.69
Condition, n (%)				
RA	95 (77.2)	51 (78.5)	44 (75.9)	0.90
PsA	34 (27.6)	17 (26.2)	17 (29.3)	0.85
Years since RA/PsA diagnosis, mean (SD)	5.9 (6.7)	6.2 (7.8)	5.6 (5.4)	0.63
Current RA/PsA therapy, n (%)				0.77
Biologic DMARDs	49 (39.8)	27 (41.5)	22 (37.9)	
Non-biologic DMARDs only	73 (59.3)	37 (56.9)	36 (62.1)	
Duration of current MTX use, years, mean (SD)	2.6 (3.9)	2.6 (3.8)	2.8 (4.0)	0.78
Baseline patient global PROMIS score, mean (SD)	40.6 (7.0)	41.4 (7.2)	39.8 (6.7)	0.19
Side effect experienced, n (%)				
Fatigue	51 (41.5)	0	51 (87.9)	< 0.001
Nausea	39 (31.7)	0	39 (67.2)	< 0.001

DMARD disease-modifying anti-rheumatic drug, *MTX* methotrexate, *PsA* psoriatic arthritis, *PROMIS* Patient-Reported Outcomes Measurement Information System, *RA* rheumatoid arthritis, *SCCS* self-controlled case series, *SD* standard deviation

*Statistical significance between groups of participants who report no nausea or fatigue and those who report nausea and/or fatigue, $P < 0.05$; t tests were performed for continuous variables and Chi-square tests for categorical variables; P values are nominal in nature and should be interpreted in an exploratory manner; SD values reported are 1 SD below population mean (for PROMIS scores, the population mean = 50, SD = 10)

only provides evidence for convergent validity of the quantitative PROMIS scores but also helps to avoid failing to identify important symptoms that are bothersome to a large minority of patients yet may be obscured if only reporting at a group level.

It is also noteworthy that although the SCCS design has been used to study the impact of different treatment options on disease flares and infection risk [30, 31], not many rheumatology studies of medication-related symptoms have used it. We would refer readers to the

Table 3 Change in PROMIS scores from risk to control window, stratified by baseline nausea and fatigue ($n = 123$)

Baseline selection[a]	Patient[b]	Number of paired observations/patient, n[c]	Mean (95% CI) risk[d]	Mean (95% CI) control[e]	Mean change[f] (95% CI)	P value[#]
PROMIS nausea						
Yes	39	43/25	56.9 (55.2, 58.6)	51.8 (50.1, 53.4)	5.1 (3.1, 7.1)	< 0.0001
No	84	110/59	44.3 (43.6, 45.0)	43.6 (43.0, 44.2)	0.7 (− 0.2, 1.6)	0.135
PROMIS fatigue						
Yes	51	62/35	61.1 (59.6, 62.6)	57.1 (55.7, 58.6)	3.9 (1.9, 6.0)	0.0003
No	72	92/50	49.4 (48.3, 50.4)	48.9 (48.0, 49.9)	0.4 (− 1.0, 1.8)	0.554

CI confidence interval, *N* sample size, *PROMIS* Patient-Reported Outcomes Measurement Information System, *SD* standard deviation

[#]Statistical significance of change in PROMIS nausea and fatigue scores in risk window (6–36 h) from control window (96–144 h) following oral MTX dose where participants serve as their own control and each observation is from a pair of PROMIS scores in the same week, $P < 0.05$; t tests were performed for continuous variables; P values are tests of the null hypothesis that there is no within-person change between risk and control. Note that the above estimates include an interaction term between the baseline score and time

[a]Selection on baseline (phase 1) survey (e.g., "Do you commonly feel fatigue within a day of taking methotrexate compared with other times?")

[b]Total number of phase 2 participants who made the indicated selection on baseline (phase 1) survey

[c]Number of paired risk-control PROMIS nausea/fatigue observations within the same week over the number of unique phase 2 participants who provided them

[d]Mean (SD) risk score for paired observations

[e]Mean (SD) control score for paired observations

[f]Mean change (CI) in PROMIS nausea/fatigue score between risk and control windows, calculated from mixed models analysis

Strengthening the Reporting of Observational Studies in Epidemiology (i.e., STROBE) guidelines for good reporting of observational data that may make it particularly suitable for the assessment of certain health outcomes [32, 33]. In particular, the SCCS design is well suited to the assessment of temporal associations between transient exposures and symptoms and AEs [23], particularly those with abrupt onset such as those examined in this study.

The findings of this study should be considered in the context of certain limitations. Patients were recruited via an online community; therefore, there may be some bias in the patients who took part. For example, individuals who have experienced MTX-associated side effects might be more likely to participate in a study like this one, which may increase the frequency of these symptoms in the cohort. We acknowledge attrition between the various phases of the study but nevertheless note a substantial number of patients who reported no nausea or fatigue and participated in the longitudinal aspect of the study. Attrition in a digital health study similar to this is likely to decrease if patients are encouraged by their treating physician to participate and if the results are to be used for clinical care, as current ArthritisPower initiatives could facilitate in the future. Our findings may not be representative of all US patients with these conditions and are based on participants' self-reported diagnosis,
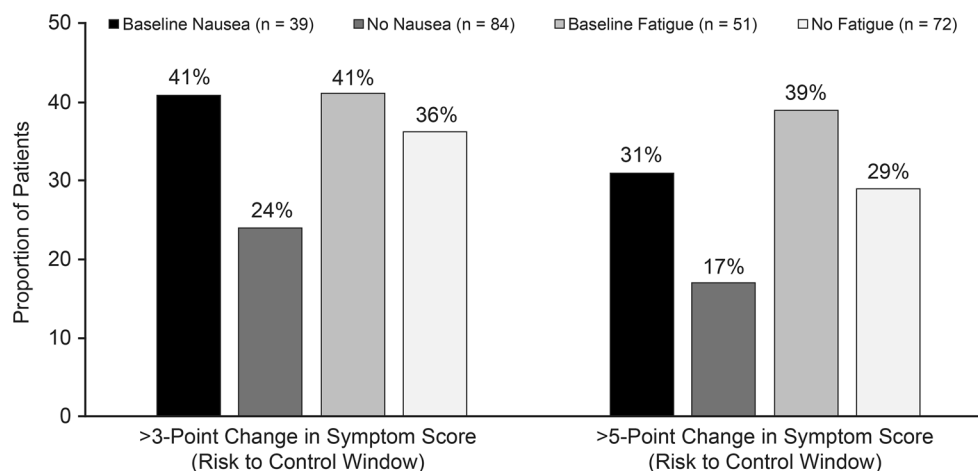
Fig. 3 Proportions of patients who had > 3-point or > 5-point change in symptom scores between risk window and control window* after oral MTX by baseline symptom status. *Risk window is 6- to 36-h period after MTX dose and control window is 96- to 144-h period after MTX dose. *MTX* methotrexate

treatment, and experiences. In addition, recall bias is a well-known limitation of self-reporting and may have impacted the results obtained from the cross-sectional survey contributed by past MTX users but would not affect the prospective, longitudinal component of the study deployed among current MTX users. Because the cutoff point at which patients become tolerant to side effects associated with MTX is unknown, we made a somewhat arbitrary decision about MTX duration and tolerance, initially specifying a 3-year cutoff, then increasing it to a 10-year cutoff. This was done to ensure adequate sample size while limiting the number of patients who had well-established MTX tolerance. Sample size did not allow us to examine the impact of duration of MTX therapy on tolerance, but we speculate that limiting it to patients on MTX for a shorter duration or new users may result in greater PROMIS score changes than what was observed here, and a higher proportion of patients with bothersome MTX-associated symptoms. Our results may thus reflect a conservative estimate of nausea, fatigue, and other MTX-associated symptoms. Finally, the limited sample size did not allow for a detailed analysis of shorter versus longer duration of MTX use.

Future research is needed to better understand the effective implementation of digital strategies and remote patient monitoring to improve detection of suboptimal patient experience with medications due to associated tolerability issues. We would anticipate a framework such as that used in this study, deployed as part of routine clinical care, can improve patient–physician communication and subsequent medication adherence and has the potential to significantly impact clinical outcomes.

CONCLUSIONS

Digital remote patient monitoring presents an opportunity to detect and address medication tolerability in real-time. In patients living with chronic autoimmune conditions such as RA and PsA, MTX is an important treatment option often prescribed by physicians to optimize disease control. However, many patients experience undesirable, temporally-based side effects, resulting in poor adherence, which may lead to suboptimal disease management.

In this self-controlled cohort of RA and PsA patients, we show that patients frequently experienced MTX side effects such as nausea and fatigue. Further research is required to manage patient perception and experience of MTX use, and improvements in treatment

adherence are likely to have a significant impact on long-term clinical outcomes. A smartphone-based strategy that implements remote patient monitoring to capture medication-related symptoms appears both feasible and acceptable to patients.

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practices/clinical-trial-data-sharing-request/
Journals.

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