ACR Open Rheumatology
Vol. 4, No. 11, November 2022, pp 935–941
DOI 10.1002/acr2.11467

American College of Rheumatology
Empowering Rheumatology Professionals

Side Effects of Methotrexate and Tumor Necrosis Factor Inhibitors: Differences in Tolerability Among Patients With Psoriatic Arthritis and Rheumatoid Arthritis

Alexis Ogdie,[1] Ervant J. Maksabedian Hernandez,[2] Yomei Shaw,[3] Bradley Stolshek,[2] and Kaleb Michaud[4]

Objective. To examine the prevalence of side effects with methotrexate (MTX) and tumor necrosis factor inhibitors (TNFi) among patients with psoriatic arthritis (PsA) and rheumatoid arthritis (RA).

Methods. This retrospective analysis, conducted between January 2000 and January 2019, used data from the FORWARD databank. Adult patients enrolled in the registry with self-reported and physician-confirmed diagnosis of PsA or RA were included if they had completed at least one questionnaire before initiating and within 12 months following initiation of MTX or a TNFi. The primary outcome was to examine the prevalence of side effects with MTX and TNFi within the year following treatment initiation. Multivariate logistic regression analysis was performed to examine the association between PsA and RA and the reporting of their side effects.

Results. Overall, 116 patients with PsA and 4247 patients with RA newly initiated MTX, and 124 patients with PsA and 4361 patients with RA newly initiated a TNFi. Patients with PsA were more likely to report MTX-related side effects than those with RA (44.8% vs. 29.4%), whereas similar proportions of patients with PsA and RA reported TNFi-related side effects within the first year (24.2% and 22.8%, respectively). Additionally, patients with PsA initiating MTX were more likely to report nausea, vomiting, abdominal pain, depression, and tinnitus than patients with RA initiating MTX or those with PsA or RA initiating a TNFi.

Conclusion. Patients with PsA reported more side effects than patients with RA, and this difference was more pronounced in those receiving MTX versus TNFi.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal condition that accompanies psoriasis. Early diagnosis and effective treatment are key to improve patient quality of life and slow the progression of disease. PsA is treated with oral small molecules, such as methotrexate (MTX), as well as biologic therapies, including tumor necrosis factor inhibitors (TNFi). Traditionally, MTX has been used as a first-line therapy in rheumatoid arthritis (RA) and PsA; however, recent treatment guidelines from the American College of Rheumatology and National Psoriasis Foundation suggest that patients with PsA could use TNFi as a first-line therapy (1). This change was driven not only by the low efficacy in available evidence but also by concerns around tolerability and side effects of MTX (2–4). A recent study found that 58.3% of newly diagnosed patients with PsA in the United States were initially treated with MTX; however, only 34.1% continued MTX monotherapy at the end of the first year (5). Another study identified shorter MTX persistence among patients with PsA than those with RA in the United States (6), although few other studies have found similar MTX persistence in PsA and RA (7,8). One of the reasons for poor persistence may be related to differences in the tolerability of MTX. MTX has many well-documented side effects (eg, nausea, fatigue, malaise, and elevated liver enzymes) (8–11), and it is assumed that patients with PsA are sensitive and have these side effects. MTX is generally well tolerated in RA, but little is known about its tolerability in PsA.

[1]Alexis Ogdie, MD, MSCE: Hospital of the University of Pennsylvania, Philadelphia; [2]Ervant J. Maksabedian Hernandez, PhD, Bradley Stolshek, PharmD: Amgen Inc., Thousand Oaks, California; [3]Yomei Shaw, PhD: FORWARD, The National Databank for Rheumatic Diseases, Wichita, Kansas, and University of Michigan, Ann Arbor; [4]Kaleb Michaud, PhD: FORWARD, The National Databank for Rheumatic Diseases, Wichita, Kansas, and University of Nebraska Medical Center, Omaha.

This study was funded by Amgen Inc.

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr2.11467&file=acr211467-sup-0001-Disclosureform.pdf.

Address correspondence to Alexis Ogdie, MD, MSCE, Department of Medicine, Division of Rheumatology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, White Building Room 5023, 3400 Spruce Street, Philadelphia, PA 19104. Email: ogdiea@pennmedicine.upenn.edu.

Submitted for publication January 11, 2022; accepted in revised form March 28, 2022.

SIGNIFICANCE & INNOVATIONS

- Although it is one of the most commonly used therapies in the treatment of psoriatic arthritis (PsA) and rheumatoid arthritis (RA), patients with PsA and RA discontinue methotrexate (MTX) because of poor tolerability.
- In this analysis of data from the FORWARD databank, we found that patients with PsA generally report more side effects than those with RA, and this is particularly evident in those initiating MTX.
- Treatment burden extends beyond the ontology used in randomized controlled trials and should be assessed in future studies of patients with PsA and RA.

Treatment burden is a complex construct that incorporates tolerability, side effects, adverse events (AEs), and other aspects related to the burden of receiving a medication. In essence, it reflects the patient's experience with the medication and, particularly, any challenging experiences. A recent systematic review defined treatment burden as "actions and resources patients devote to their health care including difficulty, time, and out-of-pocket costs dedicated to health care tasks such as adhering to medications, dietary recommendations, and self-monitoring" (12). Treatment burden is of substantial importance to patients but has rarely been studied from a patient's perspective unlike with AEs (13,14). When prescribing a new therapy, physicians are taught to discuss the risks and benefits of that drug. However, this risk-to-benefit profile has a different connotation for patients because, although a therapy may improve certain aspects of their disease, it may also add a new symptom that can have a substantial impact on their quality of life. Even though AEs are recorded by ontology in clinical trials, this does not necessarily reflect patients' concerns (15,16). Treatment burden, as reported by patients, is not generally captured in randomized controlled trials. Therefore, it is important to capture the burden of the medications available for patients, to make better treatment decisions, especially for those commonly used for the treatment of PsA. Our study aimed to fill this gap in the knowledge of treatment burden of MTX and TNFi in PsA and RA by describing the relative prevalence and types of side effects using patient-reported data from the FORWARD databank.

PATIENTS AND METHODS

Data source and study design. This was a retrospective cohort study conducted between January 2000 and January 2019 using data from the FORWARD databank (also known as The National Databank for Rheumatic Diseases)—the largest patient-reported, nonprofit observational registry in the United States, with over 30,000 records of patients with rheumatic diseases and over 10,000 patients completing a questionnaire every 6 months (17). Patients were primarily recruited through rheumatology clinics and completed biannual, comprehensive questionnaires that collected detailed information about treatments used, including start and end date, average days used per month, reasons for stopping, and any reported side effects. Key variables collected included sociodemographic characteristics, clinical and disease activity measures, treatments and treatment response, physical function scores (eg, the Health Assessment Questionnaire [HAQ] and the HAQ-II), health-related quality of life measures (eg, European Quality of Life 5 Dimensions [EuroQoL-5D], Short Form 36), direct costs, indirect costs including disability and lost opportunity to participate in work, comorbidities assessed using the Rheumatic Disease Comorbidity Index (18), symptoms, hospitalizations, and mortality rate.

Participants were questioned about experienced side effects by type of medication including type of side effect and its severity (mild, moderate, and severe), start date and its duration, lost time from work (if any), hospitalization due to side effects (if any), and respondents' certainty of the drug causing the side effect. Data about length of medication exposure, concomitant medications used, and reasons for discontinuation were also captured.

The study protocol was approved by the Institutional Review Board at the Via Christi Hospitals Wichita, Inc., and was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), as well as the guiding principles of the Declaration of Helsinki 1964 and its later amendments. Informed consent was obtained from all participants.

Study population and eligibility criteria. Among adult patients enrolled in FORWARD with a self-reported, physician-confirmed diagnosis of PsA or RA, we selected patients that reported current or past use of MTX and/or TNFi at the time of survey completion or 6 months before survey completion were included if they had completed at least 1 questionnaire before initiating and within 12 months following initiation of MTX or a TNFi. New users of MTX and/or TNFi were defined as such if they reported new use of the medication and the target medication was not listed in a prior visit/questionnaire. Patients were defined as monotherapy users if only one of these target medications was being used (eg, a patient initiating a TNFi and not on MTX during the same period would be considered a TNFi new user as a monotherapy) and a combination therapy user if they were already on one of these medications and the other was added (eg, a patient previously on MTX but who initiated adalimumab would be considered a TNFi new user as a combination therapy). Because some patients who initiated a second TNFi could have reported more than one treatment episode (one for each drug), we conducted a sensitivity analysis to assess only those patients who enter the cohort for episodes related to the first new TNFi initiation. Patients who restarted disease-modifying antirheumatic

drugs (DMARDs) and those who did not receive a DMARD at any point during the study period were excluded.

Outcomes. The primary outcome was to examine the prevalence and types of reported side effects of MTX and a TNFi within 12 months of treatment initiation. The secondary outcome included examining the prevalence of symptoms that could conceivably be related to treatment burden as reported in a symptom inventory, and the exploratory outcome included patient-reported outcomes (PROs) at a visit when a patient reported a side effect versus visits for which no side effects were reported.

Statistical analysis. Patient characteristics among new initiators of MTX and/or a TNFi are descriptively reported along with the prevalence and types of side effects, and the report of symptoms that may be considered side effects over 12 months since treatment initiation. The prevalence of side effects was stratified by diagnosis (PsA or RA) and treatment regimen (initiation of MTX monotherapy, TNFi monotherapy, or MTX-TNFi combination therapy). Multiple imputation was used in cases in which data were missing for key variables.

We evaluated the association between diagnosis (PsA vs. RA) and the reporting of side effects using univariate and multivariate logistic regression analysis. In multivariate logistic regression models, having PsA (vs. RA) was the exposure, and the outcome was a side effect reported over the next 12 months after initiation of the medication. We used a univariate approach to look at covariates that could be considered potential confounders. We then created a directed acyclic graph (Supplementary Figure 1) to form a plausible multivariate model that considered potential confounders (age, sex, and body mass index [BMI]) (19). We created 1 model each for MTX and TNFi and explored this association for both the main analytical cohort and for those in the sensitivity analysis of new TNFi initiators. All analyses were conducted using Stata Statistical Software Release 15.0 (StataCorp, College Station, Texas).

RESULTS

Study population. Of the eligible patients, 116 with PsA and 4247 with RA were new initiators of MTX, and 124 with PsA and 4361 with RA were new initiators of a TNFi. Demographics and clinical characteristics are shown in Table 1. Among new initiators, the mean age of patients with RA was higher than the mean age of those with PsA (except in TNFi initiators), and most patients were women with relatively higher proportion observed in those with RA versus PsA. Patients with PsA had a higher BMI than those with RA. The mean number of comorbidities was comparable between patients with PsA and RA although the prevalence of depression and physician-diagnosed fibromyalgia was higher in patients with PsA than in those with RA.

Reported side effects and symptoms. Among new initiators of MTX, 44.8% (95% confidence interval [CI]: 35.8%-53.9%)

Table 1. Demographics and baseline characteristics of new initiators of MTX and TNFi

Characteristic	MTX initiators		TNFi initiators[a]	
	PsA (N = 116)	RA (N = 4247)	PsA (N = 124)	RA (N = 4361)
Age, y, mean (SD)	53.5 (10.8)	59.1 (12.3)	53.8 (11.8)	49.6 (12.2)
Female, n (%)	81 (69.8)	3,467 (81.6)	87 (70.2)	3,554 (81.5)
Duration, y, mean (SD)	11.2 (9.5)	13.5 (10.9)	12.3 (9.4)	14.8 (10.8)
College educated, n (%)	71 (61.2)	2,408 (56.7)	38 (30.6)	1,699 (39.0)
BMI, kg/m^2, mean (SD)	31.4 (8.0)	28.1 (6.8)	31.1 (8.0)	28.3 (6.8)
Obesity, n (%)	57 (49.1)	1,282 (30.2)	58 (46.8)	1,362 (31.2)
Comorbidity count, mean (SD)	1.6 (2.4)	1.4 (1.6)	1.5 (1.5)	1.4 (1.6)
Count of symptoms reported, mean (SD)	9.3 (6.9)	8.0 (6.0)	9.2 (6.4)	8.2 (6.0)
Depression, n (%)	32 (27.6)	679 (16.0)	30 (24.2)	666 (15.3)
Fibromyalgia[b], n (%)	10 (8.6)	115 (2.7)	10 (8.1)	110 (2.5)
Concomitant MTX, n (%)	—	—	58 (46.8)	2,410 (55.3)
Concomitant TNFi, n (%)	90 (77.6)	3,424 (80.6)	—	—
Subcutaneous MTX, n (%)	24 (21)	946 (22)	11 (8.9)	592 (13.6)
Dose of MTX				
Median (IQR)	15.0 (12.5-20.0)	15.0 (10.0-15.0)	15.0 (12.5-20.0)	15.0 (12.5-20.0)
Mean (SD)	15.5 (4.8)	13.7 (5.1)	16.2 (5.8)	15.3 (5.4)

Note: Baseline characteristics are reported from the questionnaire phase during which patients reported their first MTX or TNFi use.
Abbreviations: BMI, body mass index; IQR, interquartile range; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.
[a]TNFi inhibitor characteristics are at the time of the first TNFi. Among TNFi initiators, 68% had only one TNFi course in the study, whereas 25% had two, and 7% had three or more observed TNFi courses. TNFi initiated include etanercept (RA 1871/PsA 60), adalimumab (RA 1458/PsA 60), certolizumab (RA 308/PsA 17), golimumab (RA 293/PsA 14), and infliximab (RA 2196/PsA 29).
[b]Physician-diagnosed fibromyalgia.

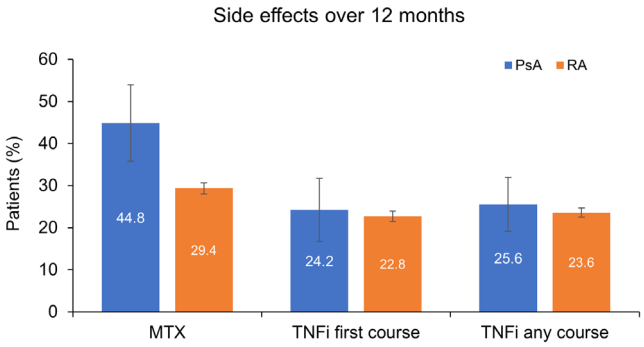

Figure 1. Proportion of patients reporting side effects within 12 months of initiating therapy. Error bars represent 95% confidence intervals. "TNFi first course" includes only those patients who were TNFi naïve; "TNFi any course" includes patients who had received multiple TNFi courses. MTX, methotrexate; RA, rheumatoid arthritis; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitor.

of patients with PsA compared with 29.4% (95% CI: 28.0%-30.7%) of patients with RA reported side effects with MTX during the first year of use. Among new initiators of TNFi, side effects reported within 12 months of initiating therapy were similar between patients with PsA and those with RA (24.2% [95% CI: 16.7%-31.7%] and 22.8% [95% CI: 21.5%-24.0%], respectively; Figure 1). Similar trends in the prevalence of side effects were observed among MTX and TNFi users receiving medication either as monotherapy or in combination (Figure 2).

In the 12 months after initiation, patients with PsA initiating MTX were more likely than those with RA to report numbness/tingling (49.1% vs. 36.5%), muscle weakness (43.1% vs. 33.7%), headache (33.6% vs. 28.3%), depression (32.8% vs. 20.1%), nausea (28.4% vs. 17.4%), tinnitus (27.6% vs. 22.1%), constipation (26.7% vs. 17.2%), nervousness (24.1% vs. 17.5%), oral ulcers (24.1% vs. 14.2%), pain/cramps of abdomen (21.6% vs. 13.8%), and vomiting (10.3% vs. 3.5%) (Figure 3A). Among patients initiating a TNFi, the prevalence of symptoms within the first 12 months was similar between patients with PsA and those with RA, although some symptoms, including nausea, headache, diarrhea, depression, nervousness, and numbness/tingling, were still generally higher among patients with PsA (Figure 3B). Furthermore, the prevalence of muscle weakness, depression, nausea, tinnitus, constipation, oral ulcers, abdominal pain or cramps, and vomiting were higher in patients with PsA initiating MTX than patients with RA initiating MTX or those with PsA or RA initiating a TNFi. Across MTX and TNFi initiators, a higher proportion of patients with RA experienced easy bruising than those with PsA (Figure 3A and B).

Of the variables analyzed, univariate analysis found that reporting side effects with MTX and TNFi was associated with depression, gastrointestinal (GI) symptoms, anxiety, and having some college education (Supplementary Table 1). After adjusting for our prespecified potential confounders (age, sex, and BMI), the likelihood (odds) of experiencing side effects with MTX was 1.8-fold higher in patients with PsA versus those with RA (odds ratio [OR]: 1.77, 95% CI: 1.21-2.60). We did not find a significant difference in the proportion of patients who reported side effects among new initiators of TNFis (OR: 1.12, 95% CI: 0.73-1.72; Table 2). Men were less likely to report side effects and/or symptoms associated with either therapy (Supplementary Table 1). When analyzed by disease category (PsA and RA), we found that the variables associated with higher likelihood of reporting side effects with MTX among patients with PsA were depression, GI symptoms, anxiety, subcutaneous administration, symptom count, and having some college education, whereas the variables associated with side effects in patients with RA were symptom count and having some college education (Supplementary Table 2a). Likewise, the variables associated with side effects with TNFi among patients with PsA were depression, GI symptoms, and having some college education, whereas the variables associated with higher odds of reporting side effects in patients with RA were depression, anxiety, and number of comorbidities (Supplementary Table 2b).

PROs. In an analysis of all users of MTX or TNFi medications (not just initiators), irrespective of the treatment class,

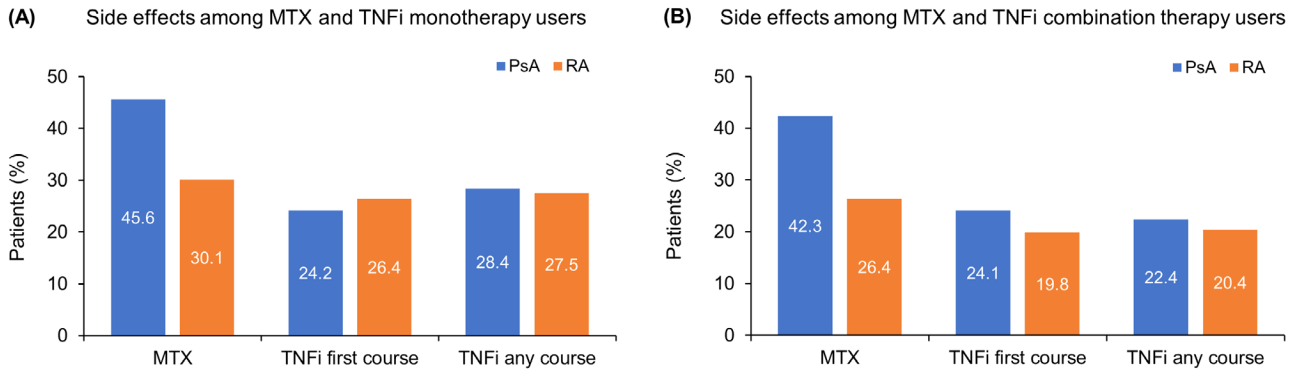

Figure 2. Patient-reported side effects of MTX or TNFi among (**A**) monotherapy users and (**B**) combination therapy users. MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

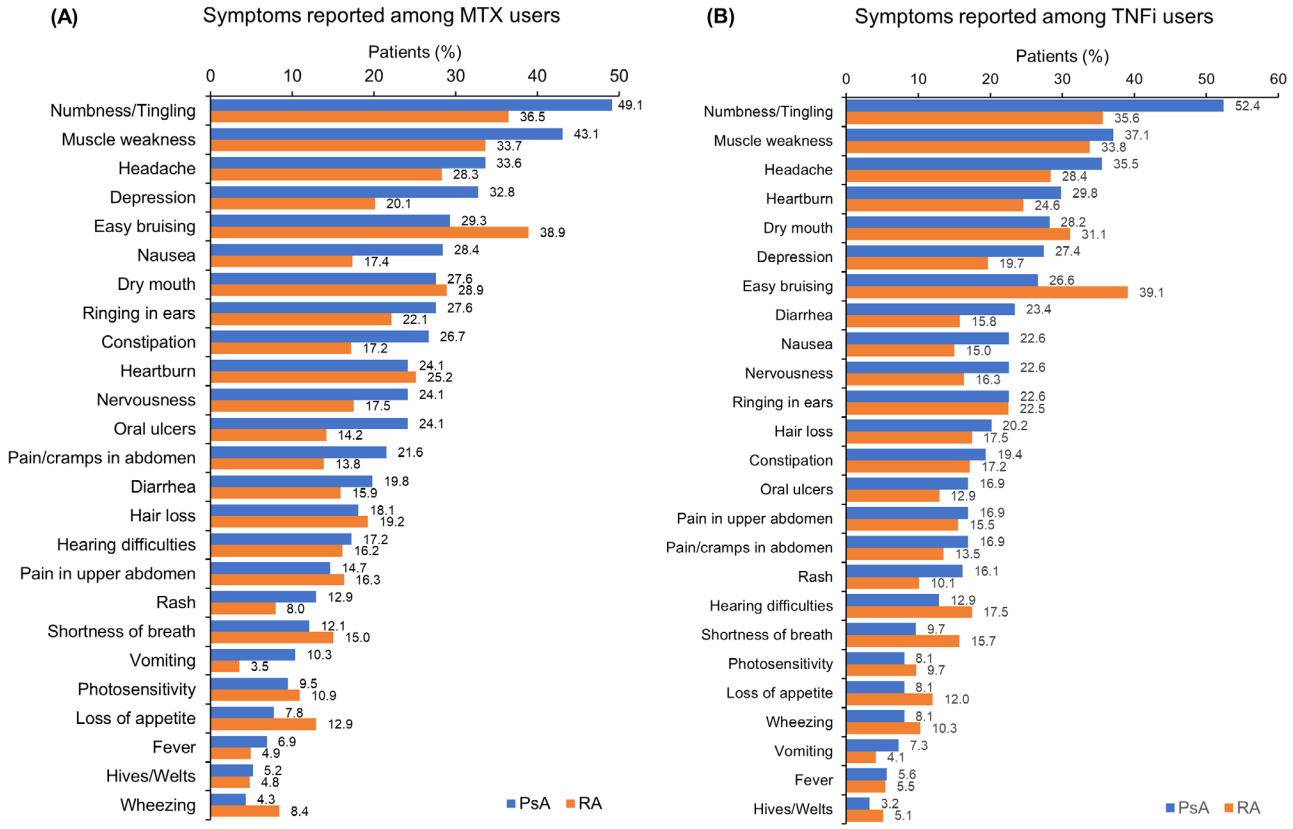

Figure 3. Patient-reported symptoms among new initiators of (**A**) MTX and (**B**) TNFi. MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

for most of the PROs (except Health Thermometer, Patient-Reported Outcomes Measurement Information System [PROMIS] Physical Function, PROMIS Anxiety, and PROMIS Social Participation) the mean scores for patients who reported side effects were relatively higher than those not reporting side effects. Among MTX users, the mean scores of PROs (except Health Thermometer, PROMIS Sleep Disturbance, PROMIS Anxiety, and PROMIS Social Participation) were numerically higher among patients with PsA who reported side effects versus those with RA who reported side effects. The Patient Activity Scale (PAS)-II score was also numerically higher in patients with PsA who reported side effects than in those with RA who reported side effects, indicating the disease severity in patients with PsA (Supplementary Table 3). In addition, the HAQ-II, PROMIS Physical Health (Pain Interference and Sleep Disturbance), and PROMIS Mental Health (Depression) scores were numerically higher than the normative values in the general population, demonstrating the impact of the disease on physical function and quality of life in patients with PsA.

Table 2. Multivariate analysis of association between patient characteristics and reporting of side effects

	MTX			TNFi		
	Univariate	Age and sex adjusted	Age, sex, and BMI adjusted	Univariate	Age and sex adjusted	Age, sex, and BMI adjusted
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
PsA vs. RA	1.95 (1.35-2.84)	1.82 (1.24-2.67)	1.77 (1.21-2.60)	1.08 (0.71-1.64)	1.07 (0.70-1.63)	1.12 (0.73-1.72)
Age	0.97 (0.96-0.97)	0.97 (0.97-0.98)	0.97 (0.97-0.98)	0.98 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.98-0.99)
Male (vs. female)	0.59 (0.49-0.71)	0.64 (0.53-0.77)	0.64 (0.52-0.77)	0.57 (0.47-0.70)	0.60 (0.49-0.73)	0.58 (0.47-0.72)
BMI	1.01 (1.00-1.02)		1.00 (0.99-1.01)	1.00 (0.99-1.01)		0.99 (0.98-1.00)

Abbreviations: BMI, body mass index; CI, confidence interval; MTX, methotrexate; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

DISCUSSION

In this analysis, we examined patient experience with MTX and TNFi in RA and PsA using self-reported data from patients enrolled in the FORWARD databank between January 2000 and January 2019 and found that, among initiators of MTX, a lower proportion of patients with RA reported a side effect in the first year of use than those with PsA. Among initiators of TNFi, the proportion of patients reporting a side effect in the first year remained similar between the RA and PsA cohorts. Our analysis also showed an association between having PsA and reporting MTX-related side effects, whereas no such association was identified for TNFi users.

Our study is different from traditional studies assessing side effects because it uniquely analyzes patients' experience with MTX and TNFi therapies. While prior studies of MTX focused on hepatotoxic effects and comparisons of treatment persistence rates in psoriatic disease versus RA (6,8,11,20,21), our study compares the treatment burden from a patient's perspective of the two most common therapies used for RA and PsA. To our knowledge, only the Study of Etanercept and Methotrexate in Subjects with Psoriatic Arthritis (SEAM-PsA), a randomized controlled trial, has compared MTX with a TNFi in PsA (22), whereas several such trials have been conducted in RA (23,24). However, these studies examined AEs using standard ontologies as opposed to treatment burden from a patient's perspective. In PsA, the SEAM-PsA trial found a numerically higher prevalence of nausea, vomiting, and diarrhea among patients receiving MTX monotherapy than those receiving etanercept monotherapy (22). While clinical trials help answer causal questions on the efficacy and safety for common AEs, many of the symptoms and side effects recorded in clinical trials use ontology for AEs, which may not capture symptoms of importance to patients. These side effects instead are either picked up in a review of systems or in discussion with the patient rather than through discrete data entry, thus potentially compounding the issue of gathering data on medication tolerability that may be most relevant to patients.

Our study found that patients with PsA, in general, reported more symptoms than patients with RA. In particular, patients with PsA more commonly reported having nausea, numbness/tingling, GI symptoms (pain/cramps in abdomen, constipation, and diarrhea), and depression than those with RA. Patients with PsA were also more likely to have a higher BMI, concomitant fibromyalgia, and depression, which may all contribute to the symptom profile and side effects to medications. Adjusting for BMI decreased the effect of PsA compared with RA, which suggests that it is a meaningful confounder in this relationship and may have implications for side effects to therapy, and MTX in particular. Obesity has previously been associated with liver toxicity related to MTX (11,20).

Strengths of this study include the use of a large patient registry that has rich data on symptoms and side effects, socioeconomic status, patient characteristics and outcomes, and disease confirmed by physicians. Furthermore, the data were captured prospectively without patients being aware of the study hypothesis or the reason for collection, thereby decreasing the risk of observer bias. Although the FORWARD databank has many advantages in data collection for RA and PsA, there are also limitations. First, the databank does not contain physician measures of disease activity. However, our study's aim was not to stratify by disease activity in RA or PsA but rather to present the patient's perspective with respect to side effects and symptoms associated with the initiation of MTX or a TNFi. Next, as this is an observational study, there may be unmeasured confounders, selection bias (those who participate in a patient registry may be potentially more engaged in their care and more likely to report symptoms), recall bias (questionnaires are sent every 6 months, and it is possible that patients may not recall symptoms experienced at the beginning of treatment interval), confounding by indication (patients at high risk for poor outcomes will not be prescribed the therapy of interest), and order effect (ie, patients may be more or less tolerant of side effects as they progress through lines of therapy). Furthermore, selective sampling of patients into the FORWARD databank might occur; however, we believe that selection bias and recall bias should have an overall minimal impact on the comparisons between RA and PsA and between therapies as these biases would apply to all exposure groups, biasing toward the null. Finally, some of the subgroups in our study contain relatively few observations, which limited the ability to detect meaningful differences between groups in such cases.

To conclude, treatment burden is of substantial importance to patients but has been rarely studied from a patient perspective. We identified symptoms of medications that have meaning for patients in terms of managing their condition and found that they differ between PsA and RA. In particular, we found a higher frequency of side effects reported for MTX among patients with PsA versus those with RA. Such symptoms and side effects may lead to poor treatment adherence, persistence, increased health care use, and worse clinical and patient outcomes. Hence, future studies are needed to further characterize the patient experience with respect to treatment burden, and a more thorough examination of side effects critical to patient outcomes should be considered for measurement in clinical trials.

ACKNOWLEDGMENTS

Medical writing and editorial assistance was provided by Julie Wang, DPM, of Amgen Inc., and Lakshmi Narendra Bodduluru, PhD, of Cactus Life Sciences (part of Cactus Communications), funded by Amgen Inc.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final

version to be published. Dr. Ogdie had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ogdie, Shaw, Michaud.
Acquisition of data. Maksabedian Hernandez, Stolshek.
Analysis and interpretation of data. Ogdie, Shaw, Michaud.

ROLE OF STUDY SPONSOR

The study sponsor collaborated with the investigators on the study design, interpretation of the data, the writing of the manuscript, and the approval of the submitted manuscript. KM, AO and YS were responsible for collection and analysis of the data and Amgen was not involved in these activities.

REFERENCES

1. Singh JA, Guyatt G, Ogdie A, Gladman DD, Deal C, Deodhar A, et al. Special Article: 2018 American College Of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Rheumatol 2019;71:5–32.
2. Rajitha P, Biswas R, Sabitha M, Jayakumar R. Methotrexate in the treatment of psoriasis and rheumatoid arthritis: mechanistic insights, current issues and novel delivery approaches. Curr Pharm Des 2017;23:3550–66.
3. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol 2020;16:145–54.
4. Merola JF, Ogdie A. SEAM-PsA: seems like methotrexate works in psoriatic arthritis? Arthritis Rheumatol 2019;71:1027–9.
5. Maksabedian Hernandez EJ, Tkacz J, Lopez-Gonzalez L, Higgins K, Ogdie A, Stolshek BS. Psoriatic arthritis treatment patterns and costs among pharmacologic treatment-naive patients. Am J Manag Care 2020;26:e252–7.
6. George MD, Baker JF, Ogdie A. Comparative persistence of methotrexate and tumor necrosis factor inhibitors in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2020;47:826–34.
7. Nikiphorou E, Negoescu A, Fitzpatrick JD, Goudie CT, Badcock A, Ostor AJ, et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol 2014;33:609–14.
8. Lie E, van der Heijde D, Uhlig T, Heiberg MS, Koldingsnes W, Rodevand E, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:671–6.
9. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Risk of liver injury among methotrexate users: a meta-analysis of randomised controlled trials. Semin Arthritis Rheum 2015;45:156–62.
10. Jay R. Methotrexate revisited: considerations for subcutaneous administration in RA. Clin Rheumatol 2015;34:201–5.
11. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. Clin Exp Rheumatol 2009;27:1017–25.
12. Alsadah A, van Merode T, Alshammari R, Kleijnen J. A systematic literature review looking for the definition of treatment burden. Heliyon 2020;6:e03641.
13. Orbai AM, de Wit M, Mease P, Shea JA, Gossec L, Leung YY, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. Ann Rheum Dis 2017;76:673–80.
14. Orbai AM, de Wit M, Mease PJ, Callis Duffin K, Elmamoun M, Tillett W, et al. Updating the psoriatic arthritis (PsA) core domain set: a report from the PsA workshop at OMERACT 2016. J Rheumatol 2017;44:1522–8.
15. Calasan MB, van den Bosch OF, Creemers MC, Custers M, Heurkens AH, van Woerkom JM, et al. Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. Arthritis Res Ther 2013;15:R217.
16. Striesow F, Brandt A. Preference, satisfaction and usability of subcutaneously administered methotrexate for rheumatoid arthritis or psoriatic arthritis: results of a postmarketing surveillance study with a high-concentration formulation. Ther Adv Musculoskelet Dis 2012;4:3–9.
17. Michaud K. The National Data Bank for Rheumatic Diseases (NDB). Clin Exp Rheumatol 2016;34:S100–1.
18. England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. Arthritis Care Res (Hoboken) 2015;67:865–72.
19. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008;3:17.
20. Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis 2010;69:43–7.
21. Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Investig 2006;26:55–62.
22. Mease PJ, Gladman DD, Collier DH, Ritchlin CT, Helliwell PS, Liu L, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol 2019;71:1112–24.
23. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: a network meta-analysis. Cochrane Database Syst Rev 2016:CD010227.
24. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375–82.