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ORIGINAL ARTICLE

Use of Oral and Subcutaneous Methotrexate in Rheumatoid Arthritis Patients in the United States

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Objective. **To examine the patterns of methotrexate (MTX) use among rheumatoid arthritis (RA) patients.**
Methods. **Using data from RA patients enrolled in a US commercial health plan and the US Medicare program, we identified RA patients initiating oral MTX. Persistence with MTX (oral or subcutaneous [SC]) was defined as no gap for ≥90 days.**
Results. **New oral MTX users in Medicare (n = 20,431) were 76.9% women, had a mean ± SD age of 69.7 ± 11.7 years, and contributed a median followup of 2.6 years (interquartile range 1.7–3.5 years). Only 38% received dosages ≥20 mg/week at any time. Approximately 50% of patients discontinued MTX at 1 year, although more than one-third of patients subsequently restarted. New commercially insured oral MTX users (n = 4,048) were similar to Medicare patients, except for age. Among Medicare patients, 19% starting oral MTX subsequently initiated a biologic agent, mostly anti–tumor necrosis factor (85%). Of these, only 50% received MTX at a dosage of ≥20 mg/week, and only 21% of individuals switched to SC MTX (4%) or received hydroxychloroquine (8%), sulfasalazine (5%), or leflunomide (8%) prior to biologic agents. In commercially insured patients, 35% initiated a biologic agent, mostly anti–tumor necrosis factor therapies (90%). Of these, 43% never received MTX ≥20 mg/week.**
Conclusion. **Titration to a higher-dose oral MTX and use of SC MTX among RA patients were infrequent and may have been underutilized. Further work to optimize MTX dosing before patients are switched to a biologic agent may be warranted.**

INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist and is the most commonly used medication for the treatment of rheumatoid arthritis (RA). It is also used to treat other inflammatory conditions, such as psoriasis, psoriatic arthritis, sarcoidosis, and inflammatory bowel disease. MTX is the first-line medication recommended to treat newly diagnosed RA patients (1). For patients who do not respond sufficiently, biologic agents and/or other nonbiologic disease-modifying antirheumatic drugs (DMARDs) may be added or substituted.

MTX can be given orally, subcutaneously (SC), or via intramuscular injection. When taken orally, its bioavailability varies considerably (2). On average, two-thirds of MTX taken orally is bioavailable (3), although variability (21–96%) in the bioavailability of MTX can be even larger when higher dosages (between 25 and 40 mg/week) of oral MTX are used (2). Because parenteral MTX allows more complete absorption of MTX, the effect of switching from oral to parenteral MTX has been examined among RA patients with insufficient response to their initial oral MTX; in small studies, switching has been shown to be safe and effective (4–8). Some evidence suggests that

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Significance & Innovations

- Although methotrexate (MTX) is considered an anchor drug for rheumatoid arthritis (RA), its use, titration, and receipt of oral versus subcutaneous MTX has not been well-characterized in real-world settings.
- In this large cohort of nearly 25,000 RA patients initiating oral MTX, a large proportion of patients did not receive dosages of 20 mg/week or higher, even among the subgroup of patients who went on to initiate a biologic agent. Few patients ever used subcutaneous MTX.
- On the basis of patterns of use characterized in this analysis, further refinement of the optimal use of MTX appears warranted.

MTX given SC can increase longer-chain MTX polyglutamates, which correlates with clinical efficacy (9,10).

Among MTX-naive patients, the comparative effectiveness of oral versus SC MTX in RA patients was examined in a recent randomized trial starting with 15 mg/week of MTX. In this trial, a somewhat higher proportion of patients receiving SC MTX compared with oral MTX achieved the American College of Rheumatology (ACR) 20% improvement criteria (ACR20; 78% versus 70%) and ACR70 (41% versus 33%) responses, although the difference in the ACR50 response was negligible; the ACR20 difference (89% versus 63%) was more pronounced in patients who had a disease duration of ≥12 months (6,11). In addition to variable bioavailability, oral MTX sometimes is associated with gastrointestinal side effects, and patients who experience this condition may benefit from parenteral administration (12). A retrospective cohort study reported that switching from oral MTX to SC MTX improved clinical response, regardless of whether the switching reason was inefficacy or poor gastrointestinal tolerability (13).

Switching to parenteral MTX has been advocated by some to be a cost-effective alternative prior to stepping up to biologic agents (5). However, there are little data examining the use of MTX in RA patients in routine practice in the US. In the present study, we aimed to examine the epidemiology of MTX use among RA patients initiating MTX, including dosing, method of administration (oral versus SC), and persistence, and compare the effectiveness of 2 strategies in regard to delaying or avoiding use of biologic agents: switching to SC MTX or adding another nonbiologic DMARD.

PATIENTS AND METHODS

Patient population. To examine a more diverse cohort, we studied RA patients enrolled in 2 different health insurance programs: commercial health plans offered by a national health insurer (2005–2012) and Medicare with Part A and B, with a Part D drug plan, and no enrollment eligibility criteria with the intention to capture patients who initiated oral MTX monotherapy. Within each payment plan, we identified individuals who initiated oral MTX after a continuous 6-month period with medical and pharmacy benefits. Patients were required to have at least 2 RA diagnosis codes from a physician and could not have received any of the following RA medications during the 6-month baseline period or on the index date: MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide (LEF), or any biologic agent. The use of prior HCQ, SSZ, and LEF excluded 35% of the commercially insured patients and 33% of the Medicare-enrolled patients that would have otherwise been eligible for the analysis, and 3.6% of the commercially insured patients and 1.8% of the Medicare enrollees who started MTX and biologic agents on the same day. All pharmacy data in and prior to the 6-month baseline period were searched to exclude patients with any prior use of MTX. The median amount of preceding data used to exclude prior MTX exposure was 21.4 months (interquartile range [IQR] 12.4–32.8 months) for commercially insured patients and 19.1 months (IQR 11.3–30.1 months) for Medicare enrollees. Followup started at the time of oral MTX initiation, defined as the index date, and ended when the patient lost coverage or at the end of the study period.

Ascertainment of RA medication use. Use of MTX, other nonbiologic DMARDs, and biologic agents was determined based on records of filled prescriptions identified using national drug codes for pharmacy-filled medications or Healthcare Common Procedure Coding System codes for infused medications received at physician offices or hospitals. For each day during followup, medication exposure to MTX and other nonbiologic DMARDs was determined based on the prescription date and days of supply. The weekly oral MTX dose was calculated based on the amount prescribed divided by the days of supply.

Patterns of MTX use. We examined a number of descriptive outcomes to characterize the use of MTX. We examined the frequency of MTX used at various doses among all filled prescriptions of oral MTX, the proportion of patients who increased their oral MTX dose or switched to SC MTX, the peak (i.e., maximum) MTX dose and peak MTX dose among the subgroup of patients who later initiated a biologic agent, and the proportion of patients who added HCQ, SSZ, or LEF. Persistence with MTX was defined as remaining on MTX (in any formulation, oral or SC) without a gap in therapy of ≥90 days. The dose of SC MTX was not estimated, given the uncertainty in the data regarding the relationship between the volume of MTX dispensed, the dose prescribed by the provider, and the potential of some volume being wasted by the patient.

Association between addition of a biologic agent and use of an increased dose of oral MTX, SC MTX, and nonbiologic DMARDs. We subsequently evaluated time to initiating a biologic agent conditional to patients following

main exposure variables of interest: increasing the oral MTX dose; adding HCQ, SSZ, or LEF to oral MTX; or switching from oral MTX to SC MTX. For this analysis, patients were censored if they discontinued all MTX use (oral or SC). Each of these 3 treatment strategies was considered as time varying, and patients who adopted >1 were considered exposed to both. For example, a patient who switched to SC MTX and then added HCQ was considered exposed and contributed person time to the 2 treatment changes. The start of followup for this analysis began at the first date that a patient adopted any of these 3 treatment strategies.

Statistical analysis. We examined the distribution of patient demographics and MTX use during the entire followup period. We used Kaplan-Meier graphs to examine persistence on MTX and compared the commercially insured to the Medicare-enrolled RA patients using Wilcoxon's rank sum test. Finally, we used Cox proportional hazards regression to examine whether the 3 treatment strategies were different with regard to time to initiation of biologic agents, adjusting for potentially confounding variables that were selected based upon content expertise and hypothesized associations with initiation of biologic agents. These variables included age, sex, use of oral glucocorticoids, nonsteroidal antiinflammatory drugs (NSAIDs), narcotics, inpatient and outpatient visits during baseline, and dose of oral MTX; in the Medicare population, 2 additional covariates were included: the original reason for Medicare enrollment (e.g., disability) and receipt of state subsidy (as a proxy for low income). All analyses were done in SAS, version 9.2. The university Institutional Review Board approved the study, and use of the data was governed by data use agreements with the Centers for Medicare and Medicaid Services and the commercial health plan.

RESULTS

Among RA patients enrolled in the commercial health plan, we identified a total of 4,048 new MTX users who were eligible to be included in the analysis (Table 1). Among these patients, the mean ± SD age was 51 ± 12 years and 74% were women. The median followup was 2.4 years (IQR 1.6–3.6 years). Patients enrolled in Medicare were considerably older (mean ± SD age 70 ± 12 years), but both the proportion of women (77%) and duration of followup (median 2.6 years [IQR 1.7–3.5 years]) were similar. Steroid use was relatively comparable between cohorts. Medicare patients were less likely to take prescription NSAIDs and more likely to take narcotics.

Table 1. Characteristics of RA patients initiating oral MTX by type of health insurance program (commercial insurance versus Medicare)*

Patient characteristics†	Commercial data source (n = 4,048)	Medicare data source (n = 20,431)
Demographics		
Age, mean ± SD years	51.1 ± 11.9	69.7 ± 11.7
Women, %	74.2	76.9
Duration of followup, median (IQR) years	2.4 (1.6–3.6)	2.6 (1.7–3.5)
Clinical characteristics		
COPD, %	10.5	14.9
Diabetes mellitus, %	12.4	18.4
Charlson Comorbidity Index, %		
0	64.6	51.3
1–2	30.1	39.4
≥3	5.3	9.3
Hospitalized during baseline period, %	8.0	18.5
No. of physician visits during baseline, mean ± SD	12.9 ± 10.0	10.7 ± 8.4
Oral glucocorticoid use (daily average dose in prednisone equivalents), %		
None	42.0	38.5
≤7.5 mg	38.3	50.0
>7.5 mg	19.8	11.5
Any use of NSAIDs, %	41.7	34.0
Any use of narcotics, %	46.9	60.8
Enrolled in Medicare for reasons other than age (e.g., disability), %	N/A	36.4
Receipt of low income subsidy, %	N/A	34.0

* RA = rheumatoid arthritis; MTX = methotrexate; IQR = interquartile range; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal antiinflammatory drugs; N/A = not applicable.
† All factors measured in the 6-month baseline period prior to the start of followup, which began when patients initiated oral MTX.

Table 2. MTX use among commercially insured and Medicare-enrolled RA patients*

	Commercially insured (n = 4,048)	Medicare (n = 20,431)
Starting MTX dosage, mean ± SD mg/week	13.6 ± 8.7	13.1 ± 8.7
All MTX prescriptions combined, %		
<10 mg/week	8.7	17.5
≥10 and <15 mg/week	30.0	33.5
≥15 and <20 mg/week	34.4	28.0
≥20 mg/week	26.9	21.0
Peak MTX dosage anytime during followup		
<10 mg/week	5.7	11.2
≥10 and <15 mg/week	18.6	25.1
≥15 and <20 mg/week	28.0	25.5
≥20 mg/week	47.8	38.3
Patients who initiated a biologic agent at any time	35.3	19.1

* Values are the percentage unless indicated otherwise. MTX = methotrexate; RA = rheumatoid arthritis.

MTX use during followup. Among patients enrolled in the commercial health plan, the most commonly taken MTX dosages were between 15 and <20 mg/week, accounting for approximately one-third of all MTX prescriptions (Table 2). When the peak MTX dose was examined, nearly half of the patients received dosages ≥20 mg/week. In contrast, among patients enrolled in Medicare, the most common dosage of MTX was between 10 and <15 mg/week. Almost 40% of the Medicare patients received a maximum dosage of MTX of ≥20 mg/week. However, in contrast to commercially insured patients, more than one-third of patients never received 15 mg/week of MTX or higher.

MTX use prior to initiating biologic agents. In commercially insured RA patients, 35% initiated a biologic agent, compared with 19% in the Medicare population (Table 3). Most of the initial biologic agents used were anti–tumor necrosis factor (anti-TNF) therapy (84–90%). In this subgroup of patients, and prior to initiating biologic agents, more than one-third of the patients (43% and 50%, respectively) never received MTX at doses ≥20 mg. In both RA populations, ~80% of patients were treated with only oral MTX and did not add or switch to other nonbiologic DMARDs; <5% of patients received SC MTX in either cohort.

Persistence with MTX. Approximately 50% of patients discontinued MTX at one year, regardless of the route of administration (Figure 1). The proportion discontinuing was numerically similar between the Medicare and com-

Table 3. MTX use among commercially insured and Medicare-enrolled RA patients who initiated a biologic agent during followup*

	Commercially insured (n = 1,429)	Medicare (n = 3,922)
Initiated an anti-TNF biologic agent (rather than a biologic agent with a different mechanism of action), %	90.3	84.3
Months from initiation of MTX to initiation of biologic agent, median (IQR)	7.2 (3.5–14.8)	7.1 (3.2–14.6)
Median oral MTX dose increase before initiating biologic agent, median (IQR) mg/week	2.5 (0.0–7.5)	0.0 (0.0–5.0)
Peak MTX dose before initiating biologic agent, mean ± SD	19.3 ± 6.6	18.0 ± 6.6
<10 mg/week, %	3.0	6.5
≥10 and <15 mg/week, %	12.7	17.6
≥15 and <20 mg/week, %	26.9	26.3
≥20 mg/week, %	57.4	49.6
Treatment change before initiating biologic agents, %†		
Stayed only on oral MTX	81.1	79.0
Switched to SC MTX	2.1	3.9
Added HCQ	8.8	8.3
Added SSZ	4.6	4.5
Added LEF	7.9	8.4

* MTX = methotrexate; RA = rheumatoid arthritis; anti-TNF = anti–tumor necrosis factor; IQR = interquartile range; SC = subcutaneous; HCQ = hydroxychloroquine; SSZ = sulfasalazine; LEF = leflunomide.

mercially insured patients, although this was statistically significant (P = 0.0003). Among the subgroup of patients discontinuing MTX who had at least one subsequent year of followup (n = 2,419 commercially insured patients and n = 15,216 patients enrolled in Medicare), the median followup time was 26.1 months (IQR 17.9–38.7 months) for commercially insured patients, and 30.0 months (IQR 21.1–40.8 months) for Medicare enrolled patients. Following MTX discontinuation in this subgroup, 37% of the commercially insured patients and 41% of the Medicare patients subsequently restarted MTX within the next 12 months. The changes in oral glucocorticoid use after starting MTX are shown in Figure 2. Among patients who previously received oral glucocorticoids in the 6 months prior to initiating MTX, ~25–35% of patients were able to stop altogether, and even more patients were able to use glucocorticoids at lower doses.

Effect of switching to SC MTX, adding other nonbiologic DMARDs, or increasing MTX dose on time to initiation of biologic agents. Comparing the treatment strategies of any dose increase of oral MTX, adding a nonbiologic DMARD, or switching to SC MTX, the adjusted Cox regression analysis in commercially insured RA patients showed no significant difference in the time to initiation of biologic agents between the 3 treatment strategies (Table 4). The corresponding analysis in the Medicare data found that those who added HCQ compared with those who increased oral SC MTX dose were less likely to initiate a biologic agent (hazard ratio 0.69 [95% confidence interval 0.53–0.90]), but there were no other significant differences between the groups after multivariable adjustment.

DISCUSSION

MTX has been commonly described as the anchor drug in RA (14) and its use has increased appreciably over time (15–17). In this study of ~25,000 RA patients initiating oral MTX, we found that the use of oral MTX at dosages of at least 20 mg/week and switching to SC MTX were somewhat uncommon, even for patients who went on to require a biologic agent.

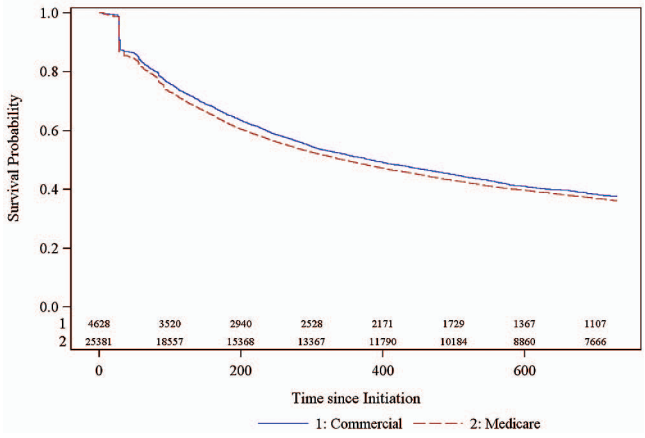

Figure 1. Persistence with methotrexate (oral or subcutaneous) among new users for rheumatoid arthritis patients enrolled in Medicare or a commercial health plan. The time since initiation was measured in days. The values listed above the x-axis represent the number of patients at risk, stratified by whether they were commercially insured or enrolled in the Medicare program. Per-

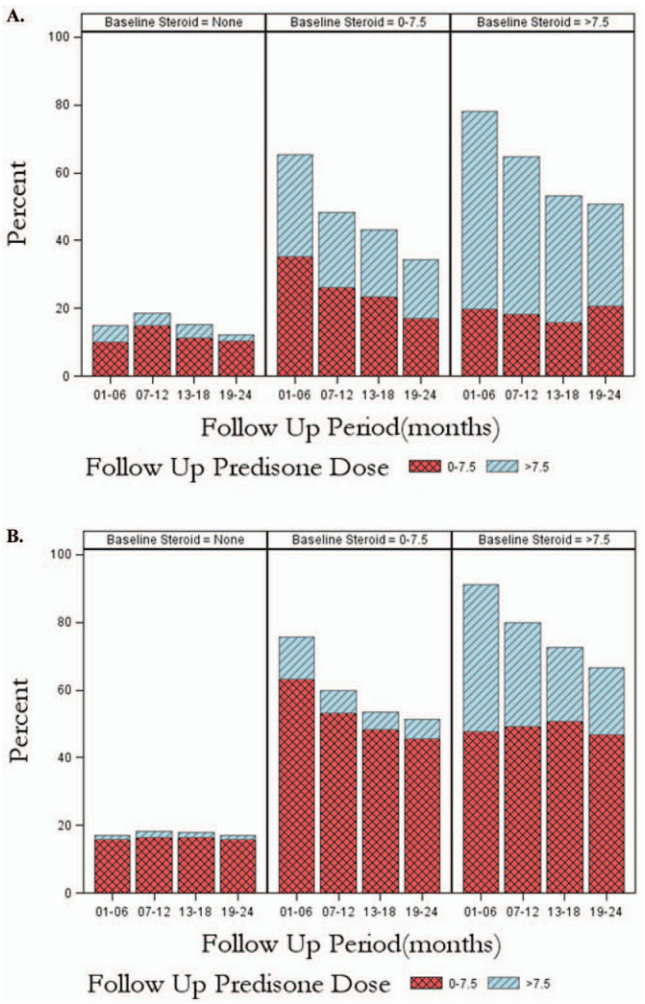

Figure 2. Changes in oral glucocorticoid use after initiation of oral methotrexate among commercially insured rheumatoid arthritis patients (**A**) and Medicare enrollees (**B**). Period refers to 6-month intervals following the start of oral methotrexate.

We found that, although ~50% of patients discontinued MTX (either oral or SC) within 1–2 years after starting, between one-third and one-half of these patients subsequently restarted therapy, reinforcing MTX as a relatively well-tolerated anchor drug in RA. Prior studies have found that persistence with MTX was comparable to our observations (16) or even better (17–20). Some variability in the proportion of patients considered adherent exists because of differences in the definition of adherence, source of data about adherence (e.g., patient self-report, clinician report, pharmacy data, Medication Event Monitoring System cap devices), practice settings, and extent of followup. In general, studies that have shown better long-term persistence were generally derived from smaller single-center RA populations using methods that may be more subjective (e.g., patient self-report) or obtained in settings that may not be generalizable to the majority of typical RA patients. We

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