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Original Article

Using subcutaneous methotrexate to prolong duration of methotrexate therapy in rheumatoid arthritis

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Abstract

Objective: Our study aims to determine whether the use of subcutaneous methotrexate (SC MTX) is associated with prolonged MTX use and lower incidence of hepatotoxicity in rheumatoid arthritis (RA) patients on MTX monotherapy and multiple drug therapy.

Methods: We conducted a retrospective cohort study using national databases of a large hospital system. Subjects had been diagnosed with RA and treated with MTX between September 30, 1999, and October 1, 2009. Outcomes of interest were the amount of time on MTX monotherapy or multiple disease-modifying anti-rheumatic drug (DMARD) therapy before addition of additional DMARDs or biologic agents, respectively. We conducted Cox regressions and Kaplan-Meier curves for association between SC MTX use and length of time before therapeutic change. We conducted chi-square tests for association between SC MTX use and elevated liver function tests (LFT).

Results: MTX monotherapy: SC MTX was associated with a significantly lower likelihood of therapeutic change (HR 0.64, 95% CI 0.52-0.78). Multiple DMARD therapy: SC MTX was not associated with a lower risk of adding a biologic (HR 1.13, 95% CI 0.97-1.31). Liver enzymes: There was no significant association between use of SC MTX and decreased frequency of abnormal LFTs [p=0.09 for alanine aminotransferase (ALT), p=0.924 for aspartate aminotransferase (AST)].

Conclusion: Use of SC MTX is associated with longer duration of MTX monotherapy before addition of other DMARDs/biologic agents in RA patients. Use of SC MTX is not associated with significantly longer duration of multiple DMARD therapy before addition of biologic agents. Use of oral MTX is not significantly associated with increased frequency of elevated LFTs.

Keywords: Methotrexate, rheumatoid arthritis, antirheumatic agents

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Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory disease, affecting an estimated 1 million adults in the United States (1). RA progresses to permanent disability without intervention. However, early diagnosis and treatment reduces symptoms, slows joint damage, and increases the chance of remission (2-5).

In the last several decades, methotrexate (MTX) has become a mainstay of treatment for RA (6, 7). It has been shown to be effective with a relatively low risk to benefit ratio (8). Additionally, MTX has been shown to have better long-term retention rates than other disease-modifying anti-rheumatic drugs (DMARDs) (9). Adverse effects are the most common reason for MTX discontinuation, especially in early stages of treatment. Severe adverse effects are rare, and most RA patients are able to tolerate high doses of MTX for long periods (9). Ineffectiveness is the second most common reason for discontinuation of MTX therapy (9). When MTX is ineffective, it may be switched for another agent (either a traditional DMARD or biologic agent) or an additional drug may be added to therapy (6). Clinical trials have shown that higher doses of MTX control RA more effectively, and aggressive treatment with higher doses of MTX can improve therapeutic response (3, 4). When used at appropriate doses, traditional DMARD therapy for RA can be as effective as newer and more expensive biologic agents (10, 11). However, higher doses of MTX are also associated with increased frequency of adverse events, including hepatotoxicity and gastrointestinal (GI) symptoms (4, 12).

Recent recommendations by the American College of Rheumatology state that MTX should be used when initiating therapy. Additional DMARDs or biologic drugs may be considered in patients who

have failed MTX monotherapy (13). Previously, it has been recommended that oral MTX should be used when initiating therapy, and subcutaneous (SC) MTX should be considered in patients with poor compliance, GI symptoms, or inefficacy (14). However, it is unclear whether SC MTX prolongs the duration of DMARD therapy in patients with RA or reduces the incidence of adverse effects such as GI symptoms and hepatotoxicity. Our study aims to determine whether the use of SC MTX is associated with longer use of MTX therapy in patients receiving both MTX monotherapy and multiple traditional DMARD therapy with an MTX component. Additionally, we will compare the frequency of liver enzyme abnormalities in patients using oral MTX versus SC MTX.

Methods

Study design and population

Our retrospective cohort study used data collected from national administrative databases of a large nationwide hospital system. Ethical approval was obtained from the regional Healthcare System Institutional Review Board under approval MIRB #00671. As this was a retrospective cohort study using a database, it was not possible to obtain informed consent from subjects and a waiver of informed consent was obtained from the IRB. Individuals included in the study cohort met all of the following criteria: (a) seen between October 1, 1999, and September 30, 2009, with two or more RA diagnostic codes (ICD9 714) at least 6 months apart, (b) received a RA diagnostic code (ICD9 714) in the last rheumatology clinic encounter, (c) prescribed an anti-rheumatic agent (ARA) for a total duration of at least 6 months (including MTX, azathioprine, leflunomide, sulfasalazine, hydroxychloroquine, gold, minocycline, adalimumab, etanercept, infliximab, golimumab, certolizumab, abatacept, anakinra, rituximab, and/or tocilizumab), and (d) received MTX monotherapy 90 days on one occasion.

The follow-up period spanned the time from cohort entry to date of death or September 30, 2009, whichever came first.

Subject groups

Therapeutic change versus MTX monotherapy

We defined MTX monotherapy as treatment with MTX exclusively. We defined therapeutic change as switching to another ARA, adding another ARA, or increasing steroid dosage to ≥2.5 mg/d of prednisone at any point during the follow-up period.

Multiple traditional DMARD therapy versus biologic therapy

We defined multiple traditional DMARD therapy as simultaneous treatment with MTX and at least one other traditional DMARD. Biologic therapy was defined as either switching to or adding a biological DMARD to multiple traditional DMARD therapy.

SC MTX therapy

We defined SC MTX therapy as use of SC MTX for at least 30 days prior to therapeutic change or addition of a biologic agent.

Determination of MTX dosing

MTX dose was calculated from the hospital pharmacy benefits database using previously described methods (15). To look for MTX monotherapy use, the entire study period was scanned for segments of MTX use for at least 90 days, which did not overlap with other ARAs. MTX did not have to be the first ARA used.

Dosage

In the MTX monotherapy group, we defined maximum MTX dose as the peak MTX dose reached at any point during the follow-up period. In the therapeutic change groups, we defined maximum dose as the peak MTX dose before therapeutic change/addition of a biologic drug. The MTX doses at which therapeutic change occurred were also recorded.

Covariates

Age

Age was calculated at each event that was analyzed. We developed five categories as follows: <45, 45-54, 55-64, 65-74, and >75 y.

Ethnicity

Ethnicity is cataloged in the VA database as follows: Caucasian, African American, other (Hispanic and Asian American), and unknown/missing.

Laboratory results

Abnormal laboratory results were defined as follows: serum creatinine >1.5 mg/dL, hemoglobin <10 g/dL, leukocyte count <2,000/microliter, serum alanine aminotransferase (ALT) >80 U/L, and serum aspartate aminotransferase (AST) >120 U/L.

Gastrointestinal adverse events

Records were analyzed for gastrointestinal (GI) events that are known to be associated with MTX use, which includes nausea, vomiting, and apthous ulcers. We searched for GI events 90 days before a therapeutic change event using ICD-9 codes. Codes used were 787.0 (nausea and vomiting); 787.01 (nausea with vomiting); 787.02 (nausea alone); 787.03 (vomiting alone); 528.7 (apthous ulcer); and 528.5 (diseases of lips). To verify that these diseases were not chronic, it was ensured that these codes were not found in the chart for 180 days before the event that we identified.

Charlson Comorbidity Index (CCI)

We created a modified CCI by removing arthritic/connective tissue disease from the criteria. Modified CCI score was categorized into five groups as follows: 0, 1, 2, 3, 4+.

Statistical analysis

All analyses were performed using Stata Statistical Software: Release 14 (College Station, TX, USA: StataCorp LP).

MTX monotherapy

Descriptive statistics were used to characterize subjects across route of administration of MTX. We used a chi-square test to assess the association between route of administration and these covariates. A chi-square test was performed for the relationship between new onset GI symptoms and use of SC MTX. A crude Cox regression was performed to determine association between the use of SC MTX and risk of therapeutic change. A second Cox regression was then performed to adjust for other variables. Gender, race, age categories, start dose categories, max dose categories, CCI score, laboratory abnormalities, new onset GI symptoms, and use of SC MTX were included in the second regression. A Kaplan-Meier curve was created comparing duration of MTX monotherapy in the oral versus SC MTX groups.

Multiple traditional DMARD therapy

As in the MTX monotherapy group, we used descriptive statistics to characterize subjects across oral and SC MTX groups. We used a chi-square test to assess the association between route of MTX administration and covariates. We performed a crude Cox regression to determine the association between a variety of patient characteristics and the length of time using traditional multiple DMARD before adding a biologic agent. A second Cox regression was performed to adjust for other variables. Gender, race, age category, and use of SC MTX were included as independent variables in the second regression. A Kaplan-Meier curve was created comparing the duration of multiple traditional DMARD therapy before addition of biologics in oral versus SC MTX groups.

Laboratory values

We performed a chi-square test for the relationship between abnormal liver function test (LFT) results and SC MTX.

Results

MTX monotherapy

A total of 7,017 subjects were identified as having been on MTX monotherapy for at least 90 days. Of the 7,017 subjects, 6,831 received oral MTX only and 186 received SC MTX. About 3,910 subjects required a therapeutic change-3,808 treated with oral MTX only and 102 treated with SC MTX (Figure 1). There was a significant association between patient age and route of administration of MTX (Table 1). Subjects on oral MTX were generally older than those on SC MTX. There was also a significant association between race, starting dose, and maximum dose and route of MTX administration. A larger percentage of subjects on oral MTX was African American compared with subjects on SC MTX (13.9% vs 7.8%). Generally, subjects taking SC MTX were taking higher starting and maximum doses than those on oral MTX (>15 mg starting dose and >20 mg maximum dose).

In the crude Cox regression, the use of SC MTX was associated with a lower risk of therapeutic change (HR 0.72, 95% CI 0.59-0.87) (Table 1). In the adjusted Cox regression model using therapeutic change as the event, the use of SC MTX at maximum dose was associated with a significantly lower likelihood of therapeutic change (HR 0.64, 95% CI 0.52-0.78) (Table 1). The Kaplan-Meier curve corresponds with the Cox regression (Figure 2). At all time points in the follow-up period, the SC MTX group had significantly fewer "MTX failures" than the oral MTX group.

Multiple DMARD therapy

A total of 6,541 subjects were identified as having been on more than one traditional DMARD at any point in time and 3,586 had used MTX as a component of multiple DMARD therapy. Of the 3,586 subjects, 1,837 eventually added or switched to a biologic drug (Figure 1). Of those 1,837 patients, 1,640 were taking oral MTX and 197 were taking SC MTX. Demographically, there was a significant association between race and route of administration of MTX (Table 1). A larger percentage of subjects on oral MTX were African American compared with subjects on SC MTX.

In the crude Cox regression model using addition of a biologic drug as the event, the use of SC MTX was associated with a significantly higher likelihood of therapeutic change (HR 1.18, 95% CI 1.02-1.37). However, the adjusted Cox regression showed no significant difference in risk of adding a biologic in subjects using SC MTX (HR 1.13, 95% CI 0.97-1.31)

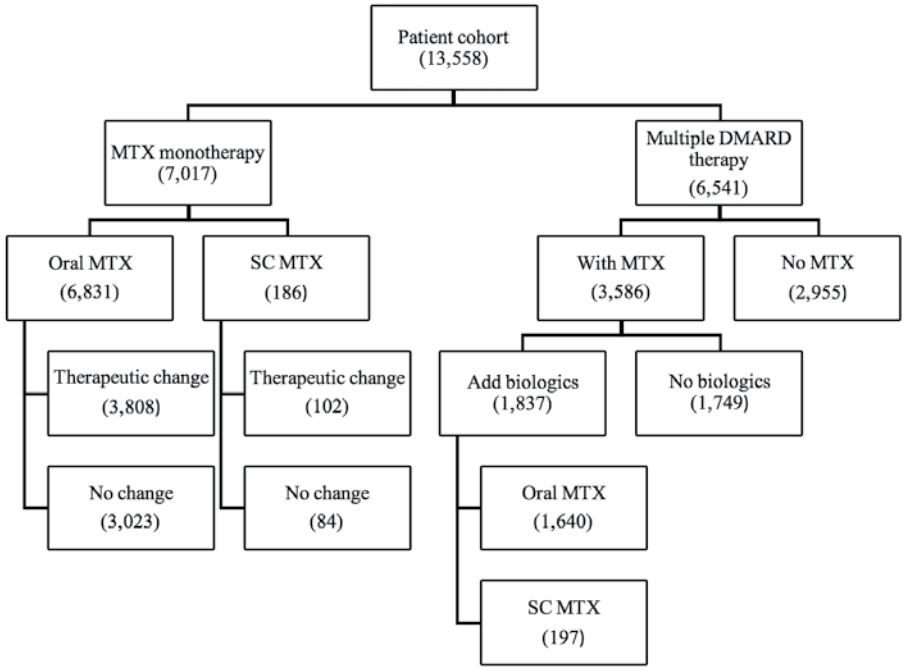

Figure 1. Patient flow diagram showing subjects sorted into methotrexate (MTX) monotherapy and multiple disease-modifying anti-rheumatic drug (DMARD) groups as well as oral and subcutaneous (SC) methotrexate groups; also, shown are patients who did not undergo therapeutic change in the MTX monotherapy group or patients who never had biologics added to therapeutic regimen in the multiple DMARD group, who were excluded from the study

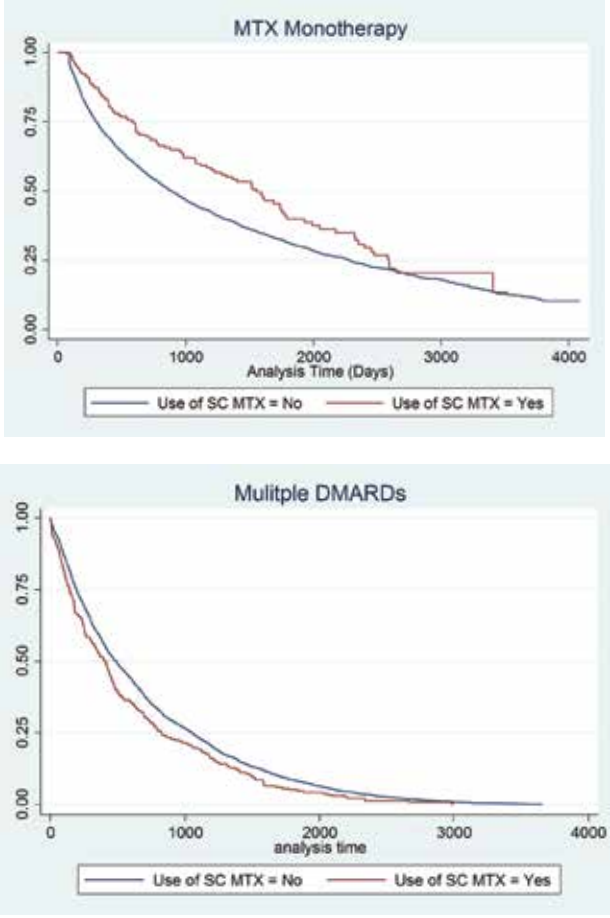

Figure 2. Kaplan-Meier survival curves for both methotrexate (MTX) monotherapy and multiple disease-modifying anti-rheumatic drugs (DMARDs) groups showing length of MTX therapy before therapeutic change in patients on subcutaneous methotrexate (SC MTX) and oral MTX

Table 1. Subject demographics

MTX Monotherapy group					
		Patients requiring therapeutic change			
	All patients (n=7017)	All (n=3910)	Oral MTX (n=3808)	SC MTX (n=102)	p
Gender					
Female	650 (9.3%)	438 (11.2%)	422 (11.1%)	16 (15.7%)	0.146
Male	6367 (90.7%)	3472 (88.8%)	3386 (88.9%)	86 (84.3%)	
Age					
<45	432 (6.2%)	224 (5.7%)	211 (5.5%)	13 (12.8%)	<0.001
45-54	1173 (16.7%)	686 (17.5%)	670 (17.6%)	16 (15.7%)	
55-64	2070 (29.5%)	1384 (35.4%)	1334 (35.0%)	50 (49.0%)	
65-74	1865 (26.5%)	912 (23.3%)	898 (23.6%)	14 (13.7%)	
>75	1477 (21.0%)	704 (18.0%)	695 (18.3%)	9 (8.8%)	
Race					
Caucasian	5509 (78.5%)	2976 (76.1%)	2898 (76.1%)	78 (76.5%)	<0.001
African American	847 (12.1%)	539 (13.8%)	531 (13.9%)	8 (7.8%)	
Other	334 (4.8%)	216 (5.5%)	213 (5.6%)	3 (2.9%)	
Unknown	327 (4.7%)	179 (4.6%)	166 (4.4%)	13 (12.8%)	
Starting MTX dose					
<10 mg/week	2145 (30.6%)	1213 (31.0%)	1191 (31.3%)	22 (21.6%)	<0.001
10-15 mg/week	2844 (40.5%)	1608 (41.1%)	1580 (41.5%)	28 (27.5%)	
>15 mg/week	2028 (28.9%)	1089 (27.9%)	1037 (27.2%)	52 (51.0%)	
Maximum MTX dose					
<15 mg/week	2055 (29.3%)	1034 (26.4%)	1032 (27.1%)	2 (2.0%)	<0.001
15-20 mg/week	2870 (40.9%)	1584 (40.5%)	1572 (41.3%)	12 (11.8%)	
>20 mg/week	2092 (29.8%)	1292 (33.0%)	1204 (31.6%)	88 (86.3%)	
Charlson comorbidity score					
0	3386 (48.2%)	1822 (46.6%)	1769 (46.5%)	53 (52.0%)	0.214
1	1901 (27.1%)	1080 (27.6%)	1054 (27.7%)	26 (25.5%)	
2	820 (11.7%)	472 (12.1%)	456 (12.0%)	16 (15.7%)	
3	539 (7.7%)	309 (7.9%)	304 (8.0%)	5 (4.9%)	
4+	371 (5.3%)	227 (5.8%)	225 (5.9%)	2 (2.0)	
Multiple DMARD group					
			Oral MTX (n=1640)	SC MTX (n=197)	p
Gender					
Female			201 (12.3%)	27 (13.7%)	0.56
Male			1439 (87.7%)	170 (86.3%)	
Age					
<45			124 (7.6%)	24 (12.2%)	0.07
45-54			343 (20.9%)	40 (20.3%)	
55-64			684 (41.7%)	87 (44.2%)	
65-74			319 (19.5%)	34 (17.3%)	
>75			170 (10.4%)	12 (6.1%)	
Race					
Caucasian			1251 (76.3%)	165 (85.1%)	<0.001
African American			228 (13.9%)	7 (3.6%)	
Other			90 (5.5%)	10 (5.2%)	
Unknown			71 (4.3%)	12 (6.2%)	

Demographic and clinical characteristics of subjects in the methotrexate (MTX) monotherapy group and multiple disease-modifying anti-rheumatic drug (DMARD) group, including gender, age, race, starting methotrexate dose, maximum methotrexate dose, and Charlson comorbidity score, on both oral and subcutaneous (SC) methotrexate

Table 2. Cox regression for methotrexate monotherapy group

	Hazard ratio	p	95% CI	
Unadjusted SC MTX	0.72	<0.01	0.59	0.87
Gender				
Female (reference)	--	--	--	--
Male	0.80	<0.01	0.72	0.90
Race				
White (reference)	--	--	--	
Black	1.03	0.52	0.94	1.14
Other	1.09	0.24	0.95	1.25
Unknown	1.14	0.11	0.97	1.34
Age				
<45 (reference)	--	--	--	--
45-54	0.97	0.69	0.83	1.13
55-64	0.88	0.11	0.76	1.03
65-74	0.55	<0.01	0.47	0.65
>75	0.43	<0.01	0.36	0.50
Start dose				
Reference	--	--	--	--
2	1.07	0.07	0.99	1.16
3	1.05	0.31	0.96	1.15
Max dose				
<15 mg/week (reference)	--	--	--	--
15-20 mg/week	0.85	<0.01	0.78	0.92
>20 mg/week	0.79	<0.01	0.72	0.86
Charlson comorbidity score				
0 (reference)	--	--	--	--
1	1.03	0.44	0.95	1.11
2	1.05	0.33	0.95	1.17
3	1.12	0.08	0.99	1.26
4+	1.03	0.73	0.89	1.18
Lab values				
Creatinine	0.99	0.92	0.86	1.15
Hemoglobin	1.11	0.52	0.81	1.53
White blood cell count	2.23	0.26	0.56	8.93
Alanine aminotransferase	1.08	0.58	0.82	1.43
Aspartate aminotransferase	2.97	0.03	1.10	8.04
SC MTX	0.64	<0.01	0.52	0.78
Gastrointestinal symptoms	1.53	0.02	1.07	2.17

Results of Cox regression for various demographic characteristics in the methotrexate (MTX) monotherapy group; all hazard ratios are adjusted for all other variables in the table, with the exception of the unadjusted subcutaneous methotrexate (SC MTX) hazard ratio

(Table 3). The Kaplan-Meier curve corresponds with the Cox regression (Figure 2). The SC MTX group had more "MTX failures" than the oral MTX group, but there was no significant difference in the number of MTX failures between groups.

Liver enzymes

In the chi-square analysis between elevated ALT and AST levels and use of SC MTX at maximum dose, p-values were 0.09 for ALT and 0.924 for AST (Table 4).

Among patients identified in our analysis, the use of SC MTX in MTX monotherapy was associated with a significantly longer duration of therapy than oral MTX. This is consistent with findings of other analyses, which also showed increased therapeutic benefit and retention with SC MTX when compared to oral MTX (16). It also suggests that the use of SC MTX may allow patients to maintain good disease control with MTX monotherapy for a longer period of time before adding other DMARDs or expensive biologic agents and that it may be an effective treatment strategy, as suggested by others (17). We found that patients on SC MTX monotherapy were taking higher doses of MTX than those on oral therapy, and it has been shown that higher doses of MTX are associated with longer duration of MTX therapy (3). Subjects who were on SC MTX had likely been prescribed a subcutaneous route of administration because of suboptimal disease control or adverse effects (e.g., GI symptoms) on oral MTX therapy, as is recommended by RA treatment guidelines (13). Our analysis of pharmacy data and exclusion of subjects with periods of prescription fill gaps minimized the inclusion of noncompliant subjects in the study, which is another potential reason for switching a patient from oral to SC MTX. Longer monotherapy duration in older patients may be due to less aggressive treatment of RA in elderly patients (18-21). We also found that the use of SC MTX was associated with increased frequency of GI symptoms, contrary to the findings of other analyses (22). This may be related to the higher bioavailability of SC MTX when compared to oral MTX or other confounders such as additional medications or illnesses that we were unable to account for in our model (15, 23).

In patients on multiple traditional DMARD therapy, the use of SC MTX was not associated with significantly longer duration of traditional DMARD before addition of a biologic drug to therapy. In fact, there was a trend toward shorter duration of MTX therapy before adding a biologic in patients using SC MTX. This does not contradict the findings in patients on MTX monotherapy. Patients on multiple DMARD therapy typically have more severe disease than those on MTX monotherapy, and MTX failure or therapeutic change is more likely due to poor response to MTX rather than adverse effects. These findings suggest that patients who have poor response to multiple traditional DMARD therapy are unlikely to experience prolonged traditional DMARD therapy when using SC MTX.

In both patients receiving MTX monotherapy and those receiving multiple traditional DMARD therapy, there was no significant association between use of SC MTX and elevated ALT and AST levels. This suggests that the route of administration of MTX does not have an effect on the incidence of hepatotoxicity.

We observed that older patients were less likely to be taking SC MTX. There is no definitive explanation for these findings. It is possible that physicians are more cautious about

Table 3. Cox regression for multiple DMARD[1] group

	Hazard ratio	p	95% CI	
Unadjusted SC MTX[2]	1.18	0.025	1.02	1.37
Gender				
Female (reference)	--	--	--	--
Male	0.95	0.51	0.82	1.10
Race				
White (reference)	--	--	--	--
Black	0.86	0.03	0.74	0.99
Other	0.89	0.27	0.73	1.09
Unknown	1.38	<0.01	1.10	1.72
Age				
<45 (reference)	--	--	--	--
45-54	0.91	0.36	0.75	1.11
55-64	0.85	0.08	0.71	1.02
65-74	0.77	<0.01	0.63	0.94
>75	0.73	<0.01	0.58	0.91
SC MTX	1.13	0.11	0.97	1.31

[1]Disease modifying anti-rheumatic drug
[2]Subcutaneous methotrexate
Results of Cox regression for various demographic characteristics in the multiple disease-modifying anti-rheumatic drugs (DMARD) group. All hazard ratios are adjusted for other variables in the table, with the exception of the unadjusted subcutaneous methotrexate (SC MTX) hazard ratio

Table 4. Chi square for LFTs

	Normal	Abnormal	p
ALT			
Oral MTX	12,272 (98.4)	205 (1.6)	0.09
SC MTX	524 (9.4)	14 (2.6)	
Total	12,796 (98.3)	219 (1.7)	
AST			
Oral MTX	12,452 (99.4)	74 (0.6)	0.924
SC MTX	534 (99.4)	3 (0.6)	
Total	12,986 (99.4)	77 (0.6)	

Results of chi-square analysis for association between use of subcutaneous methotrexate (SC MTX) and abnormal liver function tests (LFT), including alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

prescribing MTX to older patients because of concerns regarding adverse medication effects or ease of use (especially regarding oral vs. SC administration). In fact, it has been found that patients with elderly onset RA are less likely to receive treatment with biologics than those who are diagnosed with arthritis at younger ages (21). We also found that African Americans were less likely to be on SC MTX than Caucasian patients. It has been previously shown that African American patients are less likely to be prescribed biologic agents than Caucasians and are also less likely to achieve clinical remission than Caucasian patients (24). However, it is unclear whether this is due to the fact that RA may be more aggressive in some ethnic groups, differences in patient preference regarding treatment, or some bias in prescribing (25-27).

The advantages in our study were: (a) a large cohort of patients, (b) long follow-up period, and (c) the ability to accurately monitor the dose and duration of MTX therapy for each subject using the hospital pharmacy data. Since this is an observational study based on administrative data, it has several known limitations: (a) the inability to control for confounding factors like disease severity, (b) issue with generalization to a wider population as the patient population of this hospital system is predominantly male, Caucasian, and older, and (c) although steps were taken to reduce the effects of potential confounders by adjusting for covariates such as gender, age, race, abnormal lab results, and GI symptoms, there may possibly be unknown confounders.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the regional Healthcare System Institutional Review Board (MIRB #00671).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.N.; Design - B.N.; Supervision - B.N.; Resources - B.N.; Materials - B.N.; Data Collection and/or Processing - B.N.; Analysis and/or Interpretation - E.H.; Literature Search - E.H.; Writing Manuscript - E.H.; Critical Review - E.H., B.N.

Conflict of Interest: The authors have no conflict of interest to declare.

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