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Subcutaneous Methotrexate Is Associated With a Significantly Longer Duration of Methotrexate Monotherapy Compared With Oral Methotrexate in Patients With Rheumatoid Arthritis: Observations From the U.S. Veterans Affairs Database

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BACKGROUND

Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment, however, limitations of systemic exposure of oral MTX can affect its efficacy. The bioavailability of oral MTX is less than that of subcutaneous (SC) MTX at doses ranging from 10-25 mg, and plateaus at doses ≥15 mg.[1] The improved bioavailability of SC MTX may result in better efficacy, and SC MTX has been proven to be well tolerated, even at high doses of up to 25 mg/week.[1]

A previous analysis performed using the national administrative databases of the Department of Veterans Affairs (VA) suggested that the use of injectable MTX was associated with a higher likelihood to remain on MTX monotherapy.[2]

OBJECTIVES

- To identify patients in the VA database who were treated with injectable MTX after experiencing intolerance or inefficacy with oral MTX, and to determine whether these patients remained on MTX monotherapy longer than those treated only with oral MTX
- To compare the rates of liver enzyme abnormalities between patients using injectable MTX monotherapy and those using oral MTX monotherapy

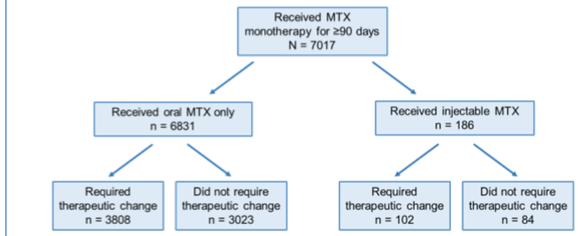
METHODS

- National administrative databases of the Department of VA, including inpatient and outpatient files, vital status files, and pharmacy benefits management and decision support system laboratory files, were used to identify patients
- Key inclusion criteria:
  - Patients seen between October 1, 1999, and September 30, 2009, having at least 2 RA diagnostic codes (International Classification of Diseases, Ninth Revision [ICD9] codes of 714) at least 6 months apart
  - Having an RA diagnostic code entered in the encounter of the last rheumatology clinic visit
  - Being at any time prescribed an antirheumatic agent for a total duration of at least 6 months, including MTX, azathioprine, leflunomide, sulfasalazine, hydroxychloroquine, gold, minocycline, adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, abatacept, anakinra, rituximab, and/or tocilizumab
  - Having received MTX monotherapy for at least 90 days
- The duration of MTX monotherapy before a therapeutic change was compared between patients treated with injectable MTX for at least 30 days and those who were treated only with oral MTX, using a Wilcoxon-Mann-Whitney test
- Therapeutic change was defined as (1) switching to or adding one or more other antirheumatic agents; or (2) an increase in steroid dosage equivalent to 2.5 mg of prednisone at any time point within the follow-up period
  - Patients who did not meet these criteria were placed in the MTX monotherapy group
- Factors that could potentially influence the duration of MTX monotherapy were assessed using a log-rank test and Kaplan-Meier curves; in order to correct for patient variables, linear regression models were also run
  - These factors included the use of injectable MTX, gender, age, race, starting MTX dose, maximum MTX dose, and modified Charlson comorbidity score
- Liver enzyme abnormalities were compared between patients on injectable and oral MTX who received MTX monotherapy for ≥90 days; abnormal alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels were defined as exceeding twice the upper limit of normal (>80 IU/L and >120 IU/L, respectively)

RESULTS

- Overall, 7017 patients were identified who had been on MTX monotherapy for at least 90 days (**Figure 1**)
  - 6831 Patients had received MTX as an oral formulation only, and 186 had received injectable MTX
  - 3910 Patients required a therapeutic change (3808 treated with oral MTX only and 102 treated with injectable MTX)

Figure 1. Patient Population



MTX, methotrexate.

- The majority of patients were male (90.7%), ≥55 years old (77.1%), and Caucasian (78.5%) (**Table 1**)
  - Among the 3910 patients who required a therapeutic change, route of administration was significantly associated with age (P<0.001), race (P<0.001), starting MTX dose (P<0.001), and maximum MTX dose attained (P<0.001), but not gender (P=0.146) or Charlson comorbidity score (P=0.214)

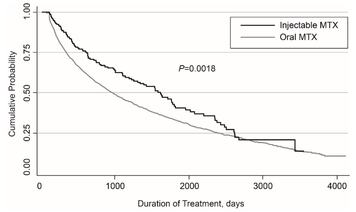
Table 1. Patient Demographics

	All Patients	Patients Who Required a Therapeutic Change			
	Total N = 7017	All n = 3910	Oral MTX n = 3808	Injectable MTX n = 102	*P* Value*
Gender, n (%)					
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, n (%), years					
<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, n (%)					
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/missing	327 (4.7)	179 (4.6)	166 (4.4)	13 (12.8)	
Starting MTX dose, n (%)					
<10 mg/week	2145 (30.6)	1213 (31.0)	1191 (31.3)	22 (21.6)	<0.001
10 to <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 attained, n (%)					
<15 mg/week	2055 (29.3)	1034 (26.4)	1032 (27.1)	2 (2.0)	<0.001
15 to <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, n (%)					
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)	

MTX, methotrexate.
*P values are for the comparison between oral MTX and injectable MTX.

- Among patients who required a therapeutic change, those treated with oral MTX remained on MTX monotherapy for a mean (SD) of 627 (636.5) days compared with 962 (786.6) days for those treated with injectable MTX monotherapy (P<0.001)
- Based on log-rank tests, the use of injectable MTX was significantly associated with longer duration of MTX monotherapy (P=0.0018) (**Figure 2**)
  - Additionally, race (P<0.001), age (P<0.001), starting dose of MTX (P=0.0197), and gender (P<0.001) were significantly associated with longer duration of MTX monotherapy

Figure 2. Duration of MTX Monotherapy



MTX, methotrexate.

- When adjusted for patient variables using linear regression analysis, the longer duration of MTX monotherapy was significantly associated with use of injectable MTX (P<0.001) (**Table 2**)
  - Age, race, starting MTX dose, and maximum MTX dose were also significantly associated with duration of MTX monotherapy

Table 2. Associations of MTX Monotherapy Treatment Duration With Patient Characteristics

	Coefficient (SE)	*P* Value	95% Confidence Interval
Gender			
Female	–	–	–
Male	27.8 (33.8)	0.411	-38.5 – 94.0
Race			
Caucasian	–	–	–
African American	27.3 (30.3)	0.368	-32.1 – 86.7
Other	109.5 (44.6)	0.014	22.1 – 196.9
Unknown/missing	-91.5 (50.6)	0.071	-190.7 – 7.8
Age			
<45 years	–	–	–
45-54 years	37.1 (49.2)	0.450	-59.2 – 133.5
55-64 years	75.1 (47.3)	0.112	-17.6 – 167.7
65-74 years	135.2 (49.9)	0.007	37.2 – 233.1
≥75 years	222.2 (51.5)	<0.001	121.2 – 323.2
Starting MTX dose			
<10 mg/week	–	–	–
10 to <15 mg/week	-146.6 (24.3)	<0.001	-194.3 – -98.9
≥15 mg/week	-240.2 (28.7)	<0.001	-296.4 – -183.9
Maximum MTX dose			
<15 mg/week	–	–	–
15 to <20 mg/week	223.9 (26.8)	<0.001	171.4 – 276.5
≥20 mg/week	385.1 (29.1)	<0.001	328.0 – 442.2
Charlson comorbidity score			
0	–	–	–
1	15.6 (24.6)	0.527	-32.7 – 63.8
2	-34.9 (33.5)	0.298	-100.5 – 30.8
3	-52.9 (39.6)	0.181	-130.5 – 24.7
4	27.6 (45.4)	0.543	-61.4 – 116.5
Injectable MTX use			
No	–	–	–
Yes	249.1 (64.7)	<0.001	122.4 – 375.9
Gastrointestinal symptoms			
No	–	–	–
Yes	57.1 (111.5)	0.609	-161.5 – 275.6
Laboratory tests			
Creatinine	-15.6 (45.7)	0.734	-105.2 – 74.1
Hemoglobin	-128.6 (101.2)	0.204	-327.0 – 69.7
White blood cell count	-353.7 (442.8)	0.424	-1221.8 – 514.4
ALT	79.5 (90.4)	0.379	-97.8 – 256.8
AST	-257.0 (316.5)	0.417	-877.6 – 363.5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTX, methotrexate; SE, standard error.

- Of the patients treated with MTX who also had ALT and/or AST levels assessed, the rates of abnormal ALT and AST levels were not significantly different between those receiving oral and injectable MTX (P=0.870 and P=0.056, respectively; **Table 3**)
- Density plots of ALT and AST levels are shown in **Figure 3A** and **Figure 3B**, respectively

CONCLUSIONS

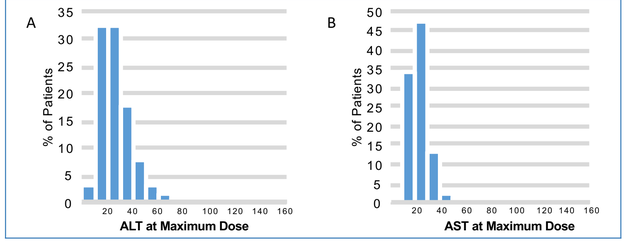
- Among patients identified in the VA database, the use of injectable MTX was associated with a significantly longer duration of MTX monotherapy compared with oral MTX
- No differences in liver enzyme abnormalities were found between patients treated with injectable MTX and oral MTX
  - This was observed despite the association of this patient population (predominantly male patients within the VA system), with increased rates of alcoholism,[3] which may therefore increase the expected incidence of liver function abnormalities
- Despite the advantage of improved bioavailability with injectable MTX compared to oral MTX, injectable MTX is only used by an estimated <5% of patients with RA in the United States[4] and is an underutilized treatment option
- Routine use of injectable MTX may allow patients to continue to achieve good disease control with MTX before adding other therapies
  - Delaying the initiation of biologic therapies in the treatment of RA may result in significant cost savings to the VA system

Table 3. ALT and AST Levels

	Normal	Abnormal
ALT level, n	6806	83*
Oral MTX	6622	81
Injectable MTX	184	2
AST level, n	6903	7†
Oral MTX	6720	6
Injectable MTX	183	1

Only includes patients who had ALT and AST levels measured. *P* values are for the comparison between rates of abnormal liver enzymes between oral MTX and injectable MTX.
*P=0.870.
†P=0.056.

Figure 3. ALT and AST Density Plots



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DISCLOSURES

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