Original article

Influence of methotrexate on gastrointestinal symptoms in patients with rheumatoid arthritis

Short running title: Influence of MTX on GI symptoms in RA

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Author contributions

SA designed the study, conducted statistical analyses, and drafted the manuscript. All authors contributed to interpretation of data, manuscript preparation, and manuscript review; approved the draft for publication; and agree to be accountable for all aspects of the work.

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Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

Abstract

Aim: This study aimed to determine the influence of methotrexate (MTX) on gastrointestinal (GI) symptoms in patients with rheumatoid arthritis (RA).

Methods: This cross-sectional study examined 529 consecutive patients with RA receiving oral MTX in our department between April 1 and September 30, 2017. GI symptoms were evaluated by the Gastrointestinal Symptom Rating Scale (GSRS); a score of ≥ 2 was considered "symptomatic." Prevalence of GI symptoms was compared between patients receiving ≤ 8 mg/week (low-dose) versus > 8 mg/week (high-dose) of MTX.

Results: Of our study population, 313 (59%) received low-dose MTX at a median (IQR) dose of 6 (6-8) mg/week, whereas 216 (41%) received high-dose MTX at a median (IQR) dose of 12 (10-12) mg/week. Relative to the low-dose MTX group, the high-dose MTX group exhibited a higher prevalence of reflux (32% vs 24%, *P*=0.043) and abdominal pain (28% vs 18%, *P*=0.007). There was no significant group-dependent difference in the prevalence of indigestion, diarrhea, and constipation. Multivariate logistic regression analysis revealed that high-dose MTX (> 8 mg/week) was independently associated with reflux [odds ratio (OR): 1.62, 95% confidence interval (CI): 1.07-2.43] and abdominal pain (OR: 1.60, 95% CI: 1.04-2.43), and that the odds ratios for reflux and abdominal

pain among those receiving high-dose MTX (> 8 mg/week) were similar to those using NSAIDs.

Conclusion: High-dose MTX is independently associated with the prevalence of upper GI symptoms in Japanese patients with RA.

Keywords: rheumatoid arthritis, methotrexate, gastrointestinal symptoms, quality of life, patient-reported outcomes

Introduction

Methotrexate (MTX) is an important anchor drug for patients with rheumatoid arthritis (RA), both as monotherapy as well as in combination with other drugs [1]. A systematic literature review of MTX monotherapy recommended starting oral MTX at 10-15 mg/week, and then increasing this up to 20-30 mg/week depending on clinical response and tolerability [2]. Toxicity can drive patients to either limit MTX usage or discontinue MTX therapy [3, 4], and gastrointestinal (GI) events are encountered frequently as a toxicity of MTX [4, 5].

GI symptoms are some of the most common comorbidities that can adversely affect quality of life (QOL) in patients with RA [6]. Relative to their healthy counterparts, patients with RA face an increased risk of upper and lower GI events, as well as increased GI-related mortality [7]. Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are known risk factors for GI symptoms [7-9], while acid-suppressive drugs such as proton pump inhibitors reportedly decrease NSAID-related GI symptoms [10, 11]. Older age and renal impairment are generally considered risk factors for developing MTX-related toxicities [12, 13]. Previous randomized controlled studies found that MTX dose tended to be associated with GI symptoms [14, 15]; however, certain confounding factors such as NSAID use and renal function complicated the

findings of these studies. The present study, therefore, aimed to determine the influence of MTX on GI symptoms in patients with RA while taking into consideration known risk factors.

Materials and Methods

Patients

This cross-sectional study included 529 consecutive patients with RA who were treated with oral MTX in our department between April 1 and September 30, 2017. All patients met the 1987 American College of Rheumatology (ACR) classification criteria or the new ACR/European League Against Rheumatism (EULAR) diagnostic criteria, and received oral MTX according to the drug label and Japan College of Rheumatology guidelines for treatment. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine (2017-0204) and complied with principles set forth by the Declaration of Helsinki. Informed consent was obtained by an opt-out procedure. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled.

Gastrointestinal Symptom Rating Scale (GSRS)

Patients were asked to complete a Gastrointestinal Symptom Rating Scale (GSRS) questionnaire to evaluate the presence and severity of GI symptoms. The GSRS is a disease-specific QOL scale and a self-administered questionnaire including 15 items with a seven-point Likert-type scale ranging from 1 (no discomfort at all) to 7 (very severe discomfort). The five subscales include reflux (heartburn and acid regurgitation), abdominal pain (abdominal pain, hunger pain, and nausea), indigestion (borborygmus, abdominal distension, eructation, and increased flatus), diarrhea (diarrhea, loose stools, and urgent need to defecate), and constipation (constipation, hard stools, and feeling of incomplete evacuation) [16]. The GSRS was shown to have good reliability and construct validity in patients with dyspeptic symptoms in a multinational study [17]. Each subscale score is calculated as the mean score of individual items in the subscale. We defined "symptomatic" as a score ≥ 2 on GSRS subscales according to a previous study [18] because it is well known that normal individuals have GSRS scores < 2 [19].

Data collection

Demographic and clinical data were collected from clinical records. Cigarette smoking was defined as daily smoking regardless of the amount. Alcohol drinking and

coffee drinking were defined in the same manner as cigarette smoking. Disease activity of RA was measured using Disease Activity Score in 28 joints using the C-reactive protein (DAS28-CRP), with DAS28 remission defined as DAS28-CRP < 2.3 [20]. Data on drug use included that for drugs prescribed in all departments of our institute.

Statistical analysis

Patients were divided into two groups based on median MTX dose: ≤ 8 mg/week (low-dose MTX group) and > 8 mg/week (high-dose MTX group). Continuous variables are expressed as median and interquartile ranges (IQR), while categorical variables are expressed as percentages. Baseline data, GSRS subscale scores, and prevalence of GI symptoms from the high-dose and low-dose MTX groups were compared by the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Additionally, patients were divided into four groups based on quartiles of MTX dose: ≤ 6 mg/week, > 6 and ≤ 8 mg/week, > 8 and ≤ 10 mg/week, and > 10 mg/week. Trends for the prevalence of GI symptoms across each quartile of MTX dose was assessed by the Cochran-Armitage trend test.

Factors associated with a score ≥ 2 on GSRS subscales were assessed with stepwise forward multivariate logistic regression models with the following variables:

age, gender, body mass index, serum albumin, estimate glomerular filtration rate (eGFR), cigarette smoking, alcohol drinking, coffee drinking, disease duration, MTX dose, duration of MTX use, DAS28 categories (remission or not) or DAS28 components [tender joint count and swollen joint count on 28 joints, serum CRP levels, general health on a visual analogue scale (GH-VAS)], and use of folic acid, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) other than MTX, biological disease-modifying antirheumatic drugs (bDMARDs), glucocorticoids, NSAIDs, acetaminophen, bisphosphonate, proton pump inhibitors, histamine H2 receptor antagonists, and prokinetic agents.

The Cochran-Armitage trend test was performed with EZR version 1.36 (Saitama Medical Centre, Jichi Medical University, Saitama, Japan) [21]. All other statistical analyses were performed with SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Demographic and clinical characteristics of all patients included in this study are shown in Table 1. Of 529 patients, 313 (59%) received low-dose MTX at a median (IQR)

dose of 6 (6-8) mg/week, whereas 216 (41%) received high-dose MTX at a median (IQR) dose of 12 (10-12) mg/week. Relative to the low-dose MTX group, the high-dose MTX group was more likely to be younger [median (IQR), 63 (50-71) vs. 67 (57-72) years, P=0.001], have a higher eGFR [78 (67-91) vs. 72 (62-82) mL/min/1.73 m^2, P<0.001], shorter disease duration [9 (5-15) vs. 10 (6-20) years, P=0.001], shorter duration of MTX use [6 (3-10) vs. 8 (4-12) years, P<0.001], and lower rate of DAS28 remission (60% vs. 72%, P=0.006). Regarding concomitant medications, the high-dose MTX group used folic acid, csDMARDs other than MTX, and NSAIDs at a higher rate, whereas bDMARDs were used at a lower rate.

GSRS score

Figure 1 shows the cumulative probability plot of GSRS subscale scores. According to the Mann-Whitney U test, GSRS subscale scores for reflux and abdominal pain in the high-dose MTX group were significantly higher than that in the low-dose MTX group (P=0.034 and 0.029, respectively). There were no significant group-dependent differences in GSRS subscale scores for indigestion (P=0.116), diarrhea (P=0.113), or constipation (P=0.669).

Across all patients, prevalences of reflux, abdominal pain, indigestion, diarrhea,

and constipation, which were defined as a score ≥ 2 on GSRS subscales, were 27%, 22%, 29%, 26%, and 45%, respectively. The high-dose MTX group had a higher prevalence than that in the low-dose MTX group for reflux (32% vs 24%, *P*=0.043) and abdominal pain (28% vs 18%, *P*=0.007) (Fig. 1). There was no significant group-dependent difference in the prevalence of indigestion, diarrhea, or constipation. According to the Cochran-Armitage trend test, the prevalence of reflux tended to increase with MTX dose (*P*=0.062), and the prevalence of abdominal pain increased significantly with MTX dose (*P*=0.004) (Fig. 2).

Factors associated with GI symptoms

Odds ratios for scores ≥ 2 on GSRS subscales were calculated using multivariate logistic regression analysis. Table 2 shows factors significantly associated with a score ≥ 2 on GSRS subscales. MTX dose was treated as a categorical variable (≤ 8 mg/week vs. > 8 mg/week) in Models 1 and 3, and as a continuous variable in Model 2. DAS28 category (remission or not) was entered as a variable in Models 1 and 2, whereas all DAS28 components were entered as variables in Model 3. High-dose MTX was independently associated with reflux in Model 1 (OR: 1.62, 95% CI: 1.07-2.43) and Model 2 (OR: 1.07, 95% CI: 1.01-1.14), and abdominal pain in Model 1 (OR: 1.60, 95%

CI: 1.04-2.43), Model 2 (OR: 1.08, 95% CI: 1.01-1.15), and Model 3 (OR: 1.60, 95% CI: 1.04-2.43). Odds ratios for reflux and abdominal pain with high-dose MTX (> 8 mg/week) were similar to that for NSAID use. MTX dose was not associated with indigestion, diarrhea, or constipation. GH-VAS was independently associated with reflux (OR: 1.01, 95% CI: 1.00-1.02), indigestion (OR: 1.02, 95% CI: 1.01-1.02), diarrhea (OR: 1.01, 95% CI: 1.01-1.02), and constipation (OR: 1.02, 95% CI: 1.01-1.03), but not with abdominal pain.

Discussion

This study clearly demonstrated the influence of MTX on GI symptoms in patients with RA. Use of NSAIDs and glucocorticoids has been identified as a risk factor for GI symptoms in patients with RA [7, 8]. Furthermore, age and renal impairment have been shown to be risk factors for developing MTX-related toxicities [12, 13]. Our multivariate analysis revealed that high-dose MTX was associated with upper GI symptoms such as reflux and abdominal pain independently of known risk factors. As this study was cross-sectional in design, causality cannot be proven in the strict sense; however, consistent with previous studies [4, 5, 14, 15], high-dose MTX can evidently cause GI symptoms. The definition of GI symptoms was ambiguous in previous studies

that investigated the relationship between MTX dose and GI symptoms [14, 15]. Our study is the first to demonstrate that upper GI symptoms increase in a MTX dose-dependent manner, using a validated patient-reported questionnaire.

In addition to hepatic disorders, GI symptoms are common adverse events in patients with RA receiving MTX. Several studies reported a prevalence of 20-40% for GI symptoms in patients with MTX administered both as monotherapy [3, 4, 14, 15] or as combination therapy with other DMARDs [22, 23]. In this study, the prevalence of GI symptoms, defined as a score ≥ 2 on GSRS subscales, was comparable to that in previous reports. Accordingly, this definition of GI symptoms with GSRS may be clinically reasonable in patients with RA. The prevalence of lower GI symptoms was equivalent to or higher than upper GI symptom in this study, while upper GI symptoms were dominant in previous studies [14, 22]. Lower GI symptoms may not be due to MTX because there was no relationship between MTX dose and lower GI symptoms. Further comparison of patients treated with and without MTX will be needed to clarify the influence of MTX on lower GI symptoms.

GI symptoms in patients with RA are affected by various factors. Several concomitant drugs can affect GI symptoms in patients undergoing RA treatment. NSAIDs and glucocorticoids are well known to cause GI adverse events [7-9]; furthermore,

concurrent use of NSAIDs and glucocorticoids is associated with a 15-fold greater risk of peptic ulcer disease than use of either drug class alone [24]. A previous study estimated that the use of proton pump inhibitors reduced NSAID gastropathy by 18% in patients with RA [10]. Bisphosphonates also can cause GI symptoms in 10-30% of patients with RA [25]. Age and renal impairment influence MTX toxicities as well. Specifically, increasing age has been shown to be associated with an increased risk of MTX treatment termination associated with a major toxicity [12]. A systematic literature review revealed that the odds of developing severe toxicity were increased roughly 4-fold in patients with renal impairment [13]. This study showed that high-dose MTX was associated with reflux and abdominal pain independently of the above-mentioned potential confounders. The odds ratios for reflux and abdominal pain in a patient given a MTX dose > 8 mg/week (vs. ≤ 8 mg/week) were about 1.6, similar to that reported for NSAID use. Accordingly, MTX > 8 mg/week can affect upper GI symptoms as much as NSAID use.

According to a recent study, gastroesophageal reflux disease increases GH-VAS in patients with RA [26]. In this study as well, GH-VAS was independently associated with reflux. Notably, high-dose MTX was not associated with reflux in the multivariate analysis with GH-VAS as a variable, but was independently associated with reflux in the multivariate analysis without GH-VAS as a variable. The univariate analysis revealed that

the prevalence of reflux did not increase significantly in accordance with MTX dose. Although not significant, the prevalence was highest in patients receiving MTX > 8 and ≤ 10 mg/week (Figure 2). This may be because patients receiving MTX > 8 and ≤ 10 mg/week were more likely to have a high GH-VAS [median (IQR), 22 (9-45)] compared to those receiving MTX ≤ 6 mg/week, > 6 and ≤ 8 mg/week, and > 10 mg/week [20 (6-46), 14 (5-30), and 17 (6-48), respectively].

Notably, the dose of MTX [median (IQR), 8 (6-10) mg/week] in the present study was lower than doses recommended for the treatment of RA [2], even after considering that the average body weight of patients in Japan is 20-30% less than that of patients in Western countries. The MTX dose approved by the Japanese Ministry of Health, Labor, and Welfare has an upper limit of 16 mg/week. However, a prospective study on certolizumab pegol in Japan, in which MTX was initiated at a dose of 8 mg/week and was increased to 16 mg/week at week 8 by protocol, showed that MTX dose used in actual clinical settings remains ≤ 12 mg/week, owing to adverse events [22]. Concentrations of erythrocyte MTX polyglutamate, a potential biomarker for MTX therapy, were reported to be markedly higher in the Japanese study than what was reported by a US study, suggesting that a lower dose of MTX may be sufficient for Japanese patients [27].

The primary goal of treating patients with RA is to maximize long-term health-

related QOL [28]. Patients in remission have a better QOL than those with higher disease activity [29]. However, a recent study suggests that intensive treatment and remission improve physical but not mental QOL [30]. In addition, upper GI symptoms such as dyspepsia and abdominal/epigastric pain reportedly reduce QOL including mental health in patients with RA or osteoarthritis [6]. Accordingly, in order to improve not only physical but mental QOL as well, improvement of GI symptoms is important during RA treatment. GSRS scores are correlated with the Medical Outcomes Study Short Form-36 Health Survey and the Psychological General Well-being, which are comprehensive QOL scales [16]. This study showed that GSRS subscale scores for reflux and abdominal pain in the high-dose MTX group were significantly higher than those in the low-dose MTX group. Our findings suggest the importance of paying attention to both upper GI symptoms during MTX treatment and to patient QOL.

Various measures can be taken to reduce GI symptoms caused by MTX. Several studies reported that intramuscular MTX has the potential to reduce GI side effects observed in oral treatment [31, 32]. Unfortunately, as intramuscular MTX is not approved in Japan, none of the present study patients received this treatment. A systematic literature review revealed that supplementation with folic acid or folinic acid reduced the risk of GI side effects by 26% [33]. Folic acid use was not statistically associated with any GI

symptoms, potentially because most patients used folic acid in this study. Canadian recommendations suggest oral split doses of MTX to minimize non-serious GI side effects [34]; however, there is no clear evidence to suggest that this is effective. If GI symptoms persist even after changing the mode of administration or concomitantly using folic or folinic acid, reducing the MTX dose may be the only countermeasure to reduce GI symptoms.

This study has some limitations worth noting. First, our analysis did not include data regarding endoscopic findings of the gastric mucosa and prior GI events, both of which are generally associated with GI symptoms [10, 11]. Additionally, we could not obtain data concerning medicine prescribed in other hospitals; however, almost all drugs available for RA treatment are prescribed at our hospital. Second, as this is a cross-sectional study, it is not clear whether GI symptoms are reduced by decreasing MTX dose. Further longitudinal studies will be needed to clarify this issue.

In conclusion, high-dose MTX is associated with upper GI symptoms independently of known risk factors in patients with RA. Moreover, a MTX dose > 8 mg/week influences upper GI symptoms as much as NSAID use in Japanese patients. Our findings suggest that it is necessary to pay attention to GI symptoms during MTX treatment and to patient QOL.

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1 Table 1. Demographic and clinical characteristics of patients

	Total	MTX ≤ 8 mg/week	MTX > 8 mg/week	
	n=529	n=313	n=216	*P* value†
Age, years	65 (54-72)	67 (57-72)	63 (50-71)	0.001
Gender, female, %	81	82	79	0.284
Body mass index	21 (20-24)	21 (19-24)	21 (20-24)	0.723
Serum albumin, g/dL	4.0 (3.8-4.2)	4.0 (3.8-4.2)	4.0 (3.8-4.2)	0.022
eGFR, mL/min/1.73 m^2	74 (64-86)	72 (62-82)	78 (67-91)	< 0.001
Cigarette smoking, %	7	5	9	0.131
Alcohol drinking, %	9	9	9	0.953
Coffee drinking, %	62	63	61	0.725
Disease duration, years	10 (5-19)	10 (6-20)	9 (5-15)	0.001
MTX dose, mg/week	8 (6-10)	6 (6-8)	12 (10-12)	< 0.001
Duration of MTX use, years	7 (4-11)	8 (4-12)	6 (3-10)	< 0.001
DAS28-CRP	1.8 (1.4-2.6)	1.7 (1.3-2.4)	2.0 (1.5-2.7)	< 0.001
DAS28 remission, %	67	72	60	0.006
Tender joint count (0-28 scale)	0 (0-1)	0 (0-1)	0 (0-1)	< 0.001

Swollen joint count (0-28 scale)	0	(0-1)	0	(0-1)	0	(0-1)	0.008
CRP, mg/dL	0.11	(0.03-0.31)	0.10	(0.03-0.26)	0.12	(0.04-0.43)	0.019
GH-VAS, 0-100 mm	17	(6-40)	17	(5-35)	20	(7-45)	0.225
Drug use, %							
Folic acid	88		84		93		0.003
csDMARD other than MTX	16		10		23		< 0.001
bDMARD	29		35		20		< 0.001
Glucocorticoid	24		21		27		0.097
NSAID	34		30		39		0.041
Acetaminophen	3		4		1		0.134
Bisphosphonate	15		15		14		0.832
Proton pump inhibitor	18		16		22		0.073
H2 antagonist	6		7		5		0.317
Prokinetic agent	2		3		1		0.067

MTX, methotrexate; eGFR, estimated glomerular filtration rate; DAS28-CRP, Disease Activity Score in 28 joints using the C-reactive protein; GH-VAS, general health on a visual analogue scale; csDMARD, conventional synthetic disease-modifying antirheumatic drug; bDMARD, biological disease-modifying antirheumatic drug;

NSAID, nonsteroidal anti-inflammatory drug; H2 antagonist, histamine H2 receptor antagonist. Data are presented as median (interquartile range), unless otherwise stated. †*P* values were determined using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables.

Table 2. Factors associated with score ≥ 2 on GSRS subscales

	Model 1	Model 2	Model 3
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Reflux			
Female	1.94 (1.11-3.39)	1.89 (1.08-3.30)	1.92 (1.11-3.33)
Body mass index†	1.12 (1.06-1.19)	1.13 (1.06-1.20)	1.11 (1.05-1.18)
Disease duration, years†	1.03 (1.01-1.05)	1.03 (1.01-1.05)	-
MTX ≤ 8 mg/week	1.00 (reference)	-	-
MTX > 8 mg/week	1.62 (1.07-2.43)	-	-
MTX dose, mg/week†	-	1.07 (1.01-1.14)	-
NSAID use	1.70 (1.12-2.57)	1.70 (1.12-2.56)	1.71 (1.13-2.60)
GH-VAS, mm†	-	-	1.01 (1.00-1.02)
Abdominal pain			
MTX ≤ 8 mg/week	1.00 (reference)	-	1.00 (reference)
MTX > 8 mg/week	1.60 (1.04-2.43)	-	1.60 (1.04-2.43)
MTX dose, mg/week†	-	1.08 (1.01-1.15)	-
NSAID use	1.80 (1.16-2.78)	1.78 (1.15-2.75)	1.80 (1.16-2.77)
Indigestion			

Proton pump inhibitor use	2.00 (1.26-3.17)	2.00 (1.26-3.17)	1.81 (1.13-2.91)
GH-VAS, mm†	-	-	1.02 (1.01-1.02)
Diarrhea			
Alcohol drinking	1.96 (1.04-3.67)	1.96 (1.04-3.67)	1.89 (1.01-3.56)
Glucocorticoid use	1.66 (1.07-2.57)	1.66 (1.07-2.57)	-
GH-VAS, mm†	-	-	1.01 (1.01-1.02)
Constipation			
Age, years†	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.04)
csDMARD use	0.39 (0.23-0.65)	0.39 (0.23-0.65)	0.36 (0.21-0.62)
Serum albumin, g/dL†	-	-	2.17 (1.12-4.20)
GH-VAS, mm†	-	-	1.02 (1.01-1.03)

GSRS, Gastrointestinal Symptom Rating Scale; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; GH-VAS, general health on a visual analogue scale; csDMARD, conventional synthetic disease-modifying antirheumatic drug. Odds ratios (OR) were calculated using step-wise forward multivariate logistic regression models. †OR for 1-unit increase in each item.

Figure legends

Figure 1. Cumulative probability plot of Gastrointestinal Symptom Rating Scale (GSRS) subscale scores for reflux (a), abdominal pain (b), indigestion (c), diarrhea (d), and constipation (e) stratified by methotrexate doses of ≤ 8 mg/week and > 8 mg/week. The percentage in the figure shows the prevalence of a score ≥ 2 on GSRS subscales. MTX, methotrexate.

Figure 2. Prevalence of a score ≥ 2 on Gastrointestinal Symptom Rating Scale (GSRS) subscales stratified by methotrexate dose. MTX, methotrexate.