Treatment patterns in rheumatoid arthritis after discontinuation of methotrexate: data from the Ontario Best Practices Research Initiative (OBRI)

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Abstract

Objective

In active rheumatoid arthritis (RA) patients with inadequate response to methotrexate (MTX), guidelines support adding or switching to another conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) and/or a biologic DMARD (bDMARD). The purpose of this analysis was to describe treatment practices in routine care and to evaluate determinants of regimen selection after MTX discontinuation.

Methods

Biologic-naïve patients in the Ontario Best Practice Research Initiatives registry discontinuing MTX due to primary/secondary failure, adverse events, or patient/physician decision were included.

Results

Of 313 patients discontinuing MTX, 102 (32.6%) were on MTX monotherapy, 156 (49.8%) on double, and 55 (17.6%) on multiple csDMARDs. Patients on MTX monotherapy were older than patients on double or multiple csDMARDs (p=0.013), less likely to have joint erosions (p=0.009) and had lower patient global assessment (p=0.046) at MTX discontinuation. Post-MTX discontinuation, 169 (54.0%) transitioned to, or added new DMARD(s) (new csDMARD(s): 139 [44.4%]; bDMARD: 30 [9.6%]), and 144 (46.0%) opted for no new DMARD treatment. Patients on MTX monotherapy transitioning to other treatment, switched more to other csDMARD monotherapy, whereas patients on combination csDMARDs switched more to new csDMARDs and bDMARD combination therapy. Early RA ($_{adj}$OR [95%CI]: 3.07 [1.40–6.72]) and treatment with multiple csDMARDs vs. MTX monotherapy (4.15 [1.35–12.8]) at MTX discontinuation were significant predictors of transitioning to or adding new csDMARD(s)/bDMARD treatment versus opting for no new DMARD treatment.

Conclusion

Differences in subsequent treatment patterns exist between patients discontinuing MTX when used as monotherapy versus in combination with other csDMARDs where the former are more likely to use a subsequent monotherapy treatment.

Key words

disease-modifying anti-rheumatic drugs, biological therapy, methotrexate, registries, rheumatoid arthritis

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Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory arthritis (1), affecting up to 1% of the population (2). RA negatively impacts health-related quality of life (3, 4), poses considerable economic burden (5), is associated with numerous comorbidities (6, 7) and reduces life expectancy (8).

In recent years, new approaches to treatment strategies comprising conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs) have greatly enhanced the care of persons with RA (9). International 'treat-to-target' recommendations for achieving remission include measuring disease activity regularly and adjusting therapy accordingly to optimise outcomes for patients (10). Methotrexate (MTX) remains the most commonly recommended csDMARD initial treatment for patients with low or moderate to high disease activity (9, 11, 12). Approved bDMARDs for RA include anti-tumour necrosis factor (anti-TNF) inhibitors, T cell costimulatory inhibitors, B lymphocyte-depleting agent, as well as interleukin (IL)-6 and IL-1 antagonists (9).

The aim of this study was to determine clinical practice patterns by analysing treatment regimens in biologic-naïve patients followed under routine care that discontinued MTX when used as monotherapy or in combination with other csDMARDs. Patient characteristics associated with treatment at the time of first MTX discontinuation and variables predicting transition to a new treatment regimen after discontinuation of treatment with MTX were identified.

Methods

Study design and data source

The Ontario Best Practices Research Initiative-Rheumatoid Arthritis (OBRI-RA) is an ongoing multicentre registry collecting data from both physicians and RA patients followed under routine care, including regular telephone interviews. Fifty-seven sites in Ontario, Canada, are currently participating. Patients are eligible for inclusion in the OBRI if they are ≥18 years at the time of enrolment, have a confirmed diagnosis of RA after the age of 16 years, and have at least one swollen joint. Institutional ethics approval was obtained, and informed consent was provided by all patients prior to study enrolment. This study was conducted in compliance with the Helsinki Agreement.

Study population

At the time of analysis, a total of 2,635 patients with RA were enrolled in OBRI of whom 2,591 had available physician assessments and information on medications. Of these, 313 biologic-naïve patients that discontinued MTX treatment due to an adverse event or side effect, primary or secondary failure, or patient/physician decision after enrolment in the registry were included in the analysis. Patients who were treated with a biologic prior to MTX discontinuation were excluded, as were patients with unknown start dates for MTX.

Parameters assessed included patient socio-economic, demographics, disease attributes, health insurance information, number of comorbidities, treatment regimens at the time of MTX discontinuation, reasons for discontinuing MTX treatment, and treatment regimens after discontinuation (csDMARDs or bDMARDs).

Statistical analyses

All statistical analyses were conducted using STATA v. 10. Descriptive statistics including the mean and standard deviation for continuous variables and counts and proportions for categorical variables were produced. The Kruskal-Wallis and Chi-square (or Fisher's exact test, as appropriate) tests were used to compare profiles of patients discontinuing different types of MTX regimens as well as profiles of patients transitioning to different treatment regimens post-MTX discontinuation.

To identify determinants of treatment post-MTX discontinuation, a stepwise approach was followed where potential confounders were first identified based on whether they showed a statistical trend ($p<0.200$) in both their univariate association with types of discontinued MTX regimens (MTX monotherapy or MTX + 1 or more csDMARDs) and the

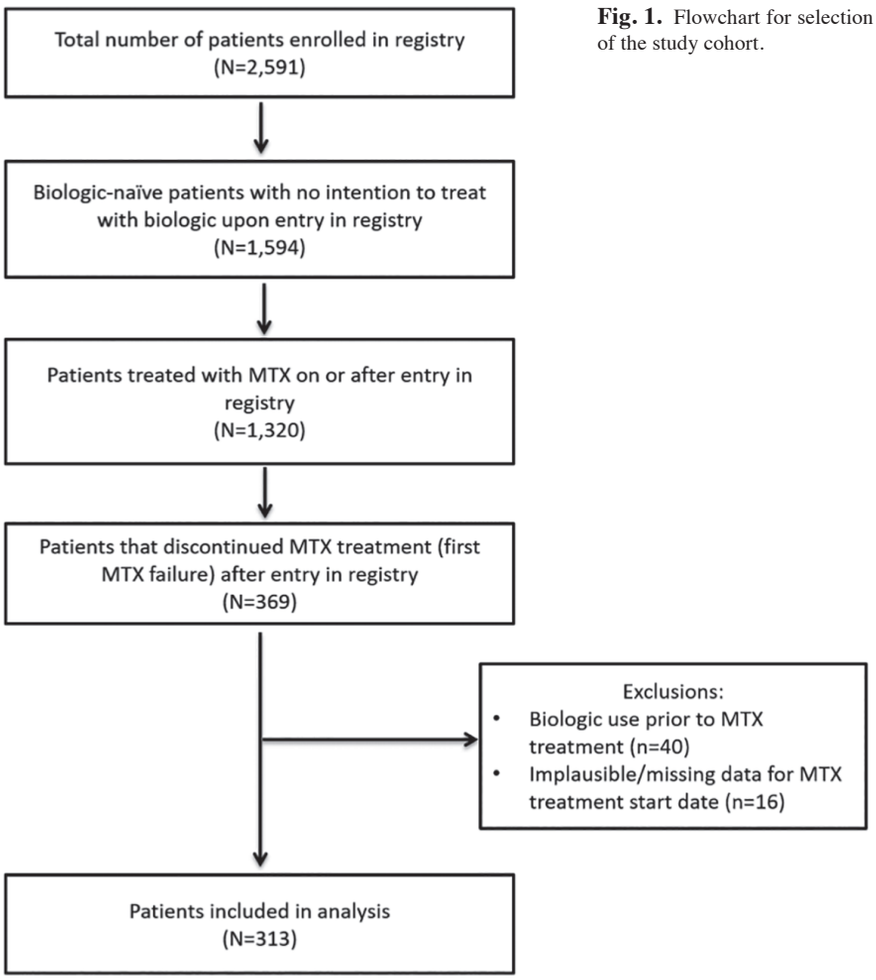

Fig. 1. Flowchart for selection of the study cohort.

choice of regimen post-MTX discontinuation. These potential confounders were then considered in multivariate logistic regression. Two different types of multivariate models were produced, a saturated model containing all variables considered and a reduced model using backward variable selection.

Results

Study cohort selection

A total of 313 biologic-naïve patients that discontinued MTX when used alone or in combination with other csDMARDs were included in the analysis cohort (Fig. 1). Patient characteristics, sociodemographic factors, and disease parameters of the analysis cohort at the time of MTX discontinuation were compared among patients that were taking MTX monotherapy (n=102, 32.6%), double csDMARDs therapy (MTX + 1 csDMARD; n=156, 49.8%) or multiple csDMARDs therapy (MTX + 2 or more DMARDs; n=55, 17.6%) (Table I). The mean duration of MTX treatment prior to discontinuation was 15 months, without any significant differences between treatment groups. Patients discontinuing MTX monotherapy were significantly older than those patients discontinuing MTX combined with double csDMARDs therapy or multiple csDMARDs therapy (p=0.013), were more likely to be treated with oral MTX (p=0.002) and were less likely to have used prior csDMARDs other than MTX (p<0.001) (Table I). Patients discontinuing MTX used in combination with multiple other csDMARDs were more likely to have joint erosion(s) (p=0.009) and had higher patient global assessment of disease activity (p=0.046). No significant differences between treatment regimens were observed in other patient demographics, annual income class, smoking status, health insurance or prescription drug coverage. Most discontinuations of MTX therapy were due to adverse events, irrespective of treatment regimen. The composition of the different treatment regimens at the time of MTX discontinuation is described in Table II.

Treatment patterns post-MTX discontinuation

After MTX discontinuation, several different treatment patterns were observed. A new treatment regimen comprising 1 or more new csDMARDs or a bDMARD was chosen for 169 (54.0%) patients (Table III). Among these, 30 (9.6%) patients were prescribed bDMARD therapy, and 139 (44.4%) received new csDMARD(s). Proportionately more patients discontinuing MTX monotherapy transitioned to monotherapy with another csDMARD (Fig. 2: white shaded segment), whereas patients who discontinued MTX when on double or multiple combination therapy transitioned to treatment regimens comprising other csDMARDs combinations (Fig. 2: black and grey shaded segments) or a biologic combination therapy (Fig. 2A: checkered white shaded segments). For the remaining 144 (46.0%) patients, no new csDMARDs or bDMARDs were added to their regimen over a mean follow-up of 14.8 months (Table III); of these, 28 (19.4%) were switched to non-DMARD therapy, including NSAIDs and/or steroids, 47 (32.6%) continued treatment with the backbone csDMARD therapy, 49 (34%) re-added MTX in their regimen, and 20 (13.9%) patients that discontinued MTX monotherapy had no documented RA treatment presumably due to being between treatments. The composition of the treatment regimen for these patients post-MTX discontinuation is described in Figure 2B.

Patient characteristics, socio-economic, demographic factors, and disease parameters at the time of MTX discontinuation were grouped according to the new treatment regimens selected after MTX discontinuation (Table III). Patients that received no further new treatment with either drug class (csDMARDs or bDMARDs) had significantly longer disease duration than the others (p=0.02), and were taking fewer

Table I. Patient characteristics by treatment regimen at MTX discontinuation.

	Analysis cohort (n=313)	Treatment regimen			
		MTX monotherapy (n=102)	MTX + 1 csDMARD (n=156) cs	MTX + multiple DMARDs (n=55)	*p*-value*
Age, years, mean (SD)	58.8 (13.2)	61.9 (13.5)	57.7 (13.4)	56.3 (10.6)	**0.013**
Female (%)	78.0	72.6	81.4	72.6	0.244
Education, % (n=302)†					
High school or less	47.0	49.0	47.0	43.4	0.820
Post-secondary	53.0	51.0	53.0	56.6	
Annual household income class, % (n=216)†					
< $50,000 CAD	43.5	46.8	36.9	55.6	*0.119*
≥ $50,000 CAD	56.5	53.2	63.1	44.4	
Smoking history, % (n=292)†					
Never smoker	48.3	43.9	51.0	48.9	0.647
Former smoker	38.0	43.9	34.0	38.3	
Current smoker	13.7	12.2	15.0	12.8	
Health insurance, % (n=292)†					
Public	31.2	35.7	31.3	21.3	0.537
Private	23.3	20.4	25.2	23.4	
Both	43.1	40.8	42.2	51.1	
None	2.4	3.1	1.4	4.3	
% prescriptions covered by insurer, mean (SD) (n=279)†	81.2 (32.2)	81.5 (32.7)	81.7 (30.4)	79.1 (36.9)	0.581
Ever applied for Trillium coverage, % (n=247)†	7.7	5.9	6.4	14.6	0.266
Disease duration (years), mean (SD)	6.7 (8.2)	7.5 (8.9)	6.8 (8.3)	4.5 (5.8)	0.276
Early RA, %	30.4	37.3	25.6	30.9	*0.142*
Rheumatoid Factor positive, % (n=293)†	62.9	54.9	66.7	67.3	0.367
Anti-CCP positive, % (n=112)†	19.8	15.7	21.8	21.8	0.635
Presence of erosion, % (n=309)†	43.5	43.1	37.2	61.8	**0.009**
28 tender joint count, mean (SD) (n=242)†	3.4 (5.0)	3.6 (5.4)	3.1 (4.3)	3.8 (6.0)	0.955
28 swollen joint count, mean (SD) (n=246)†	3.0 (4.0)	3.3 (4.6)	2.7 (3.6)	3.1 (4.1)	0.842
DAS28 ESR, mean (SD) (n=207)†	3.5 (1.5)	3.5 (1.4)	3.5 (1.6)	3.7 (1.6)	0.802
Physician Global (1-10), mean (SD) (n=223)†	3.0 (2.4)	2.8 (2.3)	2.9 (2.5)	3.4 (2.6)	0.429
Patient Global (1-10), mean (SD) (n=232)†	3.9 (2.9)	3.5 (2.8)	3.9 (3.1)	4.8 (2.7)	**0.046**
HAQ-DI, mean (SD) (n=204)†	0.91 (0.78)	0.93 (0.76)	0.84 (0.77)	1.05 (0.85)	0.431
Presence/number of comorbidities‡ (n=291)†					
mean (sd)	2.0 (1.4)	2.3 (1.4)	1.9 (1.4)	1.8 (1.4)	*0.090*
≤ 1 comorbidity, %	40.9	37.1	44.0	39.6	0.577
> 1 comorbidity, %	59.1	62.9	56.0	60.4	
Use of prior csDMARDs other than MTX					
mean, sd	0.34 (0.5)	0.14 (0.35)	0.38 (0.52)	0.62 (0.68)	**<0.001**
None, %	68.7	86.3	64.1	49.1	**<0.001**
One or more, %	31.3	13.7	35.9	50.9	
Current use of steroids, %	14.7	16.7	10.9	21.8	0.110
Reason for MTX discontinuation, %					
Primary failure	6.4	9.8	5.8	1.8	0.397
Secondary failure	12.1	12.8	11.5	12.7	
Adverse events	40.9	42.2	39.7	41.8	
Patient decision	24.0	16.7	26.3	30.9	
Physician decision	16.6	18.6	16.7	12.7	
Duration of MTX treatment (months), mean (SD)	15.0 (20.8)	13.7 (21.8)	15.5 (21.3)	16.3 (17.4)	0.206
MTX administration route, %					
Oral	54.6	67.7	51.9	38.2	**0.002**
SC	43.5	31.4	46.8	56.4	
MTX dose (mg/week), mean (SD)	18.5 (5.9)	17.9 (6.1)	18.9 (5.8)	18.8 (6.2)	0.380
Treatment added after MTX discontinuation, %					
No new csDMARDs or bDMARD	46.0	54.9	50.6	23.6	**0.028**
New csDMARDs	44.4	42.2	39.1	56.4	
bDMARD	9.6	2.9	10.3	20.0	

*Statistically significant values ($p \leq 0.05$) are highlighted in bold. Statistical trends ($p < 0.2$) are italicised.
†Indicates the number of patients with available information if there are missing data.
‡Comorbidity: Heart disease, hypertension, lung disease, diabetes mellitus, gastrointestinal disease, kidney disease, haematologic diseases, cancer, depression, osteoarthritis, psoriasis, back pain, and liver disease.
Anti-CCP: anti–citrullinated protein antibody; bDMARD: biologic disease-modifying anti-rheumatic drug; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire disability index; MTX: methotrexate; RA: rheumatoid arthritis.

Table II. Treatment regimens at MTX discontinuation.

	Analysis cohort (n=313)
MTX monotherapy, %	**32.6**
MTX double therapy (MTX + 1 csDMARD), %	**49.8**
MTX + HCQ	28.1
MTX + LEF	13.4
MTX + SSZ	8.0
MTX + AZA	0.3
MTX combination therapy (MTX + multiple csDMARDs), %	**17.6**
MTX + HCQ + SSZ	9.3
MTX + HCQ + LEF	6.1
MTX + SSZ + LEF	0.6
MTX + HCQ + AZA	0.3
MTX + HCQ + SSZ+LEF	1.0
MTX + HCQ + LEF + AZA	0.3

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; AZA: azathioprine; HCQ: hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine.

RA medications other than DMARDs ($p<0.001$). The follow-up time after MTX discontinuation for this same patient group was also significantly shorter ($p<0.001$). Those that transitioned to a bDMARD had higher tender and swollen joint counts, DAS28 (ESR), as well as physician and patient global assessments of disease activity compared to those who received no further new treatment ($p=0.025$, 0.008, 0.012, <0.001, and 0.039, respectively). Patients that transitioned to other csDMARDs had disease activity that was intermediate between the two aforementioned patient groups.

Two logistic regression models were developed, one for the addition of new csDMARD(s) or a bDMARD *versus* no new DMARD treatment (Table IVA) and the other for the selection of a bDMARD- *versus* a new csDMARD-based treatment regimen among the former patients (Table IVB). In the first analysis, early RA ($_{adj}$OR=3.07; $p=0.01$) and discontinuation of MTX + multiple csDMARDs *versus* MTX monotherapy ($_{adj}$OR=4.15; $p=0.01$) were identified as significant independent predictors of transitioning to a subsequent new treatment regimen compared to no addition of new csDMARD(s) or a bDMARD (Table IVA). In terms of selecting a bDMARD *versus* csDMARD-based treatment

Table III. Patient characteristics and disease parameters at MTX discontinuation by treatment regimen used post-MTX.

	No New csDMARDs or bDMARD added (n=144) *p*-value*	Treatment regimen post-MTX New csDMARDs/bDMARD added (n=169)		*p*-value*
		New csDMARDs(s) (n=139)	bDMARD (n=30)	
Age years, mean (SD)	58.9 (13.7)	58.8 (13.1)	59.0 (10.9)	0.950
Female (%)	81.3	75.5	73.3	0.380
Education status, % (n=302)†				
High school or less	40.3	51.1	60.7	0.060
Post-secondary	59.7	48.9	39.3	
Annual income class, % (n=216)†				
< $50,000	38.1	49.5	40.9	0.270
≥ $50,000	61.9	50.5	59.1	
Smoking history, % (n=292)†				
Never smoked	52.9	43.0	50.0	*0.180*
Former smoker	38.3	38.2	35.7	
Current smoker	8.8	18.8	14.3	
Health insurance, % (n=292)†				
Public	36.8	29.7	10.7	*0.180*
Private	19.9	26.6	25.0	
Both	41.1	41.4	60.7	
None	2.2	2.3	3.6	
% prescription(s) covered by insurer, mean (SD) (n=279)†	78.4 (34.5)	82.6 (30.6)	87.8 (27.3)	*0.070*
Ever applied for Trillium coverage, % (n=247)†	9.8	7.9	16.7	0.560
Disease duration (years), mean (SD)	8.3 (9.3)	5.2 (6.5)	5.2 (7.7)	**0.002**
Early RA, %	22.2	36.7	40.0	**0.020**
Rheumatoid Factor positive, % (n=293)†	59.4	75.9	63.0	**0.010**
Anti-CCP positive, % (n=112)†	48.1	68.9	40.0	**0.050**
Presence of erosion, % (n=309)†	37.3	48.2	56.7	*0.060*
DAS28 low disease activity (DAS ≤3.2), % (n=207)†	29.2	28.6	30.0	*0.140*
DAS28 remission (DAS ≤2.6), % (n=207)†	18.1	16.7	16.6	*0.160*
28 tender joint count, mean (SD)	2.3 (3.8)	4.1 (5.7)	4.8 (5.5)	**0.025**
28 swollen joint count, mean (SD)	2.1 (3.1)	3.5 (4.5)	4.4 (4.5)	**0.008**
DAS28 ESR, mean (sd)	3.1 (1.4)	3.7 (1.5)	4.2 (1.7)	**0.012**
Physician Global (1-10), mean (SD)	2.3 (2.2)	3.4 (2.4)	4.1 (2.7)	**<0.001**
Patient Global (1-10), mean (SD)	3.5 (3.0)	4.1 (2.7)	5.2 (3.5)	**0.039**
HAQ-DI, mean (sd)	0.83 (0.74)	0.93 (0.8)	1.2 (0.88)	0.312
Number of comorbidities‡, mean (SD) (n=291)†	2.0 (1.3)	2.1 (1.5)	2.1 (1.5)	0.840
Number of prior csDMARDs used other than MTX, mean (SD)	0.3 (0.5)	0.3 (0.5)	0.6 (0.7)	*0.18*0
Number of RA medications after MTX discontinuation, mean (SD)	0.94 (1.1)	2.4 (1.4)	2.5 (1.6)	**<0.001**
Reason for MTX discontinuation, %				
Primary failure	4.2	9.4	3.3	*0.150*
Secondary failure	15.2	8.6	13.3	
Adverse events	34.0	46.0	50.0	
Patient decision	27.8	20.2	23.4	
Physician decision	18.8	15.8	10.0	
MTX duration (months), mean (SD)	17.5 (24.1)	12.1 (17.4)	16.8 (16.4)	**0.004**
Follow-up time after MTX discontinuation (months), mean (SD)	14.8 (15.5)	31.5 (20.8)	28.6 (19.0)	**<0.001**
Number of physician visits after MTX discontinuation, mean (SD)	3.0 (3.2)	7.3 (4.7)	6.6 (4.0)	**<0.001**
Number of interviews after MTX discontinuation, mean (SD)	4.7 (3.4)	7.6 (3.5)	6.9 (4.0)	**<0.001**

*Statistically significant values (p≤0.05) are highlighted in bold. Statistical trends (p<0.2) are italicised.
†Indicates the number of patients with available information if there are missing data.
‡Comorbidity: Heart disease, hypertension, lung disease, diabetes mellitus, gastrointestinal disease, kidney disease, haematologic diseases, cancer, depression, osteoarthritis, psoriasis, back pain, and liver disease.
Anti-CCP: anti–citrullinated protein antibody; bDMARDs: biologic disease-modifying anti-rheumatic drug; csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire disability index; MTX: methotrexate; RA: rheumatoid arthritis.

regimen, patients discontinuing MTX and multiple csDMARDs therapy had borderline non-statistically significant higher odds (OR=3.84; *p*=0.060) of transitioning to a bDMARD compared to csDMARDs (Table IVB). No additional potential predictors of regimen selection were identified.

Discussion

This study provided insight into which clinical and demographic factors might determine treatment regimens after first MTX discontinuation.

In Canada, guidelines recommend MTX monotherapy or initial combination therapy (9). In addition, the Canadian Rheumatology Association (CRA) guidelines state that combination therapy should be considered in patients who have an inadequate response to monotherapy, while csDMARD and biologic therapies should be adjusted every 3–6 months as long as treatment goals have not been achieved. Generally, if an inadequate response is observed, the addition of a csDMARD to an existing regimen or a switch to a biologic is recommended (9).

Patients who have used only MTX monotherapy are not eligible for reimbursement from the provincial drug plan and only some private insurers will reimburse patients for a biologic after use of only one csDMARD. Therefore, it is less likely that patients discontinuing MTX monotherapy would receive a biologic as their subsequent treatment. Comorbidity, drug-related side effects, lack of tolerability or other patient factors may play a role in the decision to intensify therapy (10).

Recommendations seldom address access and coverage of high-cost biologics for RA (13–15). TNF inhibitors are covered in the Ontario Drug Benefit Formulary, yet their use is limited to patients with RA that have severe active disease (≥5 swollen joints, and at least one of: rheumatoid factor positive, anti-CCP positive, and/or radiographic evidence of RA, and that have experienced treatment failure, intolerance, or have a contraindication to adequate trials (at least 3 months) of conventional synthetic DMARDs (MTX at 20 mg/week, at least one combination

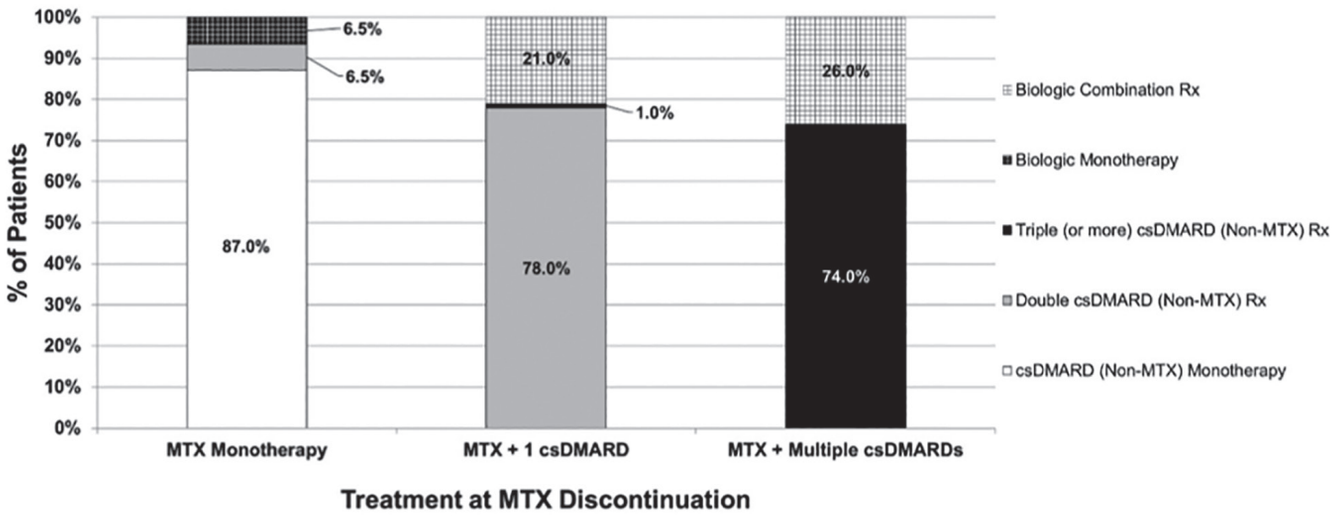

Fig. 2A. Treatment profile after MTX discontinuation by treatment pattern at time of MTX discontinuation among patients who selected a new csDMARD/bDMARD treatment regimen (n=169).

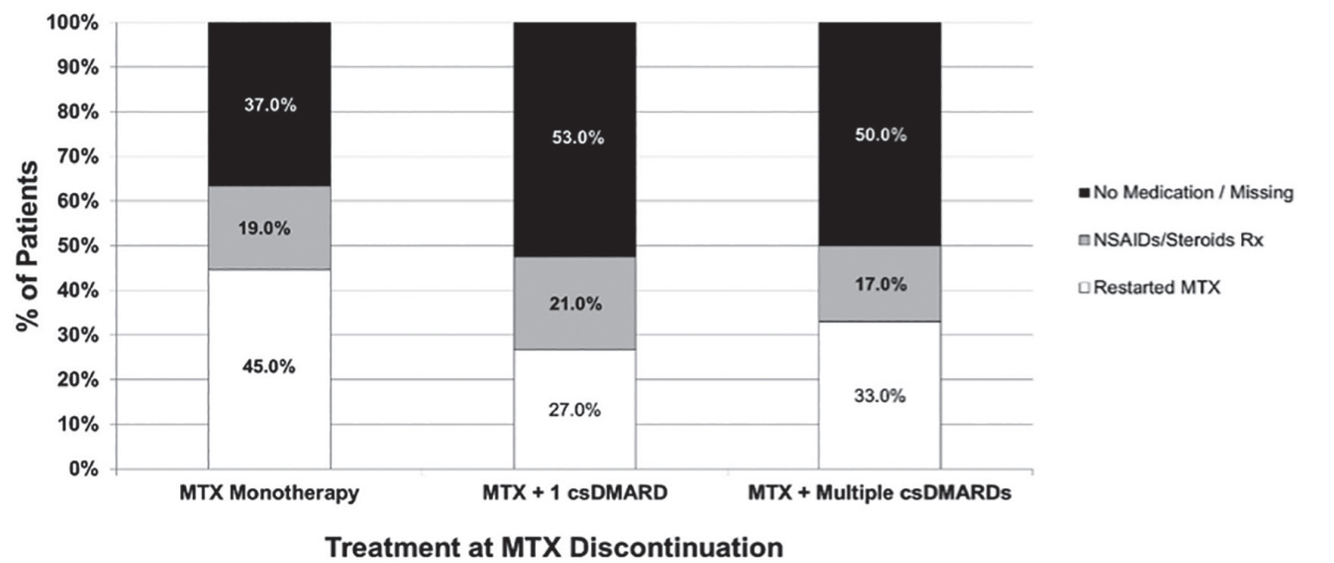

Fig. 2B. Treatment profile after MTX discontinuation by treatment pattern at time of MTX discontinuation among patients who did not select a new csDMARD/bDMARD treatment regimen (n=144).

of DMARDs and leflunomide, or, more recently, triple therapy) (16, 17).

Post-MTX treatment, over half transitioned to a regimen containing another csDMARD or bDMARD treatment, and those with combination treatment seemed to obtain a subsequent combination. The monotherapy patients seemed to be mainly serial switchers (serial monotherapy) when MTX was discontinued. These data support previously published North American studies that show considerable treatment variability for patients living with RA (18–22).

We previously reported that older-onset RA patients have greater disease activity, and treatment consists of less combination csDMARDs initially and subsequently less biologic treatment (23). In the current study, we found that patients discontinuing MTX monotherapy were older but had less erosions and lower disease activity and global assessment ratings. Early RA and use of multiple csDMARDs at the time of MTX discontinuation increased the likelihood of further treatment intensification with a bDMARD and/or new csDMARD(s). These findings are different from those of a previous study in early RA where predictors for transitioning to other csDMARDs regimens were HAQ-disability, poor mental health, and extra-articular disease; however, multiple csDMARDs therapy predicted a lower likelihood of transitioning to a regimen containing a new csDMARD in both studies (24). We also determined that the number of comorbidities was not a significant predictor for transitioning to a new treatment regimen, yet a study comprised of an international cohort recently reported that the odds of transitioning to a biologic treatment decreases for each additional chronic morbidity, while the odds of transitioning to a csDMARD-based treatment increases (25). Im-

Table IV A. Multivariate analysis for adding *vs*. not adding new csDMARDs/bDMARD post-MTX discontinuation.

Subjects n=313	Univariate analysis OR (95% CI), *p*-value	Multivariate analysis (saturated)* OR, *p*-value	Multivariate analysis (reduced)** OR, *p*-value
Medication pattern at MTX discontinuation			
MTX monotherapy	1.00	1.00	-
MTX + 1 csDMARD	1.13, 0.65	1.65, 0.189	1.67, (0.77–3.65), 0.20
MTX + Multiple csDMARDs	**4.03, < 0.001**	**4.23, 0.01**	**4.15 (1.35–12.8), 0.01**
Age (years)	1.00, 0.98	-	-
Early RA	2.08, **0.004**	2.94, **0.01**	**3.07 (1.40-6.72), 0.01**
Erosion	1.66, **0.03**	1.87, 0.08	1.87 (0.91-3.82), 0.09
Patient global score	1.10, **0.04**	1.03, 0.57	-
Number of comorbidities	1.05, 0.55	-	-
Annual income class			
< $50,000	1.00	1.00	1.00
≥ $50,000	0.67, 0.150	0.61, 0.16	*0.55 (0.27-1.14), 0.11*
Number of prior csDMARDs used other than MTX			
None	1.00	-	-
One or more	1.20, 0.45		

*Saturated multivariate model: n=157.
**Reduced multivariate model using backward variable selection with additional adjusting for age and sex. Statistically significant values ($p \leq 0.05$) highlighted in bold. Statistical trends ($p < 0.2$) are italicised.

Table IV B. Multivariate analysis for adding bDMARD *vs*. new csDMARD(s) post-MTX discontinuation.

Subjects n=169	Univariate analysis OR (95% CI), *p*-value	Multivariate analysis (saturated)* OR, *p*-value	Multivariate analysis (reduced)** OR, *p*-value
Medication pattern at MTX discontinuation			
MTX monotherapy	1.00	1.00	-
MTX + 1 csDMARD	**3.87, 0.04**	2.06, 0.300	2.46 (0.62-9.72), 0.20
MTX+ Multiple csDMARDs	**5.16, 0.02**	*3.18, 0.117*	*3.84 (0.92-16.0), 0.06*
Age (years)	1.00, 0.90	-	-
Early RA	1.15,0.735	-	-
Erosion	1.41, 0.40	-	-
Patient global score	*1.14, 0.166*	*1.12, 0.157*	*1.13 (0.96-1.33), 0.140*
Number of comorbidities	1.02, 0.88	-	-
Annual income class			
< $50,000	1.00	-	-
≥ $50,000	1.41, 0.47		
Number of prior csDMARDs used other than MTX			
None	1.00	1.00	-
One or more	*1.71, 0.195*	1.34, 0.543	

*Saturated multivariate model: n=130.
**Reduced multivariate model using backward variable selection with additional adjusting for age and sex. Statistically significant values ($p \leq 0.05$) highlighted in bold. Statistical trends ($p < 0.2$) are italicised.

portantly, a systematic review of eight clinical trials examining protocol-driven escalation of specific MTX/csDMARDs combinations has concluded that a treatment strategy is more important than a specific drug (27).

Nearly 10% received treatment intensification with a biologic after MTX discontinuation. Two recent surveys of Canadian patients and rheumatologists suggest that treatment patterns for initiating biologic therapy vary greatly (19, 31). Provided that there was unrestricted access, 57% of rheumatologists reported that they would start treatment with an anti-TNF after 3–6 months of MTX combination therapy, 31% after 3–6 months on MTX monotherapy 20–25 mg per week, and 16% immediately in patients with moderate to severe RA (19). Patients in our analysis cohort were taking MTX for an average of 15 months before MTX was discontinued, and there was no significant difference in time lapsed among treatment groups. The exact reasons for changes in treatment are not fully known. Other research questions related to pharmacoepidemiology, drug costs, and access are being considered.

There are limitations in this study. Reasons underlying the physician or patient's decision to discontinue MTX treatment were not routinely recorded. In addition, nearly half (46.0%) of patients in this study cohort that discontinued MTX opted for no treatment intensification with a biologic or a new csDMARD but the inclusion criteria were OBRI RA patients who discontinued MTX so this is not generalisable to patients who add further treatment to MTX which is frequent in routine practice. Even though the exact reason for this decision is unknown, it is possible that these patients were awaiting access to another treatment (52% of patients were treated with the backbone csDMARD(s) or with non-DMARD therapy), potentially due to delays in drug benefit plan reimbursement, used bridging therapies with a corticosteroid or NSAIDs (19.4% were treated with NSAIDs/steroids), or were waiting for an adverse event to resolve (34% re-added MTX in their regimen). For 20 (13.9%) patients, no RA treatment was documented, presumably due to being between treatments.

Conclusions

We conclude that there are different treatment pathways when MTX is discontinued. Patients with monotherapy are more apt to have sequential monotherapy, while patients on multiple csDMARDs change to a subsequent multiple csDMARDs regimen or a bDMARD.

Surprisingly, almost half of patients who stopped MTX did not receive other added or alternative treatment possibly due to low disease activity.

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