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Treatment Strategies in Early Rheumatoid Arthritis Methotrexate Management: Results From a Prospective Cohort

Cristiano S. Moura,[1] Orit Schieir,[2] Marie-France Valois,[1] Carter Thorne,[3] Susan J. Bartlett,[1] Janet E. Pope,[4] Carol A. Hitchon,[5] Gilles Boire,[6] Boulos Haraoui,[7] Glen S. Hazlewood,[8] Edward C. Keystone,[9] Diane Tin,[3] Vivian P. Bykerk,[10] and Sasha Bernatsky,[1] on behalf of the Canadian Early Arthritis Cohort Investigators

Objective. To assess real-world practice patterns surrounding treatment initiation and adjustments over time for methotrexate (MTX) and non-MTX–based treatment strategies in early rheumatoid arthritis (RA).

Methods. We studied a multicenter, incident early RA cohort (enrolled 2007–2017 within 1 year of symptoms) who fulfilled American College of Rheumatology/European League Against Rheumatism criteria. Adult patients with RA were eligible if treatment with MTX (± other disease-modifying antirheumatic drugs [DMARDs]) was initiated within 90 days of cohort entry. We compared time until treatment change for 4 initial MTX-based therapies and time to second treatment change after the first change. The definition of treatment change included changing of route for MTX monotherapy, adding or stopping a DMARD or biologic, and changing dose/frequency of a DMARD or biologic.

Results. There was great variability of treatment at initiation and during therapy adjustment. In 1,484 patients with early RA, the majority initiated MTX monotherapy (oral or subcutaneous [SC]). Patients receiving SC MTX monotherapy changed treatment less (45% versus 79%) and remained on treatment longer (hazard ratio [HR] 0.52 [95% confidence interval (95% CI) 0.4–0.67]) than those receiving oral MTX monotherapy. Most therapy adjustments involved adding a DMARD or changing to a non-MTX DMARD. Those adults taking biologics and who were receiving triple therapy had a longer time without treatment change (HR 0.26 [95% CI 0.16–0.42] and HR 0.57 [95% CI 0.38–0.85], respectively).

Conclusion. We found large variability in the way MTX-based therapies are prescribed in clinical practice. Our findings support the use of SC MTX monotherapy or MTX combination as initial therapy. For subsequent treatment after initial MTX-based therapy, those patients initiating either biologics or triple therapy had a longer time to treatment change than oral MTX monotherapy.

INTRODUCTION

Over the past decades, treatment of rheumatoid arthritis (RA) has improved due to more aggressive therapeutic strategies combined with early diagnosis and intervention and tight monitoring of disease activity (1). These principles are part of the treat-to-target recommendations that promote adaptation of therapy if the target, remission, or low disease activity is not achieved (2). Treatment with disease-modifying antirheumatic drugs (DMARDs) should start right after the diagnosis of RA in order to prevent long-term joint damage and improve function (3,4). While clinical practice guidelines often recommend early initiation of methotrexate (MTX) as the "anchor drug" in RA treatment (5,6), MTX management is complex and requires rheumatologists to make multiple decisions regarding optimal dosing, route of administration, and co-prescription with other DMARDs. In patients with early RA who are MTX naive, subcutaneous (SC) MTX monotherapy seems to be superior to oral MTX monotherapy in terms of clinical efficacy

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[1]Cristiano S. Moura, PhD, Marie-France Valois, MsC, Susan J. Bartlett, PhD, Sasha Bernatsky, PhD: McGill University, Montreal, Quebec, Canada; [2]Orit Schieir, MSc, PhD: University of Toronto, Toronto, Ontario, Canada; [3]Carter Thorne, MD, Diane Tin, BSC: Southlake Regional Health Center, Newmarket, California; [4]Janet E. Pope, MD: Western University, London, Ontario, Canada; [5]Carol A. Hitchon, MD, MSc: University of Manitoba, Winnipeg, Canada; [6]Gilles Boire, MD, MSC: Université de Sherbrooke, Sherbrooke, Quebec, Canada; [7]Boulos Haraoui, MD: Institut de Rhumatologie de Montréal, Montreal, Quebec, Canada; [8]Glen S. Hazlewood, BSc, MD: University of Toronto, Toronto, Ontario, Canada, and University of Calgary, Calgary, Alberta, Canada; [9]Edward C. Keystone, MD: Mount Sinai Hospital, Toronto, Ontario, Canada; [10]Vivian P. Bykerk, MD: Mount Sinai Hospital, Toronto, Ontario, Canada, and Hospital for Special Surgery, New York, New York.

SIGNIFICANCE & INNOVATIONS

- We studied real-world practice patterns and duration of methotrexate (MTX)–based treatment (along with subsequent treatment changes) in a large, early rheumatoid arthritis (RA) cohort.
- Patients initiating treatment with subcutaneous MTX alone or MTX-combined therapy had a longer time to treatment change versus those initiating oral MTX monotherapy. For subsequent treatment after initial MTX-based therapy, those initiating either biologics or triple therapy had a longer time to treatment change than those initiating oral MTX monotherapy.
- These findings support the use of initial subcutaneous MTX-based or MTX-combined therapy, as well as initiating either biologics or triple therapy in RA patients in whom initial MTX monotherapy failed.

and tolerability (7). The use of SC MTX monotherapy following oral MTX monotherapy failure can also delay the eventual need for further adjustments in therapy with biologics, with potential for cost savings (8). Nonetheless, initiation of treatment by oral administration is generally preferred, and use of SC MTX monotherapy in clinical practice may be suboptimal (9,10).

Considerable variability exists in the way MTX is prescribed, and studies describing the real-world practice patterns that surround initiation and duration of initial MTX-based treatment strategies along with treatment adjustment over time are sparse. Therefore, the objective of the present study was to assess real-world practice patterns surrounding treatment initiation and treatment adjustments over time for MTX-anchored treatment regimens in a large pan-Canadian cohort of patients with early RA followed up in rheumatology routine care settings.

MATERIALS AND METHODS

Population. Data were from patients with early RA who were enrolled in the Canadian Early Arthritis Cohort (CATCH) study between January 2007 and March 2017. CATCH is a national multicenter, longitudinal, observational cohort of patients with early-onset inflammatory arthritis (11) (see Appendix A for a list of CATCH investigators). Clinical data, routine laboratory studies, and patient-reported outcomes are collected according to a standardized protocol. Patients are followed up every 3 months in the first year, every 6 months through the second year, and annually thereafter, with treatment at the discretion of their rheumatologists. We studied adult patients in the CATCH study (ages ≥18 years) within 1 year of symptom onset who fulfilled either the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism RA criteria (12,13). Patients were eligible for analysis if treatment with MTX (with or without other conventional synthetic DMARDs [csDMARDs]) was initiated for the first time within 90 days of cohort entry and if they had no previous exposure to biologic DMARDs and had ≥1 follow-up visits.

Exposure. First, patients being treated with MTX were classified according to their initial therapy, which included oral MTX monotherapy, SC MTX monotherapy or MTX combined with another csDMARD, MTX double therapy, and MTX triple therapy. Each treatment group was followed up until a change in therapy occurred. Patients whose initial therapy was changed during follow-up were then reclassified according to their subsequent treatment, including oral MTX monotherapy, SC MTX monotherapy, MTX double therapy, MTX triple therapy, biologic DMARD, and non-MTX csDMARDs only. Patients were subsequently followed up for the next occurrence of the outcome as defined below. Although glucocorticoids are used in combination therapy with csDMARDs in early RA, they were not included as an additional exposure category. In Canada, patients frequently start and stop treatment with glucocorticoids according to their needs, which makes these medications not a durable choice of change in therapy and, therefore, not suitable for the analysis of treatment change.

Outcomes. The primary measure of interest in the present study was treatment change of both the initial and subsequent treatment strategies. The treatment change definition included change of route for MTX monotherapy, adding or stopping a csDMARD and/or a biologic DMARD, and changing dose/frequency of a csDMARD and/or a biologic DMARD due to inefficacy or a serious adverse event. Reasons for stopping/modifying the current treatment, as indicated by the treating physician, included dose, route, or frequency change; loss of efficacy (either due to primary or secondary failure); side effects; or other miscellaneous reasons (e.g., patient's or physician's preferences). Tapering

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Address correspondence to Sasha Bernatsky, PhD, Research Institute of the McGill University Health Centre, 5252 Boulevard de Maisonneuve Ouest, 3F.51, Montréal, QC H4A 3S5 Canada. Email: sasha.bernatsky@mcgill.ca.

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treatment was not captured as a reason for treatment change; however, some of the changes included in the analysis (e.g., discontinuing a csDMARD on double therapy) may be associated with treatment tapering.

Covariates. Patient characteristics that were measured at baseline and considered as potential confounders were selected a priori and were adjusted for in the multivariable models. These characteristics included sociodemographic variables (age, sex, race/ethnicity, and education), year of cohort entry (2007–2017), smoking status, number of comorbidities, presence of radiographic erosions, symptom duration, Disease Activity Score in 28 joints (DAS28), DAS28 using the erythrocyte sedimentation rate (ESR) or DAS28 using the C-reactive protein (CRP) level (in case ESR measurement was unavailable due to limited access), seropositivity (either positivity of rheumatoid factor or anti–citrullinated protein antibody), Health Assessment Questionnaire disability index (HAQ DI), dose of MTX (<15 mg, ≥15 mg to <20 mg, ≥20 mg to <25mg, ≥25mg, and no MTX), and use of oral glucocorticoids, nonsteroidal antiinflammatory drugs. and cyclooxygenase 2 inhibitors. Multivariable models for subsequent treatment were further adjusted for previous DMARD use.

Statistical analysis. Baseline characteristics of patients were described in terms of mean ± SD for continuous variables, while percentages were used for categorical variables. Descriptive statistics were used to summarize cohort characteristics and frequency of treatment change. Times to treatment change of the initial and subsequent therapies were derived using Kaplan-Meier methods and compared using log rank test.

Multivariable Cox proportional hazards models were used to estimate associations between treatment groups (initial and subsequent regimens) and change of therapy adjusted for covariates, including potential confounders. Follow-up time was calculated from cohort entry until the date of first treatment change. Among the subset of patients who changed therapy, a new time zero was then defined as the date of the first treatment change until the occurrence of the second change of therapy. In all analyses, patients were right censored in case of loss of follow-up or end of the study period (March 2017). In all analyses, the reference category was oral MTX monotherapy.

To account for treatment center characteristics that may potentially influence the association between medication choice and outcomes, we performed an additional Cox proportional hazards frailty model using treatment center as a random effect. In additional sensitivity analyses, we explored the effect of replacing the DAS28 with the Clinical Disease Activity Index (CDAI) or by the Simplified Disease Activity Index (SDAI) as the measurement of disease activity, excluding HAQ DI scores and erosions from the models, including a covariate representing the type of DAS28 measurement used (either CRP or ESR), and restricting the studied population to a subset of patients with at least 6 months of follow-up. All statistical analyses were performed using SAS, version 9.4.

RESULTS

Of 2,822 CATCH patients, 1,484 met eligibility criteria and were included in the initial analysis (Figure 1). Overall, patients were followed up for a median of 37.4 months (interquartile range [IQR] 17.3–68.3 months). Those changing initial treatment were

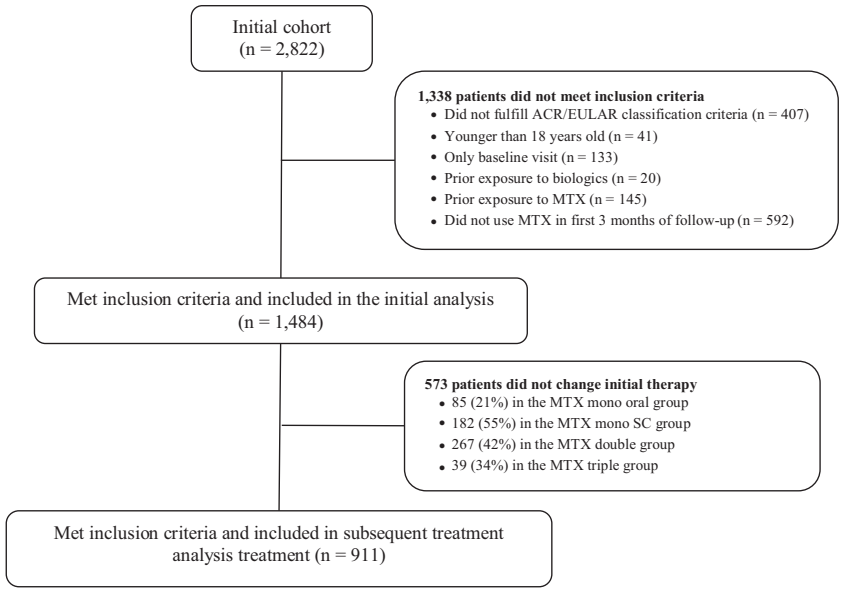

Figure 1. Flow chart of included and excluded patients. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; MTX = methotrexate; SC = subcutaneous.

Table 1. Demographic and clinical characteristics at baseline for patients divided in the initial and subsequent therapies*

Characteristic	Initial therapy				Subsequent therapy					
	Oral MTX mono (n = 398)	SC MTX mono (n = 328)	MTX double (n = 642)	MTX triple (n = 116)	Oral MTX mono (n = 58)	SC MTX mono (n = 89)	MTX double (n = 300)	MTX triple (n = 126)	Biologics (n = 100)	non-MTX csDMARDs (n = 238)
Age, years	56.3 ± 15	55.0 ± 14	54.0 ± 15	51.4 ± 14	52.6 ± 12	53.5 ± 13	54.9 ± 14	53.6 ± 16	51.9 ± 14	52.0 ± 16
Women, %	68	70	72	72	72	70	74	68	72	73
No. of comorbidities	2.0 ± 1.8	2.1 ± 1.9	2.0 ± 2.0	1.6 ± 1.8	2.2 ± 2.0	2.0 ± 1.7	2.1 ± 1.9	2.1 ± 2.0	1.9 ± 1.8	1.8 ± 1.8
Smoking status, %										
Never smoker	41	44	42	44	33	43	41	45	37	43
Ex-smoker	43	41	40	41	43	46	41	35	39	40
Current smoker	16	15	18	16	24	11	18	20	23	16
White, %	85	79	84	78	79	87	82	78	89	82
Education, %										
High school or less	50	41	43	35	40	44	48	43	44	41
Postsecondary	50	59	57	65	60	56	52	57	56	59
Symptom duration, months	5.2 ± 2.8	5.3 ± 2.9	5.6 ± 2.8	6.1 ± 3.2	5.9 ± 2.9	5.4 ± 2.5	5.6 ± 2.9	5.6 ± 2.7	5.8 ± 2.9	5.6 ± 2.9
Seropositive (RF or ACPA), %	66	64	65	81	78	67	66	65	67	72
Erosions present on hand or foot radiographs, %‡	23	20	24	20	29	28	20	21	32	24
HAQ DI	1.0 ± 0.7	1.2 ± 0.7	1.1 ± 0.7	1.3± 0.8	1.1 ± 0.8	0.9 ± 0.6	1.1± 0.7	1.1 ± 0.7	1.3 ± 0.7	1.1 ± 0.7
CDAI	27.1 ± 13.1	30.4 ± 12.7	30.1 ± 14.6	25.5 ± 14.3	24.4 ± 11.9	28.4 ± 13.1	28.6 ± 13.2	29.5 ± 15.3	36.4 ± 14.0	28.9 ± 14.8
SDAI	28.2 ± 13.3	32.3 ± 13.3	31.7 ± 15.2	26.9 ± 15.6	25.7 ± 12.6	30.1 ± 14.0	29.9 ± 13.7	31.4 ± 16.5	37.8 ± 14.5	30.0 ±14.9
DAS 28	5.1 ±1.4	5.3 ±1.4	5.3 ± 1.4	5.0 ±1.4	4.9 ±1.3	5.1±1.4	5.2 ± 1.3	5.3 ± 1.5	5.9 ± 1.3	5.2 ± 1.4
MTX dose of initial treatment, %										
<15 mg	20	4	16	0	21	12	11	9	24	–
≥15 mg to <20 mg	39	9	22	3	29	28	25	20	24	–
≥20 mg to <25 mg	34	16	42	55	36	33	43	51	33	–
≥25 mg	7	71	20	42	14	27	21	20	19	–
MTX dose of second treatment, %										
<15 mg	–	–	–	–	9	9	5	8	5	–
≥15 mg to <20 mg	–	–	–	–	16	16	17	15	11	–
≥20 mg to <25 mg	–	–	–	–	33	41	38	39	18	–
≥ 25 mg	–	–	–	–	42	34	40	38	11	–
No MTX	–	–	–	–	0	0	0	0	55	–
Steroids use, %										
Oral	34	23	42	39	24	34	35	44	47	39
Parenteral	24	46	26	45	29	34	33	30	28	32
Use of NSAIDs, %	50	60	52	66	74	61	52	47	52	58
Use of COX-2, %	18	16	14	15	19	20	16	14	18	16

* Values are the mean ± SD unless indicated otherwise. MTX = methotrexate; mono = monotherapy; SC = subcutaneous; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; HAQ DI = Health Assessment Questionnaire disability index; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; DAS28 = Disease Activity Score in 28 joints; NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2 inhibitor.
† At baseline or at 3 months if baseline is missing.

followed up for a median of 47.5 months (IQR 23.4–73.0 months), and individuals censored were followed up for a median of 22.8 months (IQR 10.3–45.8 months).

Demographic and clinical baseline characteristics are summarized in Table 1 for the initial and subsequent therapies. Most patients (92%) started on MTX monotherapy (oral or SC) or on MTX plus a second csDMARD. Patients receiving MTX triple therapy were younger than those in the other groups (mean ± SD age 51.4 ± 14 years), while those receiving oral MTX monotherapy had the shortest symptom duration and received lower doses of MTX than the other groups. Proportions of female patients ranged from 68% in the oral MTX monotherapy group to 72% in MTX double and MTX triple therapy groups for initial therapy, and from 68% in the MTX triple therapy group to 74% in the MTX double therapy group for subsequent therapy. Important differences were also noted for seropositivity (66% in oral MTX monotherapy group and 81% in the MTX triple therapy group) and dose of MTX in the initial and subsequent therapies. Missing data was minimal (<1%) for most of the baseline characteristics except for seropositivity (6%), erosions present on hand or foot radiographs (9%), DAS28 (4%), and SDAI (10%).

Figure 2 shows treatment changes during follow-up. Among patients starting MTX-based therapy, 911 (61.4%) had a change in their initial therapy (Figure 2). Another 573 patients continued receiving their original initial therapy during follow-up. Therapy was changed most often for patients starting on oral MTX monotherapy (as compared to those starting on other MTX-based treatments). The difference was particularly remarkable when compared to the SC MTX monotherapy group: 79% of patients starting on oral MTX monotherapy changed their treatment versus only 45% in the SC MTX monotherapy group. Among patients initiating MTX double therapy, 58% changed their treatment, and among those initiating MTX triple therapy, 66% changed their treatment. Most patients (46%) who initiated MTX monotherapy changed to MTX double therapy. Patients who initiated MTX double therapy most often changed to a non-MTX csDMARD treatment (40%), whereas 47% of those receiving MTX triple therapy changed to MTX double therapy. Among the 911 patients who changed their initial treatment, 595 had a subsequent treatment change (Figure 2). Among patients in whom non-MTX csDMARDs were initiated as a subsequent therapy, 79% had a second treatment change; this is twice as many changes that were observed in the biologic group (37%). The frequency of changes in all of the other groups was ~65%. The group receiving oral MTX monotherapy was more likely to switch to either SC MTX monotherapy (33%) or MTX double therapy (31%) in their second treatment change, while 53% of those patients who were receiving SC MTX monotherapy changed to MTX double therapy. Patients receiving double (27%) or triple (44%) therapy with MTX or those receiving a non-MTX csDMARD (40%) changed to MTX double therapy. As might be expected, patients who initiated a biologic as the second treatment were more likely to progress to a second biologic in the third treatment regimen (32%) than patients who had not been exposed to biologics previously.

The frequency of any side effects was similar in the groups of patients receiving MTX monotherapy (between 18% and 26%) and higher in those receiving MTX triple therapy (50%). In the subsequent therapy, 10% of patients stopped their current treatment because of loss of efficacy or a serious adverse event. The frequency of any side effects was higher in patients receiving MTX double therapy and MTX triple therapy (33% and 38%, respectively), whereas the frequency of side effects in patients receiving MTX monotherapy, biologics, or non-MTX csDMARDs was more similar (between 19% and 22%).

Times to first treatment change and subsequent treatment change are shown in Figure 3. In multiple comparisons using the log rank test, patients receiving SC MTX monotherapy

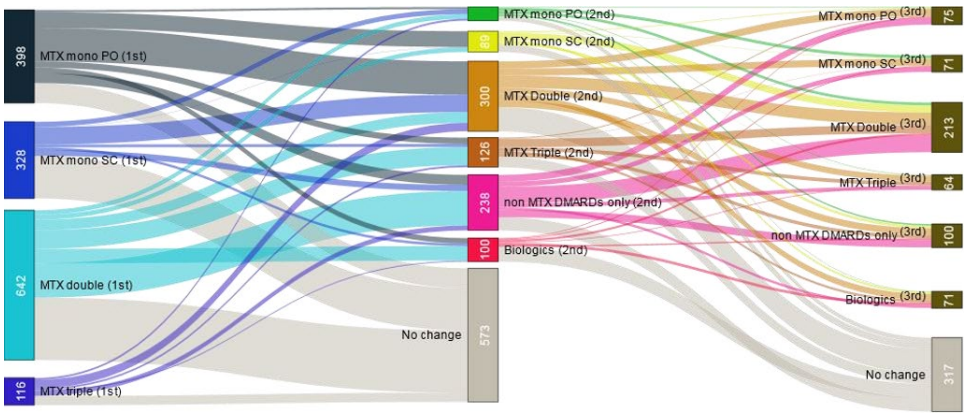

Figure 2. Frequency of treatment change after initial methotrexate (MTX)–based therapies and the subsequent treatments. The number of patients in the treatment group for initial MTX-based and subsequent therapies is shown in the colored boxes. Links connecting the same category of treatment represent changes in dose/frequency. mono = monotherapy; PO = by mouth; SC = subcutaneous; DMARDs = disease-modifying antirheumatic drugs.

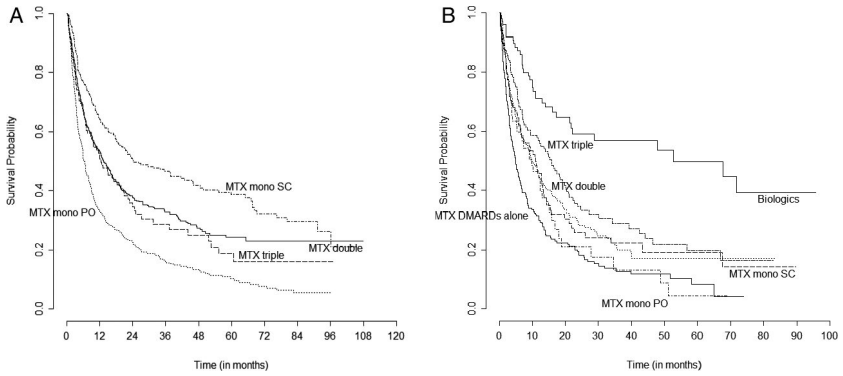

Figure 3. Kaplan-Meier survival curves for treatment duration per treatment group of initial methotrexate (MTX)–based treatment strategy (**A**) and subsequent therapy (**B**). Mono = monotherapy; SC = subcutaneous; PO = by mouth; DMARDs = disease-modifying antirheumatic drugs.

were treated significantly longer (median time to therapy change 24.5 months [IQR 7.1–96.2 months]) than patients using other strategies (Figure 3A). Patients receiving MTX double or MTX triple therapy had similar treatment duration (median time to therapy change 13.5 months [IQR 4.3–57.9 months] and 12.6 months [IQR 3.5–51.6 months], respectively), while those receiving oral MTX monotherapy changed their treatment in the shortest period of time (median 6.3 months [IQR 2.9–20.1 months]). Times to treatment change for the subsequent therapy are shown in Figure 3B. Patients on biologics stayed on therapy longer (median time to therapy change 52.9 months) than patients using other strategies. Patients initiating non-MTX DMARDs alone had the lowest median time for treatment change, at a median of 4.9 months (IQR 1.9–14.1 months) than all the other groups. Those patients receiving oral MTX monotherapy, SC MTX monotherapy, MTX double, and MTX triple therapy had similar time on therapy (median time ranging from 9.8 months [IQR 3.0–18.0 months] for oral MTX monotherapy to 15.8 months [IQR 5.0–44.2 months] for MTX triple therapy).

Cox regression models that were adjusted for baseline characteristics and controlled for MTX dose and other indicators of disease activity showed that all MTX strategies initiated at cohort entry had longer time to treatment change compared to oral MTX monotherapy (Table 2). The hazard ratio (HR) for the comparison between SC MTX monotherapy and the reference category was 0.52 (95% CI 0.41–0.66). The Cox regression analysis for the patients with subsequent treatment suggested that those receiving biologics (HR 0.26 [95% CI 0.16–0.42]) and those receiving triple therapy (HR 0.57 [95% CI 0.38–0.85]) had a longer time to treatment change, compared to the group receiving oral MTX monotherapy. When treatment center was included as a random effect in the frailty model, the association was still significant for all MTX initial therapies compared to oral MTX monotherapy and for patients in whom biologic or MTX triple therapy was initiated as a subsequent therapy. In additional sensitivity analyses, replacing the disease activity measurement (CDAI or SDAI instead of the DAS28), excluding HAQ DI or erosions from the models, including a covariate representing the type of DAS28 measurement used, or restricting the studied population to a subset of patients with at least 6 months of follow-up did not significantly change the results observed in the main analysis (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.23927/abstract).

DISCUSSION

The present study showed large variability in the way that MTX-based therapies are prescribed in routine care/practice.

Table 2. Unadjusted and adjusted hazard ratios (HRs) for time to treatment change per treatment group*

Treatment	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)†
Initial therapy‡		
Oral MTX mono	Reference	Reference
SC MTX mono	0.42 (0.35–0.50)	0.52 (0.41–0.66)
MTX double	0.61 (0.53–0.71)	0.62 (0.52–0.73)
MTX triple	0.66 (0.52–0.85)	0.68 (0.52–0.89)
Subsequent therapy§		
Oral MTX mono	Reference	Reference
SC MTX mono	0.84 (0.57–1.24)	0.82 (0.53–1.27)
MTX double	0.83 (0.60–1.15)	0.84 (0.59–1.20)
MTX triple	0.68 (0.47–0.97)	0.57 (0.38–0.85)
Biologics	0.33 (0.21–0.51)	0.26 (0.16–0.42)
Non-MTX csDMARDs	1.25 (0.90–1.74)	1.06 (0.75–1.51)

*95% CI = 95% confidence interval; mono = monotherapy; SC = subcutaneous; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.
†Adjusted for baseline characteristics: age, sex, comorbidities, smoking, race, education, symptom duration, presence of radiographic erosion, Disease Activity Score in 28 joints, Health Assessment Questionnaire disability index, dose of methotrexate (MTX), seropositivity, year of cohort entry, glucocorticoids, nonsteroidal antiinflammatory drugs, and cyclooxygenase 2 inhibitors.
‡ Number of observations used in the analysis = 1,352.
§ Subsequent therapy further adjusted for the initial treatment group; number of observations used in the analysis = 830.

Patients receiving oral MTX monotherapy as initial therapy had a higher frequency of treatment discontinuation than other MTX-based strategies. Compared to patients receiving oral MTX, fewer patients who received SC MTX monotherapy group had their treatment changed, either by combining other csDMARDs, in double or triple therapy, or by switching to or adding a biologic DMARD.

Our results also showed that patients receiving oral MTX monotherapy had the shortest treatment duration compared to all other initial MTX therapies. A prolonged period without change of therapy may reflect better disease control. These results are in line with the findings of other studies showing that the use of parenteral MTX monotherapy or MTX combination therapy is associated with higher efficacy, better tolerability, and longer time for therapy change when compared to oral MTX (14–16). A large-scale study using the Department of Veterans Affairs database demonstrated that the use of parenteral MTX monotherapy compared to oral MTX monotherapy was associated with lower risk of therapeutic change (switch or addition of ≥1 other antirheumatic agents) (14). In a head-to-head, 24-week study of MTX-naive individuals, significantly more patients who received SC MTX monotherapy than oral MTX monotherapy achieved a response according to the ACR criteria for 20% improvement and 70% improvement in disease activity (17). These findings are also consistent with an earlier CATCH study by Hazlewood et al (15), who found a significantly higher proportion of treatment failure in patients initiating treatment with oral MTX monotherapy compared to those who received SC MTX monotherapy. In our study, we expand this analysis to compare other treatment regimens.

In our analysis of subsequent therapy after MTX-based therapy, all patients, except those receiving biologics, had a high frequency of subsequent treatment change (i.e., initiation of a third treatment). Individuals receiving MTX triple therapy or biologics had a longer time until therapy change compared to those receiving oral MTX monotherapy. In the past, several trials have demonstrated the benefits of adding either a tumor necrosis factor inhibitor or other csDMARD to MTX in patients with active disease despite MTX treatment (18–20). However, the question of which is the preferred combination, after partial or suboptimum response to MTX monotherapy, remains unresolved.

Recent studies have suggested that triple therapy with sulfasalazine, hydroxychloroquine, and MTX is at least as effective as adding a biologic to MTX (21–23). Patients in the Treatment of Early Aggressive RA (TEAR) study (21), who had an inadequate response to MTX treatment and who were randomly allocated to receive combination therapy with a biologic (etanercept) or triple therapy, showed similar responses after 1-year of follow-up, except for less radiographic progression with etanercept. In the Swedish pharmacotherapy trial (22,24), patients with newly diagnosed RA were initially given MTX, and if a good response was not achieved at 3 months, they were randomized to either triple therapy or infliximab. After 12 months, the DAS28 score was superior for infliximab (24), but after 2 years the gain on quality-adjusted life years was not significantly different between the 2 strategies (22). As observed in the TEAR trial, radiographic progression was greater with conventional therapy than with the biologic agent. Similarly, the Behandel Strategieën study (25) demonstrated lower disease activity and less radiographic progression for infliximab versus triple therapy at 1 year, but improvement in disease activity and functional ability was similar at 2 years. Findings from a recent network meta-analysis evaluating a range of outcomes beyond radiographic progression suggested that, in both MTX-naive RA patients and in those with inadequate response, triple therapy is not statistically different from MTX plus biologic therapy for controlling disease activity (26). Our study, reflecting real-world practice, corroborates these findings by showing that patients who initiated on triple therapy had similar time on therapy than those on treatment with biologic drugs.

Our study has many strengths. This is a large, prospective, multicenter cohort with standardized data collection methods across the centers. In our analysis, we accounted for important baseline potential confounding factors that may play a role in treatment choice and/or treatment interruption, such as age, sex, comorbidities, smoking, race, education, symptom duration, erosions, and disease activity. However, our study also has important limitations. As in any observational study, we cannot rule out the possibility that differences in treatment choices and discontinuation might be due to unidentified confounders, which prevents us from drawing conclusions about causality. Physician or patient preferences, local guidelines, and differences in standards of medical practices in medication coverage, as well as other unmeasured factors play an important role in treatment choices and persistence that are not fully captured in our model. As previously reported (15), treatment centers participating in the CATCH study manifested strong preference for their initial therapy (either SC MTX monotherapy or MTX combination). Nevertheless, our findings were robust to sensitivity analysis that included the random effect of treatment center. Some of the changes observed may be attributed to previous treatment strategy planned by the treating physician. In provinces such as Ontario, patients are often required to have had a failed response to both MTX and leflunomide (and at least 1 combination of csDMARDs with MTX or triple therapy) before being prescribed an advanced therapeutic. On the other hand, studies like ours reflect how patients are treated in real life, and these data may serve as a valuable addition to evidence generated by randomized trials.

In summary, in this early RA population, patients who were initially exposed to oral MTX monotherapy had shorter time to treatment change than all other initial MTX-based strategies, including SC MTX therapy. For patients with a subsequent treatment after MTX, those initiating either on biologics or on triple therapy had longer time to treatment change than those patients receiving oral MTX monotherapy. Since lower rate of and longer time for treatment change may reflect better disease

control, our findings support the use of SC MTX monotherapy or MTX combination as initial MTX-based therapy in patients with early RA and the use of additional therapy (either biologic or csDMARDs) in RA patients in whom initial MTX-based therapy had failed.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bernatsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Moura, Schieir, Bykerk, Bernatsky.

Acquisition of data. Thorne, Bartlett, Pope, Hitchon, Boire, Haraoui, Hazlewood, Keystone, Tin, Bykerk.

Analysis and interpretation of data. Moura, Schieir, Valois, Hazlewood, Bernatsky.

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APPENDIX A: CATCH INVESTIGATORS

The CATCH investigators are as follows: Murray Baron, Louis Bessette, Ines Colmegna, Sabrina Fallavollita, Derek Haaland, Paul Haraoui, Shahin Jamal, Raman Joshi, Bindu Nair, Peter Panopoulos, Christopher Penney, Laurence Rubin, Edith Villeneuve, and Michel Zummer.