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Original article

Retention of triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine compared to combination methotrexate and leflunomide in rheumatoid arthritis

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ABSTRACT

Objective. – There are various combination conventional synthetic disease-modifying-antirheumatic drug (csDMARD) treatment strategies used in rheumatoid arthritis (RA). A commonly used csDMARD combination is triple therapy with methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ). Another approach is double therapy with MTX and leflunomide (LEF). We compared the real-world retention of these two treatment combinations.

Methods. – Patients with RA from the Ontario Best Practices Research Initiative (OBRI) who received triple or double therapy on or after OBRI enrolment were included. Retention rates were compared between these two groups. We also analyzed which medication in the combination was discontinued and the reasons for treatment discontinuation. Disease activity was assessed at baseline, 6 and 12 months after treatment initiation as well as at time of discontinuation. Risk factors for treatment discontinuation were also examined.

Results. – Six hundred and ninety-two patients were included (258 triple and 434 double therapy). There were 175 (67.8%) discontinuations in the triple therapy group and 287 (66.1%) discontinuations in patients on double therapy. The median survival for triple therapy was longer (15.1 months; 95% CI: 11.2–21.2) compared to double therapy (9.6 months; 95%CI: 7.03–12.2). However, this was not statistically significant. Disease activity at 6 and 12 months, measured by 28-joint count Disease Activity Score based on erythrocyte sedimentation rate (DAS28-ESR) was lower with triple therapy (mean DAS28 at 6 months 3.4 vs. 3.9, $P < 0.0001$ and at 12 months 3.2 vs. 3.5, $P = 0.0005$).

Conclusion. – Patients on triple therapy remained on treatment longer than patients on double therapy. However, this difference was not statistically significant.

1. Introduction

The treatment of rheumatoid arthritis (RA) is based on a "treat-to-target" strategy to achieve adequate disease control. There are multiple disease-modifying antirheumatic drugs (DMARDs) currently approved for treatment, including conventional and targeted synthetic DMARDs (csDMARDs and tsDMARDs, respectively) as well as biologic DMARDs (bDMARDs). Methotrexate (MTX) is considered to be the cornerstone first-line DMARD in RA[1]. Although MTX monotherapy is an effective strategy, many patients require combination DMARD therapy to achieve remission or low-disease activity. Combinations of csDMARDs have been demonstrated to be superior to monotherapy [2–5]. A frequently used combination strategy is triple therapy with MTX, sulfasalazine (SSZ), and hydroxychloroquine (HCQ). This combination has been shown to

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be very effective in treating early RA [6]. Another approach is to combine MTX and leflunomide (LEF) which has been reported to be effective in patients with persistently active RA despite MTX monotherapy [7].

The current criteria to obtain coverage for tsDMARDs or bDMARDs in Ontario, Canada includes failure of either triple therapy with MTX, SSZ, and HCQ or combination MTX or LEF. There are no current recommendations in the guidelines for choosing double therapy vs. triple therapy. However, based on their judgment, physicians may decide to choose double therapy in patients with specific comorbidities for whom triple therapy may be associated with higher risk of adverse events.

To the best of our knowledge, there is currently no data available directly comparing these two treatment approaches head-to-head to determine the preferable strategy. Given the lack of such comparative data, clinical decision-making regarding which combination strategy to try in a specific patient is often based on physician preference rather than being evidence-based.

Retention of DMARD therapy in RA is a valuable outcome that encompasses efficacy, durability, and safety of a specific therapy. Comparison of retention rates between therapies provides insight into potentially preferable treatment paradigms.

In RA, a previous study reported a low persistence rate of 18% in patients on triple therapy with MTX, SSZ, and HCQ at 1 year, which was most often due to adverse drug events from SSZ [8]. Cummins et al. reported in 2015 that a combination of any 3 of MTX, SSZ, HCQ or LEF had better survival than with traditional therapy with MTX, SSZ, and HCQ [9]. A retrospective study in 2016 evaluated the effectiveness and safety of LEF with MTX in patients who had failed triple therapy with MTX, SSZ, and chloroquine (CQ) [10]. This study reported a retention rate of 70.6% of the MTX-LEF combination therapy in this population despite previous studies in other populations demonstrating concerns of potentially serious adverse events, in particular hepatotoxicity and leukopenia with this treatment approach. Finally, a more recent study compared LEF and SSZ-based triple therapy in an open-label randomized controlled trial which reported that LEF-based combination therapy was non-inferior to SSZ-based combination therapy, and retention rates were similar in both arms [11].

To our knowledge, there is currently no published literature comparing the retention (or relative safety and efficacy) of triple therapy with MTX, SSZ, and HCQ versus combination MTX and LEF. Given the clinical equipoise regarding these two treatment strategies, we aimed to assess the retention of triple therapy with MTX, SSZ, and HCQ compared to combination MTX and LEF. In addition, the effectiveness of these treatment strategies was compared at baseline, 6 and 12 months after treatment initiation. Another aim was to investigate the reasons for discontinuation of therapy and which agent of the combination was discontinued. Finally, we examined risk factors for discontinuation of therapy.

2. Methods

2.1. Data source

The Ontario Best Practice Research Initiative (OBRI) is a multicenter registry across Ontario, Canada, collecting data from both rheumatologists and patients with RA at enrolment and at follow-up (http://www.obri.ca/). It incorporates rheumatologist assessments from approximately one-third of rheumatologists in the province of Ontario. Patients are eligible to be enrolled if they are $\geq$ 16 years of age at the time of diagnosis, $\geq$ 18 years of age at enrolment, have a rheumatologist confirmed RA diagnosis, and have at least one swollen joint. Enrolled patients are interviewed and are seen by their rheumatologist as per routine care. This information is collected on paper or electronic case report forms (CRF) which are faxed to the data management centre. Patients are also contacted by trained telephone interviewers at baseline, every three months for the first two years, and every six months for the following three years, using a secured computer assisted telephone interview system.

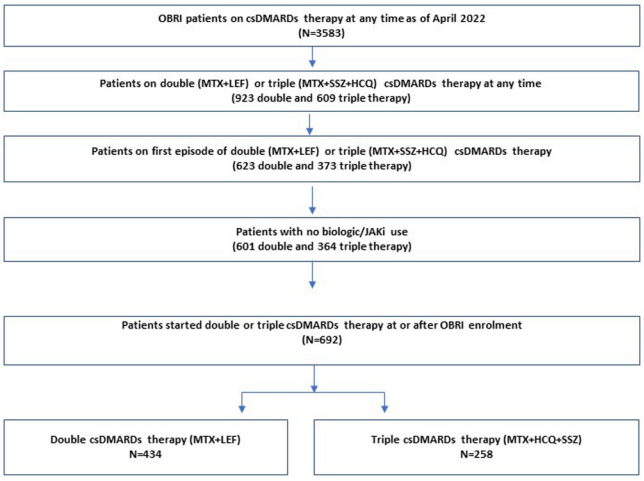

Fig. 1. Cohort flowchart.

2.2. Data collection

At enrolment, patients are asked for their general medical history including comorbidity status. Rheumatologists are also expected to report any history of previous comorbidity including cardiovascular disease (CVD), RA disease activity, and inflammatory markers, tender and swollen joint counts. Data on sociodemographics, smoking status, height, weight as well as any prior and current medications are recorded during the rheumatologist enrolment visit or during the patient's interview. Patient-reported outcomes for functional status are also collected through designed questionnaires.

At follow-up visits, all the aforementioned information is updated. RA medication changes (including discontinuation and reasons for discontinuation) between visits are also captured. Rheumatologists report any incident of comorbidity and reassess disease activity during every follow-up visit.

For this study, biologic/JAK inhibitor naïve patients who received their triple (MTX, HCQ, and SSZ) or double (MTX and LEF) therapy on or after OBRI enrolment were included (Fig. 1). The study period was between 1st January 2008 and 1st January 2021. The 6- and 12-month follow-up data for this study were retrieved by identifying a reference window of $\pm$ 2 months from the 6- and 12-month visit point.

Patients were allowed to be previously on any monotherapy or other combination therapy other than the combinations groups we are looking at. Start date was defined as the latest DMARD start and stop date as the earliest stop of any component in double or triple therapy, respectively. Discontinuation of any component of the combination therapy represented lack of retention. The addition of a new csDMARD was also considered as lack of retention as the indication to add any additional therapy would be for an inadequate response to the combination they were using. The reasons for discontinuation of therapy were determined (e.g., primary or secondary failure, adverse event, patient choice, etc.). In addition, disease activity at the time of failure of therapy was analyzed.

Covariates for this analysis included age, gender, health insurance coverage, smoking status, rheumatoid factor (RF) and

anti-citrullinated protein antibody (ACPA) status, disease duration, physical function status (health assessment questionnaire-disability index (HAQ-DI) and pain), number of comorbidities, prior DMARDs treatment, concomitant use of steroids and NSAIDs, dose and route of MTX administration (oral versus subcutaneous) and disease activity measures at initiation of either triple therapy with MTX, HCQ, and SSZ or combination MTX and LEF. Disease activity at 6 and 12 months after treatment initiation as well as at time of discontinuation was also analyzed in the groups for those patients with available of disease activity data.

2.3. Statistical analysis

All analyses were conducted on the main analysis population. Descriptive statistics, specifically mean and standard deviation (SD) for continuous variables and counts and proportions for categorical variables, were produced for all baseline characteristics. Comparisons between patients were conducted using the independent-samples *t*-test for continuous variables and the Chi-square or the Fisher's Exact test for categorical variables. Time to discontinuation was assessed using Kaplan-Meier survival analysis for triple vs. double therapy and Cox proportional hazards regression (HR) analysis.

3. Results

The analytic sample included 692 subjects (434 double and 258 triple csDMARDs therapy). The majority were female (76.0%) with a mean (± SD) age of 57.4 (± 13.0) years. Compared to triple csDMARDs therapy, patients with double therapy were significantly older (mean 58.6 vs. 55.3 years), more likely to have private health insurance coverage (83.2% vs. 74.6%), had longer disease duration (mean 8.4 vs. 5.8 years), higher ESR (mean 26.3 vs. 23.0), more comorbidity (43.5% vs. 35.7%) and higher disease activity scores as measured by DAS28-ESR (4.6 vs. 4.3) (Table 1). A total of 287 (66.1%) discontinuations due to any reason were identified in patients using double csDMARDs and 175 (67.8%) cases were identified in those using to triple csDMARDs therapy.

Proportion of MTX discontinuation was similar for the two treatment strategies (double: 67/434; triple 46/258). An adverse event was the reason for discontinuation of MTX for 41.8% patients with double csDMARD therapy and 28.3% patients with triple csDMARDs therapy (Table S1). The proportion of LEF discontinuation in double csDMARDs therapy was 50.7% with adverse events as the most common reason for discontinuation. The proportion of SSZ discontinuations in triple csDMARDs therapy was higher (37.2%) than MTX (17.8%) and HCQ discontinuations (19.4%) (Table S1).

3.1. Disease activity status at initiation, 6 and 12 months after treatment and at time of discontinuation

Using the Clinical Disease Activity Index (CDAI), overall, 20% of patients were at low-disease activity or remission at initiation of therapy with no significant difference between double (LDA/REM: 19%) and triple csDMARDs therapy (LDA/REM: 23.5%) (Table 2). The proportion of LDA for whole cohort increased at 6 and 12 months (45.3% and 55.2%, respectively). Interestingly, the proportion of patients with LDA/REM at 6 months was significantly higher in triple compared to double csDMARDs therapy (50.7% vs. 42.2%; $P = 0.04$). However, disease state was similar between the two groups 12 months after treatment initiation. At time of discontinuation, there was a higher proportion of patients in LDA/REM status in the triple csDMARDs therapy group (43.5%) compared to the double csDMARDs therapy group (36.1%) (Table 2). Disease activity at 6 and 12 months, measured by DAS28, was also significantly different between the two groups (mean DAS28 at 6 months 3.9 vs. 3.4, $P < 0.0001$ and at 12 months 3.5 vs. 3.2, $P = 0.0005$) (Table S2).

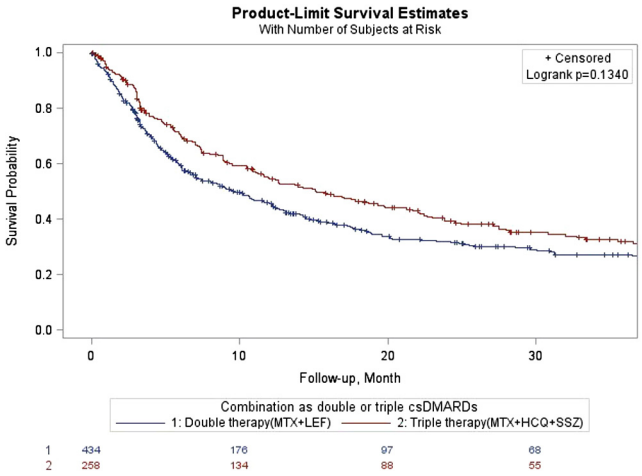

Fig. 2. Drug survival of double vs. triple csDMARDs therapy. csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine.

3.2. Time to discontinuation

The overall median survival was 11.6 months (95% CI: 9.33–13.3) with a longer median for triple csDMARDs therapy (15.1 months; 95% CI: 11.2–21.2) compared to double csDMARDs therapy (9.6 months; 95% CI: 7.03–12.2) (Table 3 and Fig. 2). The probability of drug survival for triple csDMARDs therapy at different time points was higher compared to double csDMARDs therapy (Table 3). Six months after treatment initiation, 70.3% of patients in the triple csDMARDs therapy group and 59.7% of patients in the double csDMARDs therapy remain on their combination medication. At 12 months after initiation, approximately half of patients were still receiving their double therapy (45.6%) or double therapy (54.4%).

Univariable Cox regression analysis showed no statistically significant difference in discontinuation between double and triple csDMARDs therapy (HR: 0.87; 95% CI: 0.72–1.05). After adjusting for age, gender, health insurance coverage, disease duration, presence of comorbidity, disease activity and concomitant use of glucocorticoids, the difference in discontinuation remained statistically non-significant (HR: 0.86; 95% CI: 0.69–1.07) with less discontinuation in the triple therapy group (Table 4). Discontinuation was associated with being female (HR: 1.78; 95% CI: 1.37–2.32) and having at least one comorbidity (HR: 1.27; 95% CI: 1.03–1.58) in the multivariable analysis. Additional analysis on discontinuation of MTX by administration route in double and triple csDMARDs therapy did not show a significant difference for patients receiving oral versus subcutaneous MTX (Figs. S1 and S2).

4. Discussion

In this study, we investigated the persistence of triple csDMARDs therapy compared to double csDMARDs therapy. We also descriptively compared disease activity between the two groups, at 6 and 12 months after treatment initiation. We found that patients on triple csDMARDs therapy remained on their treatment longer compared to patients on double csDMARDs therapy. However, this difference was not statistically significant after adjusting for potential confounders. Attainment of low-disease activity including remission at 6 months after treatment initiation was statistically

Table 1
Baseline characteristics of double and triple csDMARDs therapy.

	Combination as double or triple csDMARDs		
Variables	Total (n = 692)	Double therapy (n = 434)	Triple therapy (n = 258)
Female (%)	526 (76.0)	331 (76.3)	195 (75.6)
Age (years)[a]			
N	692	434	258
Mean ± SD	57.4 ± 13.0	58.6 ± 12.6	55.3 ± 13.4
Education status			
N	661	412	249
Post-secondary (%)	365 (55.2)	227 (55.1)	138 (55.4)
Health insurance coverage[b]			
N	630	394	236
Public (OHIP) + private (%)	504 (80.0)	328 (83.2)	176 (74.6)
Current smoking status			
N	630	394	236
Current (%)	120 (19.0)	76 (19.3)	44 (18.6)
Disease duration (years) at initiation of treatment[a]			
N	692	434	258
Mean ± SD	7.4 ± 9.4	8.4 ± 10.0	5.8 ± 8.2
Disease onset status			
Less than 2 years (%)	210 (30.3)	123 (28.3)	87 (33.7)
Positive RF			
N	650	405	245
Positive (%)	495 (76.2)	308 (76.0)	187 (76.3)
Positive ACPA			
N	322	202	120
Positive (%)	209 (64.9)	123 (60.9)	86 (71.7)
ESR (mm/hr)[c]			
N	650	404	246
Mean ± SD	25.0 ± 19.5	26.3 ± 19.4	23.0 ± 19.7
CRP (mg/L)			
N	616	380	236
Mean ± SD	14.4 ± 22.3	14.7 ± 24.3	13.9 ± 18.5
Patient global assessment			
N	658	415	243
Mean ± SD	4.8 ± 2.7	4.9 ± 2.8	4.7 ± 2.7
Physician global assessment			
N	634	394	240
Mean ± SD	4.5 ± 2.3	4.6 ± 2.3	4.4 ± 2.2
Swollen joint counts			
N	686	430	256
Mean ± SD	5.9 ± 5.1	6.0 ± 5.0	5.8 ± 5.2
Tender joint counts			
N	680	428	252
Mean ± SD	6.4 ± 6.1	6.7 ± 6.2	5.8 ± 5.9
CDAI			
N	656	412	244
Mean ± SD	21.4 ± 13.3	21.9 ± 13.4	20.7 ± 13.2
SDAI			
N	597	368	229
Mean ± SD	23.3 ± 14.0	23.9 ± 14.0	22.3 ± 13.9
DAS28-ESR[b]			
N	654	408	246
Mean ± SD	4.5 ± 1.5	4.6 ± 1.4	4.3 ± 1.5
HAQ-DI			
N	429	276	153
Mean ± SD	1.1 ± 0.7	1.1 ± 0.7	1.0 ± 0.7
HAQ-pain			
N	429	276	153
Mean ± SD	1.4 ± 0.8	1.5 ± 0.9	1.4 ± 0.8
Number of main comorbidities			
N	692	434	258
Mean ± SD	0.8 ± 1.1	0.8 ± 1.2	0.7 ± 1.1
Presence of main comorbidity[c]			
Yes (%)	281 (40.6)	189 (43.5)	92 (35.7)
Prior csDMARDs use			
Yes (%)	642 (92.8)	405 (93.3)	237 (91.9)
Concomitant use of NSAIDs			
Yes (%)	162 (23.4)	104 (24.0)	58 (22.5)
Concomitant use of steroids			
Yes (%)	150 (21.7)	84 (19.4)	66 (25.6)

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; SD: standard deviation; OHIP: Ontario Health Insurance Plan; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; CDAI: clinical disease activity index; DAS28: disease activity score-28; HAQ-DI: Health Assessment Questionnaire -Disability Index; NSAIDs: nonsteroidal anti-inflammatory drugs.

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

Table 2
Disease activity profile (CDAI) at initiation, 6 and 12 months after treatment initiation and at discontinuation.

	Overall (*n* = 692)	Double csDMARDs therapy (MTX + LEF) (*n* = 434)	Triple csDMARDs therapy (MTX + HCQ + SSZ) (*n* = 258)
At initiation	*n* = 504	*n* = 321	*n* = 183
CDAI, mean (SD)	21.2 (12.9)	21.8 (13.0)	20.2 (12.7)
CDAI LDA/REM, *n* (%)	104 (20.6)	61 (19.0)	43 (23.5)
CDAI REM, *n* (%)	10 (2.4)	9 (3.4)	1 (0.71)
At 6 months	*n* = 605	*n* = 384	*n* = 221
CDAI, mean (SD)	14.9 (12.0)	15.6 (12.0)	13.6 (11.9)
CDAI LDA/REM, *n* (%)[a]	274 (45.3)	162 (42.2)	112 (50.7)
CDAI REM, *n* (%)	72 (11.9)	45 (11.7)	27 (12.2)
At 12 months	*n* = 576	*n* = 353	*n* = 223
CDAI, mean (SD)	12.4 (10.9)	12.7 (11.3)	11.9 (10.3)
CDAI LDA/REM, *n* (%)	318 (55.2)	195 (55.2)	123 (55.2)
CDAI REM, *n* (%)	92 (16.0)	55 (15.6)	37 (16.6)
At discontinuation	*n* = 424	*n* = 263	*n* = 161
CDAI, Mean (SD)	16.5 (12.5)	17.2 (12.4)	15.3 (12.5)
CDAI LDA/REM, *n* (%)	165 (38.9)	95 (36.1)	70 (43.5)
CDAI REM, *n* (%)	59 (18.6)	34 (16.8)	25 (21.6)

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; SD: standard deviation; CDAI: clinical disease activity index; LDA: low-disease activity; REM: remission.

[a] $P < 0.05$.

Table 3
Mean and median survival time, overall and by csDMARDs therapy.

	Overall (*n* = 692)	Double csDMARDs therapy (MTX + LEF) (*n* = 434)	Triple csDMARDs therapy (MTX + HCQ + SSZ) (*n* = 258)
Number of discontinuations	462	287	175
Mean survival (months) (SE)	30.2 (1.66)	26.2 (1.71)	30.9 (2.45)
Median survival time (months) (95% CI)	11.6 (9.33–13.3)	9.6 (7.03–12.2)	15.1 (11.2–21.2)
Probability of survival at different time points			
6 months (%, [95% CI])	63.6 (60.0–67.2)	59.7 (54.8–64.2)	70.3 (64.1–75.6)
12 months (%, [95% CI])	48.8 (44.9–52.7)	45.6 (41.0–50.4)	54.4 (47.8–60.5)
18 months (%, [95% CI])	40.0 (36.1–44.0)	36.2 (31.3–41.2)	46.4 (39.8–52.7)
24 months (%, [95% CI])	34.7 (30.8–38.6)	32.0 (27.2–37.0)	39.2 (32.8–45.6)
36 months (%, [95% CI])	28.9 (25.1–32.9)	27.2 (22.4–32.2)	31.9 (25.6–38.4)

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; SE: standard error; CI: confidence interval.

Table 4
Univariable and multivariable Cox regression models for risk of csDMARDs therapy discontinuation.

	Univariable analysis	Multivariable analysis (*n* = 561; discontinuation: 375)
	HRs (95% CI)	HRs (95% CI)
Triple csDMARDs therapy (ref = double csDMARDs therapy)	0.87 (0.72–1.05)	0.86 (0.69–1.07)
Female (ref = male)	1.66 (1.32–2.09)[a]	1.78 (1.37–2.32)[a]
Age	0.99 (0.99–1.01)	0.99 (0.98–1.01)
OHIP + private health insurance (ref = OHIP)	1.17 (0.93–1.49)	1.20 (0.92–1.58)
Disease duration	0.99 (0.98–1.01)	0.99 (0.98–1.00)
CDAI	1.01 (0.99–1.01)	1.01 (0.99–1.02)
ESR	0.99 (0.99–1.01), 0.53	0.99 (0.98–1.00), 0.06
Presence of comorbidity	1.29 (1.08–1.55)[b]	1.27 (1.03–1.58)[c]
Prior use of csDMARDs	1.16 (0.80–1.67)	1.20 (1.77–1.86)
Concomitant glucocorticoid use	0.97 (0.78–1.20)	1.11 (0.87–1.41)

csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; OHIP: Ontario Health Insurance Plan; CDAI: clinical disease activity index; ESR: erythrocyte sedimentation rate.

[a] $P < 0.001$.

[b] $P < 0.01$.

[c] $P < 0.05$.

higher in patients with triple csDMARDs therapy compared to double csDMARDs therapy.

In the triple csDMARDs therapy group, patients discontinued SSZ more often than the two other medications (MTX and HCQ) mostly due to ineffectiveness, adverse events and patient decision. This finding is similar to the study from Erhardt et al. in which they also reported that triple therapy discontinuation was most often due to adverse events from SSZ [8]. Proudman et al. also found that SSZ was the least tolerated DMARD of triple therapy [12]. In our study, patients on double csDMARDs therapy discontinued LEF more often than MTX, mostly due to adverse events.

In our previous study, we showed that of 313 patients discontinuing MTX, 32.6% were on MTX monotherapy, 49.8% on double, and 17.6% on multiple csDMARDs [13]. A previous systematic review reported rates of MTX persistence ranging between 50 to 94% at 1 year and 25 to 79% at 5 years. They did not observe any clear trends in factors that influenced MTX persistence [14]. An open label expanded randomized clinical trial (RCT) showed the persis-

tence rate of triple csDMARDs therapy at one-year follow-up was 78% compared to etanercept (ETN) plus MTX group (63%). The mean (SD) CDAI at baseline for the triple csDMARDs group was 15.5 (11.6) [15]. Our finding for persistence rate at one year was lower and disease activity was higher compared to this study. However, the observed difference may be due to the possible effect of selection bias in observational studies compared to RCTs.

Our study has limitations. Firstly, this was an observational cohort study and therefore is susceptible to the inherent biases for these types of research studies. This includes selection bias and potential unknown confounding factors that are not possible to control for. In addition, reasons for discontinuation of therapy and adverse events are susceptible to interpretation and bias from both physicians and patients. We also did not assess how specific csDMARD therapies were titrated which is common in clinical practice to achieve better tolerance, particularly gastrointestinal-related events. Similarly, we did not assess how folic acid supplementation was used in patients on MTX. Finally, it was not possible to assess physician preferences regarding combination strategies and thresholds for treatment discontinuation or escalation to bDMARDs and tsDMARDs.

In conclusion, in our study, patients on triple csDMARD therapy remained on treatment longer than patients on double csDMARD therapy. However, this difference was not statistically significant. In addition, triple csDMARD therapy was more likely to be associated with reaching low-disease activity including remission at 6 months after treatment initiation. Finally, female patients and patients with at least one comorbidity were more likely to discontinue therapy. To the best of our knowledge, this is the first study to conduct a head-to-head comparison of these two combination csDMARD strategies. This study provides practical evidence that can be used in routine patient care. These findings should be further investigated through other registry studies and ideally through well-designed randomized control trials.

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Disclosure of interest

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Ethics

All sites had ethics approval to enroll patients. All patients signed informed consent. Ethics approval: REB# is 07-0729 AE (University Health Network).

Authors' contributions

All authors contributed to the conception or design of the work, revised the work critically and approved the final version of the manuscript. M.M. conducted the data analysis. M.M. and and S.V.B. drafted the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jbspin.2024.105732.

Références

[1] Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2021;73:924–39.
[2] Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.
[3] Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
[4] Möttönen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568–73.
[5] O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287–91.
[6] Moreland LW, O'Dell JR, Paulus HE, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of early aggressive rheumatoid arthritis trial. Arthritis Rheum 2012;64:2824–35.
[7] Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–76.
[8] Erhardt DP, Cannon GW, Teng CC, et al. Low persistence rates in patients with rheumatoid arthritis treated with triple therapy and adverse drug events associated with sulfasalazine. Arthritis Care Res (Hoboken) 2019;71:1326–35.
[9] Cummins L, Katikireddi VS, Shankaranarayana S, et al. Safety and retention of combination triple disease-modifying anti-rheumatic drugs in new-onset rheumatoid arthritis. Intern Med J 2015;45:1266–73.
[10] Hodkinson B, Magomero KR, Tikly M. Combination leflunomide and methotrexate in refractory rheumatoid arthritis: a biologic sparing approach. Ther Adv Musculoskelet Dis 2016;8:172–9.
[11] Belani PJ, Kavadichanda CG, Negi VS. Comparison between leflunomide and sulfasalazine based triple therapy in methotrexate refractory rheumatoid arthritis: an open-label, non-inferiority randomized controlled trial. Rheumatol Int 2022;42:771–82.
[12] Proudman SM, Keen HI, Stamp LK, et al. Response-driven combination therapy with conventional disease-modifying antirheumatic drugs can achieve

high response rates in early rheumatoid arthritis with minimal glucocorticoid and nonsteroidal anti-inflammatory drug use. Semin Arthritis Rheum 2007;37:99–111.
[13] Pope JE, Rampakakis E, Movahedi M, et al. Treatment patterns in rheumatoid arthritis after discontinuation of methotrexate: data from the Ontario best practices research initiative (OBRI). Clin Exp Rheumatol 2018;36:215–22.
[14] Curtis JR, Bharat A, Chen L, et al. Agreement between rheumatologist and patient-reported adherence to methotrexate in a US rheumatoid arthritis registry. J Rheumatol 2016;43:1027–9.
[15] Peper SM, Lew R, Mikuls T, et al. Rheumatoid arthritis treatment after methotrexate: the durability of triple therapy versus etanercept. Arthritis Care Res (Hoboken) 2017;69:1467–72.