Sequential treatment strategies following methotrexate inadequate response in rheumatoid arthritis: a real-world retrospective cohort study

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Abstract

Objective

This study aimed to compare different treatment strategies for rheumatoid arthritis (RA) patients following inadequate response to initial methotrexate (MTX) therapy, evaluating clinical outcomes, tolerability profiles, and factors influencing treatment decisions in real-world clinical practice.

Methods

We retrospectively analysed 239 MTX non-responders from health records. Patients were grouped based on subsequent treatment: direct switch to biologic/targeted synthetic DMARDs (b/tsDMARDs) (n=45) or MTX dose escalation (n=194). Those failing dose escalation were further stratified into leflunomide (LEF) (n=37) or b/tsDMARD (n=57) groups. Treatment efficacy was assessed using modified EULAR Boolean criteria (3V-remission) at 6-month intervals.

Results

While direct b/tsDMARD initiation achieved higher 3V-remission rates than MTX dose escalation (62.2% vs. 35.0%, p<0.001), MTX dose optimisation still enabled remission in over one-third of patients. Similarly, among MTX dose escalation non-responders, LEF therapy achieved 3V-remission in 43.2% of patients, comparable to b/tsDMARDs (50.9%, p=0.469), despite higher discontinuation rates (21.6% vs. 1.8%). Importantly, sequential csDMARD optimisation did not compromise subsequent b/tsDMARD responsiveness, with similar remission rates regardless of prior treatment exposure (62.2% after initial MTX, 50.9% post-dose escalation, 46.1% post-LEF, p=0.417).

Conclusion

While b/tsDMARDs demonstrated superior efficacy and tolerability, approximately one-third of patients achieved remission through MTX dose optimisation, possibly reflecting suboptimal initial dosing. Importantly, prior csDMARD optimisation did not compromise subsequent b/tsDMARD responsiveness. These findings underscore the importance of appropriate initial MTX dosing, while indicating that csDMARD optimisation before b/tsDMARD initiation should be considered, given the predominantly mild nature of observed adverse events.

Key words

rheumatoid arthritis, methotrexate, leflunomide, biologic therapy, remission

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of autoimmune origin, characterised by persistent synovial inflammation, progressive joint destruction, and systemic complications, leading to significant morbidity and disability if not promptly and effectively treated. Currently, an extensive array of targeted pharmacological therapies is available, supported by evidence-based recommendations, with the primary goal of preventing structural joint damage, thereby avoiding severe disability associated with delayed or inadequate disease control.

It is now well established that clinicians should aim to achieve remission or, at least, low disease activity, in accordance with the 'treat-to-target' (T2T) strategy recommended by the European League of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) treatment recommendations (1, 2). For nearly three decades, the use of disease-modifying agents has enabled a reduction in glucocorticoid use, while effectively controlling disease progression both clinically and radiographically (3, 4).

Methotrexate (MTX) remains the cornerstone of RA treatment, with its optimal dosing extensively addressed in recent guidelines. However, EULAR (1, 5) and ACR (2) provide differing endorsements. The 2019 EULAR recommendations advocate for a rapid dose escalation, aiming for at least 0.3 mg/kg within 4 to 6 weeks. In contrast, the ACR guidelines conditionally recommend initiating or titrating MTX to 15 mg per week over the same period, without explicitly emphasising the way and time to reach higher doses. Nevertheless, the recommendations are consistent in strongly discouraging the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) in MTX-naive patients, as evidence has shown that their early administration does not yield superior outcomes compared to initial conventional therapy, leading to overtreatment in a large percentage of patients. In patients failing MTX, both EULAR and ACR recommend escalation to b/tsDMARDs in the presence of poor prognostic factors, while conventional synthetic DMARDs (csDMARDs) optimisation should be considered first in their absence (3, 6, 7). However, a major concern pertains to drug tolerability issues and adverse reactions, which often limit the use of csDMARDs in clinical practice (8). Also, a topic of longstanding debate has been the cost of these drugs. While csDMARDs have lower upfront costs, literature suggests that bDMARDs may be more cost-effective in the long term due to their higher success rates and reduced need for therapy adjustments (9, 10). Moreover, a study suggested that, due to a real life tendency to delay a switch to biologic therapy, patients who cycle through multiple csDMARDs before starting a bDMARD may present significantly higher healthcare costs and may be more likely to require additional therapy changes after bDMARD initiation (11). While current recommendations endorse csDMARD optimisation prior to b/tsDMARD initiation in patients lacking poor prognostic factors, real-world adherence remains inconsistent and the comparative evidence underpinning these recommendations limited.

Thus, this study aimed to evaluate early treatment strategies for RA by comparing methotrexate dose adjustments, csDMARD cycling, and switching to b/targeted synthetic DMARDs (tsDMARDs). We assessed tolerability profiles, clinical outcomes, and factors influencing treatment selection decisions using retrospective real-world data from clinical practice. Our goal was to provide guidance for optimising the therapeutic sequence following initial MTX inadequate response.

Materials and methods

We retrospectively enrolled a cohort of RA patients diagnosed according to ACR/EULAR 2010 classification criteria who demonstrated non-response to MTX as first-line immunosuppressive therapy, assessed at 6 months, between May 1992 and May 2022. Inadequate response to MTX and subsequent treatment selection were determined at the discretion of the treating rheumatologist, reflecting the real-world nature of the cohort. Given the broad timeframe

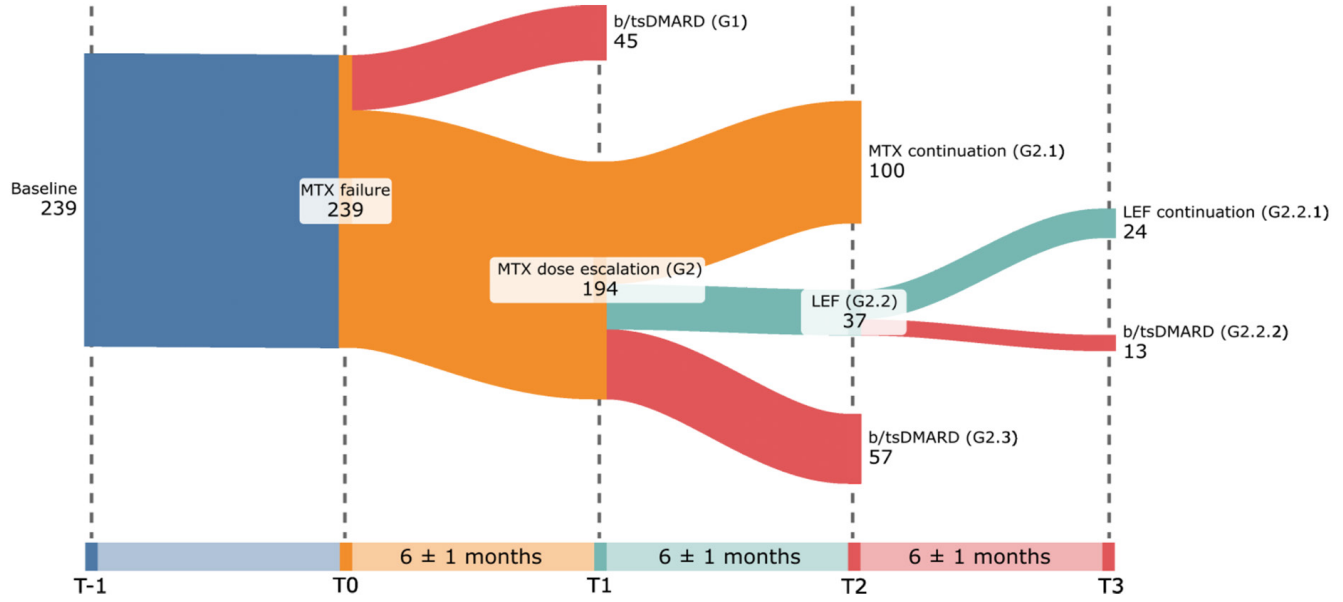

Fig. 1. Sankey diagram showing the treatment path of the groups of patients analysed and the timepoints assessed.

of the study (1992–2022), both the criteria used to define treatment failure and the available therapeutic options evolved considerably over time, particularly following the widespread implementation of the treat-to-target strategy and the progressive introduction of b/tsDMARDs into clinical practice.

To maintain population homogeneity, we excluded individuals with prior exposure to biologic therapies or other csDMARDs. We extracted comprehensive data from health records, including demographic characteristics, serological markers (rheumatoid factor, anti-citrullinated peptide antibodies), joint assessments (tender and swollen joint counts), inflammatory parameters (erythrocyte sedimentation rate - ESR, C-reactive protein - CRP), and radiographic evidence of joint erosions. Adverse events defined according to Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 were recorded.

Data collection occurred at multiple timepoints: initial MTX prescription (T-1), non-response assessment (T0), subsequent treatment modifications at 6±1 months following each therapeutic change to evaluate strategy efficacy (T1 to T3). Figure 1 illustrates the assessment timeline and treatment approaches. For analytical clarity, we designated timepoints as T (ranging from -1 to 3) and patient cohorts as 'G' followed by numerical codes representing stratification at each timepoint, as detailed in the figure, tables, and text.

Given the retrospective design of the study, while tender joint count (TJC), swollen joint count (SJC), and CRP measurements were consistently available, patient global assessment documentation proved insufficient for inclusion. Consequently, we employed a modified version of EULAR Boolean criteria, termed 3V remission criteria, incorporating only TJC, SJC, and CRP levels (12). Although less stringent than the original criteria, this modification has demonstrated reliability in predicting radiographic progression. Also, 3V-remission has been shown to be a useful tool in preventing therapy escalation in 19% of patients who did not fulfill solely the PGA criterion in 4V-remission, as a PGA >1 is not often expected to benefit from additional immunosuppressive therapy.

The study received approval from the local ethics committee (Comitato Etico Regionale Umbria CE-1413/24 20/11/2024). Due to the retrospective nature of the study, informed consent was waived by ethics committee.

Data analysis

Statistical analyses were conducted using IBM SPSS Statistics v. 26. We applied Mann-Whitney U-tests for continuous variables and Chi-squared or Fisher's exact tests for categorical variables, as appropriate. Results are presented as median (interquartile range) or absolute number (percentage).

As a sensitivity analysis, propensity score matching (PSM) was performed to account for baseline differences between groups. Propensity scores were estimated using logistic regression, incorporating age at diagnosis, ACPA positivity, baseline MTX dose, and MTX discontinuation due to adverse reactions as covariates. After exclusion of 9 subjects outside the common support region, the remaining b/tsDMARD-treated subjects (n=36) were matched 1:2 to controls using k-nearest neighbour matching with a caliper of 0.2 standard deviations of the logit of the PS. Covariate balance was assessed using the standardised mean difference (SMD). Differences in 3V-remission rates in the matched cohort were compared using Fisher's exact test.

Results

MTX dose escalation versus switch to b/tsDMARD

The study included 239 MTX non-responders, with 194 patients undergoing dose escalation (G2) and 45 transitioning to biologic agents (G1), either as monotherapy or in combination with MTX. Table I presents patient characteristics at MTX initiation (T-1) and non-response assessment (T0). The biologic agent cohort exhibited distinct

characteristics: younger age (52 *vs*. 54 years, p=0.023), higher ACPA positivity (80.0% *vs*. 56.2%, p=0.003), and higher initial MTX dosage (15 *vs*. 10 mg weekly, p<0.001). This group also demonstrated numerically higher rheumatoid factor positivity.

At treatment modification (T0), disease activity parameters showed no significant inter-group differences, although the b/tsDMARD group experienced more frequent adverse events, predominantly grade 1 gastrointestinal manifestations (Table II). Six-month outcomes (T1) revealed superior efficacy with b/tsDMARD initiation, demonstrated by significantly reduced TJC, SJC, ESR, and CRP levels compared to MTX dose escalation. Adverse event frequencies were comparable, though MTX discontinuation rates differed notably (10.8% in dose escalation *vs*. 2.2% in b/tsDMARD groups). Intuitively, the b/tsDMARD group achieved higher 3V remission rates (62.2% *vs*. 35.0%, p<0.001) (Fig. 2A).

Baseline and follow-up characteristics of MTX dose escalation patients stratified by achievement of 3V-remission are reported in Supplementary Table S1. Responders were older at diagnosis (57 *vs*. 52 years, p=0.016), had lower CRP levels (0.7 *vs*. 1.4 mg/dl, p<0.001) and a trend toward lower prevalence of erosive disease at baseline (12.7% *vs*. 25.4%, p=0.060). RF positivity, ACPA positivity, baseline MTX dose and other disease activity parameters did not differ significantly between groups at baseline. As a sensitivity analysis, PSM yielded a matched cohort of 108 subjects (36 b/tsDMARD-treated, 72 MTX dose-escalation). Post-matching covariate balance was excellent for age at diagnosis, ACPA positivity, and baseline MTX dose (SMD 0.028, 0.033, and 0.014, respectively), while MTX discontinuation due to adverse reactions remained unbalanced (SMD 0.239) owing to its absence in the control group, preventing matching. In the matched cohort, 3V-remission rates were higher in the b/tsDMARD group (69.4%) and lower in the MTX dose escalation group (18.1%) compared to the unadjusted analysis (62.2% *vs*. 35.0%), resulting in a wider between-group difference.

Table I. Patients' characteristics at diagnosis/methotrexate treatment initiation (T-1), according to future decision to escalate MTX (G2) dose or b/tsDMARD switch/add-on (G1).

	MTX dose escalation n=194 (G2–T-1)	b/tsDMARD n=45 (G1–T-1)	*p*-value
Age at diagnosis (years)	54 (45-65)	52 (34-61)	**0.023**
Sex (F)	153/194 (78.9)	38/45 (84.4)	0.400
Positive RF	119/194 (61.3)	34/45 (75.6)	0.073
Positive ACPA	109/194 (56.2)	36/45 (80.0)	**0.003**
ANA ≥1:160	46/194 (23.7)	16/45 (35.6)	0.102
Joint erosions	41/194 (21.1)	13/45 (28.9)	0.262
MTX weekly dose (mg)	10 (7.50–10)	15 (11.25–15)	**<0.001**
CRP (mg/dl)	1.3 (0.4–3.1)	1.4 (0.8-–.65)	0.293
ESR (mm/h)	31 (16–49)	35 (17.5–53.5)	0.320
TJC	4 (2–11)	4.5 (1.25–18.75)	0.643
SJC	2.5 (1.0–10)	2.0 (1.0–11.5)	0.849

Data are shown as median (interquartile range) or number (percentage).
RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; ANA: anti-nuclear antibodies; MTX: methotrexate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TJC: tender joint count; SJC: swollen joint count.

Table II. Comparison of the characteristics, disease features and adverse events at treatment change (T0) and 6 months after (T1) of patients who underwent MTX dose escalation (G2) and patients treated with b/tsDMARDs as alternative or add-on treatment (G1).

	MTX dose escalation n=194 (G2)	b/tsDMARD n=45 (G1)	*p*-value
Characteristics at the moment of treatment change (T0)			
MTX weekly dose (mg)	15 (15–15)		
CRP mg/dl	1.1 (0.4–2.5)	1 (0.4–2.0)	0.882
ESR mm/h	26 (16–39)	27 (19.5–42.5)	0.357
TJC	3 (1–10)	2 (1–10)	0.763
SJC	2 (0–5)	2 (1–6.5)	0.860
b/tsDMARD introduced			
TNF-α inhibitor		27/45 (60)	
IL-6 inhibitor		9/45 (20)	
Anti-CD20		1/45 (2.2)	
Anti-CD80/CD86		5/45 (11.1)	
JAK inhibitor		3/45 (6.7)	
ADR (CTCAE)			
AST/ALT elevation	0/194 (0)	5/45 (11.1)	**<0.001**
Nausea	1/194 (0.5)	5/45 (11.1)	**<0.001**
ADR Grade (CTCAE)	Grade 1: 1	Grade 1: 9 Grade 2: 1	
MTX withdrawal due to ADR	0/194 (0)	7/45 (15.6)	**<0.001**
Characteristics 6 months after treatment change (T1)			
CRP (mg/dl)	0.6 (0.3–1.7)	0.3 (0.10–0.75)	**0.002**
ESR (mm/h)	23.5 (13.0–40.3)	13 (3.5–28.5)	**0.001**
TJC	0 (0–2)	0 (0–1)	**0.025**
SJC	0 (0–2)	0 (0–0)	**0.012**
ADR (CTCAE)			
AST/ALT elevation	25/194 (12.9)	5/45 (11.1)	0.746
Nausea	12/194 (6.2)	0/45 (0)	0.130
Rhinitis Infective	0/194 (0)	1/45 (2.2)	1.000
Anemia	3/194 (1.5)	0/45 (0)	1.000
Leucopenia	1/194 (0.5)	0/45 (0)	1.000
Mucosal	3/194 (1.5)	0/45 (0)	1.000
Hairloss	2/194 (1.0)	0/45 (0)	1.000
Eczema	1/194 (0.5)	0/45 (0)	1.000
Headache	1/194 (0.5)	0/45 (0)	1.000
ADR Grade (CTCAE)	Grade 1: 41 Grade 2: 7	Grade 1: 5 Grade 2: 1	
New treatment withdrawal due to ADR	21/194 (10.8)	1/45 (2.2)	0.087

Data are shown as median (interquartile range) or number (percentage).
MTX: methotrexate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TJC: tender joint count; SJC: swollen joint count; b/tsDMARD: biologic/targeted synthetic disease-modifying antirheumatic drug; TNF: tumour necrosis factor; IL: interleukin; JAK: Janus Kinase; ADR: adverse drug reaction; CTCAE: common terminology criteria for adverse events; AST: aspartate transaminase; ALT: alanine transaminase.

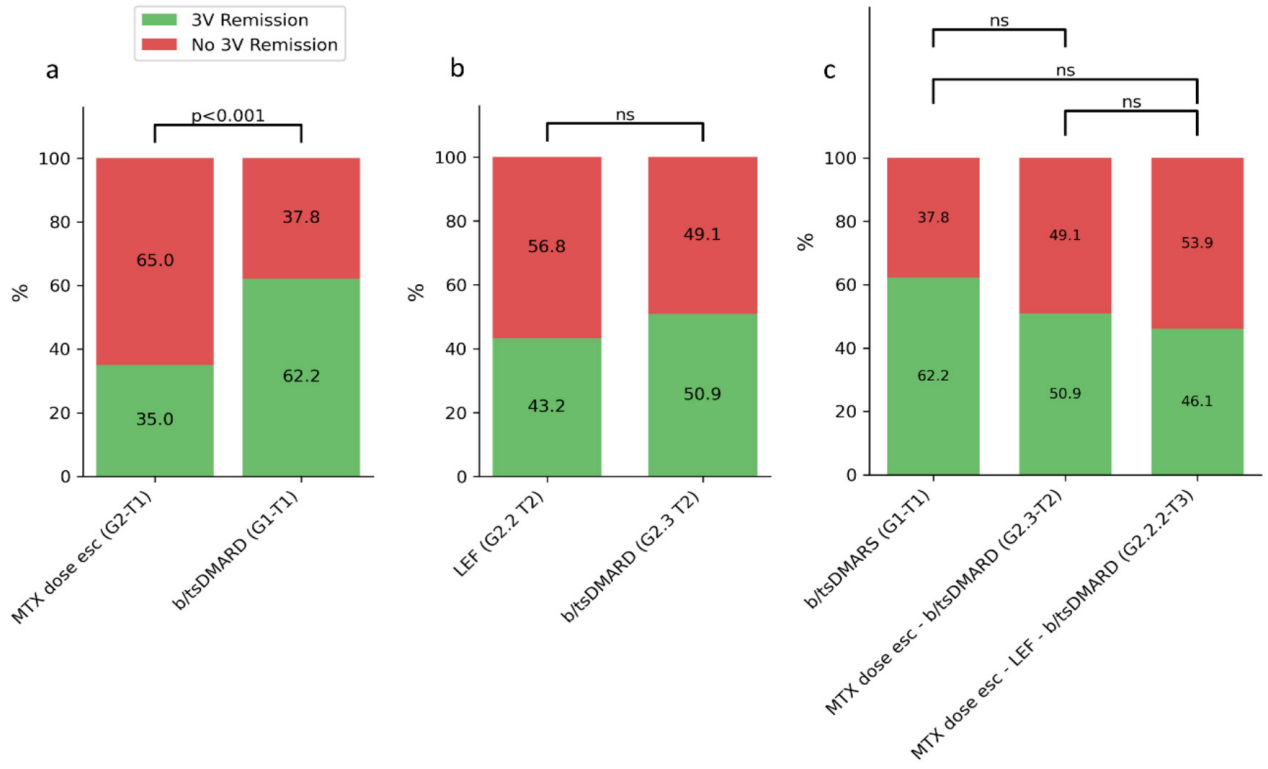

Fig. 2. Bar plots showing response rates to treatment strategies.
a: Treatment response to MTX dose escalation *vs*. direct switch to b/tsDMARD.
b: Treatment response to LEF shift *vs*. b/tsDMARDs after failure of MTX dose escalation.
c: Comparison of response rate to b/tsDMARDs according to previous treatment strategies.

Leflunomide versus b/tsDMARDs in MTX dose-escalation non-responders

Among 94 patients failing MTX dose escalation, subsequent therapy involved leflunomide (n=37, G2.2) or b/tsDMARD (n=57, G2.3). While disease activity parameters at treatment modification (T1) showed no significant differences, the leflunomide group had experienced higher adverse event rates after MTX dose escalation, particularly elevated AST/ALT (29.7% *vs*. 10.5%, p=0.018) and nausea (24.3% *vs*. 3.5%, p=0.006). Consequently, MTX discontinuation due to adverse reactions occurred more frequently in the leflunomide group (43.2% *vs*. 7.02%).

At six months (T2), the b/tsDMARD group demonstrated lower ESR levels (13 *vs*. 21 mm/hr, p=0.04) and superior tolerability (1.8% *vs*. 21.6% discontinuation rate) (Table III). 3V remission rates were comparable (43.2% *vs*. 50.9%, p=0.469) (Fig. 2B).

Leflunomide continuation versus switch to b/tsDMARDs

Analysis of leflunomide-treated patients revealed two subgroups at T3: those maintaining therapy beyond six months (n=24, G2.2.1) and those transitioning to b/tsDMARD (n=13, G2.2.2). Disease activity parameters showed no significant differences, with treatment modifications primarily driven by adverse reactions (53.8% of switches) (Table IV).

Response rates to b/tsDMARDs by previous csDMARD exposure

Comparison of b/tsDMARD response rates across treatment sequences (direct switch from baseline MTX, post-dose escalation failure, or post-leflunomide failure) revealed comparable 3V remission rates (62.2%, 50.9%, and 46.1% respectively, p=0.417) (Fig. 2C).

Discussion

Most studies on RA therapy have focused on comparing MTX efficacy with biologic DMARDs in treatment-naive patients. However, clinical trials often involve highly selected populations with greater adherence to therapy, potentially limiting generalisability to routine clinical practice (13). Few studies have explored subsequent treatment steps following initial MTX failure in real-world settings.

Our study assessed consecutive treatment strategies after initial MTX failure or intolerance in a DMARD-naive RA cohort, evaluating three common therapeutic transitions: a) MTX dose escalation *versus* direct b/tsDMARD initiation, b) LEF *versus* b/tsDMARD after MTX dose escalation failure, and c) LEF continuation *versus* b/tsDMARD switch.

Baseline characteristics of our cohort aligned with existing literature regarding demographics (female predominance, median age in sixth decade) and disease features (ACPA/RF positivity, prevalence of joint erosions, acute phase reactants levels). Patients with negative prognostic indicators (younger age, ACPA/RF positivity) and higher baseline MTX doses were preferentially transitioned directly to biologics rather than undergoing dose escalation, reflecting adherence to EULAR and ACR recommendations.

Table III. Comparison of the characteristics, disease features and adverse events at treatment change (T1) and 6 months after (T2) of patients who failed MTX dose escalation and were prescribed leflunomide (G2.2) or b/tsDMARDs as alternative or add-on treatment (G2.3).

	Leflunomide n=37 (G2.2)	b/tsDMARD n=57 (G2.3)	*p*-value
Characteristics at the moment of treatment change (T1)			
CRP (mg/dl)	1.3 (0.45–3.15)	0.93 (0.26–2.35)	0.224
ESR (mm/h)	26 (11.5–43)	28 (13.5–43.5)	0.653
TJC	1 (0–3)	2 (1–5)	0.085
SJC	1 (0–2.5)	2 (0–3)	0.181
ADR (CTCAE)			
AST/ALT elevation	11/37 (29.7)	6/57 (10.5)	**0.018**
Nausea	9/37 (24.3)	2/57 (3.5)	**0.006**
Cytopenia	2/37 (5.4)	0/57 (0)	0.152
Mucosal	2/37 (5.4)	0/57 (0)	0.152
Hair loss	0/37 (0)	2/57 (3.5)	0.518
Eczema	0/37 (0)	1/57 (1.8)	1.000
Grade (CTCAE)	Grade 1: 18 Grade 2: 6	Grade 1: 11 Grade 2: 0	**<0.001**
MTX withdrawal due to ADR	16/37 (43.2)	4/57 (7.02)	**<0.001**
Characteristics 6 months after treatment change (T2)			
CRP (mg/dl)	0.6 (0.2–2.7)	0.3 (0.1–1.25)	0.107
ESR (mm/h)	21 (11–48.5)	13 (3.5–34)	**0.040**
TJC	0 (0–1.5)	0 (0–3)	0.850
SJC	0 (0–1.0)	0 (0–1.5)	0.826
ADR (CTCAE)			
AST/ALT elevation	3/37 (8.1)	6/57 (10.5)	0.697
Nausea	2/37 (5.4)	0/57 (0)	0.152
Cytopenia	1/37 (2.7)	1/57 (1.8)	1.000
Mucosal	2/37 (5.4)	0/57 (0)	0.152
Hair loss	2/37 (5.4)	1/57 (1.8)	0.559
Maculo-papular rash	0/37 (0)	1/57 (1.8)	1.000
Grade (CTCAE)	Grade 1: 8 Grade 2: 2	Grade 1: 8 Grade 2: 1	
New treatment withdrawal due to ADR	8/37 (21.6)	1/57 (1.8)	**0.001**

Data are shown as median (interquartile range) or number (percentage).
MTX: methotrexate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TJC: tender joint count; SJC: swollen joint count; b/tsDMARD: biologic/targeted synthetic disease-modifying anti-rheumatic drug; ADR: adverse drug reaction; CTCAE: common terminology criteria for adverse events; AST: aspartate transaminase; ALT: alanine transaminase.

Table IV. Comparison of the characteristics, disease features and adverse events 6 months after initiation of leflunomide (T3), comparing subjects that were subsequently shifted to b/tsDMARDs (G2.2.2) and those who continued on leflunomide (G2.2.1).

	Leflunomide n=24 (G2.2.1)	b/tsDMARD n=13 (G2.2.2)	*p*-value
CRP (mg/dl)	0.41 (0.11–1.4)	1.53 (0.58–3.53)	0.083
ESR (mm/h)	21 (9.50–49.25)	25 (14.5–53.5)	0.441
TJC	0 (0–0.75)	1 (0–7)	0.141
SJC	0 (0–0.75)	0 (0–3)	0.387
ADR (CTCAE)			
AST/ALT elevation	0/24 (0)	3/13 (23.1)	
Nausea	1/24 (4.2)	1/13 (7.7)	
Cytopenia	0/24 (0)	1/13 (7.7)	
Mucosal	1/24 (4.2)	2/13 (15.4)	
Hair loss	1/24 (4.2)	1/13 (7.7)	
Grade (CTCAE)	Grade 1: 2 Grade 2: 1	Grade 1: 7 Grade 2: 1	
LEF withdrawal due to ADR	1/24 (4.2)	7/13 (53.8)	**0.001**

Data are shown as median (interquartile range) or number (percentage).
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TJC: tender joint count; SJC: swollen joint count; b/tsDMARD: biologic/targeted synthetic disease-modifying anti-rheumatic drug; ADR: adverse drug reaction; CTCAE: common terminology criteria for adverse events; AST: aspartate transaminase; ALT: alanine transaminase; LEF: leflunomide.

Evidence from randomised trials suggests comparable efficacy and toxicity between MTX initial doses of 7.5–15 mg weekly, while higher doses (up to 25 mg) may improve long-term outcomes without increased adverse event-related withdrawals. However, our data revealed that baseline MTX doses were unexpectedly low even in patients later transitioning to b/tsDMARDs, frequently below recommended targets (15 mg/week according to ACR; 0.3 mg/kg/week according to EULAR). Although we lacked patient weight data to fully assess EULAR recommendation adherence, the average doses appeared lower than expected for normal-weight adults. A meta-regression analysis by Bergstra *et al*. found no clear dose-response relationship for initial MTX dosing in DMARD-naive early RA patients across a dose range of 7.5–30 mg/week. However, this finding may not be directly applicable to our cohort, as it addressed initial dosing in treatment-naive patients rather than dose escalation as a rescue strategy, and was most robust for comparisons within the 15–30 mg/week range, while our patients frequently started below 10 mg/week. In this context, the remission rates observed following dose escalation may partly reflect the correction of suboptimal initial dosing rather than a true pharmacological ceiling effect of MTX, further underscoring the importance of implementing appropriate MTX doses from treatment initiation (14–17).

This finding aligns with previous real-world studies. The Italian MITRA study examining 259 RA patients confirmed MTX key role as first-line therapy (used in 85% of patients) but identified a 24-week delay in treatment initiation and outcomes frequently resulting in low disease activity rather than remission (18, 19). Similarly, the French ESPOIR cohort identified significant gaps between guidelines and practice, with 47% of severe RA patients not receiving structurally effective DMARDs within six months, indicating suboptimal care. A potential limitation observed in real-world practice, RA classification criteria (*e.g*. ACR) perform well in established disease but are less reliable in early arthritis, making it dif-

ficult to initiate treatment promptly (20-22).Furthermore, a study analysing the Norwegian NOR-DMARD registry compared outcomes between MTX and bDMARDs in RA patients. This real-world analysis examined demographic characteristics, disease activity measurements, and treatment discontinuation reasons, revealing that lack of efficacy was the primary cause (23).

The tendency toward lower initial MTX doses likely reflects concerns about adverse reactions, which occurred even at modest doses. Indeed, adverse events led to treatment discontinuation in 7/45 patients (15.6%) who subsequently switched directly to biologics. Following treatment modification, adverse event prevalence was significantly higher with MTX dose escalation compared to b/tsDMARD transition (10.8% *vs*. 2.2%).

Interestingly, disease activity did not significantly differ between groups at treatment change. However, six months later, patients receiving b/tsDMARDs demonstrated significantly lower disease activity levels. Consequently, 3V-remission rates were approximately twice as high in the biologic group, consistent with current literature. Nevertheless, bypassing MTX dose escalation could potentially lead to overtreatment, as approximately one-third of patients responded adequately to increased MTX dosing. The PSM sensitivity analysis confirmed the superior efficacy of b/tsDMARDs over MTX dose escalation after adjustment for baseline confounders, with a wider gap in 3V-remission rates compared to the unadjusted analysis (69.4% *vs*. 18.1% after PSM). This widening is consistent with the known greater efficacy of b/tsDMARDs and likely reflects the confounding effect of ACPA negativity and lower baseline MTX doses in the escalation group. Nevertheless, even after removing this confounding, a non-negligible proportion of patients achieved remission through dose escalation alone, supporting its pursuit as an initial strategy, particularly in patients without negative prognostic factors and with suboptimal baseline MTX dosing, in line with current treatment recommendations. The inability to adjust for MTX intolerance through PSM represents a residual limitation, as some b/tsDMARD-treated patients might have responded to dose escalation had they tolerated it. Consistent with this, the subgroup analysis of MTX dose escalation patients revealed that responders displayed markers of less aggressive disease at baseline, including older age at diagnosis, lower levels of CRP and a trend toward reduced prevalence of joint erosions, further supporting the notion that dose escalation represents a most reasonable strategy in patients without unfavourable prognostic features.

In the subsequent therapy step comparing patients who failed MTX dose escalation, the absence of significant disease feature differences coupled with higher rates of MTX adverse events in the LEF group suggest that many patients underwent treatment change due to MTX intolerance rather than inadequate disease control. This is supported by similar 3V-remission rates between groups at six months, despite significantly better tolerability with b/tsDMARDs.

In our final treatment step analysis comparing LEF continuation *versus* b/tsDMARD switch, the majority of patients initiating biologics discontinued LEF due to adverse events, likely representing the primary reason for treatment change.

Importantly, our analysis demonstrated comparable response rates to biologic therapy regardless of prior treatment exposure. Patients who directly switched after MTX failure showed similar outcomes to those who first attempted csDMARD optimisation, with no significant differences across all three patient groups. This finding aligns with observations from clinical trials investigating whether prior treatment exposure influences biologic response (24).

The retrospective design constitutes our study's principal strength, enabling assessment of real-world practices without therapeutic decisions being influenced by the experimental design. However, inherent limitations include the inability to account for all potential confounding variables. While we confirmed that all patients received ≤5 mg/day prednisone equivalent at each timepoint considered, detailed corticosteroid adjustment inbetween were inconsistently documented and excluded from analysis. Further limitations inherent to the retrospective design include potential selection bias in treatment allocation, incomplete capture of all adverse events, and the inability to control for unmeasured confounders such as patient preferences, comorbidities, and socioeconomic factors influencing treatment decisions.

In conclusion, our real-world data analysis demonstrates that following inadequate response to baseline MTX doses, b/tsDMARDs achieved significantly higher remission rates. However, a non-negligible proportion of MTX non-responders still attained remission through dose intensification or LEF substitution. This observation likely reflects suboptimal initial MTX dosing, as baseline doses were frequently below recommendations. Our findings underscore the importance of implementing appropriate MTX doses from treatment initiation, as recommended by current guidelines, to maximise early efficacy. It is important to underline that the absence of a control group prevents us from distinguishing genuine treatment responses from potential confounders, such as regression to the mean. Nonetheless, csDMARD optimisation prior to b/tsDMARD initiation should be considered, particularly in light of the predominantly mild nature of observed adverse reactions following MTX dose escalation. Importantly, these sequential approaches do not compromise subsequent b/tsDMARD responsiveness compared with early biologic introduction.

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