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Original article

MTX optimization or adding bDMARD equally improve disease activity in rheumatoid arthritis: results from the prospective study STRATEGE

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Abstract

Objectives. The STRATEGE (Therapeutic Strategy in Patients Treated With Methotrexate for Rheumatoid Arthritis) study aimed to describe treatment strategies in current practice in RA biologic DMARD (bDMARD)-naïve patients with an inadequate response to MTX therapy, and to compare clinical efficacy of the different therapeutic strategies on disease activity after 6 months.

Methods. The main inclusion criteria of this prospective, observational, multicentre study were confirmed RA diagnosis, treatment by MTX monotherapy and need for therapeutic management modification.

Results. The 722 patients included had a mean (S.D.) RA duration of 5.3 (6.7) years, a mean DAS28 of 4.0 (1.1); they were all receiving MTX monotherapy, 68% oral, at a mean dose of 15.0 (4.1) mg/week. Two major strategies were identified: (i) MTX monotherapy dose and/or route optimization (72%) and (ii) bDMARD initiation ± MTX (16%). MTX dosing was modified for 70% of patients, maintained (dose and route) for 28% of patients and interrupted for 2%. bDMARDs were started when the MTX mean dose was 17.4 mg/week, 56% parenterally; MTX was maintained concomitantly for 96% of patients. Six-month follow-up results adjusted by propensity score showed that both options were equally successful in improving disease activity and physical function, with 63 and 68% of good-to-moderate EULAR responses, respectively.

Conclusion. The STRATEGE study shows the importance of initial MTX treatment optimization before initiation of a biological treatment and emphasizes the importance of treat-to-target strategy.

Trial registration. ClinicalTrials.gov NCT02288520.

Key words: rheumatoid arthritis, methotrexate, optimization, treat-to-target, management

CLINICAL SCIENCE

Rheumatology key messages

- Two major strategies after initial MTX monotherapy: MTX monotherapy optimization and initiation of a biologic DMARD.
- Both strategies are equally effective on disease activity, physical function, pain and patient satisfaction at 6 months in appropriately selected patients.
- MTX was suboptimally dosed and parenteral route was underutilized at biologic DMARD initiation.

Introduction

MTX is considered the 'gold standard' of RA treatment and must be initiated in monotherapy, when there is no contraindication, immediately upon diagnosis of RA [1–3]. Guidelines recommend starting MTX at a dose of at least 10 mg/week orally and escalating in 5 mg/month increments to reach 25–30 mg/week, or the highest tolerable dose, with a subsequent switch to s.c. administration in cases of inadequate response [1–3]. However, these guidelines are not always followed, and considerable

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heterogeneity exists in prescription behaviour regarding MTX monotherapy optimization [4–7].

In addition, the guidelines only allow addition of biologic DMARDs (bDMARDs) or other conventional synthetic DMARDs (csDMARDs) to MTX treatment when monotherapy has been fully optimized (dose and route). However, evidence is scarce concerning MTX optimization in treating RA and the effect of this optimization in daily practice.

The objectives of this large nationwide observational prospective study, STRATEGE (Therapeutic Strategy in Patients Treated With Methotrexate for Rheumatoid Arthritis), were to describe treatment strategies in current practice in RA bDMARD-naïve patients with an inadequate response to MTX therapy, and to compare clinical efficacy of these different therapeutic strategies on disease activity after 6 months.

Methods

Study design, ethics and data access

STRATEGE was a prospective non-interventional multicentre study conducted in France, registered under the number NCT02288520 in ClinicalTrials.gov [8]. The therapeutic strategy is thus not assigned by the study protocol but falls within current practice.

The study was conducted in accordance with legal and regulatory requirements. The protocol was approved by the French Data Protection Authority (CNIL; Approval number 914489) and its Advisory Committee on Information Processing in Research in the Field of Health (CCTIRS). Written informed patient consent was not required. For more information, please see supplementary Data S1, available at *Rheumatology* online.

The data used in this study correspond to deidentified participant data—i.e. pseudonymized—from a dataset stored and owned by Nordic Pharma; no directly nominative data was collected. According to French law, the dataset can only be shared through a controlled access; the reuse of these health data at the individual level would require an agreement with Nordic Pharma (helene.herman-demars@nordicpharma.com), and application to the French Health Data Hub (https://www.health-data-hub.fr/), with examination by the committee of experts (CESREES, Ethics and Scientific Committee for Research, Studies and Evaluations in the field of Health) and the French National Commission for Data Protection (CNIL). The French Data Protection Act and the Public Health Code restrict access to research of public interest.

Inclusion/exclusion criteria

To be eligible for STRATEGE, patients had to (i) be aged ≥18 years; (ii) have a physician diagnosis of RA satisfying ACR 1987 and/or ACR/EULAR 2010 criteria [9, 10]; (iii) be treated by MTX monotherapy; and (iv) have a clinical, functional, structural and/or therapeutic evolution requiring a treatment modification. Patients were not eligible if they had current or previous exposure to a bDMARD for their RA treatment, if they objected to their data being collected or if they were participating in a clinical study in rheumatology.

Data collection

Data were collected on paper forms at two time points: (i) at the initial visit and (ii) ∼6 months later at a follow-up visit, in accordance with the practice of each centre.

Baseline data included sociodemographic patient characteristics, RA history, family background and comorbidities, previous treatments, current situation description, DAS28, physical function [HAQ Disability Index (HAQ-DI)], extra-articular and radiographic features and current treatment modalities, MTX dose and route, CS, folic acid, etc. The patient's options of disease management and the chosen new treatment (features and reasons) were reported.

Six-month follow-up data considered the impact of the chosen strategy on disease and treatment features, any therapeutic modifications and any adverse events (AEs).

In case of missing data, the physician was contacted to retrieve the missing information as much as reasonably possible. Missing values were not imputed.

Outcomes

To describe treatment strategies in RA patients with inadequate response to MTX therapy, we considered MTX prescription characteristics, reasons for treatment modification and the modalities of other csDMARDs and bDMARDs prescriptions. Patient characteristics at inclusion are described for the overall population and in each therapeutic strategy identified. MTX features are also described at 6 months after treatment modification.

The different strategies were compared at 6 months through efficacy outcomes assessed as change in DAS28 and HAQ-DI scores and EULAR response, and patient-reported outcomes, assessing pain (on a visual analogue scale, 0–100) and satisfaction on a four-point scale (Very satisfied, Satisfied, Unsatisfied, Very unsatisfied).

Finally, safety outcomes are presented, detailing AE related to MTX and serious AE.

Statistical analyses

Descriptive analyses are presented using frequencies and percentages for qualitative variables and means (S.D.) or medians (min–max), as appropriate, for continuous variables. Outcomes were compared between the different therapeutic strategies using analysis of covariance adjusted for baseline DAS28 and baseline HAQ-DI.

A propensity score adjustment was modelled to compare efficacy outcomes at 6 months for the two major identified therapeutic strategies. Indeed, due to the lack of randomization of the treatment optimization, patients were likely to have different clinical and demographic characteristics at the time of treatment choice,

introducing a potential indication bias. We thus estimated each patient's propensity score, reflecting the probability of receiving one of the two compared therapeutic strategies, using a binary logistic-regression model. This model included, as explanatory variables, 22 candidate predictors available at baseline *a priori* possibly explaining the therapeutic strategy assigned by the clinician (supplementary Table S1 and Figure S1, available at *Rheumatology* online); only variables shown to be related to at least one of the health outcomes were retained in the model. The adequacy of the model was approached by the c-index (area under the receiver operating characteristic curve) and the Hosmer–Lemeshow goodness-of-fit test. The individual propensity scores were then considered as explanatory variable within the linear regression model that assessed the relation between the treatment strategies and the change in DAS28 score from baseline to 6 months, as a continuous variable.

The statistical analysis used SAS 9.4 software (SAS Institute, Cary, NC, USA).

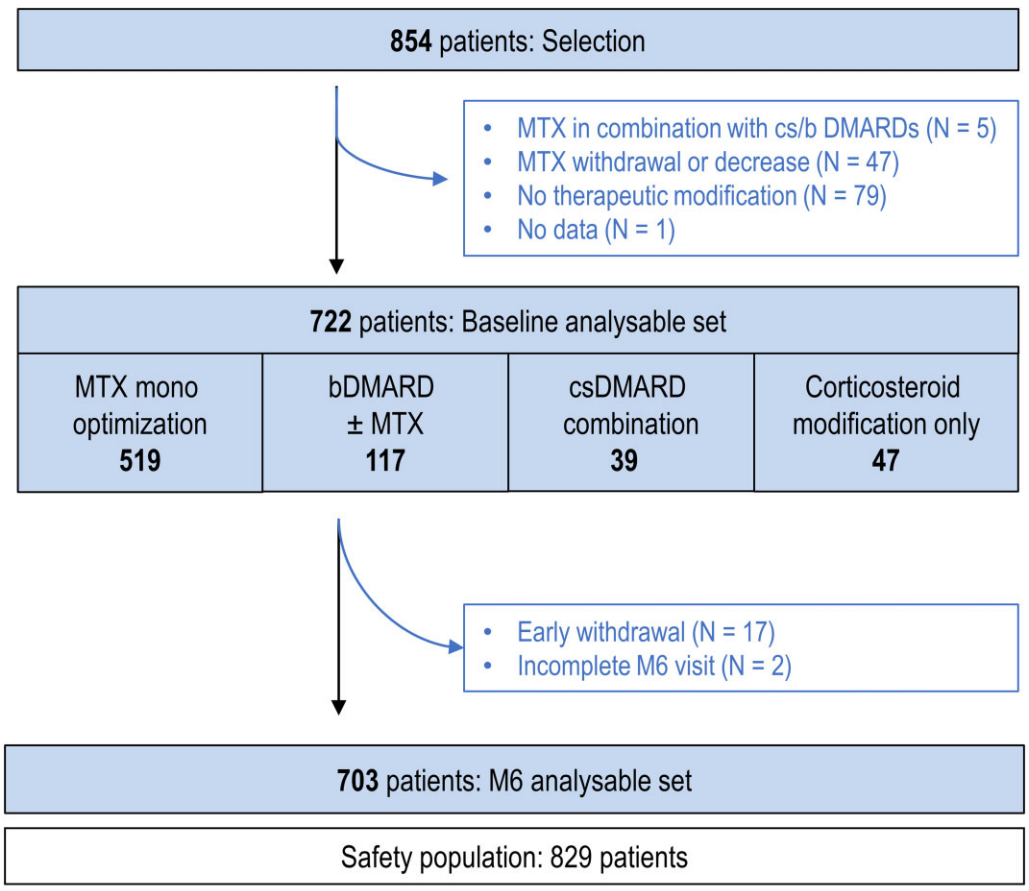
Results

Study population

Between August 2014 and September 2015, 176 rheumatologists, 90% in private practice, recruited 854 patients, 722 of whom comprised the analysable baseline set (Fig. 1). There were very few items with missing data (Tables 1 and 2). Participants had a mean (S.D.) RA duration of 5.3 (6.7) years, and a mean DAS28 of 4.0 (1.1). Disease activity levels according to DAS28 were high for 17% patients, medium for 63%, low for 12% and remission for 8%.

Patients were all receiving MTX monotherapy at inclusion, 68% oral and 32% parenterally, 30% s.c., 2% i.m., at a mean dose of 14.9 (4.1) mg/week (Table 1 and Fig. 2). Fifty percent of patients taking MTX parenterally required assistance from a nurse or caregiver to perform their injections. MTX was the first-line csDMARD in 84% of patients, of whom 66% received it in the first 3 months after diagnosis. Prior to the initial visit, 15% of

Fig. 1 Study flowchart



M6, six-months' visit

Table 1 Patient baseline characteristics

Baseline characteristics	Overall (*n* = 722)	Missing	Therapeutic strategy at the end of the initial visit				
			Two main therapeutic strategies			Other therapeutic strategies	
			(1) MTX monoth. OPT (*n* = 519)	(2) bDMARD ± MTX (BT) (*n* = 117)	P-value (OPT *vs* BT)	(3) csDMARDs combination (*n* = 39)	(4) CS modification only (*n* = 47)
Demographic characteristics							
Age, mean (S.D.), years	57.0 (13.7)	0	58.0 (14.0)	52.6 (12.5)	<0.001	54.6 (12.9)	58.3 (12.9)
Female, *n* (%)	537 (74.5)	1	377/518 (72.8)	94/117 (80.3)	0.091	28/39 (71.8)	38/47 (80.9)
RA characteristics							
RA duration, mean (S.D.), years	5.5 (6.7)	3	5.2 (6.5)	6.5 (7.1)	0.058	6.7 (8.6)	4.9 (5.3)
RF positive, *n* (%)	521 (73.9)	17	359/505 (71.1)	98/116 (84.5)	0.003	31/38 (81.6)	33/46 (71.7)
ACPA positive, *n* (%)	480 (70.1)	37	330/490 (67.3)	91/114 (79.8)	0.009	26/35 (74.3)	33/46 (71.7)
Radiographic damage, *n* (%)	278 (38.8)	5	187/515 (36.3)	58/116 (50.0)	0.006	17/39 (43.6)	16/47 (34.0)
Extra-articular manifestations, *n* (%)	74 (10.2)	0	44/519 (8.5)	22/117 (18.8)	<0.001	6/39 (15.4)	2/47 (4.3)
CRP, mean (S.D.), mg/l	12.9 (19.8)	34	12.0 (12.1)	17.6 (39.1)	0.134	11.7 (10.8)	12.0 (19.3)
ESR, mean (S.D.), mm/h	24.5 (21.6)	31	24.4 (22.9)	27.6 (17.8)	0.107	22.4 (17.2)	18.7 (17.1)
DAS28, mean (S.D.)	4.1 (1.1)	29	4.0 (1.0)	4.6 (1.1)	<0.0001	4.3 (1.2)	3.7 (1.2)
HAQ-DI, mean (S.D.)	1.0 (1.4)	108	0.9 (1.0)	1.1 (1.3)	0.074	1.5 (4.3)	1.0 (1.3)
Pain VAS, median (Q1–Q3)	50 (30–60)	7	50 (30–60)	60 (40–70)	–	40.0 (25–65)	40 (30–60)
Treatment characteristics at inclusion							
Delay between RA diagnosis and MTX initiation, mean (S.D.), years	1.7 (4.2)	5	1.6 (4.3)	1.8 (4.6)	0.653	2.1 (4.3)	1.4 (3.0)
Delay between RA diagnosis and MTX initiation, *n* (%)		0					
≤3 months	479 (66.3)		351/519 (67.6)	80/117 (68.4)	0.876	17/39 (43.6)	31/47 (66.0)
>3 months	243 (33.7)		168/519 (32.4)	37/117 (31.6)		22/39 (56.4)	16/47 (34.0)
MTX current dose, mean (S.D.), mg/week	14.9 (4.1)	7	14.1 (3.9)	17.4 (3.5)	<0.0001	17.5 (4.6)	15.8 (3.9)
MTX current dose (classes), *n* (%), mg/week		7					
≤15	509/715 (71.2)		409/515 (79.4)	53/116 (45.7)		16/37 (43.2)	31/47 (66.0)
15–20	26/715 (3.6)		18/515 (3.5)	6/116 (5.2)	<0.0001	1/37 (2.7)	1/47 (2.1)
≥20	180/715 (25.2)		88/151 (17.1)	57/116 (49.1)		20/37 (54.1)	15/47 (31.9)
Parenteral MTX, *n* (%)	230 (32.3)	10	130/513 (25.3)	65/116 (56.0)	<0.0001	16/36 (44.4)	19.0/47(40.4)
CS prescriptions, *n* (%)	377 (52.2)	0	255/519 (49.1)	62/117 (53.0)	0.451	22/39 (56.4)	38/47 (80.9)
Folic acid prescriptions, *n* (%)	598 (82.8)	0	442/519 (85.2)	95/117 (81.2)	0.285	26/39 (66.7)	35/47 (74.5)

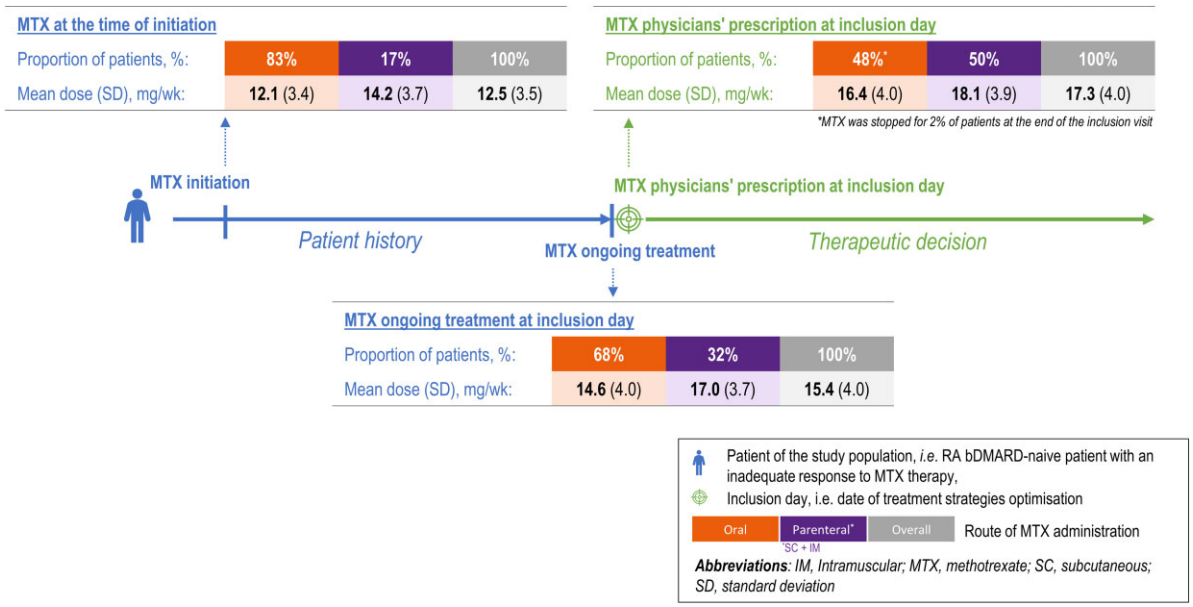
bDMARD: biological DMARDs; BT: biotherapy (i.e. bDMARD ± MTX); csDMARD: conventional synthetic DMARD; HAQ-DI: HAQ Disability Index; monoth.: monotherapy; OPT: optimization (i.e. MTX monotherapy optimization); VAS: visual analogue scale.

Table 2 MTX treatment modifications at the end of the initial visit, and reasons for modifications

MTX features	Overall		Therapeutic strategy at the end of the initial visit			
			Two main therapeutic strategies		Other therapeutic strategies	
	(n = 722)	Missing	(1) MTX monoth. OPT (*n* = 519)	(2) bDMARD ± MTX (BT) (*n* = 117)	(3) csDMARDs combination (*n* = 39)	(4) CS modification only (*n* = 47)
MTX features at the end of the initial visit						
MTX modified route and/or dose, *n* (%)	561 (77.7)	0	519/519 (100.0)	31/117 (26.5)	11/39 (28.2)	–
MTX unchanged, *n* (%)	146 (20.2)		–	81/117 (69.2)	18/39 (46.1)	47/47 (100.0)
MTX interrupted, *n* (%)	15 (2.0)		–	5[a]/117(4.2)	10[b]/39(25.6)	–
Reasons for treatment modification (more than one reason could be cited)						
Active RA (DAS28 $\geq$ 3.2), *n* (%)	530 (73.4)	0	378/519 (72.8)	99/117 (84.6)	28/39 (71.8)	25/47 (53.2)
RA not in remission (2.6 $\leq$ DAS28 $<$ 3.2), *n* (%)	73 (10.1)	0	57/519 (10.9)	4/117 (3.4)	5/39 (12.8)	7/47 (14.9)
Worsening of clinico-biological parameters, *n* (%)	234 (32.4)	0	153/519 (29.5)	49/117 (41.9)	12/39 (30.1)	20/47 (42.5)
Radiographic progression, *n* (%)	107 (14.8)	0	58/519 (11.2)	46/117 (39.3)	1/39 (2.6)	2/47 (4.2)
CS sparing, *n* (%)	81 (11.2)	0	59/519 (11.4)	18/117 (15.4)	3/39 (7.7)	1/47 (2.1)
Poor tolerance of the current treatment, *n* (%)	29 (4.0)	0	16/519 (3.1)	7/117 (5.9)	5/39 (12.8)	1/47 (2.1)
MTX	24 (82.7)	0	13/16 (81.2)	5/7 (71.4)	5/5 (100.0)	1/1 (100.0)
Other medication (NSAIDs, CS, etc.)	4 (13.8)	0	3/16 (0.6)	0/7 (0.0)	1/5 (20.0)	0/1 (0.0)
Poor treatment adherence, *n* (%)	7 (0.9)	0	6/519 (1.1)	1/117 (0.8)	0/39 (0.0)	0/39 (0.0)

[a]bDMARD monotherapy: tocilizumab for three patients, certolizumab for one patient, etanercept for one patient. [b]New csDMARD monotherapy: LEF for 10 patients. bDMARD: biological DMARD; BT: biotherapy (i.e. bDMARD ± MTX); csDMARD: conventional synthetic DMARD; monoth.: monotherapy; OPT: optimization (i.e. MTX monotherapy optimization).

FIG. 2 Patient MTX prescription: changes in route and dose



patients had MTX tapering due to gastrointestinal intolerance, liver cytolysis and other unknown reasons.

Treatment modifications in real-life in RA patients with inadequate response to MTX therapy

Four distinct treatment modification strategies were identified in RA patients with inadequate responses to initial MTX monotherapy: (group 1) MTX monotherapy optimization for dose and/or route (72%, $n = 519$); (group 2) initiation of a first bDMARD (16%, $n = 117$), for 96% in combination with MTX; (group 3) prescription of csDMARD(s) other than MTX (5%, $n = 39$), for 74% in combination with MTX; and (group 4) maintenance of MTX monotherapy (same route and dose) with only CS prescription modification (7%, $n = 47$; Table 1 and Fig. 1).

The main two reasons to justify treatment modification were active disease, in 73.4% of patients ($n = 530$), and/or worsening of clinico-biological parameters, in 32.4% of patients ($n = 234$). These reasons were the two most common justifications in each of the four strategy groups (Table 2). Remarkably, radiographic progression was cited in 40% of patients as a reason to initiate a first bDMARD for group 2, in comparison to 3–11% for other therapeutic strategies. In contrast, parenteral MTX was started mainly for efficacy reasons, safety being cited for only 5% of patients.

Regarding MTX treatment, the MTX mean dose was raised to 17.3 (4.0) mg/week from 14.9 (4.1) mg/week before modification, and the percentage of parenteral administration increased from 32 to 50% (Fig. 2). When either a bDMARD or csDMARDs were started, MTX prescription remained unmodified (dose and route) in 69 and 46% of cases, respectively. MTX was stopped for only 15 patients (Table 2).

The nature of bDMARDs and csDMARDs prescribed for strategy groups 2 and 3, respectively, are provided in Fig. 3.

The initiation of the first biologic therapy occurred at a mean DAS28 of 4.6 (1.1), after a mean RA duration of 6.5 (7.1) years when MTX mean dose was 17.4 (3.5) mg/week (45.7% of patients treated with a dose $\leq$15 mg/week, 5.2% a dose 15–20 mg/week and 49.1% a dose $\geq$20 mg/week), with 56% of s.c. administration and concomitant CS prescriptions for 53% of patients. At inclusion, s.c. administration was less used in group 1 (25.3%) and mean dose was 14.1 (3.9) mg/week (79.4%: $\leq$15 mg/week; 3.5%: 15–20 mg/week; and 17.1%: $\geq$20 mg/week) (Table 1).

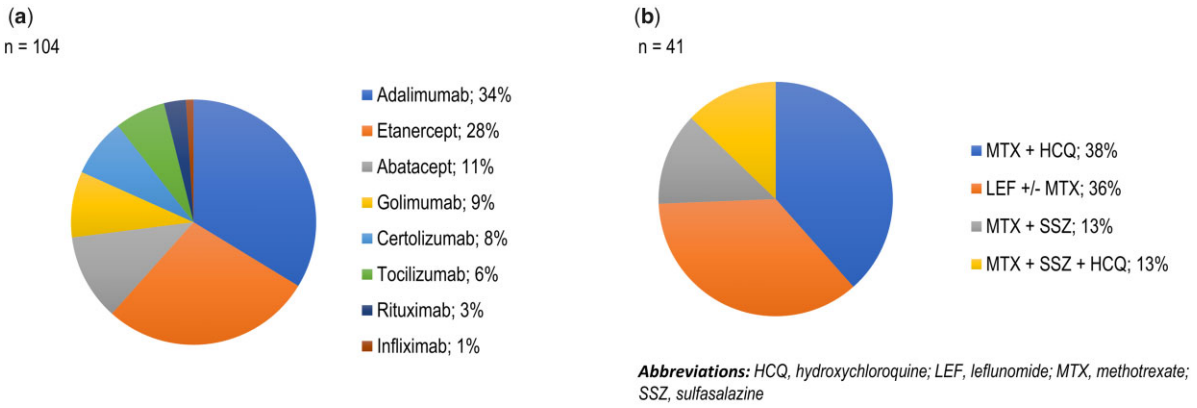
MTX features at the 6-month visit from treatment modification

Over the 6-month period, MTX prescription was maintained (dose and route) for 20% of patients ($n = 146$), interrupted for 2% ($n = 15$) and modified for 78% ($n = 561$; Table 2). An oral-to-parenteral switch was decided for 27% of patients ($n = 151$). Among these 151 patients, the MTX dose remained identical for 50% [$n = 76$; 16.4 (3.6) mg/week], was raised for 46% [$n = 69$; from 13.7 (3.1) mg/week to 18.4 (3.2) mg/week] and reduced for 4% [$n = 6$; from 20.0 (3.2) mg/week to 15.0 (3.2) mg/week].

Assessment and comparison of the 6-month efficacy outcomes for the different therapeutic strategies

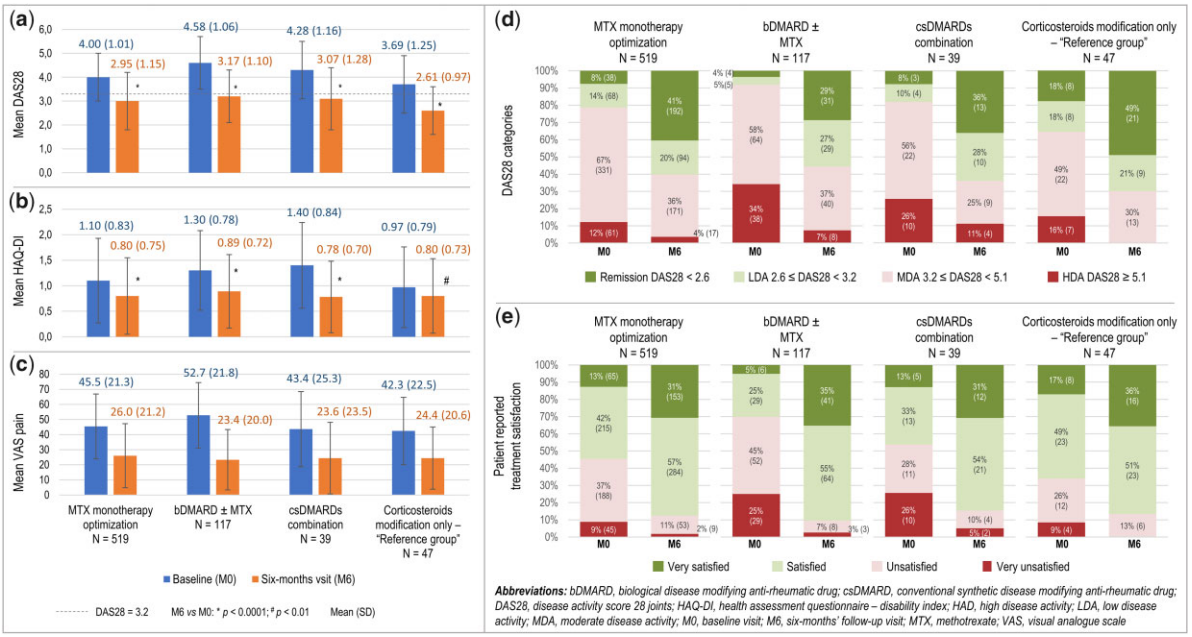
Significant DAS28 improvement was achieved after 6 months of treatment, regardless of the treatment strategy used (Fig. 4a). Mean DAS28 improved from 'active disease'

Fig. 3 Nature of bDMARDs and csDMARDs prescribed for strategy groups 2 and 3



Prescribed bDMARDs (**a**) and details of combination of csDMARDs (**b**). bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD.

Fig. 4 Evolution of clinical evaluation between the baseline and the 6-months' follow-up visit



Evolution of mean (**a**) and categorized (**d**) DAS28, HAQ-DI (**b**), self-assessed pain (**c**) and treatment satisfaction (**e**) between the baseline and the 6-months' follow-up visit.

to 'low disease activity', with the proportion of patients in remission or with low disease activity ranging from 56% to 70% for the various strategies (Fig. 4d). DAS28 comparison did not show any significant differences between the three 'active' strategies: (group 1) MTX monotherapy optimization, (group 2) bDMARD ± MTX and (group 3) csDMARDs combination, compared with (group 4) CS modification only, considered here as a reference since no disease-modifying treatment was changed ($P = 0.67$, analysis of covariance).

The percentage of patients reaching a good or moderate EULAR response was 63% for group 1 MTX monotherapy optimization, 68% for group 2 bDMARD ± MTX and 67% for the other two strategies, groups 3 and 4. All the strategies were equally ($P = 0.39$) successful in significantly improving physical function, measured by HAQ-DI (Fig. 4b) and pain (visual analogue scale; Fig. 4c). Globally, >80% of patients declared themselves satisfied or very satisfied with their treatment strategy after 6 months.

Focus on the two main therapeutic strategies, groups 1 and 2

The two most common therapeutic strategies to be compared with propensity scores for 6-month efficacy

outcomes were (group 1) MTX monotherapy optimization for dose and/or route (72%, $n = 519$) and (group 2) initiation of a first bDMARD (16%, $n = 117$).

Sociodemographic features, unrelated to disease status, were comparable among the two treatment groups except that patients proceeding to bDMARD ± MTX were younger. They also had a more active (DAS28, CRP level), more pain and more erosive disease with higher level of RF/ACPAs positivity (Table 1). The dose of MTX was higher and parenteral route was more frequent than in MTX optimization.

Efficacy outcomes were compared after adjusting baseline characteristics through individual propensity scores. Distributions of individual propensity scores are available in supplementary Fig. S1, available at *Rheumatology* online. The final model for the propensity score included the following baseline variables: patient age (±60 years old), current smoking status, ACPA and RF positivity, DAS28 and HAQ, extra-articular manifestations and radiographic damage (supplementary Table S1, available at *Rheumatology* online; c-index: 0.73, Hosmer–Lemeshow goodness-of-fit: $P = 0.73$). There was still no significant difference in DAS28 between the groups when adjusting with propensity scores ($P = 0.71$; regression coefficient: 0.06, 95% CI −0.26, 0.38). Similarly, no significant differences were found for any of the patient-reported outcome criteria after adjusting with propensity scores ($P = 0.99$ for function, 0.68 for pain and 0.327 for satisfaction).

Safety

Of the 829 patients comprising the safety population, 23.5% reported at least one AE during the 6 months of follow-up and 10% of patients reported at least one AE related to MTX. No unexpected safety concerns were raised during the study. During the study, no unexpected serious AE was reported. Three percent of patients experienced serious AE, predominantly hepatic cytolysis, neutropenia or leucopenia. There was no difference in AE frequency in the bDMARDS group *vs* the MTX optimization group.

Discussion

STRATEGE is the first large, nationwide, observational study exploring therapeutic strategies in RA patients treated with MTX monotherapy, and requiring a treatment modification for clinical, functional, structural and/or therapeutic reasons. The two major strategies were (group 1) MTX monotherapy optimization (72%) and (group 2) initiation of a bDMARD (16%), generally associated with MTX. After 6 months, both strategies appeared to be equally successful in improving disease activity (DAS28), physical function, pain and patient satisfaction.

The introduction of the treat-to-target (T2T) principal, with intensive monitoring and clearly defined therapeutic strategies, has contributed to major improvements in the treatment of RA patients [11]. Over the past two decades, several studies have searched for the optimal strategy to apply in early-diagnosed RA patients [12–14]. A recently published analysis on patients selected from the Measurement of Efficacy of Treatment in the "Era of Outcome" in Rheumatology (METEOR) international registry partly addressed this question in a real-life setting [15, 16]. Patients were included after failure on MTX monotherapy and were divided into three groups: csDMARDs ± MTX, MTX + glucocorticoids and bDMARD ± MTX. Patients were followed over 1 year of maintenance treatment. After propensity score adjustment, this study showed that bDMARD ± MTX strategy was more effective than csDMARDs ± MTX or MTX + glucocorticoids in decreasing disease activity, seeming to contradict our findings. Moreover, a bDMARD-based strategy appeared to present better treatment-survival results. However, in this study, MTX monotherapy was already optimized before inclusion. The most frequent STRATEGE option, consisting of MTX monotherapy optimization by dose raising and/or parenteral administration, was not explored in the METEOR analysis.

In our real-life study, MTX monotherapy optimization showed equally effective results on DAS28 and HAQ-DI in almost three-quarters of the patients when compared with bDMARDs initiation ± MTX. Indeed, several studies have shown that MTX optimization is a valuable choice with numerous benefits, potentially avoiding or at least delaying the introduction of costly targeted therapies [17, 18]. For instance, the efficacy of MTX dose optimization was recently demonstrated in 314 RA patients from the early arthritis Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort receiving MTX as a first DMARD (53%) [mean dose 12.2 (3.8) mg/week]. Only 26.4% had optimal MTX dose (defined as initial dose ≥10 mg/week for the first 3 months, with escalation to ≥20 mg/week or 0.3 mg/kg/week at 6 months if DAS28 remission was not obtained). In this cohort, the route of MTX administration was mainly oral (96.8% of patients). After adjustment, the optimal MTX dose was significantly more effective than a non-optimal dose in reaching remission and improving function in RA patients at 1 and 2 years (ACR-EULAR remission at 1 year: odds ratio = 4.28, 95% CI 1.86, 9.86) [15].

Another way to optimize MTX is parenteral administration. S.c. MTX has shown improved clinical efficacy [19], improved bioavailability, especially at doses >15 mg/week [20], and improved treatment survival, when compared with oral MTX [21–23]. Moreover, a retrospective cohort study on >7000 patients showed that the use of s.c. MTX, compared with oral, was associated with longer duration of MTX monotherapy before addition/switching to bDMARDs [18]. Although no randomized controlled trials have yet directly compared s.c. MTX monotherapy *vs* targeted therapies ± MTX, several observational analyses have shown that the first option was more cost effective for patients and for society as a whole [21, 24, 25].

The second most frequently used strategy in our study was bDMARD ± MTX, applied to about one-sixth of patients, preferably patients with slightly higher DAS28 and pain. More of them presented with structural damage, extraarticular manifestations and were unsatisfied with their current treatment compared with patients using other strategies. Literature data are scarce on current practice regarding MTX prescription at the moment of biologic initiation. One recent US study addressed this question, analysing Symphony Health Solutions registry data from 2009 to 2014 [8]. It showed that, consistent with our results, biologics tended to be initiated while MTX was still suboptimally dosed (15.3–15.9 *vs* 17.4 mg/week in STRATEGE). The s.c. route was chosen in only 13–16% in patients from the Symphony Health Solutions registry *vs* 56% of s.c. MTX in STRATEGE at the moment of bDMARD initiation. The higher proportion of MTX optimization in our study could be because the STRATEGE study inclusions started at the end of the inclusion period of the American registry. In our study, in contrast to patients with a MTX optimization, the group who switched to bDMARD seemed to have a former history of optimization: 56 *vs* 25.3% of s.c. administration and higher dose level, in particular in the range of dose $\geq$ 20 mg/week (49.1 *vs* 17.1%). In these patients, MTX dose was $\leq$15 mg/week for 45.7% of them and s.c. administration was not used in 44%, therefore it is likely that further MTX optimization was possible.

Finally, we found that MTX was maintained in 96% of cases upon bDMARD initiation, with no change in dose or route in 69% of cases, in line with European and National guidelines [2, 3]. However, it remains unknown whether MTX is maintained throughout the bDMARD (and recently targeted synthetic DMARD) treatment duration.

The STRATEGE study was the first investigation of current practice treatment options and their 6-month impact on RA bDMARD-naïve patients with inadequate response to MTX initial monotherapy. It emphasized the benefit of MTX monotherapy dose/and route optimization, showing the same efficacy results as the other strategies, but being more cost effective and confirming the importance of the T2T principle. We also observed that at the moment of bDMARD initiation, MTX was still suboptimally dosed and that the s.c. route was underutilized, leaving room for improvement, potentially leading to biologic treatment sparing and/or delay.

One of the strengths of this study is that we included a wide spectrum of patients with RA. The STRATEGE study aimed to include all patients with RA with inadequate response to MTX monotherapy and bDMARD-naïve regardless of disease level, age and sex, reflecting the real-life setting. Our study has some limitations. We tried to include all baseline covariates associated with treatment assignment and/or those affecting outcome. However, some confounders may have been omitted, although propensity scoring was done to reduce selection bias between groups.

The two most common therapeutic strategies should be compared with caution. It is not possible to exclude that the study is underpowered to detect a difference between the two strategies due to the lower proportion of bDMARD patients (117 *vs* 519 in the MTX monotherapy optimization strategy).

However, the absolute DAS28 change difference between MTX optimization group and biologics group was 0.36 (non-significant), and the absolute HAQ change difference was 0.11 (non-significant), below the minimal clinically important difference [26]. In addition, the biologic cohort had higher baseline values so more regression to the mean is to be expected.

The results of our study provide some evidence that MTX monotherapy optimization in patients with RA in a real-life setting could to be equally successful at 6 months in improving disease activity, physical function, pain and patient satisfaction as initiation of a bDMARD combined with MTX. These data suggest that efforts are needed to achieve a better use of MTX for RA (initiation during the first 3 months and with optimization). The STRATEGE study has shown an important role for MTX treatment optimization before initiation of a biological treatment and emphasizes the importance of a T2T strategy. By enhancing our knowledge of the use of MTX for RA, we will be able to optimize the use of this key drug in clinical practice and improve the well-being of our patients.

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Data availability statement

The dataset can only be shared through a controlled access; the reuse of these health data at the individual level would require an agreement with Nordic Pharma (helene.herman-demars@nordicpharma.com), and application to the French Health Data Hub (https://www.health-data-hub.fr/)

Supplementary data

Supplementary data are available at *Rheumatology* online.

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