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EXTENDED REPORT

Optimal methotrexate dose is associated with better clinical outcomes than non-optimal dose in daily practice: results from the ESPOIR early arthritis cohort

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ABSTRACT

Background Although methotrexate (MTX) is the consensual first-line disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis (RA), substantial heterogeneity remains with its prescription and dosage, which are often not optimal.

Objective To evaluate the symptomatic and structural impact of optimal MTX dose in patients with early RA in daily clinical practice over 2 years.

Methods Patients included in the early arthritis ESPOIR cohort who fulfilled the ACR-EULAR (American College of Rheumatology/European League against Rheumatism) criteria for RA and received MTX as a first DMARD were assessed. Optimal MTX dose was defined as ≥10 mg/week during the first 3 months, with escalation to ≥20 mg/week or 0.3 mg/kg/week at 6 months without Disease Activity Score in 28 joints remission. Symptomatic and structural efficacy with and without optimal MTX dose was assessed by generalised logistic regression with adjustment for appropriate variables.

Results Within the first year of follow-up, 314 patients (53%) with RA received MTX as a first DMARD (mean dose 12.2±3.8 mg/week). Only 26.4% (n=76) had optimal MTX dose. After adjustment, optimal versus non-optimal MTX dose was more efficient in achieving ACR-EULAR remission at 1 year (OR 4.28 (95% CI 1.86 to 9.86)) and normal functioning (Health Assessment Questionnaire ≤0.5; OR at 1 year 4.36 (95% CI 2.03 to 9.39)), with no effect on radiological progression. Results were similar during the second year.

Conclusion Optimal MTX dose is more efficacious than non-optimal dose for remission and function in early arthritis in daily practice, with no impact on radiological progression over 2 years.

INTRODUCTION

Even in the current era of biological or targeted therapies, methotrexate (MTX) remains the initial recommended disease-modifying antirheumatic drug (DMARD) and is widely prescribed for patients with rheumatoid arthritis (RA). Recent national and international recommendations support the use of MTX as the first-line DMARD for RA because of its substantial effectiveness, acceptable safety and low cost.[1–3] However, despite more than two decades of experience with the drug, considerable heterogeneity exists in rheumatologists' prescription behaviours, including the dosage and route of administration. In controlled studies of first-line biological therapy for RA, more than one-third of patients achieved clinical remission with MTX alone, but another one-third had no treatment response.[4–7] The absence of response may indicate a primary lack of efficacy or suboptimal MTX use. However, because randomised controlled studies may not reflect current clinical practice, the results should be interpreted with caution.

Starting MTX at least 10 mg/week orally, escalating with 5 mg/month to 25–30 mg/week, or the highest tolerable dose, with a subsequent switch to subcutaneous administration in case of inadequate response, seems to be the optimal evidence-based dosing and route recommendation for MTX for RA.[3 8] However, evidence is scarce concerning the impact of optimal MTX dose on symptoms and structural damage in early RA in daily practice.

We aimed to describe the optimisation of MTX in a large cohort of patients with early RA and to evaluate its symptomatic and structural impact over 2 years in a real-life setting.

PATIENTS AND METHODS

Patients

Between December 2002 and March 2005, up to 813 patients with early arthritis from 14 French regional centres were included in the ESPOIR cohort.[9] Inclusion criteria were ages 18–70 years, more than two swollen joints for >6 weeks and <6 months, suspected or confirmed diagnosis of RA and no previous intake of DMARDs or glucocorticoids (except if <2 weeks). Patients were excluded if the referring physician judged that they had other clearly defined inflammatory rheumatic diseases. Each centre acted as an observational centre and did not interfere with patient treatment, except if managing care of a patient. In this study, we excluded patients who were included in randomised controlled trials and patients not fulfilling the ACR-EULAR (American College of Rheumatology/European League against Rheumatism) criteria for RA at baseline. We considered only patients fulfilling the ACR-EULAR criteria for RA at baseline and receiving MTX as a first DMARD within the first year of follow-up (figure 1).

Patients were followed up every 6 months during the first 2 years. At baseline and at each visit, data for a set of clinical and biological variables were recorded, including the Disease Activity Score in 28 joints (DAS28),[10] Simplified Disease Activity Index (SDAI)[11] and Health

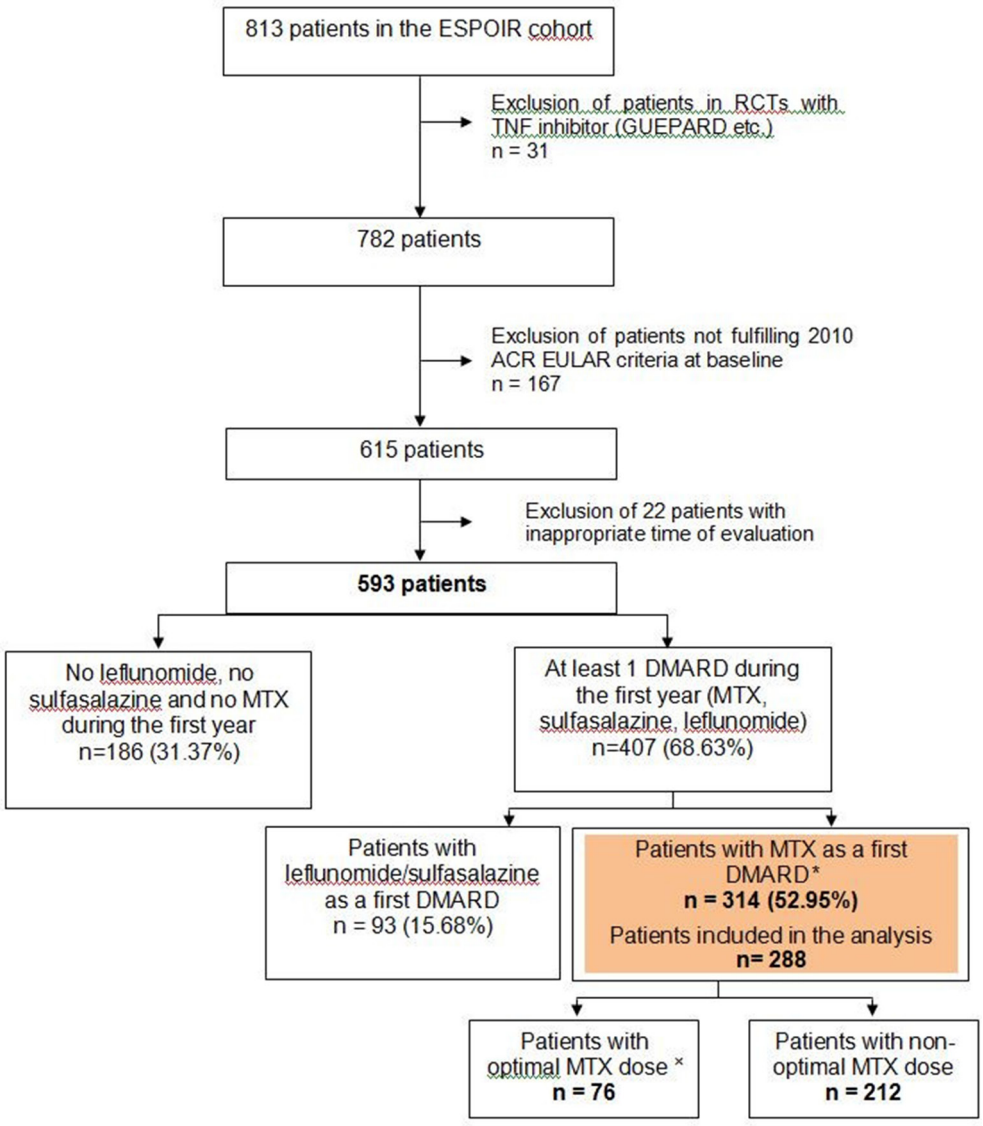

Figure 1 Flow of patients in the study. *Two patients started MTX in combination with leflunomide (n=1) and sulfasalazine (n=1). ×Introduction during the first 3 months after inclusion in the ESPOIR cohort, initially received at least by 10 mg/week and achieving at least 20 mg/week or 0.3 mg/kg/week at 6 months with DAS28 >2.6 noted at the 6-month visit in the ESPOIR cohort (or any dose noted at month 6 with DAS28 <2.6). ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; MTX, methotrexate; RCT, randomised controlled trial; TNF, tumour necrosis factor.

Assessment Questionnaire (HAQ).[12] All comorbidities and toxic effects were not systematically reported in the ESPOIR cohort. Data were collected on the alanine transaminase (ALT) and aspartate transaminase (AST), gamma-glutamyl-transpeptidase at M0 and M6, blood creatinine level at M0, severe gastrointestinal events (haemorrhage, perforation, ulcer) at M0 and M6, and bronchitis and chronic obstructive pulmonary disease at M0 and M6. However, all the patients were monitored by their treating rheumatologist and have been investigated more frequently in agreement with the recommendations.

Baseline and 1 and 2-year hand and foot radiographs were read by one experienced reader in their known chronological order, with blinding to patient identity, characteristics and treatment. Structural damage quantification involved the modified Sharp/van der Heijde score (mSHS).[13]

Optimal MTX dose was defined as fulfilling the following three criteria: (1) MTX introduction during the first 3 months after inclusion in the ESPOIR cohort; (2) initial dosage ≥10 mg/week; and (3) achieving ≥20 mg/week or 0.3 mg/kg/week MTX with DAS28 >2.6 at 6 months (or any dose with DAS28 <2.6 at 6 months).

The benefits of optimal MTX dose at 1 and 2 years of follow-up were evaluated as the proportion of patients (1) in remission according to the ACR-EULAR Boolean,[14] SDAI[11] and DAS28[10] definitions; (2) with normal functioning (ie, HAQ≤0.5); and (3) with no rapid radiographic progression, defined as ΔSHS score <5 per year.[15]

The reproducibility of the radiographic assessment was assessed in the ESPOIR cohort: intraclass correlation coefficients were >0.99 for both status and change scores. The smallest detectable change was calculated as 1.0 SHS unit.[16]

The protocol of the ESPOIR cohort study was approved by the Ethics Committee of Montpellier, France (no. 020307). All patients gave their signed informed consent before inclusion.

Statistical analysis

Data are described with descriptive statistics (mean (SD), median (IQR), minimum, maximum) and distribution of MTX doses. The route of administration was described. We compared baseline characteristics of patients by optimal and non-optimal MTX dose. Qualitative variables were compared by χ^2 test or Fisher's exact test as appropriate and quantitative variables by one-way analysis of variance or Mann–Whitney U test as appropriate.

Multivariate logistic regression was used to evaluate the symptomatic and structural efficacy of optimal MTX dose after adjustment, estimating ORs and 95% CIs. Variables potentially associated with optimal MTX dose were first analysed by bivariate analysis, then variables significant at $p \leq 0.20$ were included in the multivariate logistic regression model. Centre (hospital) and other variables known to be clinically relevant or previously used in the literature were included in the model.[17 18]

To assess the robustness of the main conclusions, sensitivity analyses were performed by mSHS score at baseline instead of presence of erosion, or DAS28 at baseline instead of swollen joint count (SJC).

All analyses involved use of SAS V.9.3 (SAS Institute). $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the population

Within the first year of follow-up, 314 of 593 patients (53%) with RA received MTX as a first DMARD (figure 1). Optimal MTX dose could be analysed in 288 patients: table 1 shows their demographic and baseline clinical characteristics. In 26 patients, optimal MTX dose could not be determined because of lack of data or inappropriate time point of evaluation, with no difference from patients included in the study (shown in online supplementary table A).

Optimal MTX dose

The mean dose of MTX at initiation was 12.2±3.8 mg/week (median 12.5, IQR 10.0–15.0, range 2.5–25 mg/week). Figure 2A shows the distribution of MTX doses at initiation. The mean dose of MTX during the first 6 months was 12.6±3.8 mg/week (median 12.5, IQR 10.0–15.0, range 2.5–25 mg/week). Figure 2B shows the distribution of the MTX doses at 6-month follow-up. The route of administration was mainly oral (96.8% of patients during the first year). Overall, 17.2% of patients had their MTX dose escalated during the first 6 months. During the first year, only 65% of the patients received folic acid supplementation (mean dose 13.0±4.8 mg/week).

Among the 288 patients, 263 (91.3%) received at least 3 months of MTX during the first 6 months and 79 (27.4%) initially received at least 10 mg/week, with escalation to ≥20 mg/week or 0.3 mg/kg/week at 6 months with DAS28 >2.6. In total, 76 patients (26.4%) fulfilled all criteria for optimal MTX dose and therefore were considered to have optimal dose. Optimal MTX dose was initiated in young patients with high C-reactive protein (CRP) level (table 1). At 6 months, more patients received folic acid supplementation with optimal than non-optimal MTX dose: 63.2% vs 49.1% (p=0.0346).

During the first year, the proportion of synthetic DMARD (sDMARD) combinations was greater with optimal than non-optimal MTX dose: 25% (n=19) vs 10.4% (n=22) (p=0.0035). These combinations were varied (including only one triple therapy MTX+salazopyrine+hydroxychloroquine with optimal MTX dose) (shown in online supplementary table B).

Table 1 Characteristics of patients in ESPOIR cohort included in this study of MTX use at baseline (n=288)

Characteristic	Optimal MTX dose* (n=76)	Non-optimal MTX dose (n=212)	p
Age (years)	44.5±12.6	50.3±11.3	**0.0008**
Female sex, n (%)	56 (73.7%)	163 (76.9%)	0.57
Symptom duration (months)†	8.8±9.7	7.7±9.2	0.20
Smoking	31 (40.8%)	104 (49.1%)	0.22
DAS28	5.3±1.3	5.5±1.2	0.057
SJC	7.5±5.7	8.8±5.7	**0.04**
TJC	7.8±6.7	10.5±7.4	**0.0025**
HAQ	1.1±0.7	1.06±0.7	0.63
C-reactive protein level‡	28.2±46.8	21.0±29.5	**0.02**
Rheumatoid factor positivity, n (%)‡	49 (64.5%)	131 (61.8%)	0.68
Anti-CCP2 antibodies positivity, n (%)‡	48 (63.2%)	116 (54.7%)	0.20
Erosions present	24 (33.3%)	92 (45.1%)	0.82
SHS score	5.9±8.3	5.7±7.3	0.75
1987 ACR criteria	57 (75%)	190 (89.6%)	**0.0017**
Use of corticosteroids in the first year§	10 (13.5%)	34 (16.2%)	0.58
Use of corticosteroids during the second year¶	4 (5.71%)	33 (17.01%)	**0.0255**
Combination with synthetic DMARDs	19 (25%)	22 (10.4%)	**0.0035**
Use of biological DMARDs			
During the first year	9 (11.8%)	16 (7.6%)	0.25
During the first 2 years	11 (14.5%)	30 (14.2%)	0.95
MTX dose			
At initiation (mg/week)	14.90±4.48	11.18±3.12	**<0.0001**
At 6 months (mg/week)	15.09±4.42	11.68±3.13	**<0.0001**
Escalation between 6 and 12 months	11 (14.47%)	52 (24.53%)	0.069
Folic acid supplementation at 6 months	48 (63.16%)	104 (49.06%)	0.0346

Data are mean±SD or n (%). Significant results are in bold type.
*Optimal MTX dose defined as fulfilling the following three criteria: (1) MTX introduction during the first 3 months after inclusion in the ESPOIR cohort; (2) initial dosage ≥10 mg/week; and (3) achieving ≥20 mg/week or 0.3 mg/kg/week MTX with DAS28 >2.6 at 6 months (or any dose with DAS28 <2.6 at 6 months).
†Symptom duration defined from the appearance of the first fixed swollen joint.
‡Baseline C-reactive protein level (normal <10 mg/L); IgM and IgA rheumatoid factor (ELISA, Menarini, France; positive >9 UI/mL) and anti-CCP2 antibodies (ELISA, DiaSorin, France; positive >50 U/mL) were detected in all patients by using the same technique in a central lab (Paris-Bichat).
§At least 7.5 mg/day equivalent prednisone for more than 3 months in the first year.
¶At least 7.5 mg/day equivalent prednisone for more than 3 months in the second year.
ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; MTX, methotrexate; SHS, Sharp/van der Heijde score; SJC, swollen joint count; TJC, tender joint count.

Among the 288 patients receiving MTX as the first DMARD, 240 (83.3%) were still receiving MTX at 12 months, with a mean dose of 15.33±4.26 vs 13.06±3.63 mg/week with optimal versus non-optimal MTX dose (p<0.0001), and 216 (75%) at 24 months, with a mean dose of 14.37±4.09 vs 13.64±4.0 mg/week with optimal than non-optimal MTX dose (p=0.227).

Optimal MTX dose, comorbidities and toxicities

At baseline, the optimal and non-optimal MTX dose groups did not differ in comorbidities (blood creatinine level, liver tests,

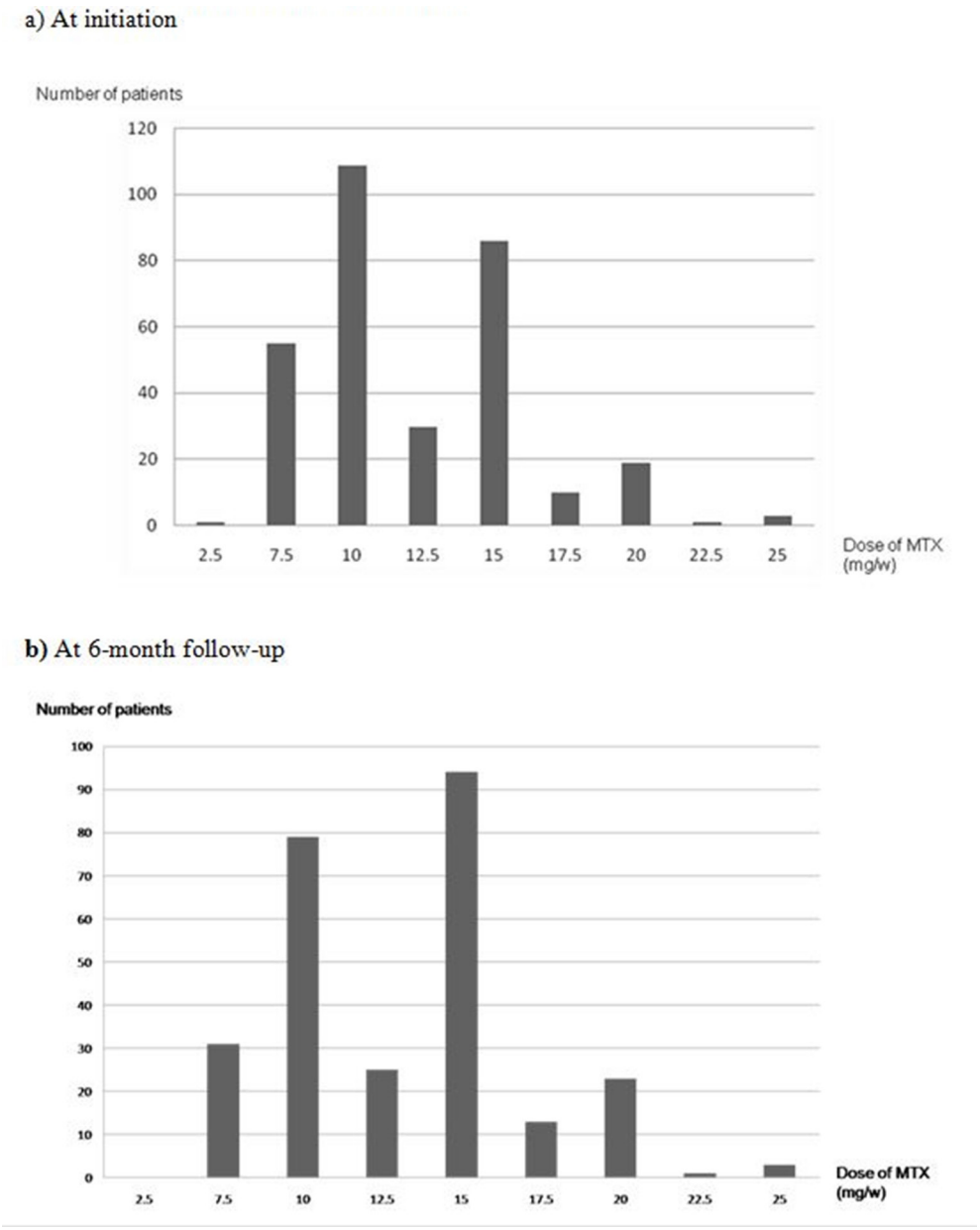

Figure 2 Distribution of the dose of methotrexate (MTX) at initiation (a) and at 6-month follow-up (b).

severe gastrointestinal events, bronchitis and chronic obstructive pulmonary disease). The toxic effects experienced by each group were limited mainly to transaminitis, severe gastrointestinal distress and bronchitis, with a trend to more abnormal level of AST and significantly more abnormal level of ALT at 6 months with optimal than non-optimal MTX dose but no difference in level ≥2 upper limit of normal (ULN) or ≥3 ULN (table 2).

Effect of optimal MTX dose on disease activity and function

On bivariate analysis, optimal MTX dose was associated with being in remission (whatever the definition used: Boolean remission, DAS28 or SDAI) and achieving normal functioning at 1 and 2 years (table 3). After adjustment (on centre, age, CRP level, SJC, positivity for rheumatoid factor (RF) or anti-CCP2 antibodies, presence of erosions, smoking, HAQ score, 1987 ACR criteria), optimal MTX dose was more efficient than non-optimal dose for achieving remission (whatever the definition used: Boolean remission, DAS28 or SDAI) and normal functioning at 1 and 2 years: ACR-EULAR remission at 1 year (OR 4.28 (95% CI 1.86 to 9.86)), normal functioning (HAQ≤0.5; OR at 1 year 4.36 (95% CI 2.03 to 9.39)) (table 3).

Effect of optimal MTX dose on radiological progression

The mean SHS score at baseline was 5.6±7.6 units (median 3 (IQR 8)). The mean change in radiographic progression at 1 year was 4.0±5.1 units (median 2 (IQR 6)). Many patients (n=170, 66.9%) showed radiographic progression (ΔmSHS>1 over 1 year), and 76 (29.9%) showed rapid radiographic progression of at least 5 units over 1 year. The mean change in radiographic progression between 1 and 2 years was 3.01±7.50 (median 0 (IQR 3)). Many patients (64.3%) did not show any radiographic progression over the second year, but 20.7% showed rapid radiographic progression during year 2.

On bivariate analysis, absence of rapid radiographic progression did not differ with optimal and non-optimal MTX dose. Results were similar after adjustment on centre, age, CRP level, SJC, positivity for RF or anti-CCP2 antibodies, presence of erosions, smoking, HAQ score and 1987 ACR criteria (table 3).

Table 2 Optimal MTX dose and comorbidities/toxic effects

Comorbidities/toxicities	Optimal MTX dose* (n=76)	Non-optimal MTX dose (n=212)	p
At baseline			
Transaminitis, n (%)			
AST≤30 U/L	6 (7.9%)	24 (11.5%)	0.514
30 U/L<AST<60 U/L	69 (90.8%)	187 (88%)	0.672
AST≥60 U/L	1 (1.3%)	1 (0.48%)	0.459
AST≥90 U/L	0 (0%)	1 (0.48%)	1
ALT≤35 U/L	7 (9.2%)	24 (11.5%)	0.673
35 U/L<ALT<70 U/L	69 (90.8%)	186 (87.5%)	0.536
ALT≥70 U/L	0 (0%)	2 (0.96%)	1
ALT≥105 U/L	0 (0%)	1 (0.48%)	1
γ-GT≤45 U/L	20 (26.3%)	61 (29.6%)	0.767
γ-GT level, U/L	37.7±42.2	43.3±54.4	0.416
Blood creatinine level, µmol/L	77.0±17.5	72.9±16.8	0.072
Severe gastrointestinal events (haemorrhage, perforation, ulcer)	2 (2.6%)	15 (7.1%)	0.255
Bronchitis and chronic obstructive pulmonary disease	1 (1.3%)	0 (0%)	0.264
At M6			
Transaminitis, n (%)			
AST≤30 U/L	6 (7.9%)	36 (17.2%)	0.059
30 U/L<AST<60 U/L	69 (90.8%)	172 (81.1%)	0.069
AST≥60 U/L	1 (1.3%)	4 (1.91%)	1
AST≥90 U/L	0 (0%)	0 (0%)	1
ALT≤35 U/L	7 (9.2%)	39 (18.6%)	0.069
35 U/L<ALT<70 U/L	69 (90.8%)	167 (78.8%)	**0.023**
ALT≥70 U/L	0 (0%)	6 (2.86%)	0.346
ALT≥105 U/L	0 (0%)	4 (1.9%)	0.576
Severe gastrointestinal events (haemorrhage, perforation, ulcer)	0 (0%)	3 (1.4%)	0.569
Bronchitis and chronic obstructive pulmonary disease	1 (1.3%)	0 (0%)	0.264

*Data are mean±SD or n (%). Significant results are in bold type.
ALT, alanine transaminase; AST, aspartate transaminase; M6, 6 months; MTX, methotrexate; γ-GT, gamma-glutamyltranspeptidase.

Sensitivity analyses

Additional analyses, conducted to test the robustness and validity of the approach, gave similar conclusions: with adjustment based on mSHS score at baseline instead of presence of erosions or on DAS28 at baseline instead of SJC, results were similar (data not shown).

Other analyses were performed with two alternative definitions of MTX optimal dose: (1) initiation of MTX during the first 3 months of follow-up, at ≥10 mg/week, and achieving ≥20 mg/week or 0.3 mg/kg/week for a minimum of 2 months during the first 6 months, with DAS28 >2.6 at M6, or any dose with DAS28 <2.6 at M6; and (2) same with achieving ≥20 mg/week or 0.3 mg/kg/week for a minimum of 3 months during the first 6 months, with DAS28 >2.6 at M6, or any dose with DAS28 <2.6 at M6. Results were similar for 73 patients with optimal MTX dose by the first definition and 72 patients with optimal MTX dose by the second definition.

DISCUSSION

This study is the first to describe the optimal dose of MTX in a large cohort of patients with early RA in daily clinical practice and to evaluate its symptomatic and structural efficacy in a real-life setting over 2 years. We found optimal MTX dose in only 26.4% of 288 patients. The definition of optimal MTX dose (initiation of MTX during the first 3 months of follow-up, at ≥10 mg/week and achieving ≥20 mg/week or 0.3 mg/kg/week at 6 months with DAS28 >2.6, or any dose noted at month 6 with DAS28 <2.6) is based on the available literature data: international guidelines for the use of MTX, starting with ≥10 mg/week orally, escalating with 5 mg/month to 25–30 mg/week, or the highest tolerable dose, with a subsequent switch to subcutaneous administration with insufficient response.[3 8] Because of the very limited number of patients who used a subcutaneous form of MTX in the ESPOIR cohort, we did not use this administration form in defining optimal MTX dose. Of note, patients were included in the ESPOIR cohort between December 2002 and March 2005, before EULAR and 3E initiative guidelines.[1 8]

Table 3 Symptomatic and structural efficacy of MTX optimisation

Outcomes	Optimal MTX dose n=76 n (%) at M12 n (%) at M24	Non-optimal MTX dose n=212 n (%) at M12 n (%) at M24	aOR* M0–M12 (95% CI)	aOR* M12–M24 (95% CI)
ACR-EULAR Boolean remission	20 (27.4) 23 (32.4)	16 (8.0) 34 (18.1)	4.28 (1.86 to 9.86)	2.75 (1.33 to 5.70)
SDAI remission	23 (31.9) 27 (38.0)	27 (10.8) 33 (17.6)	5.14 (2.27 to 11.60)	3.08 (1.54 to 6.14)
DAS28 remission	42 (58.3) 40 (57.1)	57 (28.8) 74 (39.4)	4.09 (2.01 to 8.29)	2.71 (1.35 to 5.45)
Normal functioning†	56 (73.7) 52 (68.4)	107 (50.5) 110 (51.9)	4.36 (2.03 to 9.39)	2.02 (1.03 to 3.96)
Absence of rapid radiographic progression (ΔSHS score <5)	46 (68.7) 46 (75.4)	132 (70.6) 145 (80.6)	1.17 (0.60 to 2.28)	1.70 (0.79 to 3.65)

*aOR, adjusted on age, centre, swollen joint count, C-reactive protein level, positivity for anticitrullinated protein antibody or rheumatoid factor, erosion, smoking, Health Assessment Questionnaire (HAQ) score, 1987 American College of Rheumatology criteria.
†HAQ≤0.5.
ACR, American College of Rheumatology; aOR, adjusted OR; DAS28, Disease Activity Score in 28 joints; EULAR, European League Against Rheumatism; M12, 12 months; M24, 24 months; M0, baseline; MTX, methotrexate; SDAI, Simplified Disease Activity Index; SHS, Sharp/van der Heijde score.

Of note, significantly more patients received folic acid supplementation with optimal than non-optimal MTX dose at 6 months. Side effects that could have been avoided with folate supplementation (stomatitis, gastrointestinal distress, transaminitis, and so on) could have influenced the ability of patients to accelerate MTX. Prescription of at least 5 mg folic acid per week with MTX therapy is strongly recommended.[3 8]

Second, we found more optimal dose of MTX in younger than older patients. This fact could be related to at least two elements: (1) the incidence of comorbidities and comedications increasing with age, which can lead to a bias of indication and a risk of undertreatment of older patients, and (2) increased MTX toxicity in older patients limiting the ability to increase the weekly dose.

Third, in daily practice, optimal MTX dose was more efficacious than non-optimal MTX dose in terms of remission and function in early RA but had no impact on radiographic progression over 2 years. In a previous study,[19] we confirmed the 6-month symptomatic and 12-month structural efficacy of MTX in early RA in daily clinical practice despite the suboptimal use of MTX. With optimal MTX dose, the additional benefit is essentially for clinical remission and function more than structure. However, the structural progression in the ESPOIR cohort was quite low, which may explain the lack of benefit of MTX optimisation on structural damage progression and a limited number of patients in the optimal MTX dose group may indicate lack of power.

One of the strengths of this study is that we included a wide spectrum of patients with early RA. The ESPOIR cohort aimed to include all patients with early arthritis regardless of disease level, age and sex, so our study reveals the performance of optimal MTX dose in a real-life setting. Because of the large number of baseline variables available in the ESPOIR cohort, the possibility of failure to include confounding covariates was reduced.

Our study has some limitations. We tried to include all baseline covariates associated with treatment assignment and/or that affect the outcome. However, ensuring that some confounders were not omitted is difficult. Because of a change in patient condition, data at baseline do not necessarily represent their condition at the time of the treatment decision. With a predetermined visit for follow-up, the information on DAS28 between two visits when the treatment is optimised is lacking. We extrapolated that if the patient was not in DAS28 remission at 6 months, the probability was high that the remission was not achieved before and so the MTX dose should be escalated to ≥20 mg/week or 0.3 mg/kg/week at month 6.

The description of the toxic effects experienced by each group was limited mainly to transaminitis, severe gastrointestinal distress and bronchitis, with no difference between groups except for moderate transaminitis <2 ULN at 6 months. Data on stomatitis, rash, brain fog and non-severe gastrointestinal distress were not collected, so determining to what extent common MTX toxic effects affected the ability to increase the weekly dose was difficult. However, whatever the reason of not achieving MTX optimal dose, our study is clearly showing that optimal MTX dose is more efficacious than non-optimal dose for remission and function in early arthritis in daily practice.

The proportion of sDMARD combinations used was greater with optimal than non-optimal MTX dose during the first year, including only one triple therapy with MTX+sulfasalazine+hydroxychloroquine. However, none of these combinations have clearly shown superiority to MTX monotherapy without being combined with corticosteroids.

We found no previous study concerning the use and clinical and structural efficacy of MTX optimisation in early RA in a real-life setting. Observational studies,[16 18 20 21] analysed the effect of early treatment on early RA outcome. Wiles *et al*[18 21] suggested that early MTX treatment (within 6 months of symptom onset) had a beneficial effect on long-term radiographic progression (progression of Larsen score at 5 years) and disability (HAQ score ≥1 at 5 years). However, MTX was used in only 7 of 219 patients, with sulfasalazine being prescribed in 60.7%. In a large patient population with RA, Kyburz *et al* showed that radiographic progression over 5 years was significantly lower for patients with than without early initiation of DMARDs (within the first year of symptom onset). [20] In a study of the ESPOIR cohort, Lukas *et al* showed that in daily clinical practice, a rapid (within 3 months) DMARD start (including MTX, sulfasalazine, leflunomide, tumour necrosis factor inhibitors) reduced 12-month radiographic progression.[16] Recently, Hazlewood *et al*[22] compared the effectiveness of starting with oral versus subcutaneous MTX over the first year in a cohort of 666 patients with early RA (417 oral MTX, 249 subcutaneous MTX). Initial treatment with subcutaneous MTX was associated with lower rates of treatment change, no difference in toxicity and some improvement in disease control as compared with oral MTX over the first year in these patients (lower mean DAS28 scores: mean difference (−0.38 (95% CI −0.64 to −0.10)) and small difference in DAS28 remission (OR 1.2 (95% CI 1.1 to 1.3))).[22] In the CONCERTO trial, increasing doses of MTX in combination with adalimumab demonstrated a statistically significant trend in improved clinical outcomes in patients with early RA.[23]

The results of our study help close the gap in evidence that optimal MTX dose in patients with early RA in a real-life setting is more favourable than non-optimal dose in terms of remission and function over 2 years. Such data suggest that efforts are needed to achieve a better use of MTX for early RA (initiation during the first 3 months and at optimal dose). By enhancing our knowledge of the use of MTX for RA, we will be able to optimise the use of this anchor drug in clinical practice and improve the well-being of our patients.

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Optimal methotrexate dose is associated with better clinical outcomes than non-optimal dose in daily practice: results from the ESPOIR early arthritis cohort

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Notes