Original article

Evidence of the symptomatic and structural efficacy of methotrexate in daily practice as the first disease-modifying drug in rheumatoid arthritis despite its suboptimal use: results from the ESPOIR early synovitis cohort

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Abstract

Objective. To describe the use of MTX in early arthritis (EA) in daily clinical practice and to evaluate its 6-month symptomatic efficacy and 12-month structural efficacy.

Methods. Patients included in the French observational ESPOIR cohort were assessed. Evaluation of the symptomatic and structural efficacy was performed by generalized linear regression after adjustment on propensity score (PS) in the group of patients receiving at least 3 months of MTX vs the ones receiving any other treatment except LEF, SSZ or TNF inhibitors.

Results. Within the first 6 months of follow-up of 777 EA patients, 59% received a DMARD, which was MTX in 68% ($N = 313$) of patients. The mean dose of MTX was 12.7 ± 3.8 mg/week. Only 53.7% of the patients received folic acid supplementation. MTX was initiated in patients with more active and severe disease. At 6 months, in unadjusted analysis, patients starting MTX had a significantly higher DAS-28 (3.58 vs 3.23; $P = 0.001$) and a significantly higher HAQ (0.60 vs. 0.48; $P = 0.01$) compared with controls. After adjustment by PS, there were no significant differences. Adjustment for the PS also revealed a statistically significant decrease in the radiological progression at 12 months in the MTX group [total Sharp–van der Heijde score (SHS), 1.05 ± 0.29 vs 2.02 ± 0.29, $P = 0.025$].

Conclusion. This study confirms the symptomatic and structural efficacy of MTX in EA in daily practice despite the non-optimal use of MTX, including low doses and infrequent concomitant folic acid supplementation.

Key words: methotrexate, early arthritis.

Introduction

Even in the current era of biologic targeted therapies, MTX remains the initial preferred anti-rheumatic drug and is widely prescribed for patients with RA. Recent national and international recommendations support the use of MTX as one of the first-line DMARDs for RA, based on its substantial effectiveness, good safety profile and low cost [1–3]. But despite more than two decades of experience, considerable variability exists in the way rheumatologists prescribe MTX therapy, including the dosage and route of administration. More knowledge on the optimal use is needed, as this would benefit RA patients, improve education and facilitate treatment evaluation. In published studies of first-line biologic therapy for RA more than one-third of patients achieved a clinical remission in the control groups treated with MTX alone, but

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another third had no treatment response [4–7]. The absence of a response may indicate either a primary lack of efficacy or a suboptimal MTX regimen. However, as randomized controlled studies may not reflect current clinical practice, the results should be interpreted and extrapolated with caution.

Evidence is scarce concerning the use of MTX and its efficacy on signs and symptoms and structure in early arthritis (EA) in daily practice. That is why we aimed to describe the use of MTX in a large cohort of EA patients in daily clinical practice and to evaluate its short-term (6-month) symptomatic efficacy and 12-month structural efficacy in a real-life setting.

Materials and methods

Patients

Between December 2002 and March 2005, 813 patients with EA from 14 French regional centres were included in the ESPOIR cohort [8]. Inclusion criteria were age 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 steroids (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 in charge of a patient. In this study we decided to exclude patients of the ESPOIR cohort included in randomized controlled trials with anti-TNF ($n = 36$). Thus 777 patients were involved in this analysis.

Patients were followed every 6 months during the first 2 years. At baseline and at each visit, data for a set of clinical and biologic variables were recorded, including that from the DAS for 28 joints (DAS-28), a composite index of disease activity [9], and a functional ability questionnaire, the HAQ [10]. Baseline and 1-year radiographs of hands, wrists and feet from included patients were read according to SHS, blinded to patient identity, patient characteristics and treatment, but with knowledge of the chronological order in order to increase sensitivity to change [11]. The protocol of the ESPOIR Cohort study was approved by the ethics committee of Montpellier, France. All patients gave their signed informed consent before inclusion.

Statistical analysis

Description of MTX intake and folic acid supplementation
MTX intake was defined as at least 3 months of MTX during the first 6 months of follow-up. Descriptive statistics [mean (S.D.), median (interquartile range (IQR)), minimum, maximum] and distributions of the MTX doses were computed. The route of administration was described.

The baseline characteristics of patients taking MTX were compared with those of patients receiving any other treatment, including MTX received for <3 months, during the first 6 months of the follow-up period, except LEF, SSZ or TNF inhibitors. This allowed us to consider as controls patients not receiving any DMARDs that have previously demonstrated a relevant symptomatic and structural effect. Qualitative variables were compared with the chi-square test (Fisher's exact test when appropriate) and quantitative variables with one-way analysis of variance (ANOVA) (Mann–Whitney U-test when appropriate).

Folic acid supplementation was also described [mean (S.D.), median (IQR), minimum, maximum]. To investigate whether folic acid supplementation was adapted to the dose of MTX, Spearman's product–moment correlation was calculated for folic acid dose *vs* dose of MTX.

Propensity score
In cohorts such as the ESPOIR cohort, without fixed treatment protocol, severity and activity of the disease may confound the relationship between MTX and its efficacy on signs and symptoms or radiographic progression (confounding by indication). The theory underlying propensity modelling assumes that the likelihood of MTX introduction, and thus the severity of RA in the opinion of the physician, can be approximated by taking into consideration all variables measured at baseline that the physician may or may not implicitly use to decide to introduce MTX [12]. By adjusting the relationship between MTX introduction and outcomes for individual propensity scores (PSs), confounding by indication can partly be adjusted for. Variables potentially associated with MTX use (*vs* the control group, i.e. patients receiving any other treatment, including MTX received for <3 months during the first 6 months of follow-up period, but except LEF, SSZ or TNF inhibitors) were analysed in a bivariate analysis [13, 14]. Those significant at the 0.30 level or less were selected and included in a multivariate logistic regression model. The centre (hospital) and other variables known to be clinically relevant or previously used in the literature were also included in the model [15, 16]. Balance achieved was assessed by examining the differences in distributions of confounders between the two groups after applying the PS.

Evaluation of the symptomatic and structural efficacy of MTX

The symptomatic efficacy was evaluated using DAS-28 for disease activity and HAQ for functional disability at 6 months. The structural efficacy was evaluated by the radiographic progression (SHS) at 12 months. Paired *t*-tests were used to evaluate the improvement of DAS-28 and HAQ at 6 months in both groups of patients (treated with MTX *vs* controls). Evaluation of the symptomatic and structural efficacy was performed by generalized linear regression without and after adjustment on PS in the group of patients receiving MTX *vs* the controls. Of note, 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 at 1.0 SHS unit [17].

To assess the robustness of the main conclusions, sensitivity analyses were conducted in three ways: (i) by using different PSs; (ii) by using other controls (MTX *vs* no MTX,

MTX *vs* no DMARDs); and (iii) by using another population, i.e. only patients fulfilling the new ACR/European League Against Rheumatism (EULAR) criteria for RA at baseline [18]. All analyses involved the use of SAS v9.1 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

Characteristics of the population

Table 1 shows the demographic and clinical characteristics of the 777 patients in the ESPOIR cohort baseline included in this analysis. In total, 606 (78%) patients fulfilled the new ACR/EULAR criteria for RA at baseline.

MTX intake and folic acid supplementation

Within the first 6 months of follow-up of 777 RA patients, 59% received at least 3 months of a DMARD, which was MTX in 68% ($N = 313$) of patients either as monotherapy (90%) or in combination with other DMARDs. SSZ was chosen in 52 patients and LEF in 28 patients. Other DMARDs (mainly HCQ) were prescribed in 68 patients. The mean dose of MTX at initiation was 12.5 ± 3.9 mg/week (median 12.5, IQR 10.0–15.0) with a minimum value of 5 mg/week and a maximum value of 25 mg/week, resulting in a dose of 0.19 ± 0.06 mg/kg/week (median 0.18, IQR 0.15–0.23) with a minimum value of 0.06 mg/kg/week and a maximum value of 0.34 mg/kg/week. Fig. 1 shows the frequency distribution of the mean doses of MTX at initiation. The mean dose of MTX during the first 6 months was 12.7 ± 3.8 mg/week (median 12.5, IQR 10.0–15.0) with a minimum value of 5 mg/week and a maximum value of 25 mg/week, resulting in a dose of 0.19 ± 0.06 mg/kg/week (median 0.19 IQR 0.15–0.23) with a minimum value of 0.06 mg/kg/week and a maximum value of 0.34 mg/kg/week. Fig. 2 shows the frequency distribution of the mean doses of MTX during the first 6 months. The route of administration was mainly oral (97.4% of patients, $n = 305$). There was an escalation of MTX dose in 13.4% of patients ($n = 42$) during the first 6 months. Of the 313 patients treated by MTX during the first 6 months, 223 (71.3%) were still receiving MTX at 12 months.

MTX was initiated in patients with more active and severe disease (DAS-28 5.39 ± 1.22 *vs* 4.78 ± 1.31; HAQ 1.11 ± 0.68 *vs* 0.84 ± 0.64; anti-CCP2 antibodies positive 49.8% *vs* 25.6%; CRP 24.9 ± 37.4 *vs* 14.9 ± 25.0; presence of at least one erosion 64.5% *vs* 53.0%; all $P < 0.003$) (Table 1).

Folic acid supplementation was given in only 53.7% of the patients. The mean dose of folic acid was 12.7 ± 3.8 mg/week. Correlation with the dose of MTX was moderate ($r = 0.537$; $P < 0.0001$) (Fig. 3).
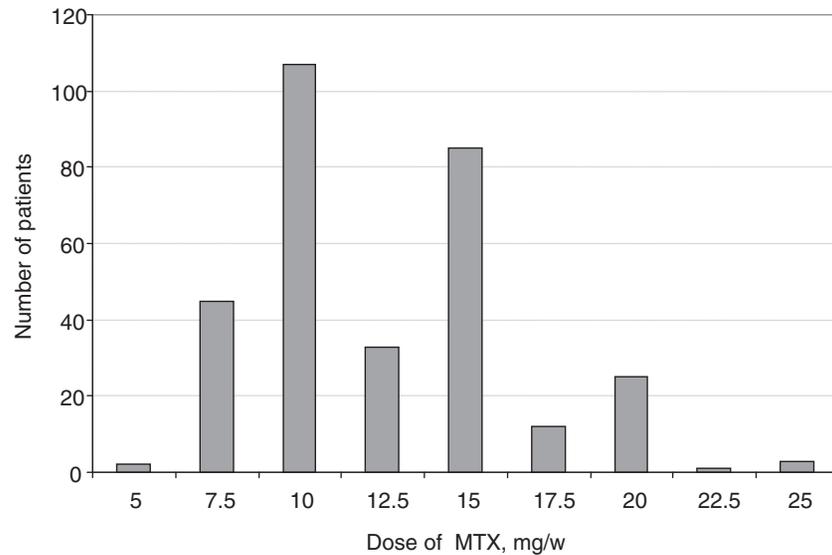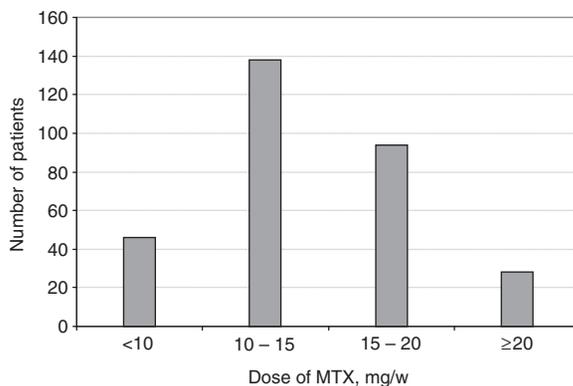
Radiographic progression

The mean SHS at baseline was 5.6 ± 7.6 U (range 0–56), with a median score of 3 (IQR 1–7) units. The mean change of radiographic progression at 1 year was 1.46 ± 4.22 (range 0–37) with a median radiographic

TABLE 1 Characteristics of patients in the ESPOIR cohort included in this study at baseline

Characteristic	All patients ($n = 777$) mean (S.D.)	MTX ($n = 313$) mean (S.D.)	Other treatments except SSZ, LEF and TNF⁻ ($n = 384$)	P^a
Age, years	48.0 (12.7)	48.8 (12.0)	47.2 (13.2)	0.164
Female sex, *n* (%)	598 (77.0)	237 (75.7)	305 (79.4)	0.242
>12 years of education, *n* (%)	245 (31.5)	97 (31.0)	125 (32.6)	0.660
Employed, *n* (%)	492 (63.3)	207 (66.1)	234 (60.9)	0.157
Smoking, *n* (%)	370 (47.6)	155 (49.5)	177 (46.1)	0.368
DAS-28	5.06 (1.30)	5.39 (1.22)	4.78 (1.31)	<0.0001
HAQ	0.96 (0.67)	1.11 (0.68)	0.84 (0.64)	<0.0001
Morning stiffness >60 min, *n* (%)	237 (30.5)	109 (34.8)	99 (25.8)	<0.004
Symptom duration, months	4.7 (5.7)	4.9 (5.9)	4.4 (5.1)	0.037
CRP level[b]	19.8 (32.0)	24.9 (37.4)	14.9 (25.0)	<0.0001
RF, *n* (%)[b]	342 (44.1)	171 (54.6)	134 (35)	<0.0001
Anti-CCP2 antibodies[b], *n* (%)	287 (37)	156 (49.8)	98 (25.6)	<0.0001
Erosion present, *n* (%)	403 (57.7)	191 (64.5)	172 (52.9)	0.003
Use of corticosteroids, *n* (%)[c]	168 (26.0)	97 (35.0)	56 (19.1)	<0.0001
Cumulative mean dose of corticosteroids during the first 6 months, mg	1186.9 (701.5)	1223.9 (719.7)	1119.3 (723.9)	0.180
Cumulative mean dose of corticosteroids during the first year, mg	2448.9 (1249.1)	2439.7 (1117.8)	2454.8 (1488.5)	0.403

[a]Comparison between patients with MTX and patients with other treatments except SSZ, LEF and TNF inhibitors (TNF⁻) at baseline. [b]Baseline CRP level (normal <10 mg/l); IgM and IgA RF (Elisa, Menarini, France; positive >9 UI/ml) and anti-CCP2 antibodies (ELISA, DiaSorin, France; positive >50 U/ml) were detected in all patients using the same technique in a central lab (Paris-Bichat). [c]Use of corticosteroids: at least 7.5 mg/day equivalent prednisone for >3 months in the first year.

Fig. 1 Frequency distribution of the mean dose of MTX at initiation.

Fig. 2 Frequency distribution of the mean dose of MTX over 6 months.

progression of 0 (IQR 0–1) units. Most patients (71.4%) did not show any radiographic progression over 1 year, but 8% showed a severe progression of at least 5 U.

PS

The logistic model used the following variables to estimate the probability of being treated with MTX during the first 6 months: centre (14 classes), age, sex, profession (6 classes), years of education (5 classes), smoking (yes/no), DAS-28, HAQ, morning stiffness (0, ⩽60 min, >60 min), symptom duration, CRP, RF present (yes/no), anti-CCP2 antibodies present (yes/no), erosions present (yes/no), use of corticosteroids (at least 7.5 mg/day equivalent prednisone for >3 months in the first year: yes/no). After adjustment for the PS, there was no difference in baseline characteristics between patients treated with MTX and patients treated with other treatments

(control group) (data not shown). There were 157 missing values for the PS (50 in the MTX group and 107 in the control group). Characteristics of patients with missing values were similar to those of patients without missing values except that patients with available PSs were older (48.7 ± 12.2 vs 45.2 ± 13.9, P = 0.007) and with less functional disability (HAQ 0.93 ± 0.67 vs 1.06 ± 0.68, P = 0.033).

Evaluation of the symptomatic and structural efficacy of MTX

There was a significant improvement in disease activity and HAQ at 6 months in patients treated with MTX: mean DAS-28 at baseline = 5.40 ± 1.22 and mean DAS-28 at 6 months = 3.58 ± 1.38 (P < 0.0001); mean HAQ at baseline = 1.11 ± 0.68 and mean HAQ at 6 months = 0.60 ± 0.56 (P < 0.0001). The patients of the control group also showed significant improvement in disease activity and HAQ at 6 months: mean DAS-28 at baseline = 4.78 ± 1.31 and mean DAS-28 at 6 months = 3.23 ± 1.35 (P < 0.0001); mean HAQ at baseline = 0.84 ± 0.64 and mean HAQ at 6 months = 0.48 ± 0.54 (P < 0.0001).

In the unadjusted analysis, patients starting MTX within 6 months showed a significantly higher DAS-28 (3.58 ± 0.08 vs 3.23 ± 0.08, P = 0.001) and a significantly higher HAQ (0.60 ± 0.03 vs 0.48 ± 0.03, P = 0.01) at month 6 as compared with controls. After adjustment for the PS, there were no significant differences (Table 2).

In unadjusted analysis, patients starting MTX within 6 months did not show a significant difference in radiographic progression score at 1 year as compared with controls. Adjustment for the PS revealed a statistically significant difference in the change in 1-year SHS: the estimated marginal means (EMMs) (standard error) were 1.05 ± 0.29 U in patients starting MTX within 6 months and 2.02 ± 0.29 U in patients starting other treatments (control

Fɪɢ. 3 Scatter plot of dose of folic acid with dose of MTX.
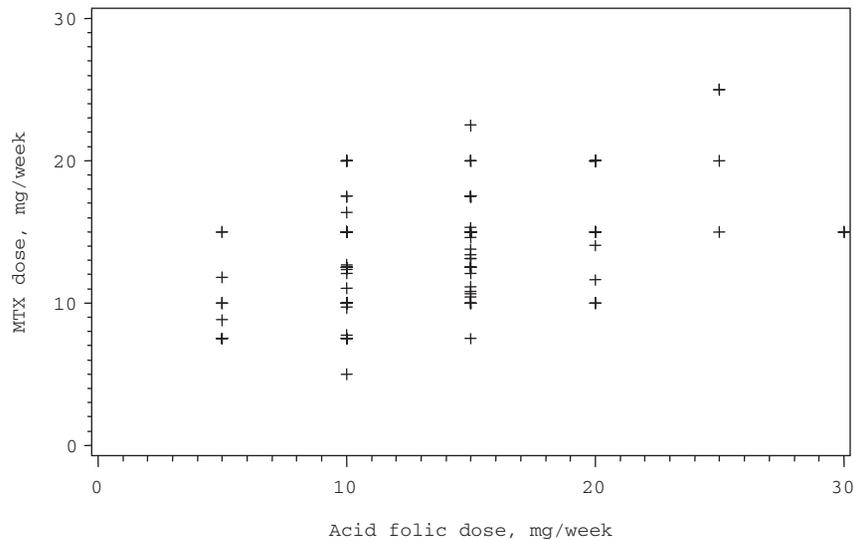
Tᴀʙʟᴇ 2 Symptomatic and structural efficacy of MTX

Outcomes	Unadjusted			After adjustment for the PS		
	MTX	Controls	*P*	MTX	Controls	*P*
DAS-28 at M6, mean (s.ᴅ.)	3.58 (0.08)	3.23 (0.08)	0.001	3.45 (0.08)	3.36 (0.08)	0.423
HAQ at M6, mean (s.ᴅ.)	0.60 (0.03)	0.48 (0.03)	0.010	0.56 (0.03)	0.52 (0.03)	0.424
Radiographic progression score[a] at M12, mean (s.ᴅ.)	1.49 (0.27)	1.52 (0.26)	0.951	1.05 (0.29)	2.02 (0.29)	0.025
Change in erosion score[a] at M12, mean (s.ᴅ.)	1.21 (0.22)	1.28 (0.21)	0.808	0.84 (0.24)	1.72 (0.24)	0.015

[a]Sharp–van der Heijde score. M6: 6 months; M12: 12 months.

group) (*P* = 0.025). Concerning the 1-year change in erosion score, after adjustment for the PS, patients starting MTX within 6 months had less erosion progression than patients starting other treatments, and EMMs were 0.84 ± 0.24 *vs* 1.72 ± 0.24 (*P* = 0.015) (Table 2).

Sensitivity analyses

Additional analyses, conducted in order to test the robustness and validity of the approach, resulted in similar conclusions. When the PS was based on the introduction of MTX *vs* other treatments within 6 months, a decreased radiographic progression was also suggested in patients who had started MTX *vs* those who had not: 1.15 ± 0.28 *vs* 1.76 ± 0.24 SHS units, *P* = 0.113, although the difference was not statistically significant. When the PS was based on the introduction of MTX *vs* no DMARD within 6 months, a decreased radiographic progression was also confirmed in patients who had started MTX *vs* patients without DMARD: 1.09 ± 0.30 *vs* 2.22 ± 0.34 SHS units, *P* = 0.019. When the population was reduced to patients fulfilling the new ACR/EULAR criteria for RA, the trend was similar: 1.19 ± 0.33 *vs* 1.75 ± 0.35 SHS units, *P* = 0.269, although the difference was not statistically significant. Other

approaches (such as the exclusion of the symptom duration and smoking status from the PS) also resulted in similar conclusions (data not shown).

Discussion

This study is the first to describe the use of MTX in a large cohort of EA patients in daily clinical practice and to evaluate its 6-month symptomatic efficacy and 12-month structural efficacy in a real-life setting using the PS.

We have demonstrated several important elements. First, use of MTX in daily clinical practice was not optimal: only 40% of patients with EA received MTX during the first 6 months of follow-up. The mean dose was lower than recommended: 12.7 ± 3.8 mg/week and 60% of patients (*n* = 184) received <15 mg/week. There was an escalation of dose only in 13.4% of patients (*n* = 42) during the first 6 months. Furthermore, only 53.7% of the patients received folic acid supplementation [19]. It should be noted that patients were included in the ESPOIR cohort between December 2002 and March 2005, before the EULAR and 3E initiative guidelines [2, 19].

Secondly, despite this non-optimal use of MTX, this study confirms the 6-month symptomatic and 12-month structural efficacy of MTX in EA in daily clinical practice. The statistically significant higher disease activity observed at month 6 in the patients who started MTX before month 6, and its disappearance after adjustment for the PS, indicated the symptomatic efficacy of MTX. Adjustment for the PS revealed a statistically significant decrease in the radiological progression at 12 months in the MTX group *vs* controls.

One of the strengths of this study is that a broad group of patients with EA was included. The ESPOIR cohort aimed to include all patients with EA regardless of disease level, age and sex, and thus our study indicates the performance of MTX in a real-life setting. The study also included a large number of patients. Due to the large number of baseline variables available in the ESPOIR cohort, the possibility of unobserved confounding covariates was reduced.

Our study has some limitations. There is a lack of consensus in the literature as to which variables to include in a PS model. Possible sets of variables for inclusion in a PS include the following: all measured baseline covariates, all baseline covariates that are associated with treatment assignment, all covariates that affect the outcome (i.e. the potential confounders), and all covariates that affect both treatment assignment and the outcome (i.e. the true confounders). Brookhart *et al.* [14] suggested that variables that do not affect exposure but that affect the outcome should always be included in the PS model. Furthermore, they noted that including variables that affect exposure but not the outcome will increase the variance of the estimated treatment effect without a concomitant reduction in bias. It should be noted that, in practice, it may be difficult to accurately classify baseline variables into the true confounders, those that only affect the outcome, those that only affect exposure and those that affect neither treatment nor the outcome. In specific settings, the published literature may provide some guidance for identifying variables that affect the outcome. In practice, in many settings, most subject-level baseline covariates likely affect both treatment assignment and the outcome. Therefore it is likely that one can safely include all measured baseline characteristics in the PS model. We tried to include all baseline covariates that are associated with treatment assignment, all covariates that affect the outcome, and all covariates that affect both treatment assignment and the outcome. However, it is difficult to make sure that no confounders had been omitted in the PS. Finally, the PS is built using patients' baseline characteristics. Due to changes in patients' conditions, data at baseline do not necessarily represent the patients' conditions at the time the treatment decisions were made.

Four PS-based methods are used in the medical literature: matching, stratification, regression adjustment and PS weighting [12]. There is no clear consensus as to which method is preferable. Given the size of the study sample, stratification and matching were not selected.

In our analysis, adjustment for PS was deemed to be valid (balance achieved, robustness of the results).

In the literature, no study concerning the use and efficacy of MTX in EA in a real-life setting was found. In a cohort of EA in Norway, MTX was selected as the DMARD of choice for 78% of the patients [20]. But this study did not assess the impact of MTX. Other observational studies [15, 18, 21] analysed the effect of early treatment on early RA outcome. Thus Wiles *et al.* [15, 21] suggested that early treatment (within 6 months of symptom onset) has a beneficial effect on long-term radiographic progression (progression of Larsen score at 5 years) and disability (HAQ score $\geqslant$ 1 at 5 years) after adjusting for the PS. But SSZ was the drug of 'first choice,' being prescribed in 60.7% of patients, and MTX was used in only 7 of 219 patients. Furthermore, short-term efficacy on signs and symptoms and 1-year radiographic progression were not assessed. Diego Kyburz *et al.* [22] showed in a large patient population with RA that the radiographic progression over 5 years is significantly lower in patients with early initiation of DMARD treatment (within the first year of symptom onset). In a recent study on the ESPOIR cohort, Lukas *et al.* [17] showed that in daily clinical practice, a rapid DMARD start (within 3 months) reduces 12-month radiographic progression.

The results of our study add to the sparse evidence that treatment with MTX during the first 6 months in patients with inflammatory arthritis in a real-life setting is favourable with regard to signs and symptoms at 6 months and 1-year radiographic progression. Such results have been observed despite a suboptimal use of MTX and, in particular, a weekly dose lower than the recommended one. Such data suggest that efforts have to be made in order to achieve a better (more frequent and at an optimal dose) use of MTX in early RA.

> ### Rheumatology key messages
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> - MTX is efficacious on 6-month disease activity and disability in EA in a real-life setting.
> - MTX is efficacious on 12-month structural progression in EA in a real-life setting.
> - The use of MTX was suboptimal during the first 6 months in a real-life setting.

Acknowledgements

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