SHORT COMMUNICATION

Folate Supplementation During Methotrexate Therapy: A Population-based Retrospective Cohort Study

Canelle MAZAUD[1] and Laurence FARDET[1,2]*
[1]Department of Dermatology, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, FR-94010 Créteil, and [2]EA 7379, EpiDermE, UPEC Université Paris Est Créteil, Créteil, France. E-mail: laurence.fardet@aphp.fr
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Methotrexate (MTX) is a well-established therapy for many dermatological conditions (e.g. psoriasis) and non-dermatological conditions (e.g. rheumatoid arthritis). Prescribed at an immunomodulatory dosage (i.e. ≤30 mg/week), MTX is inexpensive and has a good efficacy-toxicity ratio. Serious adverse events are rare and no more frequent than those observed with placebo (1). However, minor adverse events, such as mild increases in transaminase level or gastrointestinal symptoms, are more frequent with the drug, which results in a 30% increase in the rate of discontinuation of MTX compared with placebo (1). Two meta-analyses have shown that some of these adverse events may be limited by folate supplementation (2, 3), without lowering MTX efficacy (3–5). Furthermore, folate supplementation may relieve MTX-related hyperhomocysteinaemia (4). Finally, folate supplementation is usually inexpensive and is not, in itself, associated with adverse events. Therefore, guidelines recommend prescribing at least 5 mg folic or folinic acid weekly for all patients with dermatological conditions requiring MTX prescriptions (6–11). However, very few data are available regarding adherence to these recommendations. The aims of this study were to assess the prevalence of adequate folate supplementation in individuals exposed to MTX ≤30 mg/week, to define determinants of good practices, and to analyse association between folate supplementation and early MTX withdrawal.

METHODS

Data were extracted from the French medico-economic database Echantillon Généraliste de Bénéficiaires (EGB), a representative 1/97th random sample of the French population (12). For this study, all patients who had at least one reimbursement for MTX were identified (ATC codes L04AX03 or L01BA01) during 2006 to 2016. Only incident users (defined by reimbursement of MTX during a given year with no previous prescription in the preceding year) were included in this cohort study. For all these patients, we searched for co-prescription of folate (i.e. folic or folinic acid, ATC codes B03BB01 or V03AF03) during MTX exposure. Adequate folate supplementation was defined as a mean weekly dose of folate ≥5 mg over the MTX exposure. Covariates of interest that were analysed included: (*i*) patient sex and age, (*ii*) the underlying condition requiring MTX, (*iii*) data on MTX exposure, (*iv*) data on co-prescription of systemic glucocorticoids during the first 3 months of MTX exposure, and (*v*) data on MTX prescriber. Baseline variables are reported as mean ± standard deviation (SD) or median (interquartile range; IQR) for continuous variables and number (%) for categorical variables. Groups were compared using a χ^2 test for categorical variables and Student *t*-test or Kruskal–Wallis test for continuous variables. A logistic regression model was used to assess determinants of good practice. A Cox proportional hazard model was used to assess whether adequate folate supplementation was associated with early (i.e., <3 months after MTX initiation) discontinuation of MTX. Linearity for continuous variables was checked. The proportional-hazard assumption for the Cox model was checked graphically. All statistical analyses were 2-tailed and were tested at the significance threshold $\alpha = 0.05$. All analyses were performed using Stata 14.0. The study was approved by the national Institut des Données de Santé committee (number 291/216).

RESULTS

During the study period, 771,190 individuals were recorded for at least one day in the EGB. Among them, 3,771 individuals (0.49%) were incident MTX users (64.2% women; mean age 54.1 ± 17.8 years) (Table SI[1]). The median weekly MTX dose was 12.2 mg (9.3–16.0); the dose varied widely according to patients' and prescribers' characteristics (Table SII[1]). The median duration of exposure was 614 days (164–1,526). MTX was most frequently prescribed orally (71.8%), mainly for rheumatoid arthritis (28.3%) or psoriasis/psoriatic arthritis (23.3%).

Overall, 2,774 individuals (73.6%) had adequate folate supplementation. These patients were older (63.0% of those ≤40 years received adequate supplementation by comparison with 78.2% of those aged ≥60 years), received MTX at a higher dosage (59.5% and 79.9% for those prescribed MTX <10 mg/week or ≥10 mg/week received adequate supplementation, respectively) and for a longer time, and probably had more severe disease (indirectly assessed using concomitant systemic glucocorticoid prescriptions) than those with inadequate folate supplementation (**Table I**). Furthermore, prescribers probably more familiar with MTX prescriptions (i.e. dermatologists, rheumatologists, internists, gastroenterologists and hospital-based physicians) were more likely to adequately prescribe folates. Adequate folate supplementation was associated with less early discontinuation of MTX (adjusted hazard ratio (HR): 0.46 (95% confidence interval (95% CI) 0.39–0.55), $p < 0.001$). The results were similar when accounting for an adequate folate supplementation over the first 3 months of exposure (adjusted HR 0.48 (0.41–0.57)).

DISCUSSION

Folate supplementation decreases the number of patients with adverse events (1). The relative risk of gastrointestinal

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Table I. Folate supplementation (suppl.) with methotrexate (MTX) prescription: multivariable analysis

	OR [95% CI]	*p*-value
Sex, female vs. male	1.09 [0.92–1.29]	0.31
Age		
0–18 years	0.23 [0.16–0.35]	<0.001
19–50 years	1	–
51–70 years	1.29 [1.08–1.55]	0.006
>70 years	1.56 [1.23–1.97]	<0.001
MTX dose, per 1 mg/week increase	1.14 [1.12–1.16]	<0.001
Route of MTX administration, oral vs. subcutaneous	1.05 [0.87–1.26]	0.62
Duration of MTX use		
0–3 months	1	–
4–6 months	2.43 [1.78–3.30]	<0.001
7–9 months	3.83 [2.62–5.60]	<0.001
10–12 months	3.55 [2.33–5.41]	<0.001
>12 months	3.44 [2.75–4.31]	<0.001
Underlying disease		
Rheumatoid arthritis	1	–
Psoriasis/psoriatic arthritis	0.75 [0.59–0.96]	0.02
Crohn's disease or ulcerative colitis	1.52 [0.88–2.62]	0.13
Combination of several diseases	0.98 [0.77–1.24]	0.84
Other or unknown	0.58 [0.46–0.73]	<0.001
Prescriber's specialty		
Rheumatologist	1	–
General practitioner	0.75 [0.60–0.94]	0.01
Dermatologist	1.11 [0.76–1.61]	0.60
Gastroenterologist	0.94 [0.27–3.26]	0.92
Internist	0.90 [0.47–1.72]	0.75
Other	0.70 [0.53–0.92]	0.01
Prescriber's mode of practice		
Hospital	1.52 [1.19–1.93]	0.001
Community	1	–
Hospital and community	1.30 [0.96–1.75]	0.08
Unknown	1.66 [1.25–2.20]	<0.001
Co-prescription of systemic glucocorticoids, yes vs. no	1.34 [1.13–1.58]	0.001

adverse events (e.g. nausea, vomiting) was 26% (95% CI 8–41%) lower in patients receiving concomitant adequate, compared with inadequate, prescription of folate (3). Folate supplementation is also protective against abnormally elevated serum transaminase level, with a 36–77% reduction in risk (2, 3). Two meta-analyses did not show a statistical benefit of folate supplementation for mucocutaneous adverse events, although there was a trend in favour of supplementation (2, 3). They were also unable to draw meaningful conclusions on the effect of folate supplementation on haematological adverse events due to poor reporting of this outcome in included trials. More importantly, in a previous study, the risk of withdrawal from MTX treatment was notably lowered by folate co-prescription (relative risk 0.39 (0.28–0.53)) (3). We found similar results. Few similar data are available. Two declarative surveys of dermatologists showed contradictory results, with 26–81% of those who responded declaring prescribing folate systematically or almost systematically in patients exposed to MTX (13, 14). In a population-based study of 2,467 new MTX users older than 65 years, 73% were prescribed adequate folate along with their first prescription of MTX; a finding similar to ours (15).

There is some debate about whether young patients or those receiving MTX ≤10 mg/week should receive folate supplementation, as they may be less prone to MTX-induced adverse events, and perhaps less likely to have folate deficit. The results of our study may reflect this debate. However, to date and to our knowledge, available guidelines recommend prescribing folate supplementation to all MTX-exposed patients, no matter their age or the dose they receive.

Our study has several strengths, including the use of a large population-based sample of individuals initiating MTX, representative of the whole French population. However, the study has also limitations, most of them inherent to the use of an administrative database. This study assessed what was done by patients, not what was prescribed. We cannot rule out that some patients were adequately prescribed folate supplementation, but did not buy it at the pharmacy. In addition, some included individuals may have been misclassified as incident MTX users. However, these patients may represent a very small proportion. Finally, we were unable to adjust the analyses on several potential confounding factors, such as baseline comorbidities (e.g., overweight, alcohol intake), because this information is not recorded in the EGB.

In conclusion, folate supplementation could be enhanced in the youngest patients and during the first days/weeks of MTX exposure. Since this study demonstrates that lack of folate supplementation is strongly associated with early withdrawal from MTX treatment, less experienced prescribers should be better informed about the benefits of folate supplementation with MTX prescription.

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