(Bi)Weekly folic acid supplementation might be inferior to a daily folic acid dosing schedule in the prevention of methotrexate-related toxicity in patients with rheumatoid arthritis

Sirs,

Although methotrexate (MTX) has been proven effective in the treatment of rheumatoid arthritis (RA), treatment can be complicated by folate related adverse events; mainly elevation of transaminases (in 20–58% of patients) and gastrointestinal (GI) complaints (in 20–60% of patients) (1, 2). Based on multiple trials, co-administration of folic acid in doses from 1–5 mg per day during 5 to 7 days per week (3-7) is recommended to minimise adverse effects (8). In practice, however, a pragmatic (bi)weekly dosing schedule of folic acid is often applied (9, 10). However, there is no evidence that supports the efficacy of this (bi)weekly dosing schedule in reducing adverse effects. Therefore, we have compared the rate of occurrence of abnormal liver enzyme findings and GI complaints between patients using folic acid 1 mg/day or 10 mg/weekly (in 1–2 doses/week) in the Nijmegen early RA inceptions cohort (initiated in 1985) with RA patients treated with MTX in the period between January 2000 and June 2008. Before January 1st 2004, patients using MTX were prescribed folic acid in a dose of 1 mg/day. Due to changing insurance regulations, the folic acid regimen of 1 mg/day abruptly changed on that date to 10 mg/weekly in 1–2 doses (one and four days after methotrexate administration) for almost all the patients, resulting in a natural quasi experiment.

Of the 347 RA patients (ACR-1987 classified) starting with MTX who were included, 193 (56%) had weekly folic acid supplementation (of whom 133/193 received 5 mg twice-weekly), and 154 daily 1mg. The 347 patients contributed 26,625 weeks of observation time, with a mean of 77 weeks. 171 liver enzyme abnormalities (defined as any elevation of the serum value of ALT and/or AST exceeding the upper limit [UL]) were found in 71 patients: 20 (13%) in the patients on 1 mg/day and 51 in the 193 (26%) patients on 10 mg/week, with an adjusted between-group hazard ratio of 1.67 (0.97–2.88). (Table I). More stringent definitions for liver enzyme abnormalities were also analysed (Table I), resulting in lower and non-significant HRs (Table I). GI complaints occurred in 8 (5.2%) patients of the daily dose group and 19 (9.8%) patients in the weekly dose group, with an adjusted between-group hazard ratio of 4.2 (1.2–15) (Table I, Fig. 1).

To investigate whether our results are biased because the earlier 1 mg daily patients might be treated with lower MTX dosages (calendar time bias), MTX doses and DAS28 scores were plotted showing comparable MTX dosages and disease activity levels over time. In our models, we also corrected for MTX dose by means of a time-dependent covariate. A dose-related increase in toxicity was however not found. Combining above-mentioned information of DAS28 and MTX doses, we inferred that a time induced bias did not seem to occur.

In conclusion, in RA patients treated with MTX, taking 10 mg folic acid weekly (in 1–2 doses) *versus* 1 mg daily significantly raises the hazard of GI complaints. For liver enzyme abnormalities no significant difference was found, although this might be a type 2 error, in light of the trend towards higher risk of liver enzyme abnormalities in the (bi)weekly dosage group. Our findings, combined with the established effectiveness of 1 mg once daily folic acid in a randomised clinical trial, and absence of RCT level evidence of effectiveness of (bi)weekly folic acid, indicates that (inter-) national folic acid guidelines should prefer daily 1 mg instead of (bi) weekly folic acid schemes until a randomised clinical trial proves non-inferiority of a (twice-)weekly regimen compared to a daily regimen.

Table I. Between-group differences for liver enzyme elevations and gastro-intestinal complaints

		Hazard ratio (CI)		
	Events (%)[1]	Crude	Corrected	Variables in final model
Primary outcome				
LF events, n (%)[2]	71 (20.5%)	1.59 (0.93-2.64)	1.67 (0.97-2.88)	Center, AST
LF events, n (%)[3] (definition 2)	26 (7.5%)	1.19 (0.51-2.77)	1.18 (0.50-2.81)	Center, ESR, AST (propensity score)
LF events, n (%)[4]	22 (6.3%)	1.47 (0.57-3.79)	1.20 (0.46-3.10)	Center, ESR
Secondary outcome				
GI events, n (%)	27 (7.8%)	4.20 (1.25-14.13)	4.22 (1.19-14.98)	Center, RA duration, DMARD use (propensity score)

[1]Reported events are included events (first event for each patient) in survival analysis; [2]Percentual serum values of AST and/or ALT of either >1 times more than the UL; [3]Percentual serum values of AST and/or ALT of either >2x UL, or <2x but >1x UL, occurring on at least 2 of 4 consecutive evaluations; [4]Percentual serum values of AST and/or ALT of either >3x UL, or <3x but >2x UL, occurring on at least 2 of 4 consecutive evaluations.

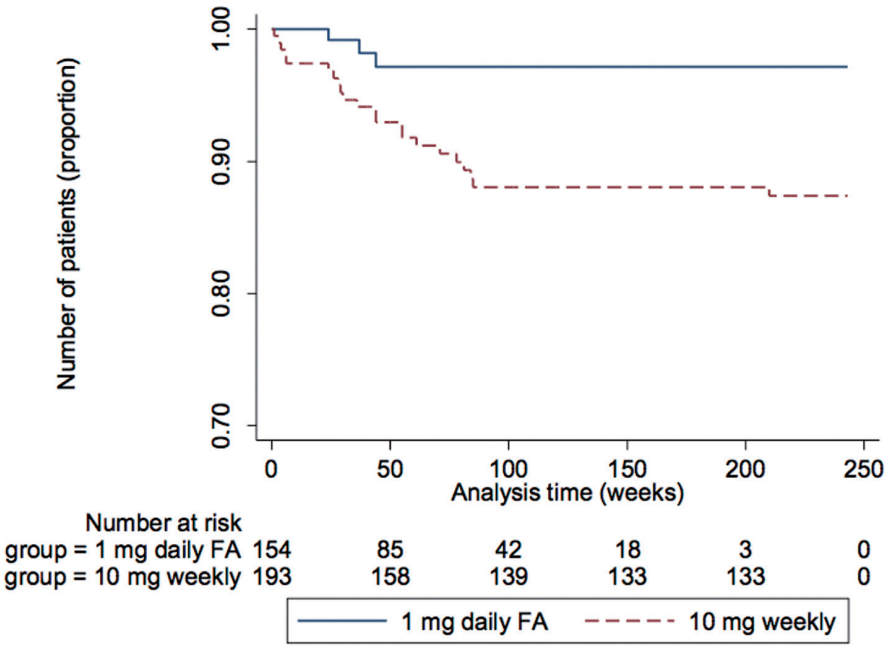

Fig. 1. Time gastro-intestinal event: daily versus (twice-) weekly folic acid.

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Competing interests: none declared.

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