Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis

M Hoekstra, A E van Ede, C J Haagsma, M A F J van de Laar, T W J Huizinga, M W M Kruijzen, R F J M Laan

EXTENDED REPORT

Objective: To study factors associated with toxicity, final dose, and efficacy of methotrexate (MTX) in patients with rheumatoid arthritis (RA).

Methods: Data were used from a randomised clinical 48 week trial on 411 patients with RA all treated with MTX, comparing folates and placebo. Logistic regression was used to study the relation between baseline variables and various dependent factors, including hepatotoxicity (alanine aminotransferase ≥3× upper limit of normal), MTX withdrawal, final MTX dose ≥15 mg/week, and MTX efficacy.

Results: Addition of folates to MTX treatment was strongly related to the lack of hepatotoxicity. Next to this, high body mass index was related to the occurrence of hepatotoxicity. Prior gastrointestinal (GI) events and younger age were related to the adverse event, diarrhoea. Hepatotoxicity and GI adverse events were the main reason for MTX withdrawal, which in turn was associated with the absence of folate supplementation, body mass index, prior GI events, and female sex. Renal function (creatinine clearance ≥50 ml/min) was not associated with toxicity. Reaching a final dose of MTX of ≥15 mg/week was related to folate supplementation and the absence of prior GI events. Efficacy of MTX treatment was associated with low disease activity at baseline, male sex, use of non-steroidal anti-inflammatory drugs (NSAIDs), and lower creatinine clearance.

Conclusions: MTX toxicity, final dose, and efficacy are influenced by folate supplementation. Baseline characteristics predicting the outcome of MTX treatment are mainly prior GI events, body mass index, sex, use of NSAIDs, and creatinine clearance.

Methotrexate (MTX) is an effective disease modifying antirheumatic drug (DMARD). Its effectiveness has been proved in placebo controlled trials and in comparison with other DMARDs. MTX in a weekly dose can be used for years and its use is mainly limited by toxicity. Renal impairment and age are generally considered risk factors for developing MTX toxicity, but studies show conflicting results. A rise in liver enzymes, in particular the transaminases, occurs frequently during MTX treatment. Dose, obesity, alcohol use, and lack of folate supplementation are considered to be associated with hepatotoxicity. Gastrointestinal (GI) side effects also often occur during MTX treatment. Folinic acid supplementation reduced the occurrence of GI side effects. Overall toxicity scores, including both hepatotoxicity and GI side effects, have also been reduced by the addition of folate.

Pulmonary toxicity is less common. Pre-existing pulmonary disease and age have been shown to increase the risk of pulmonary side effects, although one other study did not show this. Pancytopenia was found to be related to renal impairment and central nervous system toxicity was more common in elderly patients with mild renal insufficiency.

Disease duration, disease activity, sex, functional class, and prior DMARD use are suggested to be related to treatment response, whereas age and renal function are not. Supplementation with folates has raised questions about the reduced efficacy of MTX, but most studies did not show a negative effect.

In MTX treatment a dose-response relation exists, but the optimal dose is individually determined. For clinical practice it is relevant to predict toxicity, final dose, and efficacy. Therefore, we aimed at studying the relation between baseline factors and toxicity, reaching a final dose ≥15 mg/week, and efficacy of MTX treatment.

METHODS

Data were used from a 48 week randomised placebo controlled multicentre trial, comparing the influence of placebo, folic acid, and folic acid on the toxicity and efficacy of MTX treatment. In this randomised clinical trial (RCT), selection of patients as well as MTX treatment reflected daily rheumatological care. The primary end point of the trial was the effect of folates on MTX withdrawal due to adverse events. Four hundred and eleven patients with rheumatoid arthritis (RA) were included. Exclusion criteria were prior MTX use, a creatinine clearance <50 ml/min (Cockcroft formula), liver disorders, leucopenia, thrombopenia, alcohol abuse, and treatment with folic or folic acid.

MTX was started in all patients at a dose of 7.5 mg/week, and increased every six weeks by 2.5 mg to a maximum of 25 mg/week until a significant decrease in disease activity (change in disease activity score ≥1.08) was obtained. When adverse events occurred the MTX dose was adjusted. The action following an adverse event was indicated in the protocol. Dose adjustments at the discretion of the attending rheumatologist were allowed. Patients were randomly allocated into one of three groups receiving either folic acid (1 mg/day), folic acid (2.5 mg/week), or placebo. At a MTX dose of ≥15 mg/week folate doses were doubled. This study has been described in detail elsewhere.

Baseline variables included folate supplementation, age (years), sex, creatinine clearance (ml/min), disease duration (months), rheumatoid factor, disease activity score (DAS),...
body mass index (BMI) (kg/m²), alcohol use (>4 U/week), smoking, non-steroidal anti-inflammatory drug (NSAID) use, corticosteroid use, and prior GI events. Prior GI events included prior peptic ulcers and abdominal surgery.

The following dependent variables were studied: severe hepatotoxicity (defined as a rise in alanine aminotransferase > three times the upper limit of normal, which according to the protocol rules, was a reason for MTX withdrawal), the 10 most commonly reported adverse events (nausea, dizziness, headache, rash, fatigue/malaise, abdominal pain, stomatitis, cough, alopecia, and diarrhoea), MTX withdrawal due to toxicity, reaching a final MTX dose of >15 mg/week, and efficacy.

For the analysis of efficacy we used the European League Against Rheumatism (EULAR) response criteria. A good response was defined as a DAS improvement from baseline of >1.2 in combination with a DAS <2.4.

### Statistical analysis
Data were analysed using SPSS for Windows, version 10.0. Univariate analyses were performed. The relation between baseline variables and dependent variables was studied by a backward stepwise conditional logistic regression analysis. The independent variables in this model were selected on the basis of outcome of the univariate analyses and data from the literature. A general set of baseline variables (age, disease duration, DAS, creatinine clearance, and rheumatoid factor) was included in every analysis. A variable was excluded when the p value was >0.10. Results are given as odds ratios with 95% confidence intervals. A p value of <0.05 is considered significant.

### RESULTS
The preceding analysis of the RCT showed no differences between the two folate supplemented groups. In the present study the two groups were therefore merged. Table 1 describes the baseline characteristics. There were no significant differences in baseline variables in the folate and placebo groups. Table 2 lists the 10 most common adverse events. Table 3 gives the results of the univariate and multivariate analysis.

Hepatotoxicity leading to MTX withdrawal, was associated with absence of folate supplementation and high BMI. Severe

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**Table 1** Baseline demographic and clinical variables

<table>
<thead>
<tr>
<th></th>
<th>Folate supplementation (n=274)</th>
<th>Placebo (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (standard deviation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>55.4 (12.7)</td>
<td>57.2 (12.7)</td>
</tr>
<tr>
<td>Disease duration [months]</td>
<td>42 (0–600)</td>
<td>49.5 (1–324)</td>
</tr>
<tr>
<td>Disease activity score</td>
<td>4.62 (0.94)</td>
<td>4.63 (0.94)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.6 (4.2)</td>
<td>26.0 (4.1)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>77.4 (13.9)</td>
<td>77.0 (15.7)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>89.8 (23.1)</td>
<td>90.2 (28.4)</td>
</tr>
</tbody>
</table>

**Table 2** Most frequently reported subjective adverse events. Results are shown as No (%) of patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Folate supplementation (n=274)</th>
<th>Placebo (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>154 (37)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>100 (24)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>99 (24)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>90 (22)</td>
<td></td>
</tr>
<tr>
<td>Fatigue/malaise</td>
<td>81 (20)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>79 (19)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>71 (17)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>70 (17)</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>53 (13)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>43 (10)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Univariate and multivariate logistic regression analysis (backward stepwise conditional)

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>OR (CI)</td>
</tr>
<tr>
<td><strong>Hepatotoxicity (ALT &gt;3×ULN)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate supplementation</td>
<td>&lt;0.001</td>
<td>0.12 (0.06 to 0.24)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.02</td>
<td>1.08 (1.01 to 1.16)</td>
</tr>
<tr>
<td>Prior GI events</td>
<td>0.03</td>
<td>2.04 (1.07 to 3.89)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>0.01</td>
<td>0.97 (0.94 to 0.99)</td>
</tr>
<tr>
<td>MTX withdrawal due to toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate supplementation</td>
<td>&lt;0.001</td>
<td>0.27 (0.17 to 0.44)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.02</td>
<td>1.81 (1.10 to 2.98)</td>
</tr>
<tr>
<td>Prior GI events</td>
<td>0.02</td>
<td>1.07 (1.01 to 1.13)</td>
</tr>
<tr>
<td>Men</td>
<td>0.12</td>
<td>0.47 (0.26 to 0.85)</td>
</tr>
<tr>
<td>DAS0</td>
<td>0.02</td>
<td>1.34 (1.04 to 1.72)</td>
</tr>
<tr>
<td>MITX dose &gt;15 mg/week</td>
<td>&lt;0.001</td>
<td>3.33 (2.17 to 5.12)</td>
</tr>
<tr>
<td>Folate supplementation</td>
<td>0.02</td>
<td>0.61 (0.40 to 0.93)</td>
</tr>
<tr>
<td>Prior GI events</td>
<td>&lt;0.001</td>
<td>0.52 (0.40 to 0.66)</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS0</td>
<td>&lt;0.001</td>
<td>1.79 (1.16 to 2.76)</td>
</tr>
<tr>
<td>Men</td>
<td>0.01</td>
<td>1.79 (1.16 to 2.76)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; ULN, upper limit of normal; prior GI events, prior gastrointestinal events, including peptic ulcers and abdominal surgery; NS, not significant; *DAS0, disease activity score at baseline.
Use of methotrexate in patients with RA

hepatotoxicity occurred in 36/137 (26%) of the placebo group, and 11/274 (4%) of the folate group. In patients with a BMI of 20–25 hepatotoxicity occurred in 16/190 (8%), in patients with a BMI of 30–35 this occurred in 10/51 (20%). The mean BMI in this study was 25 (range 20–40).

Diarrhoea was associated with prior GI events and lower age. The other nine adverse events were not related to any of the baseline variables.

Pneumonitis and leucopenia occurred in two and three patients, respectively. These numbers were too small for reliable assessment of predictive factors.

MTX was withdrawn in 126 patients. In 91 patients this was due to toxicity (52 in the placebo group, 39 in the supplemented folate group). Absence of folate supplementation, prior GI events, and BMI are related to MTX withdrawal. The mean final MTX dose was 17.6 mg/week in the folate group and 15.0 mg/week in the placebo group—a significant difference (p<0.001). An MTX dose ≥15 mg/week was reached in 221 (54%) of all 441 patients. Reaching such a final “high” dose is related to folate supplementation and absence of prior GI events.

The DAS at baseline (DAS50) was associated with a good response. The probability of a good response is higher with a lower disease activity at baseline. Moreover, efficacy was better in men and in patients who used NSAIDs. In men a good response was reached in 57/121 (47%) and in women in 95/289 (33%). In the group receiving NSAIDs a good response was reached in 144/375 (38%), in contrast with 8/32 (25%) in the group who did not use NSAIDs. There was a significant inverse correlation with creatinine clearance and efficacy.

DISCUSSION

Our data show that next to folate supplementation a higher BMI is related to hepatotoxicity. Prior GI events and younger age are related to the occurrence of diarrhoea, and MTX withdrawal is related to the absence of folate supplementation, prior GI events, BMI, and female sex. Reaching a final MTX dose of ≥15 mg/week is associated with the use of folates as well as with prior GI events. A good response to MTX treatment is related to the DAS at baseline, the use of NSAIDs, male sex, and creatinine clearance.

The data from the RCT that we used were obtained by applying a treatment protocol designed to mirror clinical practice with MTX. Clinical trials are not the best way to draw conclusions about predicting toxicity, especially with respect to rare side effects. In this study we were interested in common toxicity limiting the use of MTX. The magnitude of the trial as well as its design makes it suitable to address the questions of the present study. One of the few points that prevented generalisation of our data to clinical practice is the exclusion of patients with a creatinine clearance <50 ml/min. Although in routine care patients with impaired renal function are not likely to be treated with MTX, this has to be taken into account.

An increase in transaminase was reduced significantly by folates. This is in agreement with the findings of Shiroky et al.12 The influence of folic acid on transaminase levels was not specifically mentioned in the studies by Morgan et al.11,12 In preceding studies a relation between obesity or weight and rise in transaminase or severe liver disease was found, which was confirmed by our observations.11,12 An explanation for this may be the association between obesity and a fatty liver, increasing the susceptibility to MTX related toxicity. In accordance with a meta-analysis on 496 patients by Felson, as well as a study on 469 patients by Bologna, we found no relation between age, renal function, and a rise in transaminase.8,9

In contrast with the study by Shiroky, which showed a marked reduction of GI side effects due to folinic acid supplementation, our trial did not reveal a relation between either folic acid or folinic acid and GI side effects. Our data showed an association between prior GI events, a lower age, and diarrhoea. Bologna et al. also reported a lower incidence of GI side effects in the older age group,7 whereas in another study of 235 patients with RA treated with MTX GI symptoms were reported more frequently in the older age group.7 In both studies these GI side effects have not been specified in detail, so the part explained by diarrhoea is not known.

Hepatotoxicity and GI side effects were the main reason for MTX withdrawal and it is therefore not surprising that a relation between folate supplementation, BMI, prior GI events, and MTX withdrawal was found. No relation between age and MTX withdrawal was found. In accordance with a 13 year retrospective study of 144 patients with RA our study confirmed that MTX withdrawal was related to female sex.7 In contrast, our data did not show a relation between age and MTX withdrawal, which coincides with the results of the study by Bologna et al.9

The addition of folates increases the chances of reaching a higher MTX dose. This is probably determined by a reduction of side effects, but may also be due to a lower efficacy. With a history of prior GI events the chance of reaching a higher dose is smaller, which can be explained by the occurrence of GI side effects. Renal function and age were not related to the dose reached.

Anderson et al studied factors influencing response to treatment in a meta-analysis of 1435 patients. In their multivariate analysis, disease duration as well as patient global assessment of disease activity were significantly related to treatment response.23 In contrast with this, we found no relation between disease duration and efficacy, the mean disease duration being lower in our study. The assessment of disease activity in our study comprised apart from the patient's global assessment, the Ritchie articular index, the 44 joint count, and the erythrocyte sedimentation rate. The DAS combines these four variables. A good EULAR response is not easily achieved when the DAS is high at baseline. In accordance with the study of Anderson et al, efficacy of MTX was better in men. Concomitant use of NSAIDs was associated with increased efficacy. A study by Cush et al showed a positive effect of NSAIDs on disease activity.24 In contrast with others we found a relation between renal function and good response. The response was better in patients with a lower creatinine clearance. This was not explained by the MTX dose, but may be explained by a longer MTX exposure due to renal impairment.

CONCLUSIONS

Apart from the beneficial effect of folate supplementation on the occurrence of hepatotoxicity and MTX withdrawal due to toxicity, side effects were associated with BMI, prior GI events, and female sex. Prior GI events and a lower age are related to the occurrence of diarrhoea. Renal function (creatinine clearance ≥50 ml/min) was not associated with toxicity and MTX withdrawal due to toxicity.

Reaching a final dose of MTX of ≥15 mg/week is particularly related to folate supplementation and to a lack of prior GI events. This is probably explained by a reduction of toxicity. A good response to MTX treatment is mainly related to the DAS at baseline, and to a lesser extent to the use of NSAIDs, male sex, and creatinine clearance. Efficacy was not influenced by age.

As a result of this study a suggested approach for daily practice might be that in patients with RA, who do not have prior GI events or a high BMI and have a calculated creatinine clearance ≥50 ml/min, one can start with 15 mg/week MTX, provided that folates are added to the treatment.
REFERENCES


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