Interruption of Long-term Methotrexate Treatment in Psoriasis

Evaluation of Clinical Course and Laboratory Parameters after Discontinuation and Re-introduction of Weekly Oral Methotrexate

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The effects of interval treatment were evaluated in 10 psoriatic patients on long-term treatment with low-dose oral methotrexate (MTX). In all patients, the dosage of MTX had already been tapered off as much as possible. After interruption of MTX treatment, the clinical course and changes in laboratory parameters were evaluated. The mean MTX-free period was 17 weeks, and the mean reduction in cumulative MTX dose was 76 mg ($p = 0.05$). However, only 3 patients preferred interval treatment to a continuous schedule. During the first 3 weeks of discontinuation, a significant decrease in the serum transaminases was observed, indicating a direct toxic influence of MTX on the liver parenchym.

We conclude that interruption of long-term MTX treatment leads to a substantial reduction of the cumulative MTX dose and reduces the hepatotoxic load of MTX. It is necessary to motivate patients on long-term MTX treatment for regular treatment interruptions to establish a further reduction in their cumulative MTX dose. *Key words: cumulative dose; toxicity.*

The efficacy of low-dose oral methotrexate (MTX) in severe psoriasis is well established (1, 2). Beside gastro-intestinal complaints, the most notorious side-effects of MTX therapy concern haematological abnormalities and hepatic damage (2–7). For the treatment of psoriasis MTX is often continued for many years, especially when the achieved clinical result is satisfactory and no major side-effects occur. However, a high cumulative dose of MTX is associated with an increased frequency of liver damage (4, 8).

The aim of the present study was to investigate whether treatment with MTX in intervals is better than a continuous schedule. The MTX regimen was temporarily discontinued in 10 psoriatic patients on long-term treatment with oral MTX according to the Weinstein schedule (9). At the moment of discontinuation all patients were in a stable clinical condition with minimal skin lesions, and their weekly MTX dose had already been tapered off to an optimal dose with respect to efficacy and side-effects. The clinical course after discontinuation and re-introduction of MTX was evaluated. MTX was re-introduced at the moment of a partial relapse, according to well-defined criteria. The possible reduction in cumulative dose of MTX due to the temporary discontinuation was calculated, as well as effects on important laboratory parameters. The opinion of the patients concerning the interruption and re-introduction of treatment was evaluated by means of a short questionnaire.

PATIENTS AND METHODS

Patients

The study was carried out in the period June 1993–May 1994. Eight males and 2 females with severe psoriasis vulgaris for 25–55 years were included. The age of the patients was 51–72 years and the mean treatment period was 12.7 years (0.8–21.5 years). All patients had been treated according to the Weinstein schedule (a weekly divided oral dose with a maximum of 15 mg per week) (9, 10). All patients responded well to MTX therapy, and the weekly dose was individualized by tolerance and efficacy in each patient. The mean cumulative dose of MTX at the moment of discontinuation was 6,471 mg (400–10,790 mg). As it was our purpose to reach maximal similarity to the treatment situation in daily practice, the patients were allowed to continue their topical anti-psoriatic treatment in the same amounts as before interruption of MTX treatment. This topical treatment comprised sparse use of topical corticosteroids or calcipotriol and unlimited use of bland emollients.

Assessment of disease progress

At discontinuation and subsequently every 2 weeks during the first 2 months and later every 4 weeks, the area (percentage of total body area) and the severity of the psoriatic lesions were estimated by one and the same clinician. The area involved was assessed by using the "rule of hand", in which the area covered by the examiner's hand represents roughly 1% of the skin surface (11). The severity score was assessed by grading erythema, scaling and thickness of the psoriatic lesions on a 3-point scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. By summation of these three scores the severity score was calculated. The Psoriasis Severity Score was calculated according to the following formula (modified after Perkins (12)):

$$\text{Psoriasis Severity Score (PSS)} = \frac{\text{Erythema (0–3)} + \text{Scaling (0–3)} + \text{Thickness (0–3)}}{9}$$

$\times$ % surface area involved.

This scoring method is analogous to the PASI score (11), but the impact of the surface area on the overall score is more decisive in this calculation model. Treatment was re-introduced when a partial relapse of psoriasis occurred. A partial relapse was defined as an area score reaching a value of twice the initial area score with a minimum of 3% and a severity score reaching a value of more than 3 points.

Calculation of the modulation of the cumulative MTX dose due to temporary discontinuation of treatment

For each patient the difference between the expected and the real cumulative MTX dose was calculated. The expected cumulative dose is the cumulative dose that the patient would have received if treatment had not been interrupted. For patients who restarted and continued on the same dose schedule as prescribed before the discontinuation, this difference was computed by multiplying the pre-study weekly dose by the number of MTX-free weeks. For patients with severe relapsing psoriasis who needed a temporary "loading-up" dose after re-introduction to get a favourable clearing of their lesions, this additional MTX was comprised in the calculation. If the expected cumulative dose was higher than the real cumulative dose, this resulted in a reduction in
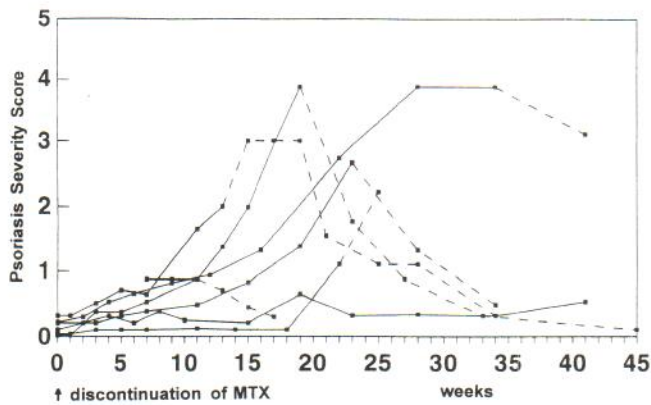
Fig. 1. Psoriasis Severity Score after discontinuation (——) and re-introduction (------) of MTX in patients with an MTX-free period >11 weeks ($n = 7$).

Fig. 2. Number of MTX-free patients in relation to the time after discontinuation of treatment.

cumulative dose due to treatment interruption. However, if the expected cumulative dose was lower than the real cumulative dose, the patient eventually received more MTX than he or she would have received without treatment interruption.

Additionally, it was investigated whether a higher number of MTX-free weeks was attended by a larger "loading-up" dose and consequently by an annulling of the "gain" in cumulative MTX dose. A possible predictive value of the pre-study MTX dose for the number of MTX-free weeks was also assessed.

Evaluation of laboratory parameters before and after discontinuation of MTX treatment

At the moments of clinical assessment (PSS) the following laboratory parameters were recorded: hemoglobin, erythrocyte mean cell volume (MCV), leucocyte count, thrombocyte count, serum folate, alkaline phosphatase, serum-transaminases (SGOT and SGPT) and gamma-glutamyltranspeptidase (gamma-GT). The values before discontinuation and possible changes during discontinuation of the MTX regimen were established.

Patients' opinion of treatment in intervals

Whether the patients preferred a continuous treatment schedule to a treatment in intervals was investigated by means of a short questionnaire. The reason for this preference was also investigated.

Statistics

Whether the mean difference between the expected and the real cumulative dose differed significantly from 0 was tested with a paired *t*-test. Possible correlations between the number of MTX-free weeks, the pre-study MTX dose and the difference between the expected and the real cumulative dose were assessed and tested using a Spearman's rank correlation coefficient. Changes in laboratory parameters were assessed by univariate linear regression analyses for each patient separately, with the value of a certain laboratory parameter as the dependent and the time period following discontinuation of MTX as the independent variable. Whether the mean change of the laboratory parameter concerned differed significantly from 0 was tested by means of a Wilcoxon signed rank test or in cases of a normal distribution a paired *t*-test.

RESULTS

Clinical relapse

Three patients experienced a quick relapse and MTX was re-introduced within 4 weeks. In 7 patients the MTX free interval was at least 11 weeks. One patient did not relapse at all within a follow-up period of 41 weeks. In 3 patients the MTX treatment had to be re-introduced before the criteria for a partial relapse
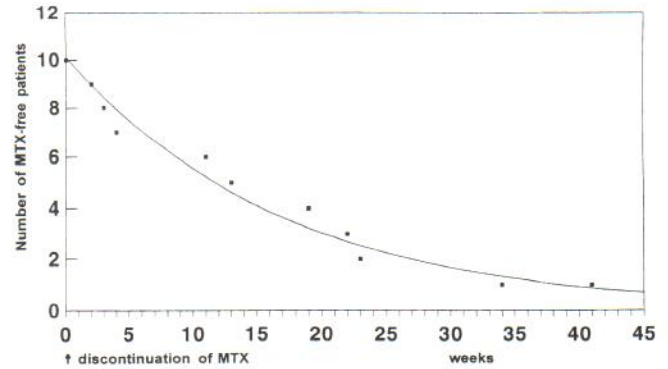
were met, because of recurrence of skin lesions at cosmetically disturbing localizations or because of rapidly progressing pin-point lesions, indicating the onset of a severe relapse. The clinical course (PSS) of the 7 patients with an MTX-free period of 11 weeks is shown in Fig. 1. The mean MTX-free period of these patients was 23 weeks (11–41, $n = 7$) The number of MTX-free patients in relation to the time after discontinuation of the treatment is shown in Fig. 2. The "overall" mean MTX-free period was 17 weeks (2–41 weeks, $n = 10$).

Cumulative MTX dose

The individual reduction or increase in cumulative MTX dose due to interruption of MTX treatment is shown in Fig. 3. One patient had to be excluded in this calculation because it appeared that she had previously been treated with arsenic; acitretin was prescribed at the moment of a relapse. The mean reduction of the cumulative MTX dose was 75 mg (−67.5–255 mg, $p = 0.05$). Recalculation for those patients with a MTX-free period of at least 11 weeks resulted in a mean reduction of the cumulative MTX dose of 117.5 mg (−23.8–255 mg, $p = 0.03$).

It appeared that a lower MTX dose before discontinuation of the MTX regimen permitted a higher number of MTX-free weeks (r (Spearman) = −0.64, $p = 0.05$). A positive correlation was observed between the number of MTX-free weeks and the difference between the expected and the real cumulative MTX dose (r (Spearman) = +0.64, $p = 0.06$).
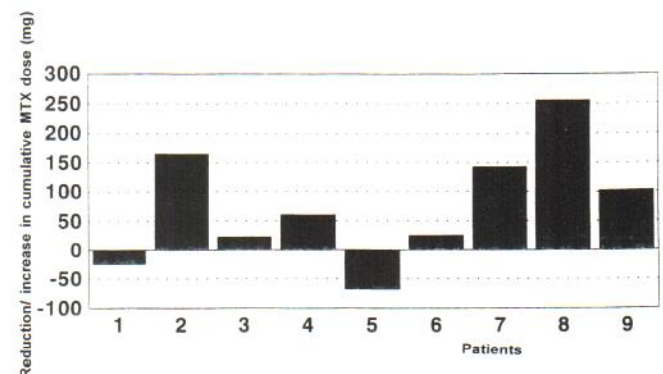

Fig. 3. Reduction (positive values) or increase (negative values) in cumulative MTX dose due to interruption of treatment for each patient ($n = 9$).

Laboratory parameters

At the moment of discontinuation 3 patients showed an elevated MCV (>100 fl), the other patients showed an MCV in the high normal range (92–100 fl), one patient had a lowered thrombocyte count (<120 × 10⁹/l), all patients had serum folate levels in the low but normal range (5.7–14 nM/l), one patient had both an elevated SGOT (27 U/l), SGPT (48 U/l) and gamma-GT (85 U/l), one patient showed an elevated SGPT (33 U/l) and one patient an elevated gamma-GT (69 U/l).

The mean changes in laboratory parameters during the whole period of discontinuation in patients with a number of MTX-free weeks >11 ($n = 7$) were evaluated. A small but statistically significant increase of serum-folate was observed (0.166 nM/week, $p < 0.05$). During the first 3 weeks after discontinuation a statistically significant mean decrease of 2.09 U/l/week in SGOT and 4.46 U/l/week in SGPT could be demonstrated ($p < 0.05$, $n = 9$; the data of one patient were not complete). Higher transaminases at the moment of discontinuation were associated with a more prominent decrease during the first MTX-free weeks. In the first weeks after re-introduction a mean increase of 1.30 U/l/week in SGOT ($p = 0.09$) and 2.31 U/l/week in SGPT ($p = 0.06$) was observed. In the other laboratory parameters no important changes were observed.

The patient with a low thrombocyte count and the two patients with an elevated gamma-GT did not show an improvement into the normal range during discontinuation of MTX.

Subjective assessment

The 3 patients resuming their MTX regimen shortly after discontinuation (within 4 weeks) all preferred a continuous treatment. Of the 7 patients with prolonged MTX-free periods, 3 patients preferred interval treatment because of the reduced toxicity potential of such a regimen. The other patients preferred a continuous treatment in spite of a long MTX-free period because of fear of a relapse and practical problems with the more cumbersome local therapy.

DISCUSSION

Clinical severity scores and safety parameters after interruption and re-introduction of long-term MTX treatment were evaluated in 10 psoriasis patients. The MTX-free period was assessed, and it was evaluated whether treatment interruption resulted in a substantial reduction of the cumulative dose. To our knowledge no similar study has been reported so far.

A considerable mean number of 17 MTX-free (2–41) weeks could be reached. Three patients asked for re-introduction of MTX treatment before the defined criterion of a relapse was met. This problem is characteristic of clinical studies and links up with day-to-day medical practice. Seven patients had an MTX-free period of at least 11 weeks. Two patients were still free of MTX after 6 months; one of them did not get a relapse at all (Figs. 1, 2). Relapse periods of 1 year or even more have been reported by other authors (10, 13). There was a negative correlation between the weekly MTX dose before discontinuation and the number of MTX-free weeks. The mean reduction in cumulative dose due to this single interruption of treatment

was 76 mg. Only in 2 patients did treatment interruption result in a small increase in cumulative MTX dose, because they needed a "loading-up" dose to reach the same clinical situation as before the treatment interruption (Fig. 3). For patients with at least 11 MTX-free weeks the mean reduction was 117 mg. A positive correlation was observed between the number of MTX-free weeks and the reduction in cumulative dose. This is an important observation and means that the "gain" in cumulative MTX-dose due to treatment interruption was not annulled by high "loading up" doses after re-introduction of treatment.

The only laboratory parameters showing significant changes during discontinuation of MTX treatment, particularly in patients with abnormal pre-study values, were the serum transaminases. After re-introduction of MTX a borderline significant increase in SGOT and SGPT was observed. The relatively high MCV values at the beginning of the study probably indicate a macrocytogenic impact of MTX on the erythrocytes (14, 15). The low normal serum folate values before discontinuation of MTX treatment and the small but statistically significant increase during discontinuation indicate a suppressive effect of MTX on the serum folate level. This is in accordance with reports in the literature (16, 17). Despite the fact that all patients in the present study were in a stable clinical situation without important side-effects, they showed clear changes in liver parenchym-derived transaminases, reflecting a direct hepatotoxic effect of MTX.

Although a mean MTX-free period of 17 weeks could be reached after interruption of MTX treatment, 7 patients preferred continuous treatment because of fear of a relapse or because local treatment was less convenient. This indicates that patients have to be carefully instructed and persuaded to become motivated for an interval treatment schedule.

In this study it was shown that treatment of severe psoriasis with MTX in intervals is a good alternative to a continuous dose schedule. Treatment interruption results in a substantial reduction of the cumulative dose and reduces the hepatotoxic load of MTX. Patients on a low maintenance MTX-dose may particularly benefit from regular interruptions of their MTX regimen. It is necessary to persuade patients on long-term MTX treatment to interrupt their regimen at regular intervals to achieve a further reduction in their cumulative dose.

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