

Discontinuation of Methotrexate in Psoriasis

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Methotrexate (MTX) is the most commonly used systemic therapy for psoriasis. The drug is a folic acid antagonist and the main effect on psoriasis is thought to be inhibition of lymphatic cell proliferation (1). Due to its anti-inflammatory effect, MTX may also have a protective effect against cardiovascular disease (2, 3). MTX is generally well tolerated, but common, minor adverse reactions are nausea, loss of appetite, and fatigue. Major toxicities include myelosuppression, hepatotoxicity, and pulmonary fibrosis (4).

Although MTX has been used in the treatment of inflammatory disorders since the 1950s (5), there have been few evidence-based studies on MTX in the treatment of psoriasis. Results from three recent randomized controlled studies of patients with psoriasis showed that MTX was as effective as cyclosporin (6), or less effective than ciclosporin (7), and less effective than adalimumab, but more effective than placebo (8). In these studies Psoriasis Activity and Severity Index (PASI)-75 (75% improvement in PASI) for the patients treated with MTX was 60% at week 16 (6), 24% at week 12 (7), and 35.5% at week 16 (8), and rates of discontinuation of MTX therapy due to adverse reactions were 28% (6), 0% (7), and 5.5% (8), respectively.

The main purpose of this study was to determine the reasons for discontinuation of MTX treatment in patients with psoriasis. Secondly, we wanted to discuss the potentially preventable or adjustable factors that might influence the specific reasons for discontinuation.

METHODS

We reviewed the records of all patients who were registered as having an International Classification of Disease (ICD-10) code of psoriasis in the years 1997–2007 at our Dermatological Department. The inclusion criteria were: diagnosis of psoriasis made by a dermatologist, minimum age of 18 years, treatment with MTX at any period between 1997 and 2007, and discontinued MTX treatment before the date of data collection. We excluded

patients treated with MTX because of palmoplantar pustulosis, nail psoriasis, psoriasis arthritis, or as a supplement to infliximab treatment. The main reasons for discontinuation of MTX therapy were recorded together with patient- and treatment-related data.

The data were evaluated using descriptive statistics.

RESULTS

In the period 1997–2007, a total of 2,221 patients with psoriasis were treated at our department. The inclusion criteria were met by 156 of these patients. Median duration of MTX therapy was 7.5 months (range 0.3–264 months), median accumulated MTX dose was 524 mg (range 15–16,925 mg), and at the end of the treatment median weekly MTX dose was 12.5 mg (range 2.5–30 mg). MTX was administered orally to 142 patients (91%) and 94 patients (60.3%) received folate supplementation. The most frequent main reason for discontinuation of MTX therapy was adverse reactions, which were reported in 89 patients (57%). Remission was the second most frequently reported main reason for discontinuation of MTX, followed by “lack of clinical response” and finally “non-drug-related reasons” (Table I).

The adverse reactions that most frequently resulted in discontinuation of MTX were reactions related to the liver and the gastrointestinal tract. Discontinuation because of other adverse reactions (infections, abnormal blood counts, fatigue, headache, etc.) occurred in 30 patients (19%) (Table I).

The 35 cases of adverse liver reactions included fibrosis in liver biopsies (the degree of fibrosis was not graded) ($n=5$), pro-collagen 3 N-terminal peptide (PIIINP) elevated above the normal range (mean 7.7 $\mu\text{g/l}$ (range 6.0–11.1; normal range 1.7–4.2 $\mu\text{g/l}$)) ($n=5$), aspartate aminotransferase (AST) greater than twice the upper limit of normal in at least two blood tests ($n=2$), and elevated AST less than twice the upper limit of normal or AST greater than twice the upper limit of normal in

Table I. Reasons for discontinuation of methotrexate (MTX) and the MTX treatment regimen. One (0.6%) was lost to follow-up

	<i>n</i> (%) [*]	Male sex	Discontinuation	Oral route of	Folate supple-	MTX dose at the end of
		<i>n</i> (%)	(age, years)	administration	mentation	treatment (mg/week)
			Mean (range)	<i>n</i> (%)	<i>n</i> (%)	Median (range)
All patients	156 (100)	94 (60.3)	53 (19–86)	142 (91.0)	94 (60.3)	12.5 (2.5–30.0)
Remission	37 (24)	18 (48.6)	59 (19–84)	36 (97.3)	20 (54.1)	7.5 (2.5–25.0)
Adverse liver reactions	35 (22)	20 (57.1)	56 (24–86)	31 (88.6)	21 (60.0)	10.0 (2.5–25.0)
Adverse gastrointestinal reactions	24 (15)	14 (58.3)	50 (19–84)	18 (75.0)	12 (50.0)	15.0 (7.5–30.0)
Other adverse reactions	30 (19)	20 (66.7)	55 (19–84)	28 (93.3)	22 (73.3)	12.5 (2.5–20.0)
Lack of clinical response	32 (21)	20 (62.5)	47 (19–82)	28 (87.5)	21 (65.6)	15.0 (5.0–25.0)
Non-drug-related reasons	26 (17)	18 (69.2)	45 (24–81)	25 (96.2)	13 (50.0)	14.0 (2.5–30.0)

^{*}Some patients reported more than one reason for discontinuation; thus, the accumulation of percentages exceeds 100%.

one blood test ($n=20$). In three patients with adverse liver reactions, the reaction was not specified.

Details on treatment regimen (including MTX dosage, route of administration, and folate supplementation) are given in Table I.

DISCUSSION

The most frequent events leading to discontinuation of MTX were adverse reactions, mainly from the liver and the gastrointestinal tract, which observation is in accordance with earlier studies (6–9). However, our data indicated a low threshold for discontinuation of MTX treatment, especially in cases with adverse liver reactions.

To detect MTX-induced liver damage, guidelines from the American Academy of Dermatology (AAD) in 1998 recommended liver biopsies for patients “having persistent significant abnormalities in liver chemistry values” (10). According to newer guidelines from the European Academy of Dermatology and Venereology (EADV) in 2009 (11), most European countries currently use PIIINP in serum as an indicator of liver fibrosis and restrict the recommendation of liver biopsies to patients in whom PIIINP levels are repeatedly elevated. Compared with these recommendations, rational reasons for discontinuation of MTX due to adverse liver reactions were found in only about one-third of the patients in our study (fibrosis, elevated PIIINP, and AST more than twice the upper limit of normal in at least two measurements).

In order to reduce adverse haematological, gastrointestinal, and hepatic reactions in MTX treatment, the AAD guidelines from 1998 (10) recommended folate supplementation, though evidence was mainly based on studies of MTX-treated patients with rheumatoid arthritis (12, 13). Moreover, clinical experience indicates that adverse gastrointestinal reactions and, to some degree, adverse liver reactions may be reduced by switching MTX therapy to parenteral administration (14). In our study, a considerable number of the patients who discontinued MTX might have tolerated MTX if these suggestions had been followed.

Efficacy, prevalence, and severity of MTX-induced adverse reactions depend on the treatment dose. The AAD guidelines from 1998 (10) recommended a weekly dosage of 7.5–30 mg, individually adjusted. Our data do not tell us whether adjustment of dosage was tried, but we found that patients who discontinued MTX due to adverse liver reactions did take a low dose of MTX at the time of discontinuation. Patients who gave up MTX due to lack of efficacy might have obtained better efficacy by raising the dose, as the weekly median dosage for these patients was only half the maximum recommended dosage. Moreover, switching to subcutaneous administration in the 28 orally treated patients who discontinued MTX because of lack of efficacy might have increased the efficacy, as reported in a study of patients with rheumatoid arthritis (15).

With this study, we highlight the importance and possibility of optimizing MTX therapy before considering giving it up.

The authors declare no conflicts of interests.

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