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ORIGINAL ARTICLE

Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment

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ABSTRACT

Objective To evaluate the efficacy, safety and side-effects of methotrexate (MTX) in psoriasis.

Design A 26-year retrospective study.

Setting Department of Dermatology, Leipzig University, Leipzig, Germany.

Patients One hundred and fifty-seven patients with extensive plaque psoriasis, erythrodermic, pustular and arthropathic forms, were treated with low-dose methotrexate (15–20 mg maximum weekly dosage [Weinstein schedule]), the majority for long-term periods. The mean cumulative dose was 3394 mg, the mean duration 237 weeks.

Results The effect of MTX treatment was good in 76%, moderate in 18% and poor in 6% of subjects; 61% experienced side-effects, most frequently due to liver function abnormalities, bone marrow suppression, nausea, gastric complaints and hair loss. In 20% of cases the subjects were forced to discontinue therapy; 9% refused therapy due to physical and psychological discomfort, 2% wanted to become pregnant, 16% were lost to follow-up, 6% died from multimorbidity and old age. Three subjects (2%) developed cancer of the lung, breast or cervix uteri, possibly in relation to long-term MTX treatment. Altogether there were no deaths or life-threatening side-effects attributable to MTX treatment, and no cases of progressive liver cirrhosis apart from two extensive skin necroses due to overdosage (misunderstanding, suicidal attempt) that were treated successfully with citrovorum factor.

Conclusion Low-dose MTX (<15–20 mg/week) is an effective therapy for extensive and severe forms of psoriasis if patients are selected carefully and monitored regularly, particularly with respect to liver and bone marrow toxicity. This helps to reduce severe side-effects even during long-term treatment. Drug interactions must be avoided. MTX therapy according to the guidelines is relatively safe and still has a place in the systemic treatment of psoriasis with 40 years of experience and an acceptable safety record.

Key words: psoriasis, methotrexate, long-term treatment, efficacy, safety, side-effects

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Introduction

In 1951, Gubner *et al.*[1] noted the rapid clearing of psoriatic skin lesions in patients with psoriatic arthritis treated with the antimetabolic drug aminopterin. Later this drug was replaced by the more stable and less toxic derivative methotrexate (MTX).[2] Despite significant progress in alternative systemic treatment regimens, such as retinoids, cyclosporin A, and photochemotherapy with UVA (PUVA), the folic acid antagonist MTX remained in clinical use as a standard systemic therapy for psoriasis. The first guidelines[3] on MTX therapy for psoriasis have been revised several times since 1972 and have been approved by the FDA.[4]

MTX inhibits dihydrofolate-reductase competitively, reducing metabolism dihydrofolic acid to tetrahydrofolic acid which results in suppression of the intracellular synthesis of various folic acid derivatives that play an important role as cosubstrate in the transport of C_1 units. Synthesis of purin, thymin and DNA is disturbed as a consequence.

The immune system is a likely target for the antipsoriatic effects of MTX.[5] In addition, MTX interferes with epidermal cell kinetics, presumably due to a temporary reduction in

Table 1 Indications (A) and efficacy (B: good, C: moderate, D: poor) of MTX therapy

	A		B		C		D	
	n	%	*n*	%	*n*	%	*n*	%
Plaque psoriasis (>20% body surface)	57	(36)	42	(74)	11	(19)	4	(7)
Erythrodermic psoriasis	36	(23)	28	(78)	6	(17)	2	(5)
Pustular psoriasis, generalized	24	(15)	19	(80)	3	(13)	2	(7)
Pustular psoriasis, localized	12	(8)	8	(66)	3	(21)	1	(13)
Arthropathic psoriasis	28	(18)	22	(79)	5	(18)	1	(3)

Combination therapies with glucocorticoids were not evaluated in this paper

Table 2 Contraindications of MTX therapy

Liver disease
Renal failure
Gastric ulceration
Cytopenia
Pregnancy
Woman wishing to become pregnant
Man wishing to procreate
Concomitant medication of interactive drugs
History of alcoholism
Infectious diseases
Immune system deficiency
Unreliability, non-compliance

DNA synthesis and induction of apoptosis in keratinocytes[6] and it inhibits the chemotaxis of neutrophils and monocytes. Finally, it impairs C_{5a}-induced skin response and LTB_4-induced intraepidermal penetration of granulocytes. Owing to the inhibition of 5 aminoimidazol-4 carboxamide ribonucleotide transformylase, MTX induces the release of adenosin. Adenosin itself inhibits O_2 generation by polymorphonuclear cells (PMN), PMN adhesion, modulation of TNFα by macrophages and lymphocyte proliferation, which again explains the anti-inflammatory and immune modulatory effects of MTX.[7]

MTX has been used in severe cases of psoriasis with great caution owing to its known side-effects, particularly hepatotoxicity. In 1971 Weinstein and Frost[8] introduced a weekly divided schedule, i.e. three doses per week at 12-h intervals. Attempts to apply MTX as a topical formulation have failed, obviously due to poor percutaneous absorption and availability of thymidilate from the salvage pathway in the folic acid metabolism.[9]

Here we report on our 26 years' experience with long-term MTX treatment of psoriasis evaluated in a retrospective study with particular respect to clinical efficacy and side-effects. During the last 26 years, treatment modalities in the Department of Dermatology at the University of Leipzig have been modified four times with regard to dosage regimen and monitoring strategies.

Materials and methods

Files of psoriasis patients treated with MTX between January 1972 and December 1998 were reviewed. The indications for MTX therapy are outlined in Table 1. Besides psoriasis we also used MTX in pemphigus vulgaris (five cases), bullous pemphigoid (nine cases), systemic lupus erythematosus (four cases), dermatomyositis (six cases), Morbus Reiter (one case), pityriasis rubra pilaris (two cases) and mycosis fungoides (two cases).

Usually the drug was administered orally as described by Weinstein and Frost.[8] In the first period, treatment was started with 25 mg per week, increased up to 40–50 mg and than tapered down to a 10–15-mg maintenance dose. In the later periods doses were initially 15 and 25 mg per week and reduced to 7.5–10 mg. In several patients the interval was prolonged from 7 days to 10–12 days. MTX was given intravenously in only 12 patients with insufficient intestinal absorption. In these patients serum concentrations were determined by fluorometry. We tried to overcome these disturbances by changing from oral to parenteral administration rather than increasing the dose of the drug.[10]

Before starting therapy the following laboratory tests were performed: full blood count, serum creatinine, urine analysis and liver function tests (including aminotransferases, alkaline phosphatase and gamma-glutamyl transpeptidase, hepatitis serology), chest X-ray, later sonography of the abdomen (after 1980), aminopropeptide of collagen type III (in selected cases).[11] The laboratory tests were monitored at 4–8 week intervals, when patients attended our outpatient department. The weekly dosage was adjusted to clinical efficacy and side-effects. In single problem cases liver biopsies were taken after approximately 1.0–1.5 gm of the cumulative MTX dose and repeated at 3.0 and 4.0 gm, respectively. Liver histologies were graded according to the guidelines between I and IV. The contraindications are listed in Table 2.

All women of child-bearing age were subjected to a pregnancy test before starting treatment and the use of contraceptives was obligatory during the treatment.

Clinical course, efficacy, side-effects, duration of treatment, cumulative doses and reasons for discontinuation of treatment were recorded. Efficacy was considered good if the skin was clear or almost clear, moderate if recurrences were seen during treatment, and poor when there was no improvement. The impact on quality of life by means of validated questionnaires was not evaluated. The goal was not predominantly to achieve the complete clearing of psoriasis, but rather to achieve adequate control at the lowest dosage possible and the longest resting period from MTX treatment and to switch to another systemic drug or PUVA as the rotational therapeutic principle before reaching a cumulative toxic range.[12]

During MTX therapy topical treatment with dithranol, tars, corticosteroids and vitamin D analogues was encouraged.

Combinations of MTX with PUVA or retinoids were not performed. In various patients folic acid (citrovorum factor) (2.5–5 mg) was given 6–12 h after MTX to reduce side-effects, such as nausea and megaloblastic anaemia, without impairing the beneficial antipsoriatic effects of MTX.[13]

Results

Patients

One hundred and fifty-seven patients (109 male, 48 female) with a median age of 48.3 years at the onset of treatment (range 19–76 years), received MTX between January 1972 and December 1998. Fifty-seven (36%) suffered from patchy recalcitrant psoriasis vulgaris covering more than 20% of the body surface, 36 (23%) were erythrodermic, 28 (18%) arthropathic, 24 (15%) had generalized pustular form, 12 (8%) a localized form (Table 1). In December 1998, 17 patients were still on MTX treament.

Patients were distinguished according to five time periods. In the beginning patients were selected for treatment more generously, at later time points more strictly.

Dosage

The weekly dosage ranged between 7.5 and 40 mg (initially), as a rule it did not exceed 22.5–25 mg. The cumulative dose ranged between 120 and 10 235 mg (mean 3394 mg). The dose required for significant improvement was 75–235 mg. In 12 patients with intestinal absorption disturbances we changed the route of application from oral to intravenous.[10] Campbell *et al.*[14] found a systemic bioavailability of 35% after oral intake vs. 93% after intramuscular administration.

Duration of therapy

The therapy lasted for between 5 and 698 weeks (mean 237 weeks). The high rates of cumulative dose and duration are based on the fact that the therapeutic regimen was discontinued anywhere from one to several times.

Efficacy

Whether patients would respond or not could usually be demonstrated within 1–3 weeks. Depending on the clinical picture of psoriasis (Table 1), the effect was good in 119 patients (76%), moderate in 28 (18%) and poor in 10 (6%) (Table 1).

Our data show similar efficacy of MTX in stabilizing different types of psoriasis. This is true for erythrodermic psoriasis; a good response was also observed in 8 out of 12 patients with persistant localized pustular psoriasis. In our experience erythrodermic psoriasis responds to MTX as well as to cyclosporin A; however, mycophenolate mofetil (Cellsept®) as a monotherapy was less effective.

Table 3 Follow-up under MTX therapy (n = 157)

Effect	n	(%)
Good	119	(76%)
Moderate	28	(18%)
Poor	10	(6%)
Clearing of the skin	48	(31%)
Switch to an alternate systemic drug (rotation)	22	(14%)
Discontinuation due to side-effects	31	(20%)
Liver toxicity	22	(14%)
Bone marrow suppression	9	(6%)
Refusal (physical and psychological discomfort)	14	(9%)
Desire for pregnancy	4	(2%)
Drop-out (moving)	26	(16%)
Deaths (not MTX related)	9	(6%)
Cancer, possibly related to MTX	3	(2%)

Quality of life was assessed subjectively by the majority of patients and turned out to be significantly improved.

Time course and follow-up

In 48 (31%) cases skin lesions were cleared within 3–5 months and remained stable (Table 3). Twenty-two (14%) subjects received alternate systemic medication to prevent and avoid side-effects after long-term MTX treatment.

However, in 31 (20%) cases therapy had to be withdrawn due to side-effects, such as liver toxicity (22 [14%]) and bone marrow suppression (9 [6%]). In addition, 14 (9%) subjects refused to continue therapy due to physical or psychological discomfort and 4 (2%) wanted to become pregnant. Over the years we could not follow-up on 26 patients (16%), who had changed their doctor or their residence. Nine patients (6%) died from multimorbidity or old age, and three (2%) from cancer of the lung, breast and cervix uteri, possibly related to long-term treatment with MTX.

Arthropathic psoriasis

In arthropathic psoriasis MTX represents the drug of first choice. Mobility of the joints and subjective features usually improved significantly after 3–4 weeks' treatment. Subsequently, we tried to withdraw MTX after 4–6 months substituting it with non-steroidal antiphlogistics or antirheumatics. This was successful in 35% of the cases. In the majority, long-term treatment with MTX was required. MTX and non-steroidal antiphlogistics were generally not combined. There were no cases of rebound phenomenon after withdrawal of MTX in psoriatic arthropathy.

Relapses

The symptom-free interval after cessation of therapy was rather short, depending on the eruptive pressure of the

Table 4 Side-effects due to MTX therapy

Side-effect	n	% of total (n = 157)
Abnormal liver function tests	40	25%
Gastrointestinal	37	24%
Nausea	29	18%
Gastric complaints	12	8%
Vomiting	3	2%
Gastric ulcer	2	1%
Haematopoietic suppression	18	11%
Leucopenia	14	9%
Thrombocytopenia	11	7%
Anaemia	7	4%
Subjective	18	11%
Fatigue	14	9%
Headache	9	6%
Dizziness	3	2%
Kidney	5	3%
Hair loss	7	4%
Infection/pneumonitis	2	1%
Ultraviolet light	3	2%
Increased sensitivity	2	1%
Phototoxic erythema	1	1%
Neoplasm	3	2%
Wound healing (delay)	3	2%
Necrosis of skin (toxic)	2	1%

disease. After 6 weeks skin lesions started to reappear in 23% of patients, after 6 months full relapses were seen in 41% of patients, comparable to results with dithranol as well as acitretin treatment.[15] Thus, alternate treatment, at least topical applications, or in the majority of cases systemic therapy according to the principle of rotating potentially harmful drugs should be taken into consideration when MTX is withdrawn. Rebound phenomenon were seen in 12 patients, but no case with transition into a pustular form.

Side-effects

In 95 cases (61%) one or more side-effects were observed (Table 4). However, it was necessary to discontinue MTX therapy in only 31 (20%).

With regard to side-effects, there was no apparent difference between cases subjected to continuous or interval treatment in our study and no obvious relation between cumulative dose or duration of MTX therapy and the frequency or severity of side-effects. Furthermore, no signs of tachyphylaxis nor recalcitrance to MTX during repeated treatment periods were observed.

Abnormal liver function

Pretherapeutic monitoring was performed with great caution. Subjects with even minor hepatic dysfunctions or prepathological findings were excluded from MTX treatment. Nevertheless 40 subjects developed increased hepatic enzyme levels or pathological signs detected by ultrasound or liver biopsy. Therefore, MTX therapy had to be discontinued in 22 cases. On the other hand, seven subjects with obesitas and/or diabetes mellitus were included. These results are the subject of separate study, performed together with gastroenterologists. Altogether, we could not find any association between individual cumulative MTX dose, liver biopsy classification and function tests. Finally, no progressive liver cirrhosis was observed in MTX treatment.

Gastrointestinal side-effects

Nausea and discomfort occurred particularly during the first 2–3 days of MTX intake. These symptoms contributed to discomfort in 14 cases leading to refusal to continue MTX therapy.

Hematopoetic suppression

Usually, haematopoetic suppression occurred at higher doses and improved after dose reduction or temporary withdrawal of MTX. Haematopoetic suppression was the reason for stopping MTX therapy in nine patients.

Subjective side-effects

Significant fatigue and headache were reported by 10 of 18 subjects, lasting longer than the first 2–3 days after MTX intake, leading to discontinuation of MTX therapy in 14 cases.

Kidney

Kidney functions were affected relatively rarely indicated by infrequent increase in blood urea nitrogen retention. Impairments were reversible after subsequent dose reduction.

Hair loss

Loss of scalp hair occurred in 11 patients and lasted between 4 and 11 months. In five patients some regrowth was observed at lower MTX doses. Interestingly the hair loss was reversible in all patients after cessation of therapy.

Infection

Pneumonia forced cessation of MTX treatment in two patients.

Neoplasm

Three patients developed cancer of the lung, breast and cervix uteri. Details of the case histories are given in Table 5. Basal cell carcinomas in three different elderly patients were not attributed to MTX therapy which had been started less than 4 years before tumour manifestation.

Delay in wound healing

Delayed wound healing was observed in three patients who presented poor granulation tissue formation after wounding.

Necrosis of the skin

Multilocular necroses could clearly be attributed to an overdosage of MTX, in one subject due to attempted suicide, in another

Table 5 Characterization of cancer patients

Patient no.	Diagnosis	Cancer	Age	Sex	MTX dosage	Duration	Intervals without treatment	Remarks
1	Generalized pustular psoriasis	Lung	52	M	7895 mg within 17 years	527 weeks	5 (361 weeks total)	Non-smoker
2	Erythrodermic psoriasis	Breast	45	F	4912 mg within 12 years	419 weeks	6 (211 weeks total)	
3	Plaque psoriasis	Cervix uteri	42	F	3378 mg within 9 years	292 weeks	8 (176 weeks total)	

due to non-professional advice to switch from weekly to daily intake. Both cases were treated successfully with 5 formyl tetrahydrofolic acid (citrovorum factor) at relatively high doses every 6 h depending on the individual conditions.[16]

Ultraviolet light

Ultraviolet sensitivity was significantly increased in two cases; one subject experienced phototoxic erythema attributed to MTX treatment.

Drug Interactions

Drug interactions are most likely to become clinically relevant in subjects with decreased renal function. Significant candidates are non-steroidal anti-inflammatory drugs, trimethoprime, sulfamethoxazole, theophylline, warfarin anticoagulants,[17,18] salicylates, barbituates, phenytoin, retinoids, dipyridamole, penicillins and colchicine.[18,19] Dipyridamole can potentiate growth inhibitory effects of MTX in human keratinocytes.[20] We made every effort to avoid such interactions or at least we took them into account and, when necessary, adjusted the MTX dosage temporarily if such co-medication could not be avoided.

Discussion

This retrospective study of our 26 years' experience treating a total of 157 cases of extensive or severe psoriasis with MTX showed that with cautious selection and careful monitoring procedures, according to established guidelines,[4] MTX is a potent and efficacious drug. Similar preliminary results were published by our group in 1986[20] and 1994.[21] In 76% and 18% of the 157 cases the effects were good and moderate, respectively. Among the psoriatic subgroups the arthropathic form responded fairly well, the pustulosis palmoplantaris relatively poorly.[22] The mean dose was 3394 mg, the mean treatment period 237 weeks, discontinuing the therapeutic regimen once or several times, in order to prevent cumulative toxic effects.[23] The maximum weekly maintenance dose rarely exceeded 15 mg.

The preferable way of application seems to be oral. However, in a few recalcitrant cases, the intravenous or intramuscular route may be preferred due to superior pharmacokinetics.[10] In terms of the appropriate age, adults over 35–40 years can be treated, but the drug is generally contraindicated in childhood.

Side-effects were observed in 61% of patients. However, undesired effects due to hepatotoxicity, haematopoietic suppression, desire for pregnancy or general poor physical and psychological feelings forced discontinuation in only 31 (20%) cases. In several cases the principle of rotating alternate systemic treatments was applied using PUVA, retinoids and cyclosporin A. The relapse rate after discontinuation of therapy was 41% after 6 months. This corresponds to our experience with dithranol[12] and also with retinoids[12,15] and cyclosporin A.[23]

In terms of pharmacoeconomics MTX (10 mg/week) costs around 2 Euro, while the daily costs of acitretin (25 mg) is around 4 Euro and cyclosporin A (200 mg) around 12.50 Euro.

According to published data and the results presented, low-dose treatment with MTX seems to be relatively safe, even as long-term therapy.[17,24,25,26] After almost 40 years rare and unexpected side-effects are not likely to occur in terms of the safety profile. Presumably, there is no apparent relation between the cumulative dose or duration of therapy and the frequency of side-effects. As they may occur in any phase of treatment, thorough monitoring is imperative.

Possible elevated risk of cancer is of particular interest. However, some patients have been exposed to both photochemotherapy or other immunosuppressants as well as to arsenic compounds for decades. These influences may interfere with tumour initiation and hamper an objective risk assessment of MTX treatment. We found cancer of different internal organs in three cases, possibly, but not definitely, related to MTX treatment and three other patients with basal cell carcinoma, presumably not attributable to MTX. This deserves special attention because a seven-fold increase in non-melanoma skin cancers has been described in a group of patients treated with MTX or photochemotherapy.[27] However, these patients had been exposed to other potential carcinogenic factors, such as arsenic drugs, radiotherapy and PUVA, whereas our cases were treated only with MTX.

We did not record any deaths due to MTX. However, we found skin necroses in two cases due to overdosage (misunderstanding and suicide attempt). Presumably, specific MTX carriers in the human epidermis, might be important in cutaneous manifestations of MTX toxicity.[28] Clinically, erosion of psoriatic plaques can be observed as a sign of MTX toxicity.[29]

Liver fibrosis and cirrhosis were neither frequent nor severe.[30] After cessation of MTX hepatic dysfunctions were

not progressive and did not significantly impair quality of life. Liver function tests, together with ultrasound and detection of the aminopropeptide of collagen III,[11] and liver biopsies in severe or uncertain cases are proper tools to monitor liver damage.

Finally, it should be mentioned that MTX treatment for severe psoriasis can also exacerbate a variety of psychological and coping problems due to the chronic relapsing character of the disease. Fatigue, headache and other subjective features have been repeatedly attributed to MTX.[31]

In summary, we want to emphasize that MTX in low doses, even as a long-term treatment with and without medication-free intervals, is efficacious and relatively safe when applied with careful monitoring and cautious selection of subjects according to the established guidelines. After nearly 40 years experience with low dose MTX new limiting aspects in terms of its safety profile are unlikely.

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