Methotrexate for Psoriasis in 2004

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Introduction

Although the exact mechanism for the pathogenesis of psoriasis is still not completely understood in 2004, T-cell activity is clearly involved in its etiology. A vicious cycle occurs in which T cells are activated, cytokines are released, and target tissues become inflamed, resulting in the activation of additional T cells. Inflammation and epidermal hyperplasia with abnormal keratinocyte differentiation follow and are seen in the psoriatic plaques. The recent new insight into the immunological processes that take place in the inflamed skin and joints has led to advances in the pharmaceutical industry. This has provided us with a number of new "biologics" for treatment of psoriasis and psoriatic arthritis without the broader suppression of the immune system produced by the more traditional therapies including methotrexate (MTX). They are drugs, which until now have been without much specific organ toxicity such as hepatotoxicity as found with MTX or nephrotoxicity as known from cyclosporine. For this reason it may be valuable to re-evaluate the status of MTX treatment for psoriasis in 2004. The purpose of this review has been to shortly present data from 45 years' experience with this drug including present knowledge of working mechanisms, results of therapy, side effects and guidelines and thereafter discuss the place for MTX in psoriasis treatment within this age of "biologics".

Working mechanism

Despite the many years of MTX use, there are still uncertainties concerning the mechanisms of action. The early assumption of interference with epidermal and epithelial cell kinetics as the main factor for antipsoriatic activity, which the weekly divided oral dose was based upon, is no longer held valid. Today, immunomodulation has a far higher priority together with a number of aspects of anti-inflammatory properties. One of the more recent theories on the main effect is induction of apoptosis in activated T cells.

Results of therapy

The original placebo-controlled study by Black and co-workers (1) from 1964 did not use any of the present low-dose schedules. However, they clearly demonstrated the efficacy of MTX in psoriasis and psoriatic arthritis; and clinical practise and a number of surveys have since contributed to the acceptance of MTX as one of the most valuable drugs for the severe skin disease and active arthritis. An improvement of more than 75% of psoriasis was found in 31–90% of patients in the literature, when reviewed by van de Kerkhof (2). In the largest study, performed by Nyfors (3) in 1978, more than 75% clearing could be seen in 90% of 248 patients. A study from the Nijmegen (4) group from 1994 on 113 patients showed that long-term treatment with a maximum weekly dose of 15 mg MTX decreased hospital admissions during treatment by a factor of 10 compared with the pre-treatment period. The Nordic Quality of Life study from 2001 (5) showed that almost 10% of Danish members of the Psoriasis Association were presently on MTX, and that their quality of life was better than quality of life of patients on cyclosporine or retinoids.

The improvement of arthritis follows after 1–3 months regarding all of the following parameters: swelling, joint tenderness, morning stiffness, grip strength and pain together with ESR. Failure to obtain good results on psoriasis or arthritis can in both cases be due to too low a dose. Dosages should be adjusted according to clinical effect and side effects.

Side effects

Serious acute toxic reactions are recognized, but can in general be avoided if the drug is correctly used. The side effects of MTX can be seen in Table I. Subjective side effects can be found from the first week as well as later during treatment. The most common – nausea and abdominal discomfort – are usually mild. Fatigue, headache, dizziness and loss of appetite are uncommon, and depression, anorexia and loss of libido are rare. Decreasing the dosage is often followed by resolution, and discontinuation gives a total disappearance of symptoms. Profylactic folic acid (5 mg) taken two to five

Table I. *Side-effects of methotrexate in patients with psoriasis*

Common and mild	Uncommon	Rare
Nausea	Fatigue	Osteopathy
Abdominal discomfort	Headache	Stomatitis
Leukopenia	Vomiting	Burning sensation
Hepatotoxicity	Thrombocytopenia	Chills
	Liver cirrhosis	Fever
		Anaemia
		Dizziness
		Depression
		Hair loss
		Anorexia
		Gastrointestinal ulcers
		Agranulocytosis
		Pulmonary fibrosis
		Pneumonitis
		Toxic epidermal necrolysis

times weekly will also be helpful, and methoclopramide can be used as therapy against nausea.

The most common long-term side effect, liver toxicity, will be dealt with in more detail. Haematopoietic suppression may occationally occur, but is not frequently encountered. Leukopenia is more frequent than thrombocytopenia, anemia rarely appeares and agranulocytosis is extremely rare. All haematopoietic side effects may arise as a result of overdosing, which may be the result of unobserved decreased renal function, interaction with other drugs or poor patient instructions.

Oral lesions of stomatitis or a burning sensation of the skin are to be considered as warning signs of a possible overdose. The severe reaction of toxic epidermal necrolysis is associated with overdosis brought forward by interactions. Hair loss, photosensitivity and pulmonary fibrosis are all considered rare, but have recently been found more common than expected. Pneumonitis, which is feared in MTX cancer therapy, seldom occurs as a complication in treatment of psoriasis. Also osteopathy is rare in psoriasis, but better known as an adverse effect when treating leukaemia. Infections are in general not a significant problem. Stern et al. (6), when studying MTX-treated psoriatics, calculated the relative risks for non-cutaneous cancer and non-melanoma skin cancer to be 0.96 and 1.2 respectively. MTX gives negative results in the Ames test and the white-ivory somatic mutation test, but the drug is teratogenic, so women should not become pregnant while taking the drug.

Hepatic toxicity

Since 1968, a substantial number of co-operative as well as single studies have shown that MTX may induce liver damage, which in some psoriatic patients will lead to fibrosis or cirrhosis. Alcohol, an important co-factor for MTX-induced liver cirrhosis, adds to folate depletion of the liver. Polyglutamates of MTX within hepatocytes competing with hepatocyte folate polyglutaminates may lead to chronic hepatocellular folate deficiency, which in part may be responsible for the toxicity. Data from the co-operative investigations indicated that increasing cumulative dosage, increased alcohol intake, the combination of diabetes and obesity and increasing age were associated with liver damage in MTX-treated psoriasis patients. Previous intake of arsenic and long-term use of other hepatotoxic agents are similarly associated with liver damage. There have been great variations in the reported frequencies of fibrosis and cirrhosis among different studies. Data from 1987 showed a frequency of 7.4% cirrhosis among 390 patients from Aarhus, 195 men and 195 women. Among these, 20 men and 9 women developed cirrhosis, all had no signs of fibrosis in their first biopsy. Besides alcohol, a high number of patients previously treated with arsenic could have contributed to the relative high frequency of cirrhosis in Danish patients. Today advanced hepatic fibrosis and cirrhosis is much less frequent.

Guidelines

Indications and contraindications for the use of MTX in psoriasis as well as the way to monitor therapy have been presented in international guidelines. The recommendations presented below are, apart from discrepancies concerning liver biopsies and a few minor details, in line with these international rules.

Indications

The decision to administer MTX

should be individualized. Each patient should be evaluated with reference to severity of disease, amount of discomfort and incapacity, and general medical and psychological conditions. Psoriasis should be pronounced and not adequately controlled by standard topical therapy. In psoriatic arthritis it is recommended as a first drug of choice for patients with active disease requiring disease-modifying agents.

Contraindications

Normal kidney, liver and bone marrow functioning are prerequisites for MTX. Pregnancy and alcohol abuse are absolute contraindications, as are an active peptic ulcer or present severe infection. Drug interactions are listed in Table II. Concomitant medication with sulphonamides (especially if combined with trimethoprim), and salicylates are absolutely contraindicated. The exception is low-dose (100–150 mg daily) aspirin. Non-steroidal anti-inflammatory agents should be avoided on MTX treatment days. For a woman in reproductive years, contraception is required during treatment and until 3 months following discontinuation of the drug. It is preferable that the patient abstains from alcohol intake during therapy, but up to three units of alcohol per week can be allowed. It is of utmost importance that the patient is reliable and cooperative.

Laboratory investigations

Table III shows laboratory examinations recommended before and during treatment. A pre-treatment liver biopsy is not recommended unless one is dealing with a high risk factor for liver disease. A baseline serum procollagen type III aminoterminal peptide (PIIINP) is preferable. PIIINP is a valuable non-invasive marker of fibrogenesis. Although the test is not organ specific and no marker for fibrosis, it has been established that as long as PIIINP is normal no significant development of fibrosis is taking place in the liver. PIIINP is recommended to be studied initially three times, and later twice yearly. If PIIINP is increased, which may take place during pronounced activity of arthritis, the rules established earlier concerning liver biopsies should be followed. These guidelines have advised at least performing a first liver biopsy, when the cumulative dose reaches 1.5 g and repeat liver biopsies at 1–1.5 g intervals of further cumulative doses.

Choice of dosage

The weekly oral single dosage schedule has recently become more popular than the divided weekly oral dosage by many dermatologists. However, other dermatologists prefer the latter in order to avoid higher peak values. There are no good comparative studies at present for a good choice. The American guidelines advise a test dose of 5–10 mg to avoid hypersensitivity reactions. Over the many years of MTX use, the author has only done this in elderly patients, and has yet to encounter a situation regretting not having performed the test dose. With the divided weekly oral dosage, a start with 5 mg at 12 h intervals three times once weekly can be given to the average adult weighing approximately 70 kg, a dose to be reduced according to weight, with the lowest dose being 2.5 mg for each of the three doses. The single weekly dose is normally not to go above 25 mg/week. Occasional patients, however, may need a maximum of 37.5 mg/week. A weekly parenteral dose, starting with 15 mg weekly, may be chosen for patients who have difficulties with uptake of the drug, or to lessen gastrointestinal problems. Up to 50 mg weekly is regarded

Table II. *Drug interactions that may increase methotrexate (MTX) toxicity*

Mechanism	Drugs
Pharmacological enhancement of MTX-toxic effect	Trimethoprim-sulfamethoxasol
	Phenylbutazol
	Ethanol
Decreased renal elimination	Nephrotoxins
	Salicylates
	Sulphonamides
	Probenecid
	Cephalosporin
	Colchicine
Displacement of MTX from plasma protein binding	Salicylates
	Probenecid
	Barbiturates
	Phenytoin
Intracellular accumulation of MTX	Probenecid
	Dipyradimol
Hepatotoxicity	Ethanol
	Retinoids
Additive antihaematopoietic effect	Cytotoxic drugs
	Chloramphenicol

Table III. *Laboratory examinations before and during treatment*

Before therapy
Haemoglobin, leucocyte and differential count, thrombocyte count
Urine analyses, serum creatinine, preferable glomerular filtration rate (GFR)
Liver transaminases, alkaline phosphatases, bilirubin
N-terminal propeptide of procollagen type III (PIIINP)
Serum albumin
Chest radiography
During therapy
Initially after a week, later monthly
Leucocyte and thrombocyte counts
Livertransaminases
2–3 times yearly
N-terminal propeptide of procollagen type III (PIIINP)
Haemoglobin
Alkaline phosphatases
Serum creatinine
Yearly
GFR (In case of increasing serum creatinine)
Serum albumine
Chest radiography
After 1.5mg accumulated MTX, in case of abnormal PIIINP
Liver bi-

as safe with a reduction according to weight.

All dosages should be adjusted according to clinical effect and side effects, including the subjective. Minor increases in liver enzymes can be tolerated, but if being persistent or major increases of 100% or more, they should lead to reduction or temporary discontinuation. The patient's alcohol consumption should also be reexplored.

A 100% clearing should not be the aim of treatment. What can be expected is an improvement to approximately 75% clearing, and thereby a pronounced improvement in quality of life. Long-term treatment beyond the clearing phase and consolidation phase of the arthritis will usually permit a gradual reduction in dose.

Combination therapy

Many patients on MTX are often so well managed by the drug, that they discontinue their topical therapy. Topical therapy, however, should be generally encouraged to help keep the systemic dose as low as possible. On the other hand ever so often, single drug therapy may fail to clear the patient sufficiently within the possible dose range, therefore other combined approaches have been sought. It is beyond the purpose of this article to go into details of this approach, but it may be mentioned that the combination of MTX and cyclosporine has been used with benefit without greater problems when adhering to the guidelines for both drugs. The same appears to the combination of MTX and some of the new single-target immunomodulatory drugs, the "biologics".

Among these can be mentioned infliximab and etanercept, both anti-TNF-α drugs, where a large number of patients over several years have benefited by this combination therapy. MTX may also be combined with efalizumab.

General considerations

If the rules for accepted control are adhered to, the risk/benefit ratio for MTX is still among the favourable, and the drug should be considered one of the most valuable for severe psoriasis. Although the biologics may achieve higher response rates and show better safety profiles as a whole, real long-term experience is still lacking, and the drugs are not without side effects. With etanercept upper respiratory symptoms have been reported frequently, and for efalizumab arthralgia and flu-like symptoms are known. Infliximab has been implicated in reactivation of latent tuberculosis, increased incidence of opportunistic infections, formation of antinuclear antibodies and demyelination. Also, the results of the biologics are not always of a higher dimension in relation to clearing, and besides all drugs until now show non-responders. Finally, with the rising cost of medication both for the individual and for society as a whole only a proportion of patients with psoriasis in the Nordic countries will be allowed to switch to one of the new therapies, and worldwide the percentage will be extremely small. Therefore the specialists should keep up their skills in using the more "old fashioned" drugs as MTX as safely and effective as possible.

Further reading

1. Zachariae H. Methotrexate. In: P. van de Kerkhof (ed.) Textbook of Psoriasis, Blackwell Publishing, Oxford 2003.
2. Cather J, Menter A. Novel therapies for psoriasis. Am J Clin Dermatol 2002; 3: 159–173.

References

1. Black R, van O'Brien W, Scott E, Auerbach R, Eisen AZ, Bunim JJ. Methotrexate therapy in psoriatic arthritis; Double-blind study on 21 patients. J Am Med Ass 1964; 189: 743–747.
2. van de Kerkhof P, Vissers W. Established treatments of psoriasis. Curr Drug Target Inflamm Allergy 2004; 2: 145–156.
3. Nyfors A. Benefits and adverse drug

experiences during long-term methotrexate treatment of 248 psoriatics. Dan Med Bull 1978; 25: 208–211.
4. van Doreen-Greebe R, Kuijpers A, Buijs W, et al. Methotrexate revisited: Effects of long-term treatment in psoriasis. Br J Dermatol 1994; 130: 204–210.
5. Zachariae H, Zachariae R, Blomqvist K, et al. Treatment of psoriasis in Nordic countries: A questionnaire survey from 5739 members of the Psoriasis Association, data from the Nordic Quality of Life study. Acta Derm Venereol 2001; 81: 116–121.
6. Stern R, Zierler S, Parrish J. Methotrexate used for psoriasis and the risk of non-cutaneous and cutaneous malignancy. Cancer 1982; 50: 869–872.

Preliminary programme for Scandinavian EB-conference 2005

Sunday 24 April

17.00 Registration

18.00 Get-together party

Monday 25 April

8.15 Registration

Plenary morning session I (Chairs: Malin Netz, Anders Vahlquist)

8.30 Official opening & A short history of EB in Sweden - *Malin Netz & Anders Vahlquist*

9.00 Classification of EB - *Robin Eady*

9.30 The pathogenesis of EB - *Leena Bruckner-Tuderman*

Plenary morning session II (Chairs: Heidi Ellingsen Silseth, Carl-Fredrik Wahlgren)

10.30 Prognosis of different EB-forms - *Dörte Koss-Harnes*

11.00 Healthcare professionals' part in the EB-patient's life - *Janice Carrera*

11.30 Multiprofessional care – Marcel Jonkman

12.00 Introduction to the workshop sessions - *Gabor Koranyi*

13.30 Workshops, session I; all workshops led by a multidisciplinary panel

Workshop A: Neonatal care + nutrition + parental support - *Carl-Fredrik Wahlgren*

Workshop B: Wound dressings + pain management + ophtalmology - *Gabor Koranyi*

Workshop C: Surgery + physiotherapy + occupational therapy - *Gerd Wohlin*

Workshop D: Psychological and social support + oral care + prophylactic skin care - *Malin Netz*

15.30 Workshops, session II (repeated with new participants)

19.00 Bus leaving for the conference dinner

19.30 Conference dinner at Restaraunt Atrium, National Museum Art Gallery

Tuesday 26 April

Plenary morning session (Chairs: Bitte Ahlborg, Kris Aaseth)

8.30 "A life time story of EB"; case studies - *Tobias Gedde Dahl*

Therapeutic summaries:

8.50 The skin - *Jackie Denyer*

9.10 Surgery - *Bryan Mayou*

9.30 Mouth and teeth - *Nina Skogedal*

9.50 "Focus on everyday-life" - Presentation of an inquiry study - *Elisabeth Wallenius*

10.10 Coffee break + poster and exhibition viewing

10.40 Introduction to EB-forum on the Internet and Professionals' forum - *Heidi Ellingsen Silseth & Anders Vahlquist*

10.50 Professionals' forum

* Physicians - *Anders Vahlquist*
* Dental professionals and speech therapists - *Mats Jontell*
* Nurses and dieticians - *Jackie Denyer & Lesley Haynes*
* Occupational- and physiotherapists - *Gerd Wohlin*
* Psychologists and social workers - *Janice Carrera*

12.10 Lunch

Plenary afternoon session I (Chair: Kristina Gustafsson-Bonnier)

13.30 "Personal experience"; panel interview of four EB-patients led by a professional journalist

14.30 Coffee break + poster and exhibition viewing

Plenary afternoon session II (Chair: Christina Eklund)

15.00 Patients' organisation/DEBRA; peer counselling, co-operation between patients, professionals and society - *Kris Aaseth*

15.20 Future therapy; gene therapy? - *Leena Bruckner-Tuderman*

16.00-16.15 End of conference - *Malin Netz & Anders Vahlquist*