Skin Therapy Letter ©

Volume 6 · Number 3 · 2000

16-JAN-2001 BSDS BOSTON SPA LS23 7BQ
SKIN THERAPY LETTER

8295.949000 VOL 6 NUMB 3

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Systemic Therapy of Psoriasis I

using methotrexate

K.C. Smith, MD FRC
Niagara Falls, Ontario, Can

ABSTRACT

If methotrexate were introduced as a new drug today, it would be hailed as a major advance in the management of psoriasis, as well as for a number of other conditions. Because the patent on methotrexate expired decades ago, this medication has not recently received the attention it deserves. When patients are properly screened and educated about the correct use of methotrexate, and appropriately monitored during treatment, this drug is a safe, inexpensive, well-tolerated and effective medication for the control of psoriasis.

KEY WORDS: *psoriasis, methotrexate, systemic therapy*

In 1951 Gubner[1] reported improvement in psoriatics treated with the folate antagonist aminopterin, but clinical use was limited by mucosal and GI side-effects. In 1958, Edmundson and Guy[2] reported good control of psoriasis with amethopterin, or methotrexate (MTX), an analog of aminopterin.

MTX can produce a number of side-effects, particularly GI and liver toxicities. However, administration of folic acid has been shown to reduce or eliminate the GI distress sometimes associated with MTX, and does not interfere with its efficacy.[4] Several different dosage schedules have been reported to be effective. The author finds 10mg of folic acid po once a week with MTX (regardless of the dosage of MTX) is both simple and effective. Folinic acid (Leucovorin), by contrast, reduces the efficacy of MTX[5], and should be administered as an antidote in cases of MTX overdose.

Studies in animals demonstrated that MTX toxicity was more closely related to duration of contact with tissues than with total dose, and in 1963, Berlin[3] suggested that an intermittent dosage schedule might improve the therapeutic index. The current practice in dermatology is to administer MTX as a single dose once a week, or in three divided doses 12 hours apart, to reduce GI discomfort. There is no evidence that three divided doses 12 hours apart is safer, and there are occasional reports of serious or lethal toxicity when patients mistakenly take MTX every 12 hours, every day of the week.

Mechanism of Action

MTX is one of the most effective systemic therapies for psoriasis, but the mechanism of action is not completely understood. The proliferating lymphoid cells THP-1 (macrophages) and MOLT-4 (T-cells) are over 1000 times more sensitive to MTX than keratinocytes at the concentrations seen in vivo with once-weekly therapy.[6] Low-dose MTX also promotes the intracellular accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) by inhibiting AICAR transformylase. Under conditions of cell injury, AICAR increases the release of the autocoid adenosine, a potent antiinflammatory agent.[7]

Patient Selection and Management

The best candidates for treatment with MTX are those patients who, in addition to lacking contraindications to methotrexate, are honest, reliable and realistic. Patients must be willing to avoid alcohol consumption while taking methotrexate, and should be willing to continue topical medications to reduce the dose of methotrexate required to obtain an adequate degree of control of their psoriasis.

Patients should be instructed to obtain ALL of their medications from a SINGLE pharmacy, to reduce the chances of drug interaction. A letter should be sent to every physician who is caring for the patient, informing them that MTX is being started, and a copy of all bloodwork should be ordered for each treating

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physician. Patients who do not have a family doctor should not be offered methotrexate unless your office is set up to deal with bloodwork abnormalities, regardless of whether you are available. Patients who do not cooperate with the regular bloodwork necessary for the safe use of this drug should be warned firmly, and a letter about this warning should be sent to each of the patient's doctors. If non-cooperation continues, MTX must be stopped. Documentation about the patient's history with regard to MTX, whether MTX was well tolerated, and the cumulative dose of this drug is important.

It is also important to document the justification for offering to prescribe MTX (e.g., the extent and location of the psoriasis, and the impact the psoriasis is having on the patient's life, employment and relations with others).

Patient Information

Prior to starting MTX, patients must be educated about the precautions necessary for the safe use. Discuss the need for contraception with women who are candidates for treatment with methotrexate. Women must avoid pregnancy while taking this drug and for 3 months after stopping it because it has been associated with teratogenicity. There is no evidence that MTX has any adverse effect on spermatogenesis or fertility in men at the doses used in dermatology, and men should be reassured about this.

Management

Prior to starting MTX, and from time to time during treatment, a list of the patient's prescription and non-prescription medications (including "natural" or herbal remedies) should be reviewed, and the patient again cautioned to avoid alcohol consumption. Laboratory studies prior to starting MTX should include CBC, SGOT, alkaline phosphatase, bilirubin, creatinine, serum albumin, and hepatitis B and C serology. As well, HIV-1 should be checked in those at risk for HIV. However, MTX has been used successfully to treat psoriasis in HIV infected patients.[8] CBC and SGOT should be repeated twice a month for the first two months of treatment, then monthly while the patient is taking MTX. The SGPT should NOT be tested. It is frequently elevated when there is no clinical problem, leading to an unacceptable number of "false alarms".

Hepatitis in low-dose therapy is not commonly seen, and may be more common in patients receiving combination therapy with etretinate, in those with heavy alcohol consumption, or in those with a higher total cumulative dose of methotrexate. Some drugs that can affect the toxicity of MTX are listed in Table 1. Liver biopsy is generally not performed prior to starting MTX in otherwise healthy patients. However, each prescription for this drug should be recorded in a flow chart, and when the total dose reaches 1.5gm, the patient should be referred to a gastroenterologist for consideration of a liver biopsy. As a general rule, a liver biopsy is not performed in healthy, young, non-obese, non-diabetic patients who have normal liver function studies. Patients should return to the gastroenterologist for reassessment each time the total dose of MTX increases by 1.5gm.

The Roenigk classification of liver biopsies (Grades 1-4)[9] has been criticized because it was adapted from a classification system developed many years ago for use in primary biliary cirrhosis where portal inflammation is the major feature. For this reason, it is not an ideal classification tool for assessing MTX toxicity, which tends to produce centrilobular changes.

The starting dose of MTX in an adult is usually in the range of 10-15mg at bedtime, once a week. Improvement in psoriasis is usually seen within 4-8 weeks. The dose may be increased to 25mg once a week if necessary. Topical medications and UVB or PUVA are usually continued in order to reduce the long-term need for MTX. Phototoxicity associated with MTX has been reported, but is very rare in clinical practice, and MTX is often used successfully with UVB or PUVA.

When a patient has improved to a satisfactory degree, the dose of MTX can be adjusted each week within a specified range (e.g., between 2.5-15mg once a week), as necessary. This is done in order to maintain adequate (but not necessarily perfect) control of the psoriasis, and often allows for a lower cumulative dose of

Effect/Mechanism	Drug
Increased hepatotoxicity of MTX	• Alcohol • Etretinate
Increased effects and toxicity of MTX	• Sulfonamides • Other antineoplastics
Reversal of MTX action	• Folinic acid (Leucovorin) (used as antidote for overdose)
Decreased renal elimination	• NSAIDS • Aspirin • Probenecid • Cyclosporin • Other nephrotoxins
Increased antifolate effect	• Phenytoin
Decreased MTX effect	• Neomycin (oral) with oral MTX

Table 1: Drugs that may effect the toxicity of methotrexate

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MTX than would be the case if the patient was maintained on a fixed dose, e.g., 15mg once a week.

Rotational Therapy

The successful use of "rotational therapy" (e.g., switching every 3-6 months between several treatments including methotrexate, cyclosporine, acitretin and PUVA) depends on many variables, including the patient's finances, ability to attend on a regular basis for UV light treatment, underlying medical conditions, and medications. The increased complexity and cost of rotational therapy is sometimes justified by the reduced long-term load on any one organ system:

- Methotrexate – liver damage
- Cyclosporine – altered kidney function
- PUVA – skin
- Acitretin – elevated lipids.

Conclusion

Methotrexate is an effective medication for the control of psoriasis. When patients are properly screened and educated about the correct use of this drug, and appropriately monitored during treatment, MTX is often very safe, simple to use, inexpensive, and well-tolerated.

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US FDA Advisory Committee Recommends Approval for Tacrolimus Ointment

The US FDA Dermatologic and Ophthalmic Advisory Committee recommended in November 2000, that Fujisawa's *Protopic* Ointment (tacrolimus) be approved for the treatment of moderate-to-severe atopic dermatitis in children and adults.

Atopic dermatitis, or eczema, is an increasingly common pruritic dermatosis that is believed to be triggered by an imbalance in the immune system. Tacrolimus is the first of a new generation of topical immunomodulators that bring about clinical improvement by modulating the patient's immune response and is the first to be recommended for approval by the FDA.

Fujisawa presented data from clinical studies conducted world-wide, in which children and adults were treated for 12 weeks to 1 year. The US clinical trials were double-blind, placebo controlled, and patients were randomized to apply either 0.03% tacrolimus, 0.1% tacrolimus or placebo twice daily. Both concentrations of *Protopic* significantly improved or completely cleared the signs and symptoms of atopic dermatitis in ≥2/3 of the patients.

The Committee recommended the 0.1% concentration to treat adults. The lower 0.03% concentration was recommended for children, and for adults who are undergoing long-term intermittent therapy, and are intolerant of, or are not adequately responsive to, conventional treatment. *Protopic* was not recommended as a first-line therapy. Committee members felt that patients should begin with treatments that have well characterized safety profiles, e.g., corticosteroids. Tacrolimus is steroid free and provides a welcome addition for the management of atopic dermatitis, since many patients, as well as parents, are loathe/afraid to use corticosteroids.

Skin burning and itching associated with the application of *Protopic* was reported, however, these events seemed to decrease as the disease improved. The effects of ultraviolet light on skin treated with *Protopic* are not known. Many committee members expressed concern about this and recommended that patients using *Protopic* should use safe sun practices to avoid exposure to natural or artificial sunlight.

Fujisawa put forward a New Drug Submission to Canada's Therapeutics Products Program (TPP) (formerly HPB-Ottawa) in July 2000, for this product, and phase III clinical trials are underway. In Japan *Protopic* 0.1% was approved in 1999. A decision by the FDA is expected in the next 6-8 weeks.

JUST ANNOUNCED! On December 8, 2000, the US FDA granted approval of this topical immunomodulator in the recommended concentrations for the treatment of atopic dermatitis. Next issue (volume 6, Issue 4) Topical Tacrolimus, S.J. Frankel and F. Kerdel.