Commentary and update: Methotrexate for psoriasis—two decades later

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As a resident in dermatology at the Cleveland Clinic 20 years ago, I wished to pursue a research project that would have clinical application, and I became interested in studying methotrexate (MTX), a dramatic systemic drug useful in treating psoriasis.

Control of severe generalized psoriasis with systemic drugs has long been a goal of dermatologists. Drugs initially used such as arsenic and systemic corticosteroids had resulted in serious adverse reactions and are generally not used today. Systemic corticosteroids often produced generalized pustular psoriasis. Antimetabolic drugs ushered in a new era in the treatment of psoriasis. Gubner et al[1] fortuitously noted in 1951 the rapid clearing of psoriatic skin lesions in a patient with rheumatoid arthritis treated with aminopterin. Clinical experience in dermatology developed with aminopterin[2]; however, it was later replaced by a more stable derivative, MTX,[3] which was used in cyclic dosages with fewer severe side effects than aminopterin. Other antimetabolic drugs such as hydroxyurea, azathioprine, azaribine, and mycophenolic acid have been used to treat psoriasis, but have not been as effective as methotrexate, which has stood the test of time despite many side effects. Recently, psoralen and UVA (PUVA) therapy and systemic retinoids have challenged MTX as the best systemic treatment for psoriasis.

The mechanism of action of MTX was well worked out when we initiated our studies with MTX.[4] We found in experimental studies of animals that a single dose of MTX was safer than divided doses. The common practice at that time was two or three tablets of MTX administered daily for five days and then resting a few days and repeating the dose. We proposed giving MTX as a single oral dose, 25 mg/wk.

Methotrexate was a cancer chemotherapy drug and for the first years (1955–1970) was the standard systemic drug for the treatment of psoriasis, although it was not approved by the Food and Drug Administration (FDA). Under the Psoriasis Task Force of the National Program for Dermatology, Roenigk, Maibach, and Weinstein[5,6] prepared guidelines for MTX treatment of psoriasis after a thorough review of the literature. Soon after these guidelines were developed the FDA used them to approve MTX for use in psoriasis. The MTX guidelines were recently revised after 10 years of experience.[7] The following represents the major points of these guidelines in the use of MTX as a systemic treatment for psoriasis.

Indications

The decision to administer MTX for the treatment of psoriasis should be made on an individual basis with regard to severity, amount of discomfort, degree of incapacity, and general medical and psychological condition. Methotrexate is indicated in the symptomatic control of recalcitrant psoriasis not responsive to topical therapy. The diagnosis of psoriasis and the need for MTX therapy should be established by dermatologic consultation.

Only patients who have severe psoriasis, which may be life-ruining physically, emotionally, or economically and cannot be adequately controlled by standard topical antipsoriatic therapy should be treated with MTX. Some examples of candidates for MTX therapy are listed in the *Table*.[7]

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Table. Methotrexate guidelines

- Candidates for MTX therapy
  - Psoriatic erythroderma
  - Psoriatic arthritis
  - Acute pustular psoriasis—Von Zumbusch type
  - Localized pustular psoriasis
  - Psoriasis in areas of body preventing economic employment
  - Extensive psoriasis
- Relative contraindications
  - Significant renal function abnormalities
  - Significant liver function abnormalities
  - Pregnancy—near absolute
  - Men or women in fertile age—appropriate steps should be taken to avoid conception during and for at least 12 weeks after discontinuing MTX therapy
  - Hepatitis, active or recent
  - Cirrhosis
  - Severe anemia, leukopenia, or thrombocytopenia
  - Peptic ulcer, active—near absolute
  - Excessive alcohol consumption
  - Active infectious diseases (i.e., tuberculosis, pyelonephritis)
  - Unreliable patient. Circumstances may arise in which contraindications must be waived, i.e., when benefits can be expected to outweigh the risks of MTX therapy in an individual patient
- Pre-MTX evaluation
  - History and physical examination
  - Laboratory
  1. Hematologic
     - Hemoglobin
     - Leukocyte count
     - Platelet count (quantitative)
  2. Renal function studies
     - Urinalysis
     - Blood urea nitrogen (BUN)
     - Serum creatinine or creatinine clearance
  3. Liver function studies
     - Routine liver function tests, such as serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, bilirubin
  4. X-ray film of chest
- Liver biopsy
- Continuing laboratory studies
  1. 1- to 4-week intervals
     - Leukocyte count
     - Platelet count
  2. 3- to 4-month intervals
     - Hemoglobin
     - Urinalysis
     - Serum creatinine
     - SGPT
     - SGOT
     - Alkaline phosphatase
  3. Yearly intervals
     - Creatinine clearance (optional)
     - Chest x-ray

A thorough history and physical examination often identify patients with preexisting risk factors such as liver disease. Chemical liver function tests identify only certain cases of existing liver disease. Recent studies[8] with quadratic multiple ordered laboratory tests have differentiated between alcoholics and nonalcoholics with different degrees of liver disease. Our initial studies[4] had identified several patients with abnormal liver function, which encouraged further studies[9] to investigate abnormalities of liver biopsies in patients before starting MTX (*Table*).[7]

The liver and methotrexate

After many years it became apparent that some patients were showing abnormal liver function study results while receiving MTX. Early studies immediately incriminated MTX although no pretreatment liver biopsies had been done and other factors such as alcohol, drugs, and hepatitis were not considered.[10] Dermatologists began doing biopsies on psoriatics with no prior MTX therapy and found a variety of abnormalities including cirrhosis.[9,11] It has been suggested that the liver was involved in the pathogenesis of psoriasis. In the late 1960s several pretreatment liver biopsies were done prospectively to determine the effects of MTX on the liver. An international meeting was held to develop criteria for classifying liver biopsies and to evaluate the data of many investigators on MTX and liver function. Weinstein et al[12] found no increase in incidence of fibrosis and cirrhosis from first to last liver biopsy. Factors found to be important in increasing liver damage due to MTX were (1) obesity, (2) increased age, (3) alcohol intake, (4) total dose of MTX, (5) frequency of administration (daily oral dosage schedule). These studies formed the basis of recommendations on follow-up of liver function studies and biopsies in the MTX Guidelines.[5–7]

Liver scans are of minimal value in detecting liver disease. The most reliable test of liver damage is the needle biopsy technique. Severe liver disease can be present, as shown by liver biopsy, in the face of a normal physical examination, liver function tests, and liver scans.

Therefore, it is advisable that a liver biopsy be done, when feasible, before starting MTX therapy. Exceptions might be: (1) advanced age, (2) marked obesity, (3) acute illness (acute pustular psoriasis), (4) medical contraindications for liver biopsy (cardiac instability, prolonged bleeding time for prothrombin time), and (5) anticipated short-term use of MTX. When these conditions change[3–5] and long-term use of MTX is anticipated, liver biopsy should be done.

The decision regarding follow-up liver biopsies during MTX therapy is made on the basis of

pretreatment liver biopsy, risk factors, and total cumulative dose of MTX. Details of management are outlined in the recent guidelines.[7]

The international cooperative study[12] published in 1973 involved 550 patients, and 81 patients had pre-MTX and post-MTX sequential liver biopsies. The second study involved 900 patients two years later. Both concluded that with increased dosage of MTX (>2200 mg), there was no significant increase in incidence of cirrhosis, but an overall slight increase in liver damage. Evaluation of single post-MTX liver biopsies showed a 3% incidence of cirrhosis.

Zachariae et al[13] and Nyfors and colleagues[14,15] suggest that longer exposure (years) to MTX and/or a higher cumulative dose of MTX leads to a higher incidence of cirrhosis. The international cooperative study[12] shows a much lower incidence of cirrhosis than Nyfors[14] (2 groups, 1977) and Zachariae.[16] All studies indicate that the incidence of cirrhosis is low with a total dose of MTX below 1.5 g.

Risk factors (alcohol, arsenic, lowered renal function, obesity, diabetes) in Zachariae's[16] (1980), and probably in all studies, increase the risk of fibrosis and cirrhosis developing with accumulation of less than 1.5 g of MTX. Nyfors[14] (1977) has the highest reported cumulative MTX dose (4000 mg) in a large group and suggests an increasing incidence of cirrhosis with cumulative increased dosage. It is our impression that the incidence of cirrhosis in the United States is much lower than recently reported (Nyfors and Zachariae), particularly when the risk factors can be minimized.

Klaber and Baker[17] have recently confirmed reports of Nyfors and Zachariae of a high incidence of fibrosis and cirrhosis after many years of MTX therapy in total cumulative dose over 5000 mg. The clinical course of cirrhosis induced by MTX seems to be nonaggressive; in fact many of these patients have been continued on MTX therapy without worsening of liver biopsy findings.[17]

Drug dosage schedules

The single oral dose that we suggested in our initial studies[4] has remained one of the two major forms of administration. Weinstein and Frost[18] did kinetic studies that confirmed a mechanism of action of MTX in psoriasis. They suggested a divided dose, intermittent oral schedule given over a 36-hour period each week. Although one liver biopsy study[19] suggested increased toxicity from this schedule, it is still used along with the single oral dose.

Drug interactions

The use of any drug in addition to MTX should be carefully evaluated and avoided, unless there are definite indications for its use.

Methotrexate is bound in part to plasma albumin and is displaced by a number of other drugs.[7] Toxicity may be altered by concomitant use of these drugs. In the dosages of MTX used in treating psoriasis, such reactions are rarely clinically significant. Concomitant therapy with irradiation or with chemical agents known to have a depressive effect on the hematopoietic system should be used with extreme caution. Corticosteroids administered systemically with MTX should be avoided when possible. The concomitant use of corticoids and MTX increases the risk of serious complications.

Adverse reactions

Other reactions to MTX noted in our early studies were nausea, headaches, and burning of the skin, and later included gastrointestinal, hematological, urogenital, and central nervous system problems.

Several single case reports of carcinoma developing during MTX therapy have been published, implicating possible immunosuppressive effects of MTX. Bailin et al[19] followed 205 MTX-treated psoriatics, but observed no increase in the incidence of internal cancer, neither general nor specific. Nyfors[20] followed 248 MTX-treated psoriatics and found 10 malignancies, again of different types and not significantly higher than the expected number of internal malignancies. Stern et al[21] found no increase in cutaneous or noncutaneous malignancies in MTX-treated patients.

Combination therapy

Although combinations of MTX with other drugs may produce adverse drug interaction, some drug combinations with MTX may have beneficial effects and reduce potential toxicity from both drugs. Topical therapy should be encouraged to keep the dose of MTX low. Patients taking MTX tend to abandon effective topical and intralesional steroids and tars; patients whose disease is *not* controlled by MTX would benefit from the full Goeckerman.

Methotrexate combined with PUVA resulted in clearing at a considerably lower amount of

UVA than is noted with PUVA alone.[22] Patients have been treated with a three-week course of MTX followed by a combination of UVB and MTX.[23] Methotrexate was stopped when the disease was controlled and maintenance was with UVB therapy alone. It is difficult and inconvenient to control severe psoriasis with UVB alone without having to restart MTX. The well-known recall of UVB-induced erythema[24] was not seen in this study.

Methotrexate combined with retinoids provides a more rapid clearing of severe generalized pustular psoriasis than either drug alone.[25,26] Further experience with these two drugs and possibly combining them with UVB or PUVA may reduce the adverse reactions of each modality by allowing rest and repair of the various organ systems targeted for toxicity during treatment with an alternative agent.

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