

Multidisciplinary Focus on Methotrexate in Psoriatic Disease

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ABSTRACT. The aim of this focus is to establish the role of methotrexate (MTX) in the treatment of psoriatic disease (PD). Despite the lack of hard evidence, MTX can be regarded as the nonbiological drug of choice for the treatment of peripheral psoriatic arthritis, although its effect on psoriatic dactylitis, enthesitis, and spondylitis needs to be further studied by means of well conducted clinical trials. MTX is effective in improving the skin involvement of PD, and can be used in moderate to severe psoriasis before starting a biological agent. Although rheumatologists consider it relatively safe in PD, dermatologists are very concerned about its toxicity and so, until more definite data are available, precautions should be taken to prevent MTX-induced liver fibrosis and cirrhosis. (J Rheumatol 2009;36 Suppl 83:56-58; doi:10.3899/jrheum.090226)

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METHOTREXATE

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RHEUMATOLOGISTS' PERSPECTIVE

Methotrexate (MTX) is the most widely used disease modifying antirheumatic drug (DMARD) for the treatment of psoriatic arthritis (PsA) peripheral joint disease¹. Although the level of evidence supporting its efficacy is weak², most rheumatologists are convinced that MTX is effective in peripheral PsA. This belief stems partially from its wide use as a DMARD in rheumatoid arthritis (RA), but to an even greater extent due to personal experience with MTX in PsA. Can we therefore consider MTX the reference nonbiological drug for psoriatic peripheral joint disease? With regard to the other clinical manifestations of PsA (enthesitis, dactylitis, and spondylitis), rheumatologists generally believe that MTX is virtually ineffective but, once again, this opinion is not supported by scientific evidence and so the question is whether we should really consider it a possible therapeutic agent in such cases.

The role of MTX in PsA: efficacy. Tumor necrosis factor- α (TNF- α) inhibitors are by far the most effective agents for controlling joint inflammation and deterioration in peripheral PsA. Unfortunately, cost and safety issues limit their use to patients with severe PsA refractory to at least one nonbiologic DMARD. MTX, sulfasalazine (SSZ), leflunomide (LEF), and cyclosporin A (CSA) are the traditional DMARD used in first line therapy. However, CSA has an unfavorable toxicity

profile and can be considered first choice only for some cases with severe skin involvement. LEF has been shown to be more effective than placebo in an appropriate trial³, but its Cohen d effect size was low³, and the number of adverse events was relatively high; further, its effect on skin disease was only slightly better than that of placebo. SSZ is the second most widely used drug in PsA¹, but a longterm observational study found that is more likely to be discontinued than MTX⁴; as is well known, SSZ also has no effect on skin manifestations. For one reason or another, CSA, LEF, and SSZ do not seem to be superior to MTX in treating peripheral PsA. Further, MTX is effective on psoriatic skin lesions, has been shown to improve joint inflammation in a number of observational studies², is considered to be effective by rheumatologists, and is relatively inexpensive. Despite its weak evidence base, MTX can therefore be considered the reference nonbiologic DMARD for treatment of psoriatic peripheral joint disease. It can also be used in combination with CSA, and might contribute to longterm survival on TNF- α antagonists.

Although no well conducted studies have investigated the effects of MTX on psoriatic enthesitis, dactylitis, or spondylitis, it is considered to be ineffective in such cases. This opinion is at least partially influenced by the assumption that "no evidence = no effect." Interestingly, MTX has been shown to be superior to nonsteroidal anti-inflammatory drugs (NSAID) in treating enthesitis related to ankylosing spondylitis (AS)⁵, improved dactylitis in a small group of patients with PsA⁶, and was more effective than placebo on inflammatory spinal involvement in AS⁷. The findings of these studies are not sufficient to support its use in treating these clinical manifestations, but they do suggest that further trials are warranted. At present, there is no reason for believing that MTX should not be considered an option in the treatment of mild cases of enthesitis, dactylitis, and spondylitis that do not respond to local corticosteroids and NSAID.

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The role of MTX in PsA: toxicity. Unlike dermatologists, rheumatologists seem less concerned about MTX toxicity in PsA, an attitude that again is probably due to their broad experience with the drug in RA. Recent evidence suggests that hepatotoxicity is more common in PsA, being reported in about 7% of cases¹; however, the real prevalence of MTX-induced liver fibrosis cannot be established only on the basis of serum transaminase abnormalities, but requires more sensitive means such as liver biopsy or preferably noninvasive elastography (Fibroscan)⁸. Nevertheless, when using MTX in PsA, it seems advisable to check for liver toxicity risk factors (alcohol, metabolic syndrome, hepatitis B and C virus infections) before starting therapy, to add folic acid supplementation, to perform routine safety tests every 2-3 months, and to evaluate the need for liver fibrosis examinations after a cumulative dose of about 3 grams. Given the low risk of severe liver damage and the existence of noninvasive techniques, liver biopsy does not seem to be advisable.

DERMATOLOGISTS' PERSPECTIVE

MTX is a synthetic structural analog of folic acid that inhibits purine and pyrimidine synthesis, and thus the synthesis of both DNA and RNA. In addition to these antiproliferative effects, MTX has an antiinflammatory effect by increasing adenosine levels. It is believed that the efficacy of MTX in psoriasis is due to decreased epidermal cell proliferation and inhibition of the immuno-inflammatory process characteristic of the disease⁹. In comparative studies^{10,11}, MTX 15 mg weekly (2.5-25 mg/week) proved less effective (and less rapid) than psoralen plus ultraviolet A therapy, with 16 week Psoriasis Activity and Disease Index 75 (PASI75) and PASI50 responses being achieved by, respectively, 60% and 75% of the patients. It is also less effective than CSA in terms of speed of action and overall efficacy, but better than acitretin.

The current dermatological indications for MTX are severe, chronic plaque-type, erythrodermic, and pustular psoriasis. The 12-hour refracted dose regimen (one-third of the total dose at 8:00 AM, one-third at 8:00 PM, and the last third at 8:00 AM of the following day) seems to be better tolerated, and is based on the pathophysiology of the psoriatic cell cycle. The efficacy and toxicity of MTX are both dose dependent. In dermatology, it is normally used at low doses (7.5-25 mg once weekly) in a single oral administration or in 3 fractioned doses. It is recommended to start with small doses (5-10 mg) and increase them slowly until reaching a satisfactory clinical response or a maximum dose of 30 mg/week. Subjective tolerability and laboratory variables should be checked frequently during the first 2 months of treatment, and the full effect of MTX is usually seen after 2-3 months. Once good clinical control has been achieved, the dose should

be reduced to the minimum effective dose. Folic acid supplementation reduces the side effects but does not seem to prevent severe toxicity. Patients refractory to oral MTX should be treated parenterally at doses of up to 25 mg once a week. Combination treatments with other systemic immunosuppressants, retinoids, or photochemotherapy are contraindicated. MTX can also be used in rotation regimens¹², but should not be given after acitretin because of its long half-life and possible liver toxicity.

Contraindications to use of MTX are liver and lung disease, impaired renal function, and pregnancy and lactation, and it should not be given to female patients of childbearing age who do not practice contraception, male patients planning to conceive, or patients with hematological abnormalities. In addition, caution is required in elderly patients, alcohol abusers, and people with active infectious diseases (including HIV infection). Despite the precautions taken before starting MTX therapy, adverse reactions may involve bone marrow (anemia, leukopenia, thrombocytopenia, pancytopenia, acute bone marrow suppression), liver (increased serum transaminase levels, fibrosis, and cirrhosis), lung (acute hypersensitivity reactions, interstitial fibrosis), and the gastrointestinal system (stomatitis, oral ulcerations, nausea, vomiting, and diarrhea).

Liver toxicity is a major concern in psoriasis and, as the discontinuation of MTX may not restore liver function or inhibit progression to cirrhosis¹³, prevention is essential. The risk factors for liver fibrosis are prolonged treatment, a cumulative dose of > 1.5 g, age > 65 years, and comorbidities (diabetes mellitus, excessive alcohol intake, obesity), but high liver enzyme levels are not necessarily predictive. The frequency of bioptic signs of cirrhosis and fatty infiltration is, respectively, 0-26% and 25%-40%, but a liver biopsy may be associated with minor risks such as bleeding (1:1000 patients), and major risks such as death (1:10,000 patients). Serum type III procollagen aminoterminal peptide (PIIINP) levels are considered reliable indicators of liver fibrosis/cirrhosis, but the test is not organ-specific (increased PIIINP levels are also found in arthritis).

MTX overdosage is another concern. The risk factors are impaired renal function, accidental association with trimethoprim-sulfamethoxazole, and incorrect administration by the patient (daily instead of weekly). The antidote is folic acid at a dose of 20 mg, which should be given immediately and then every 6 hours.

QUESTIONS AND ANSWERS

Do you suggest contraception for both females and males when starting therapy with MTX?

As MTX has been associated with miscarriage and fetal abnormalities, women of childbearing potential should be strongly encouraged to use effective contraception. In the case of men, although it is generally thought that MTX may be responsible for reduced fertility and fetal damage, the evidence for this is weak. Nevertheless, male patients starting MTX should be told there is a potential risk of problems with pregnancy and that contraception is advisable to be on the safe side.

Is MTX useful in reducing the immunogenicity of the TNF- α blockers?

It is well known that concomitant use of MTX with the TNF- α blockers (especially infliximab) in RA is associated with a lower rate of antibodies against the anti TNF- α agents, and it is likely that immunogenicity in general is slightly reduced by the concomitant use of MTX. The clinical relevance of this effect in PsA is unknown but, if a patient is already taking MTX, it seems advisable to add the TNF- α blocker without stopping MTX.

Are high-resolution computed tomography and functional tests essential to screen for pulmonary fibrosis during MTX treatment even in mild respiratory symptoms (dry cough, dyspnea)?

Pulmonary toxicity is a well known side effect of MTX and can vary from interstitial fibrosis (which is usually of little clinical relevance) to acute hypersensitivity alveolitis, which is rare but potentially lethal. These effects seem to be rarer in PsA than in RA. PsA patients taking MTX who develop pulmonary symptoms should be evaluated carefully, with specific investigations being recommended on an individual basis.

Dermatology guidelines suggest using MTX orally, but dermatologists use the parenteral route because it has been shown to be more effective. Why this difference?

The guidelines suggest oral administration because this is what has been used in the main clinical trials of MTX in psoriasis. Further, oral MTX is safer than parenteral MTX because it leads to lower peak plasma levels. The first choice in dermatology should usually be the oral route, and the parenteral route should be reserved for cases in which oral administration is inefficacious.

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