Drug Use and Toxicity in Psoriatic Disease: Focus on Methotrexate

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ABSTRACT. Methotrexate (MTX) toxicity in psoriatic disease was the focus of discussion at the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Plenary presentations and results of a Web-based opinion survey of rheumatologists and dermatologists from GRAPPA, and others from New Zealand, Australia, and Canada, provided topics of discussion for small-group breakout sessions, including hepatotoxicity, alcohol use, fertility and pregnancy, and combination therapy. As a framework, topics were considered under headings: importance, knowledge deficit, sufficient data for a recommendation, and research agenda. Breakout session conclusions/consensus were as follows: (1) Data are insufficient to recommend routine serial liver biopsy to prevent MTX-induced liver fibrosis; further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity without the need for liver biopsy. (2) Insufficient data are available to establish a dose-response relationship between alcohol use and MTX hepatotoxicity, so no safe limit of alcohol intake can be recommended. (3) Although cessation of MTX 3 months prior to conception is reasonable, inadequate data are available to specify duration or to quantify the risk of adverse fetal outcome; registries to track pregnancy outcome are potentially useful. (4) Combination therapy with anti-TNF agents or sulfasalazine is safe, but insufficient data are available for combinations with leflunomide or cyclosporine. (J Rheumatol 2008;35:1454–7)

Key Indexing Terms:
PSORIASIS PSORIATIC ARTHRITIS METHOTREXATE TOXICITY

Despite a weak evidence base, methotrexate (MTX) is one of the most common therapeutic agents for psoriatic arthritis (PsA) and has been used in the treatment of severe psoriasis since 1958[1]. Despite ready availability and decades of use in clinical practice, much remains unknown about MTX. Although many other therapeutic options are now available to patients with psoriasis and PsA, in particular biologic agents such as anti-tumor necrosis factor-α (TNF-α) drugs, MTX remains an important drug. Further, important differences exist between official recommendations for toxicity monitoring between the dermatology community[2] and the rheumatology community[3], which can be confusing for both practitioners and patients. It was therefore decided that MTX would be an appropriate focus for review by a unique combination of dermatologists and rheumatologists represented at the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

One of the intriguing issues with MTX is the difference in toxicities observed between patients with rheumatoid arthritis (RA) compared to patients with psoriasis or PsA. A recent cross-sectional study confirmed that pulmonary toxicity was more common in RA patients compared to patients with PsA, and that hepatotoxicity was more common in PsA patients[4]. A metaanalysis of longterm MTX treatment studies in RA and psoriatic disease showed a 3-fold greater risk of hepatic fibrosis in patients with psoriatic disease[5]. The reasons for such differences are unclear, but there may be justification for different toxicity monitoring for patients with psoriatic disease.

Prior to the meeting, GRAPPA members, as well as other rheumatologists and dermatologists from Australia, New

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Supported by an unrestricted financial grant from Abbott, Centocor, Wyeth, Amgen, and UCB Pharma.

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Zealand, and Canada, were surveyed to ascertain the nature of current practice and opinions regarding MTX use and to highlight possible differences in the way the drug was used between the 2 disciplines. Such variability was thought to provide a useful starting point for discussion and the development of a research agenda.

Rheumatologist and Dermatologist Survey

Current practices. A Web-based survey devised by the GRAPPA Toxicities Subcommittee was conducted among GRAPPA membership (n = 212) and among other dermatologists and rheumatologists listed in the national physician databases of e-mail addresses (NZ, Canada, Australia). Of the GRAPPA membership, 72 started the survey and 56 completed it; 32% were dermatologists. Of the national databases, 236 physicians started the survey and 184 completed it; 40% were dermatologists. The 2 surveys were combined for analysis (n = 240). Respondents were experienced (55% with 15 or more years since gaining specialist qualification) and saw many patients with psoriasis (63% of dermatologists saw more than 100 patients with psoriasis per year) and PsA (32% of rheumatologists saw more than 100 patients with PsA per year).

Rheumatologists used MTX far more often for PsA (68% of physicians used it for more than half of their patients) than did dermatologists for psoriasis (1% of physicians used it for more than half of their patients). Pretreatment chest radiography and viral hepatitis serology were undertaken by rheumatologists more frequently than dermatologists (52% vs 17%, 56% vs 39%, respectively), but lipid profile and liver biopsy were undertaken less frequently (14% vs 29%, < 1% vs 5%, respectively). Most physicians used a once-weekly dose regime, but more dermatologists (15% vs 4%) used other regimes. Dermatologists used lower weekly doses (10–15 mg or less) than rheumatologists (62% vs 30%, respectively).

Dermatologists were more conservative than rheumatologists in their advice regarding alcohol (complete abstinence recommended by 53% vs 24%, respectively); however, for those who did not recommend abstinence, there was wide variation in the amount of alcohol permitted, from one standard drink per week to 2 drinks per day as long as there were alcohol-free days each week. Dermatologists were much more likely to recommend routine liver biopsy after a 1.5 g cumulative dose of MTX, as does the 1998 Psoriasis Taskforce Guideline (29% vs 4%)[2]. Dermatologists were as likely as rheumatologists to monitor liver chemistry blood tests (even though there is little evidence that liver chemistry tests predict hepatic fibrosis in psoriatic disease). Few respondents used amino-terminal propeptide of type III collagen (PIIINP) levels to monitor for possible hepatic fibrosis (10% of dermatologists and no rheumatologists); P111NP levels were available but not used by a further 11% of respondents.

Serious liver disease (biopsy-proven cirrhosis) due to MTX had actually been observed by 40 respondents, presenting to more dermatologists than rheumatologists (27% vs 11%, respectively). This confirms that MTX hepatotoxicity is still an important problem, although some evidence is available that it has become less common in patients with psoriasis over recent decades[6].

Dermatologists tended to more often defer decision-making to the obstetric team if a woman taking MTX became pregnant (63% vs 41%, respectively), whereas rheumatologists more often recommended early termination (29% vs 17%). Although it is well described that MTX is associated with miscarriage (and in high dose is used therapeutically to induce abortion) and with fetal abnormalities for pregnancies that continue to term, there are many reports of successful pregnancies[7]; some suggest that the timing of exposure to MTX (6 to 8 weeks postconception) is critical to the development of the aminopterin syndrome[8,9]. The decision to terminate is therefore not so clear-cut. In discussion, it was emphasized that women of child-bearing potential should be strongly guided to effective contraception, and there was even a suggestion that women should undergo regular pregnancy tests while taking MTX (as is done for isoretinoin). There was fair consensus that MTX be ceased for at least 3 months prior to conception for the male partner who is taking MTX (78% of rheumatologists and 72% of dermatologists), but the evidence base for this advice is poor; subsequent discussion revealed many physicians whose male patients had fathered normal children while taking MTX.

Plenary Discussion

Hepatotoxicity. Interest has been shown in PIIINP as a surrogate marker for liver fibrosis that might usefully monitor MTX hepatotoxicity. PIIINP is cleaved during collagen synthesis, which is upregulated in active fibrogenesis. In a longitudinal study of 70 patients with psoriasis, 4 patients developed liver fibrosis; all had elevated PIIINP levels. Of 2 other patients with elevated PIIINP levels, normal liver histology was found[10]. Since active inflammation from arthritis can increase PIIINP levels, it may not be so useful in PsA. In a small study of 54 patients with PsA or psoriasis who had received an average MTX dose of 4.4 g (range 1.0–19.7) over 6.6 years (range 1.3–30), 11 patients developed Roenigk grade 3A liver histologic changes, and 27 developed grade 2 (no patients with grade 3B or 4)[11]. Seven of 11 (64%) grade 3A patients had elevated PIIINP levels, and 9/43 (21%) without grade 3A had elevated PIIINP levels. In another small study, 65 patients with 174 PIIINP assays and 30 liver biopsies were reviewed[12]. Mean cumulative dose of MTX was 2 g (SD 1.8 g) over a mean of 4.3 years (range 1–14). Of the 30 liver biopsies, 26 (86.6%) showed normal histology, 3 had focal fibrosis, and 1 had early cirrhosis. Although the median of those with abnormal

liver histology was higher than other patients, only 28% of PIIINP estimations with a value > 4.2 μg/l correlated with abnormal liver biopsy. The test does not seem sufficiently sensitive as a screening test and lacks specificity.

The relationship between other risk factors for liver disease and MTX-associated liver disease is an area of great interest. It is known from studies in RA that diabetes and other risks for hepatic steatosis can limit the usefulness of serial liver chemistry tests to predict liver fibrosis[13]. It has also been proposed that a possible reason for higher rates of MTX hepatotoxicity in psoriasis versus RA is the higher rates of comorbidities, especially dyslipidemia, obesity, diabetes mellitus, and excessive alcohol intake, in patients with psoriasis. Such additional risk factors have been shown to lead to worse MTX hepatotoxicity[14]. Nevertheless, it is unclear whether such factors can entirely explain the apparent differential toxicity.

Breakout Groups

At the GRAPPA meeting, 4 breakout groups discussed the following topics as they relate to MTX: general hepatotoxicity, alcohol guidelines, fertility and pregnancy issues, and the use of combination treatment. During their discussions, each group considered at least 2 of the following questions:

- What are the most important toxicity issues to highlight in the forthcoming review?
- Where are the gaps in our knowledge?
- Should GRAPPA issue recommendations on monitoring or toxicity issues as part of the publication?
- What topics should be placed on the agenda for future projects for the drug toxicity group?

The general conclusions from these groups are summarized in Table 1.

Research Agenda

Based upon these discussions the following research topics and specific questions were generated:

1. Prevention of MTX-induced hepatotoxicity.

- What is the risk of serious liver disease in patients with psoriasis and PsA taking MTX, and how does this relate to cumulative dose?
- Can serial monitoring of biomarkers such as PIIINP or liver chemistry identify patients at high risk of MTX hepatotoxicity?
- How do other risk factors for liver disease interact with MTX hepatotoxicity, and are such risk factors sufficient to explain differences in risk between RA, psoriasis, and PsA?

Table 1. Results of breakout discussion groups (these are not recommendations but only represent the opinions of those present at the meeting).

Topic	Conclusions
Hepatotoxicity	• Pre-treatment liver biopsy might be less satisfactory than considering a different treatment if risk factors for liver disease are present
	• Insufficient data exist to recommend or not recommend serial liver biopsies, but presence of other risk factors may help guide decision-making; a formal literature review is required in the first instance
	• There was no consensus on the use of PIIINP use to monitor possible hepatotoxicity, but further studies were recommended.
Alcohol use during treatment with MTX	• Although there are insufficient data upon which to base a recommendation, in practice small amounts of alcohol are probably safe
	• Use of large databases or registries might help us understand the dose-risk relationship between alcohol and MTX-associated hepatotoxicity
Fertility and pregnancy	• There was consensus that 3 months off treatment prior to conception for both female and male partner was appropriate, but little or no data are available to support the specific duration of ceasing treatment (especially with regard the male partner)
	• Use of registries to track pregnancies that do occur (both female and male-partner) would be useful
	• Regular pregnancy tests for fertile women taking MTX was not popular, but a pregnancy test prior to commencement or waiting until next menstrual period before starting MTX may be reasonable
	• There was no consensus view of whether termination would be recommended for a woman becoming pregnant while taking MTX
Combination therapy	• There was general agreement that the combination of MTX with sulfasalazine or with an anti-TNF agent is safe
	• Much less consensus existed regarding the combination of MTX with leflunomide or with cyclosporine, with a significant proportion of experts being uncomfortable with these combinations
	• It was felt reasonable to solicit opinions on different combination treatments from a wider group (for example, the American College of Rheumatology or the America Academy of Dermatology)
	• The issue of skin cancer was highlighted as a special problem for psoriasis or PsA patients who have been exposed to PUVA therapy, which may be especially important for patients taking cyclosporine or anti-TNF agents
	• Registries and formal literature reviews may provide good opportunities to assess the toxicity profile of different combination therapies.

PIIINP: propeptide of type III collagen; MTX: methotrexate; TNF: tumor necrosis factor; PsA: psoriatic arthritis.

• Can pharmacogenomics identify patients at high risk of MTX hepatotoxicity?
• What is the cost-utility of regular liver biopsy in preventing serious liver disease in patients with psoriasis and PsA treated with MTX?
• What is the dose-risk relationship between alcohol intake and MTX hepatotoxicity in patients with psoriasis and PsA?
2. Fertility and pregnancy issues
• What are the risks of spontaneous miscarriage or fetal malformation for a woman with psoriasis or PsA who becomes pregnant while taking MTX but discontinues it before 6 weeks postconception?
• What are the risks of spontaneous miscarriage or fetal malformation for the pregnant female partner of a man with psoriasis or PsA who is taking MTX at the time of conception?
• How long does it take for any such risk to return to background following discontinuation of MTX?

Rheumatologists and dermatologists from GRAPPA will continue to monitor and discuss the safety of methotrexate and other drugs in psoriatic disease. An ongoing search of the literature will allow us to follow new research developments.

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