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**The Australasian Psoriasis Collaboration view on Methotrexate for psoriasis in the Australasian setting**



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Key words: expert opinion, psoriasis, methotrexate, liver toxicity, monitoring

### **Abstract**

The Australasian Psoriasis Collaboration (APC), established in 2014, has reviewed methotrexate (MTX) in the management of psoriasis in the Australia/New Zealand setting. The following comments are based on expert opinion and literature review.

Low-dose methotrexate (<0.4 mg/kg/week) has a slow onset of action, has moderate-good efficacy, with an acceptable safety profile. The mechanism of action is anti-inflammatory, rather than immunosuppressive.

Pre-treatment, consider testing full blood count (FBC), liver and renal function, non-fasting lipids, hepatitis serology, HbA1c and glucose. BMI and abdominal circumference should also be measured. Optional investigations in at risk populations include HIV, Quantiferon®-TB Gold, and chest x-ray. In uncomplicated patients, repeat FBC at 2-4 weeks, then every 3-6 months and liver/renal function at 3 months and then every 6 months.

There is little evidence that a MTX test dose is of value. Adverse events are the main reason for discontinuation of MTX; once weekly folic acid may reduce these.

Low-dose MTX rarely causes clinical significant hepatotoxicity in psoriasis. The majority of treatment emergent liver toxicity is related to underlying metabolic syndrome and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Alcohol itself is not contraindicated, but it may be sensible to limit alcohol to <20 mg/day.

Although MTX is a potential teratogen post-conception, there is little evidence for this pre-conception. MTX does not affect the quality of sperm.

There is no evidence that MTX reduces healing, so there is no specific need to stop methotrexate peri-surgery. Methotrexate may be used in combination with ciclosporin, acetrein, prednisone and anti-TNF biologics.

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## **Introduction**

The Australasian Psoriasis Collaboration (APC) was established in 2014 to improve clinical outcomes in patients with psoriasis in Australia/New Zealand through a more holistic and comprehensive approach to management. Its aims include fostering independent collaborative research, developing quality statements on management issues, addressing unmet clinical and educational needs and working with the Australasian College of Dermatologists, the New Zealand Dermatological Society Inc and other professional societies to enhance psoriasis awareness and management.

The APC is made up Australian and New Zealand dermatologists with an established interest in the management of psoriasis, supported by specific specialists (e.g hepatologist, neonatal geneticist, etc).

The inaugural meeting of the APC reviewed the use of methotrexate (MTX) in the management of psoriasis in the Australia/New Zealand setting. How methotrexate is used has largely developed through custom and practice, and has not been validated with quality research; this includes the various published national/international guidelines. Renewed clinical interest in methotrexate in psoriasis has stemmed from its use as comparator to newer biologic agents, new studies including its subcutaneous administration and better knowledge regarding the causation and non-invasive monitoring of fibrotic liver disease. An improved body of data now exists to guide patient selection, folic acid supplementation and monitoring.

For the sake of brevity, our comments are listed as bullet points, with minimal explanation. The following comments by the APC are largely based on expert opinion, but references are included at the end for further reading.

### Methotrexate (MTX) in clinical practice

- Low-dose methotrexate (less than 0.4 mg/kg once per week) has a long history of use as a second-line systemic agent in the treatment of many inflammatory dermatoses, including psoriasis.<sup>1-2</sup>
- Methotrexate has a slow onset of action, has moderate-good efficacy with an acceptable safety profile for the treatment of psoriasis in all age groups. It is also beneficial for psoriatic polyarthritis and oligoarthritis.
- Methotrexate's mechanism of action is anti-inflammatory, inhibiting 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (AICAR), rather than as a tetrahydrofolate reductase inhibitor.<sup>3</sup>
- In doses used for psoriasis, MTX has minimal immunosuppressive effects and should be considered an immune-modulatory/anti-inflammatory drug, rather than an immunosuppressive.

### Baseline tests

It is appropriate to consider the following investigations prior to starting methotrexate (expert opinion and various international guidelines):<sup>2,4-5</sup>

- Full blood count, urea/electrolytes/creatinine, and liver function tests.
  - Consider calculating creatinine clearance in those at risk of renal impairment (e.g. elderly).
- Body mass index (BMI), weight, and abdominal circumference.
- Beta-HCG in women of child-bearing age.
- Non-fasting lipids, haemoglobin A1c (HbA1c), and blood sugar level.

Additional tests: the following tests should be considered in at risk patients/populations, or as part of a workup for potential future biologic therapy:

- Quantiferon®-TB Gold.
- Chest X-ray.
- Hepatitis B and hepatitis C virus serology (? all patients).
- Human immunodeficiency serology.
- Varicella zoster serology.

### Routine monitoring

In uncomplicated patients consider repeating (expert opinion and various international guidelines):<sup>2,4-5</sup>

- FBC: at 2 weeks, 4 weeks, then every 3 months.
- Liver function tests in the first 3 months (for hypersensitivity), then every 6 months.
- Renal function tests every 6 months.
- Non-fasting lipids, HbA1c every 6-12 months.
- Weight, BMI, waist circumference every 12 months.
- No need for routine lung function tests.<sup>6</sup>

#### Notes on monitoring

- Bloods ideally taken 5-6 days after the previous dose.
- Measuring AST or ALT is useful for identifying idiosyncratic drug toxicity/hypersensitivity (occurs in the first few months of therapy and is rare). With persistently elevated transaminase levels  $\geq 3$  upper limit of normal, consider stopping methotrexate.
- Albumin levels, platelet count, and coagulation abnormalities are better determinants of liver function, but only change late in disease.
- A high HbA1c in patients with liver disease is more predictive of death than a persistently high ALT.

#### **Pharmacology**

MTX enters the cell through the reduced folate carrier and forms pharmacologically active MTX polyglutamate (MTX-PG).<sup>7-8</sup>

- Absorption of methotrexate is decreased by food; however, if MTX causes nausea it can be taken with meals.
- Oral non-absorbable antibiotics such as vancomycin, neomycin, and bacitracin can decrease absorption.
- Absorption is increased by slower transit through the gut (e.g. when a patient is constipated).
- The key metabolite 7-OH methotrexate is 90-95% protein bound, hence can be easily displaced by highly plasma protein bound drugs (e.g. penicillins) and result in higher levels of free MTX.

- Serum half-life is 6 to 8 hours; however, when converted into its polyglutamate form, MTX can persist for 30 to 40 days. This explains why it has a maximal effect after 5-6 months.<sup>9</sup>
- Methotrexate is largely excreted by the kidneys as intact drug. Patients with renal impairment or reduced methotrexate clearance, are at risk of haematological toxicity (pancytopenia).
- Pregnancy category D.

### Dose

- Low dose methotrexate is considered less than 0.4mg/kg/week.
- Standard dermatological dose is 15-25 mg once per week (range 5-40 mg/week).
- There is little evidence to suggest a 5 mg test dose has value.
- Adverse events are the main reason for discontinuation of MTX, with 7% to 30% of patients discontinuing therapy in the first year.
- There is some evidence to suggest that, when higher MTX doses are needed (e.g. 25-30 mg/week), splitting the oral dose over 24 hours increases bioavailability, but it is unclear whether this has additional clinical effect.<sup>8</sup>
- Consider subcutaneous/IM methotrexate if patient compliance poor or GI adverse effects limits oral MTX, or a higher dose is needed.<sup>10-11</sup>
- If available, consider measuring trough polyglutamated methotrexate prior to dose escalation, or as a measure of patient compliance.<sup>9</sup>

### Liver toxicity and monitoring

- Methotrexate has a low inherent risk of drug induced liver toxicity.
- An increased rate of hepatic fibrosis is seen in those with Type 2 diabetes and obesity. The majority of treatment emergent liver toxicity in psoriasis patients is related to underlying metabolic syndrome and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH).<sup>5,12-14</sup>
- Liver biopsy continues to be the most reliable test of liver fibrosis/cirrhosis, but the benefit/risk ratio is negative, as MTX-induced liver damage is rare.
- Amino terminal levels of type III procollagen (P<sub>3</sub>NP) has high negative predictive value (sensitivity 74%, specificity 77%) when repeated every 3-4 months, but may not be cost-effective.<sup>15</sup>

- European Enhanced Liver Fibrosis (ELF) panel is an ELISA that measures serum levels of hyaluronic acid, tissue inhibitor of metalloproteinases-1 (TIMP-1) and P<sub>3</sub>NP. This assay shows promise as a potential tool in evaluating liver structure and function, but is not readily available.<sup>16</sup>
- FibroScan® has a high negative predictive value (specificity 88%), but results are invalid in 25-30% of patients due to obesity (even using XL probe).<sup>17</sup>
- It is worth considering a baseline FibroScan® (within 6/12 starting MTX), repeated 1-3 years later (depending on transient elastography (TE) score).<sup>18</sup>

### Folic acid supplementation

- There is some evidence that once or twice weekly folic acid supplementation decreases MTX associated adverse effects, without affecting efficacy.<sup>19</sup>
- The optimal dosing schedule of folate is unknown, but a reasonable suggestion is to recommend Methotrexate on Monday and Folic acid (5 mg) on Friday.
- Care should be taken when co-prescribing other folate antagonists such as dapsone and trimethoprim-sulfamethoxazole, with additional monitoring of FBC.

### TB prophylaxis and hepatotoxicity

- Australia/New Zealand's proximity to Southeast Asia, where TB is endemic, puts people who travel there at risk. The evidence that MTX reactivates TB is poor.
- Quantiferon Gold® (QFT-G) has become the gold standard for diagnosing both latent and active TB. Consider repeating if new relevant exposure, or every few years in people on additional immunomodulatory/immunosuppressive therapy.
- Latent TB is treated with isoniazid and rifampicin.

### How much alcohol is OK?

- Alcohol itself is not contraindicated with methotrexate. It would be sensible to limit alcohol consumption to less than 20 mg/day (1 standard drink/day females or 1-2/day for males). Unlike type 2 diabetes and obesity, alcohol has not been linked to increased risk of liver fibrosis in psoriasis patients.<sup>20</sup>
- Binge drinking or excessive alcohol consumption carries significant risk of hepatotoxicity.

## NAFLD and NASH

- 25-35% of people in the Asia-Pacific region have non-alcoholic fatty liver disease (NAFLD).
- 5-30% of patients with NAFLD will go on to develop non-alcoholic steatohepatitis (NASH)
- 15-25% of NASH will develop cirrhosis over ~2 decades. Around 30% to 40% will die from liver-related causes.
- Around 98% of patients with NASH have insulin resistance, while 87% fulfill the criteria for the metabolic syndrome and 30-70% have Type 2 diabetes. Thus, it seems that visceral adiposity and insulin resistance are universal in NASH. Patients with cirrhosis due to NASH have poor long-term outcomes.
- Among other markers, the presence of the metabolic syndrome and persistently increased ALT are significantly associated with the progression of NAFLD.
- Drug treatment is not currently effective in the treatment of NAFLD/NASH.
- Lifestyle modifications focusing on diet, exercise (3-7% reduction in body weight) and behavioural changes can successfully lead to improvements in overall NASH histologic activity, degree of steatosis, and liver chemistry.
- Obesity (and psoriasis) increases the risk for internal malignancies (but no consistent evidence that MTX does).<sup>21</sup>

## Liver disease and MTX

- The hepatotoxicity of low-dose regimens of MTX has been debated. Whilst ultrastructural change is common, clinical disease is rare. Minor ALT changes occur within 1 to 2 days of therapy initiation but are not related to the development of hepatic fibrosis.
- Traditional risk factors (although the evidence is conflicted) for MTX-related liver injury include:
  - Dose: cumulative, incremental, frequency.
  - Age >60 years (? reduced renal clearance).
  - Alcohol consumption >15 g/day.
  - Obesity, Type 2 diabetes (T2D).
  - Pre-existing liver disease (e.g. Hepatitis B and C).
  - Renal failure (decreased clearance).

- Liver disease is more common in psoriasis than in rheumatoid arthritis.
- Other drugs: Vitamin A, non-steroidal anti-inflammatory drugs (NSAIDs).
- NASH, possibly aggravated by MTX, is an important cause of liver injury in patients on long-term, 'low-dose' MTX treatment for psoriasis.
- Rarely, MTX alone can cause a NASH-like pattern of injury that is at least in part caused by a higher cumulative dose (an effect of increasing levels of adenosine).
- A high HbA1c in patients with liver disease is more predictive of death than a persistently high ALT.
- Hepatitis B vaccination is recommended in all patients. As acute Hepatitis B virus (HBV) is rare, patients who are not immunised against HBV should start their proposed anti-psoriasis treatment immediately.
- If the patient does not develop an adequate antibody response to Hepatitis B vaccination, they can give be given a double dose.

### Co-prescribing with methotrexate

The severity of psoriasis often requires additional anti-psoriasis treatments.

- Acitretin – no particular concern in low dose acitretin (e.g. 10-20 mg/day).
- Ciclosporin – monitor renal function more closely, and reduce MTX if renal impairment.
- Prednisone – no particular concern.
- Anti-TNF biologics – no particular concern. Benefit due to better drug survival and reduced antibody formation to biologics in patients on MTX has been proposed but is unproven.

### Pregnancy and methotrexate

Methotrexate is a teratogen when taken post-conception.<sup>22</sup>

- If taken post-conception:
  - Cumulative spontaneous abortion: 42% (95% CI 29.2–58.7).
  - Risk of major birth defects: adjusted OR 1.8 (95% CI 0.6–5.7).
  - Developmental delay – unknown but possibly increased.
- If taken pre-conception:
  - No increased risk of abortion or birth defects.
- Spermatogenesis<sup>23</sup>

- A few reports of oligospermia, but no effect on quality of sperm.
- No increased risk of congenital abnormalities.

### Other

- There is no evidence that MTX reduces healing, so there is no specific need to stop methotrexate peri-surgery.<sup>24</sup>
- Methotrexate remains safe and moderately effective in older patients (>65 years).<sup>25</sup>

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