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## DMARD MONITORING GUIDELINES – Reviewed 23.01.15

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The current BSR DMARD and Denosumab Monitoring Guidelines are now available via the following link: <http://www.rnhrd.nhs.uk/our-services/for-clinicians>

### **Methotrexate**

#### **A. Indications:**

**(Licensed):** RA [1, 2], Psoriasis.

**(Unlicensed):** Psoriatic arthritis [3], Crohn's disease [4], connective tissue disease (SLE, myositis and vasculitis) [5], Felty's syndrome [6].

#### **B1. Methotrexate dosage: Grade of evidence: C**

Typical dose: 7.5–25mg ONCE weekly; starting dose may vary depending on the severity of the condition and patient characteristics such as age, renal function and other comorbid conditions.

The initial dose may be 5–10 mg once weekly, increasing by 2.5–5mg every 2–6 weeks until disease stabilized [7].

The maximum licensed dose in RA is 25 mg/week. Rarely, the maximum dose can be 30 mg/week [8]. Lower doses should be considered for frail elderly patients who often have poor renal function. If maximum oral dose is not effective or causes intolerance, consider i.m. or subcutaneous route of administration before discontinuation of the drug.

#### **B2. Folic acid: Grade of evidence: A**

Typical dose: 5mg once weekly, preferably the day after the methotrexate [9]. Folic acid can be given any day as long as it is not on the same day as methotrexate. Folic acid reduces toxic effects and improves continuation of therapy and compliance [9–11].

#### **C. Route of administration**

**Methotrexate:** Oral, i.m., i.v. or subcutaneous

**Oral (licensed):** It is preferable to use only 2.5 mg tablets and patients should be reminded of the need to check the dose and strength of the tablets with each prescription.

**Parenteral (licensed):** The dose for parenteral use is usually the same as the oral although one should consider the difference in bioavailability between oral and parenteral routes of administration. [12].

**Folic Acid:** Oral.

**D. Time to response:** 6 weeks to 3 months

**E. Cautions: Grade of evidence: C**

- (1) Patients with clinically significant renal impairment from any cause (see section J).
- (2) Localized or systemic infection including hepatitis B or C and history of tuberculosis.
- (3) Unexplained anaemia and/or cytopenia associated with marrow failure.

**F. Contraindications: Grade of evidence: C**

- (1) Pregnancy and breast feeding.
- (2) Suspected local or systemic infection.
- (3) Bone marrow failure with unexplained anaemia and cytopenia.

**G. Notable drug interaction (refer to BNF and SPC)**

- (1) Phenytoin: Antifolate effect of methotrexate is increased.
- (2) Probenecid, penicillin, NSAIDs: Methotrexate excretion is reduced. (Clinically significant interaction between NSAID and methotrexate is rare).
- (3) Tolbutamide: Serum concentration of methotrexate may be increased.
- (4) Co-trimoxazole, trimethoprim: Antifolate effect of methotrexate is increased and greatly increases the risk of marrow aplasia.**

## H. Monitoring schedule: Grade of evidence: C [2]

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	<b>BSR</b>	<b>BAD</b>
<b>(a) Pre-treatment assessment</b>	<b>FBC, U&amp;E, LFT and chest X-ray (unless CXR done within the last 6 months). Pulmonary function tests should be considered in selected patients (see Section H(4)).</b>	<b>As BSR</b>
<b>(b) Monitoring</b>	<b>FBC, U&amp;E, LFT every 2 weeks until dose of methotrexate and monitoring stable for 6 weeks; thereafter monthly [9] until the dose and disease is stable for 1 year. Thereafter the monitoring may be reduced in frequency, based on clinical judgement with due consideration for risk factors including ae, comorbidity, renal impairment etc, when monthly monitoring is to continue. Re: serum pro-collagen III in patients with psoriatic arthritis – refer to Section J.</b>	<b>Initially once a week FBC, U&amp;E, creatinine, LFTs; gradually increase interval between tests until therapy stabilized; thereafter monitor every 2-3 months.</b>

## **I. Actions to be taken: Grade of evidence: C [13]**

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<b>WBC &lt;3.5 x 10<sup>9</sup>/l</b>	<b>Withhold until discussed with specialist team.</b>
<b>Neutrophils &lt;2.0 x 10<sup>9</sup>/l</b>	<b>Withhold until discussed with specialist team.</b>
<b>Platelets &lt;150 x 10<sup>9</sup>/l</b>	<b>Withhold until discussed with specialist team.</b>
<b>AST, ALT &gt; twice upper limit of reference range.</b>	<b>Withhold until discussed with specialist team.</b>
<b>Albumin- unexplained fall (in absence of active disease)</b>	<b>Withhold until discussed with specialist team.</b>
<b>Rash or oral ulceration, nausea and vomiting, diarrhoea</b>	<b>Withhold until discussed with specialist team.</b>
<b>New or increasing dyspnoea or dry cough.</b>	<b>Withhold and discuss urgently with specialist team.</b>
<b>MCV &gt; 105 fl</b>	<b>Withhold and check serum B12, Folate and TFT and discuss with specialist team if necessary.</b>
<b>Mild to moderate renal impairment</b>	<b>Withhold until discussed with specialist team (refer BNF)</b>
<b>Severe sore throat, abnormal bruising</b>	<b>Immediate FBC and withhold until the result of FBC is available.</b>

## J. Special clinical circumstances:

Table 1. Summary

Special circumstances	Grade of evidence	BSR	BAD
Alcohol	C	Caution required and advise to stay well within national recommendations	Caution required and advise to stay within 4-6 units/week [14].
Liver biopsy	B	Liver biopsy is not required in absence of pre-existing liver disease. CSLD is uncommon/rare [15,16].	Not recommended as a routine but patients with persistently abnormal pro-collagen III (>4.2 µg/l in at least three samples over a 12 month period) should be considered [17].
Serum pro-collagen III	B	Role of this test in the background of inflammatory arthritis remains unclear – not routinely recommended [18].	Recommended for early detection of liver disease [17,19].
PFT	B	Methotrexate is best avoided in established cases of ILD. If pre-treatment CXR is abnormal, consider HRCT and PFT [20-27]. TLCO can be more sensitive than CXR in some cases [28].	Lung injury in psoriasis or following treatment with methotrexate is rare. If suspected the BSR regimen may be followed.
Bone marrow failure (anaemia, neutropenia and thrombocytopenia)	C	Withdraw methotrexate: if severe, discuss with haematologist, may need immediate admission for urgent folinic acid rescue (Section M1) [13].	As BSR
Renal failure/severe dehydration	C	Patients who develop dehydration, pre-renal or acute renal failure while on methotrexate should have methotrexate	As BSR

		withheld and should be given folinic acid rescue [29] (Section M1). Methotrexate elimination is predominantly by renal excretion. If patients develop worsening chronic renal failure FBC should be monitored closely and dose reduction considered.	
Pregnancy and breastfeeding	C	Avoid conception and pregnancy, male and female. To continue contraception for at least 3 months after stopping methotrexate [2, 30, 31].	As BSR
Elective surgery	A	Therapy can be continued. Caution for early detection of infection and complications [32, 33].	As BSR
NSAIDs	C	Most NSAIDs can be continued as long as monitoring is regular and caution is exercised regarding LFT and renal function, particularly in the elderly [13].	As BSR

**(1) Alcohol:** Any patient suspected of alcohol abuse is usually unsuitable for methotrexate therapy. Dermatologists (BAD) may allow patients, receiving methotrexate, to continue taking small amounts of alcohol (4–6 units/week) [17].

Rheumatologists should advise the patients receiving methotrexate to limit their alcohol intake well within national recommendations.

**(2) Hepatotoxicity:** Methotrexate related hepatotoxicity was first reported in psoriasis patients several decades ago. A cumulative dose of 1.5 g of methotrexate might cause clinically significant liver disease [34]. Please note that liver fibrosis/cirrhosis may occur with normal liver enzymes and imaging findings [34, 35].

## **(a) Liver biopsy: Grade of evidence: B**

Current studies in patients with RA suggest that liver biopsies are not cost effective for at least the first 10 yrs of methotrexate use in patients with normal liver function values [8]. Clinically serious liver disease (CSLD) is rarely seen in RA patients receiving low dose methotrexate and routine liver biopsies are therefore not recommended [16].

BAD does not recommend routine liver biopsy on all patients receiving methotrexate. However, if there is history of pre-existing liver disease, a baseline ultrasound guided liver biopsy should be performed. This should be undertaken soon after the methotrexate is started, usually within 3–4 months [34, 35]

## **(b) Serum pro-collagen III levels: Grade of evidence: B**

Dermatologists (BAD) have recently examined the role of serological markers such as pro-collagen III amino terminal peptide (PIIINP) in detecting methotrexate induced liver damage. A recent study suggests that the patients with repeated normal levels of PIIINP are very unlikely to have significant liver damage from fibrosis/cirrhosis [17] and that follow-up liver biopsies may only be offered to patients with persistently abnormal levels of PIIINP over 4.2 ng/ml (for Orion assay)—section M2.

In rheumatology, the role of such serological markers is unclear as it can be false positive in inflammatory arthritis, such as rheumatoid or psoriatic arthritis [18].

**(3) Pulmonary toxicity:** Pulmonary toxicity related to methotrexate is often the cause for withdrawal of therapy in an otherwise stable patient with a frequency of 1:108 patient years compared with 1: 35 patient years for hepatotoxicity [21] and 1: 58 patient years for neutropenia [36].

Methotrexate pneumonitis (MP) is a potentially fatal hypersensitivity reaction and is far less predictable than hepatic or haematological toxicity. It is most frequently but not exclusively seen within the first year of treatment [28]. Many studies suggest that the incidence of MP is much higher in patients with pre-existing lung disease [20–27].

## **(4) Pulmonary Function Test (PFT): Grade of evidence: B**

PFT may be a useful investigation to detect pre-existing lung disease and is a sensitive but non-specific test in identifying occult lung disease. If pre-treatment CXR suggests abnormal shadowing it may be worth considering a high resolution computerized scan (HRCT) and PFT to ascertain the carbon monoxide transfer factor (TLCO) prior to commencing methotrexate therapy [26]. One recent study suggests carbon monoxide transfer factor (TLCO) is a more sensitive marker for detection of Interstitial Lung Disease (ILD) than CXR [36, 37]. In fact the study proposes the use of PFT as a screening test and recommends that patients with a TLCO value <70% should be subjected to a HRCT (and CXR) [27]. It is important to note that airway obstruction may not be a contraindication to the use of methotrexate but presence of interstitial lung disease certainly is, and it is better detected prior to commencement of therapy or avoided (Dr Clive Kelly, Gateshead Hospital, personal communication).

## **(5) Bone marrow failure: Grade of evidence: C**

Significant fall in cell counts can occur as a result of methotrexate-induced bone marrow suppression. It is particularly likely in the elderly and in patients with significant renal impairment or in patients with concomitant administration of anti-folate drugs. If there is a significant fall in cell count, the following actions should be taken immediately:

- (a) Withdraw the methotrexate therapy.
- (b) Give folinic acid rescue therapy: Section M1.
- (c) Consider immediate discussion with supervising specialist/team, medical on-call team or the local haematologist. However, in cytopenia due to Felty's syndrome—methotrexate might be a useful drug with good haematological outcome [6].

## **(6) Pregnancy and breast feeding: Grade of evidence: C**

All patients, male and female, should be advised against conception and pregnancy during treatment with methotrexate as it is an abortifacient as well as a teratogenic drug. If patients become pregnant inadvertently, it is appropriate to refer the patient to an obstetrician. Breast feeding should not be allowed as the drug may be excreted in the breast milk. Patients should be advised to continue contraception for at least 3 months after stopping methotrexate [30, 31].

## **(7) Surgical interventions: Grade of evidence: A**

Earlier studies suggested an increased incidence of early post-operative complications, such as infections, in a significant number of patients who continued their treatment with methotrexate within 4 weeks of surgery. Two recent studies, one prospective randomized controlled, suggest that the continuation of methotrexate treatment does not increase the risk of infection or surgical complications in patients with RA [32, 33].

## **(8) NSAIDs: Grade of evidence: C**

NSAIDs can be continued as long as monitoring is regularly undertaken. Special cautions need to be exercised if significant abnormalities are noted in liver enzymes. All patients should be regularly advised to avoid over the counter medications including aspirin and ibuprofen [2] without the knowledge of the specialist team.

## **(9) Infections: Grade of evidence: B**

In contrast to many immunosuppressive therapies, methotrexate is relatively safe and has a low risk of infection associated with its use [38]. However, infections are still reported and such infections need to be diagnosed at an early stage to prevent systemic dissemination, and methotrexate should be stopped immediately. If infection

is associated with dehydration and pre-renal failure, stop methotrexate and consider folinic acid rescue. The infections can be due to a range of organisms, from viral and bacterial to rare opportunistic infections. One recent short-term observational study (over 6 months) showed a high death rate (33%) in patients with pulmonary infections [39]. Significant mortality and morbidity can be associated with viral infections due to Herpes Zoster/Varicella.

## K. Immunization

(1) Patients receiving methotrexate should not receive immunization with live vaccines. However, the RNHRD have produced specific local guidance with regards to the varicella-zoster vaccine which can be found at <http://www.rnhrd.nhs.uk/our-services/for-clinicians>, under the heading “Zostavax GP guidelines”.

(2) Inactivated polio is available although suboptimal response may be seen.

(2) Annual flu vaccination is recommended.

(3) In patients receiving methotrexate exposed to chickenpox or shingles, passive immunization should be carried out using VZIG. The Herpes Zoster immunoglobulins can be obtained from Health Protection Agency. Tel. No: 020 8200 6868.

## L. Appendices

### (1) Folinic acid rescue: Grade of evidence: C [2, 40].

In suspected cases of methotrexate overdose, severe haematological toxicity, pre-renal or acute renal failure, consider treatment with folinic acid. The initial dose should be at least

20 mg, given intravenously. Subsequent doses of 15 mg (which may be taken orally) should be given at 6 hourly intervals until the haematological abnormalities are improved (usually not more than 2–8 doses).

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