Oxford University Hospitals NHS
NHS Foundation Trust

NHS
Oxfordshire
Clinical Commissioning Group

METHOTREXATE FOR USE IN ADULT AND PAEDIATRIC RHEUMATOLOGY
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for methotrexate therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF

Shared Care Protocol – Responsibilities

Shared care assumes communication between the rheumatology specialist, GP, District Nurse or Community Children's Nurse if required* and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. See Rheumatology Shared Care Responsibilities document for further information.

Rheumatology Specialist Team

At the start of treatment:

- Complete pre-treatment assessments, including baseline tests, in accordance to the specific shared care protocol
- Initiate treatment by prescribing the first 56 days
- Supply the patient with 3 blood cards (for FBC, U&E and LFTs) and inform patients to book and attend blood tests at 2, 4 and 6 weeks after starting treatment
- Ensure that patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly, as part of obtaining informed agreement to shared care
- Provide a copy of the drug-specific patient information leaflet (or direct patient to Versus Arthritis website https://www.versusarthritis.org/about-arthritis/treatments/drugs/)
- Provide a copy of OUHFT 'Rheumatology Shared Care Monitoring Card' to the patient and/or carer, which includes contact details for the rheumatology advice line
- Send a letter to the GP requesting shared care once dose is stable, confirming the above has been completed. Include any results from pre-treatment assessments if appropriate. Provide details of the dose to be continued. Outline shared care protocol criteria and/or direct them to the relevant document on the Oxfordshire CCG website

After 2-6 weeks of treatment:

- Check blood test results from week 2, week 4 and week 6 (available on EPR for Oxfordshire patients/contact GP practice for blood results if patient's GP practice is not in Oxfordshire)
- Ensure any abnormal results are acted upon promptly

After 4-6 weeks of treatment:

- Conduct a consultation with the patient and/or to check that the patient is not experiencing any issues or side effects.
- Confirm that the patient is stable (no side effects, tolerating the drug and established on monthly blood tests). Communicate this information in a shared care handover letter to the GP. Shared care can now commence.
- If the patient is not stable requiring change in the treatment regime, the patient will remain under the care of the specialist until they become stable, as above.

Unless any concerns are raised by the GP within 14 days, shared care will be assumed and the patient will collect the next prescription from the GP. [8]

During treatment:

- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient
- If the dose is increased, patient's bloods will be monitored as above
- If dose is decreased, additional monitoring may not be required at discretion of the rheumatology specialist - this will be clearly communicated in the clinic letter and the existing monitoring schedule should continue

GP

- Ensure that provision has been made for the patient to have blood monitoring as per local arrangements
- Prescribe medication once the dose is stable or shared care is agreed
- Ensure all monitoring is completed in accordance to 'Recommended monitoring schedule for patients taking disease-modifying anti-rheumatic drugs (DMARDs)' including referring to District Nursing service/phlebotomy service is patient is housebound and unable to attend GP surgery for monitoring*.
- Check results then advise the specialist of any deteriorations or abnormal results. Results should be recorded on the monitoring card if the GP practice is outside of Oxfordshire.
- Notify the specialist to any changes in patient's condition, any adverse drug reactions or failure to attend tests
- If a patient fails to attend for monitoring:
  - Only issue a 28 day prescription and book them in for the next available appointment for a blood test
  - If they fail to attend a second blood test then contact the specialist team for advice and to discuss suitability for continuing treatment before supplying further prescriptions
- For parenteral methotrexate, if patient/relatives/carers unable to administer and patient is housebound, provide direction to administer to District Nursing team/Community Childrens Nursing team to cover period of administration before next monitoring is due, with end date included (at which point safety monitoring and review required)

****District Nurse/Community Childrens Nurse***
NB. Input only required if patient is unable to self-administer parenteral methotrexate, relatives/carers are unable to administer and patient is housebound and unable to attend GP surgery/OUH for monitoring or administration

- Complete blood test as requested by GP (This should be done by the Community Phlebotomy service if you have one in your locality)
- Be aware of **side effects** section (see guidance document), checking with patient and escalating any concerns to GP before administering
- Complete administration of methotrexate injection as requested by GP via Direction to Administer
- Update the Primary Care Record by recording the fact of administration as a consultation (or as agreed with the patient's practice)

Plan subsequent administration dates into scheduling tool for period of administration covered by Direction to Administer – NB. Note DTA end date (where patient safety checks and review will be carried out) and do not exceed this

Patient and/or carer

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Ensure that they are booked in for blood test monitoring as per local arrangements and attend as required
- Attend all hospital and GP appointments as scheduled
- Ensure monitoring card is kept up to date and is brought to all appointments (especially patients whose GPs are out of Oxfordshire)

- Report any side effects to the GP or a member of the specialist team

BACKGROUND FOR USE

Methotrexate is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent. It is prescribed for a wide range of conditions. It is also used as a disease modifying drug and is often referred to as a steroid-sparing agent or an immunomodulator.

Indications, dose adjustments and monitoring requirements for disease modifying drugs (licensed and unlicensed indications) defined in the Oxfordshire shared care protocol are in line with national guidance published by the British Society for Rheumatology (BSR) and British Society for Paediatric and Adolescent Rheumatology (BSPAR).

Methotrexate is a disease modifying anti-rheumatic drug (DMARD) and is an established medicine with a known side effect profile. All new patients must be initiated by a specialist. Methotrexate uses in this protocol are limited to:

Adult Rheumatology

- Commonly used as a first line treatment for active rheumatoid arthritis (licensed)
- It can be used in combination with other DMARDs (such as leflunomide, sulfasalazine or hydroxychloroquine) to achieve disease remission
- Also used in combination with biological agents
- Parenteral methotrexate is licensed for rheumatoid arthritis and can be administered subcutaneously
- The use in the following conditions is unlicensed and recommended by the British Society of Rheumatology: psoriatic arthritis, early undifferentiated arthritis, juvenile idiopathic arthritis (JIA), spondyloarthropathies, Systemic Lupus Erythematosus (SLE), myositis, mixed connective tissue disease, scleroderma, vasculitis and polymyalgia rheumatica

Paediatric Rheumatology

- Commonly used as a first line treatment for active Juvenile Idiopathic Arthritis (subcutaneous form licensed)
- Also used in the following conditions: Juvenile Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Uveitis, Vasculitis and Other Connective tissues such as Scleroderma (localised & systemic), Sarcoidosis and any other rheumatological conditions (all unlicensed)
- Methotrexate should only be initiated by and under the direction of a consultant paediatric rheumatologist, or a rheumatologist with an interest in paediatric rheumatology

DOSAGE

Adult Indications:

- Typical regimen 15-25 mg weekly [1,2,3]
- Usual maximum dose 25 mg weekly, but in exceptional cases a higher dose (up to maximum of 30mg weekly) may be clinically justified [3]
- Folic acid should be prescribed routinely at a dose of 5mg once weekly but can be increased to up to 6 times a week (not on the day of methotrexate) if required due to side effects from methotrexate. Folic acid reduces the risk of hepatotoxicity and gastrointestinal side effects. Time to response is up to 3 months

Paediatric Indications:

- Dose range 10-15 mg/m^2 per week (maximum of 25mg/m^2), up to a maximum of 25 mg per week. [3,4] It is usually given on the same day each week, but on occasions there may be an agreement to give a dose a day or two either side to help compliance.
- Folic acid supplementation is not an absolute requirement. It may be used to reduce side effects at a dose of 1- 5mg per week, to be given 4 days after the methotrexate is

recommended. The frequency can be increased up to 6 times a week if needed (not on the same day as methotrexate).

PRESCRIBING INFORMATION

- Prescriptions must state the form, strength, dose and directions in full.
- If methotrexate injection is prescribed, the brand name **must** be stated.
- The use of 'as directed' in prescribing must be avoided
- Doses must be taken on the same day each week.
- If it is being used in an unlicensed indication this must be explained to patient.

Oral methotrexate

- Only 2.5mg tablets should be prescribed and dispensed to avoid potentially fatal errors
- Tablets do disperse in water [5]

Subcutaneous Methotrexate

- Consider using methotrexate by s/c administration **only** on the advice of a specialist. The dose is the same as the oral dose.

Subcutaneous methotrexate can:

  - Improve the patients quality of life and satisfaction with treatment
  - Ensure the maximum bioavailability
  - Reduce symptomatic side effects for some patients, thus increases in the therapeutic dose are better tolerated
  - Extend the time that disease is controlled before expensive anti-TNF therapies need to be introduced.

- All prescribing of subcutaneous methotrexate should be via brand name as there are a number of brand and devices available. The brand of choice within the OUH and OCCG is Metoject®.
- If the Metoject device is unsuitable, the second-line option is Nordimet®. This should only be used for paediatric patients who cannot use the Metoject® device and those with dexterity issues.
- In order for a patient to use the product under the care of the GP, they must be able to administer the injection or have made alternative arrangements for a relative / carer (or District Nurse/Community Children's Nurse if patient and relative/carer are unable to administer to do this for them). The patient will be counselled by the consultant **not** to start the injections before they have received training by the Rheumatology specialist nurse team (if injection is to be given by District Nurse or Community Children's Nurse, the patient does not require training)
- If the patient is changing from oral methotrexate to an equivalent dose of subcutaneous methotrexate, the consultant will request the GP to prescribe the initial dose and include all necessary information in the clinic letter. There is no requirement for additional blood monitoring so the patient can continue with their current monitoring schedule. Once the patient has collected their first supply of medication, they can then phone the Rheumatology Day Unit to arrange an injection technique training appointment. The number is 01865 737553.
- For paediatric patients, the patient and parents/carers will be counselled by the consultant and will receive training from the specialist nurse to administer the injections during the clinic appointment. If it is not possible for patient or parent/carer to administer the injections, alternative arrangements will be made by the specialist nurses.

<u>Disposal of sharps</u>

- Cytotoxic sharps bins (purple-topped) will be provided by the hospital specialist nurse on initiation of treatment when attending for the self-administration training
- Once the sharps box is full and has been sealed it can be dropped off at the GP for disposal or collected by the local council in exchange for an empty one. This differs in areas so make sure the patient is aware of the correct process (the GP surgery should have these details).

- Only in exceptional pre-arranged circumstances should this exchange occur as part of a planned follow up clinical appointment at the outpatient department.
- Patients are advised to return their boxes for disposal and replacement when full or approximately every 3-6 months.
- For those receiving their treatment from the District Nursing or Community Children's Service, supply and collection of sharps box will be arranged by that service, either via the Council if available, or other local arrangement depending on the area – see GP, DN and CCN guidance document for more detail.

PRE-TREATMENT ASSESSMENT BY SPECIALIST

- FBC, LFT, U&E, CRP [6]
- Chest X-ray if not done within the last 6 months (not necessary in children unless there is a specific indication)
- Lung function tests may be considered in smokers and patients with pre-existing lung disease.
- Pre-viral screen in high-risk patients: HIV, HBV (surface antigen, core antibody), HCV (antibody test) and consider herpes zoster status (if appropriate)
- Varicella zoster serology in children to determine immune status to chickenpox. Consider vaccine if susceptible
- In children and young people, live vaccines (especially if part of an immunisation schedule), can be given if patients are on doses under 15mg/m^2. If they are on higher doses, seek advice from the paediatric rheumatology team or an Infectious Diseases specialist.

ONGOING MONITORING

More information available in separate guideline; 'Recommended Monitoring Schedule for patients taking disease-modifying anti-rheumatic drugs (DMARDs)'

Baseline assessments should include height, weight, blood pressure, FBC, U&Es, LFTs and CRP.

Standard Monitoring Schedule as per British Society of Rheumatology Guidelines[6]:

- Following initiation or dose change: Check FBC, U+Es and LFTs **every 2 weeks** until on stable dose for **6 weeks**
- Once on stable dose, check FBC, U+Es and LFTs **monthly** for **3 months**
- Thereafter, check FBC, U+Es and LFTs **every 3 months**.
- More frequent monitoring is appropriate in patients at higher risk of toxicity (extremes of body weight, CKD3 or above, pre-existing liver disease, significant other medical co-morbidity, age over 80 years and previous DMARD toxicity)

British Society of Paediatric & Adolescent Rheumatology monitoring guidelines are currently under review and will be added in when available.

Exceptions and Additions to the Monitoring Schedule:

Drug	Laboratory monitoring	Other monitoring
Methotrexate	Standard monitoring schedule	In women of childbearing age: pregnancy testing should be repeated as clinically required (e.g. after any gap of contraception is reported)
Methotrexate/Leflunomide combined	Extend monthly monitoring longer term (at least 12 months)	In women of childbearing age: pregnancy testing should be repeated as clinically required (e.g. after any gap of contraception is reported)

Abnormal Laboratory Results and Action to be Taken:

Please note that in addition to absolute values for haematological indices a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance.
Some patients may have abnormal baseline values; specialist will advise if so. e.g. some patients with cirrhosis will have pre-existing pancytopenia and lupus patients may have leucopenia because of lymphopenia.

Laboratory Result	**Action**
WBC less than 3 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
Neutrophils less than 1.6 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
Platelets less than 140 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
MCV greater than 110 fl	Withhold and discuss with Rheumatology. May be able to continue if chronic increase. Check folate and $B_{12.}$ If level low, start appropriate supplementation.
Creatinine increase greater than 30% over 12 months and/or calculated GFR less than 60ml/min/1.73m^2	Discuss with Rheumatology as dose adjustments or further investigations may be required.
Adult liver function ALT greater than 2.5 x upper limit of normal or over 100U/l	Withhold and discuss with adult rheumatology.
Paediatric liver function ALT or AST greater than 120U/l	Withhold until discussed with paediatric rheumatology. Transaminase increase 3 times the upper limit of normal is common within 2 days of drug administration and may be attributable to an asymptomatic viral infection. Consider rechecking ALT at trough level. (i.e. 0-2 days prior to dose) If LFT derangement occurs more than once, contact the paediatric rheumatology team before discontinuing.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications	
Significant renal disease	Do not use in GFR less than 30 ml/min
Untreated folate deficiency, leucopenia, thrombocytopenia.	Do not use.
Chronic liver disease and alcoholism	Relative contraindication, use with caution
Severe COPD	Do not use.
Immunodeficiency	Do not use.
Suspected local or systemic infection	Treat infection vigorously. Continue methotrexate unless symptoms significant.

Precautions	
Elective surgery	Methotrexate can be continued (caution for early detection of infection and complications).
Renal impairment	Reduce the dose (avoid if GFR less than 30 ml/min).

SIDE EFFECTS AND ACTION TO BE TAKEN

SIDE EFFECTS	**ACTION**
Renal impairment	Patients who develop dehydration, pre-renal or acute kidney injury while on methotrexate should have methotrexate withheld and FBC monitored closely. Review any changes in medication particularly ACEI and ARB.
Nausea and/or vomiting	Consider: • Increasing the dose of folic acid to 5 mg daily up to 6 days a week - omitting on the day methotrexate is taken. • Splitting methotrexate dose over one evening and next morning (if on oral tablets). • A short-term anti-emetic. • Avoiding NSAID use on the day of methotrexate • If unable to tolerate refer back to specialist for review.
Hair loss	Usually mild, rarely significant. Reversible on stopping drug. Can consider increasing the dose of folic acid to 5 mg daily up to 6 days a week - omitting on the day methotrexate is taken.
Rash	Withhold treatment and discuss with specialist.
Mouth ulcers, mucositis	Mouth ulcers may respond to increasing folic acid as above. If severe despite extra folic acid stop methotrexate and refer to a specialist for advice.
Menstrual dysfunction/amenorrhoea	May occur during treatment and for a short while after cessation.
Otherwise unexplained dyspnoea or cough (especially if accompanied by fever/sweats)	Methotrexate pneumonitis may occur. Withhold treatment, arrange chest X-ray and discuss urgently with consultant.
Abnormal bruising	Withhold until FBC result available.
Sore throat or other unusual infection	Urgent FBC and withhold until FBC result available. Susceptible to opportunistic infections such as viral wart, TB and pneumocystis.
Lymphoproliferative disorders	Use with caution - discuss with haematology
Cervical dysplasia	Regular cervical smears
Diarrhoea	Consider reducing dose
Fever, chills	Withhold until FBC result available

Withholding doses of methotrexate: One weekly dose of methotrexate can be withheld without inducing a flare. Patients are advised not to take the dose if more than 24-72 hours late but take as normal the following week.

NOTABLE DRUG INTERACTIONS

(Please note that this is not an extensive list. Refer to BNF and SPC for any specific drug interaction queries)

Any anti-folates: Co-trimoxazole Trimethoprim Phenytoin Sulphonamides Fansidar®	Avoid co-prescribing: Increased anti-folate effect which may induce toxic effects of methotrexate on FBC.
Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin	Under specialist advice this combination is not contraindicated. NSAIDs and aspirin may reduce tubular excretion of methotrexate and enhance its toxicity. Over-the-counter products containing NSAIDs or aspirin are NOT recommended. Avoid in IBD as they can aggravate symptoms.
Ciclosporin	Patients co-prescribed ciclosporin with methotrexate should initially be re-stabilised by the specialist as it can increase methotrexate toxicity.
Leflunomide	Although the BNF states that leflunomide is not usually used with methotrexate, it is appropriate to use the combination in rheumatoid arthritis under specialists' advice[7]. There can be increased risks of side effects (e.g. liver and haematological), but with careful monitoring experience suggests they may be used together.
Alcohol	Safe in moderation but may cause nausea. Stay below national guidance limits.
Penicillins	Theoretical interaction whereby penicillins can increase the risk of toxicity when given with methotrexate, particularly high doses. Advise caution with use and close monitoring for methotrexate side effects is advised.
Ciprofloxacin	Possible increased risk of methotrexate adverse effects on concurrent use. Suspect ciprofloxacin as a cause should they occur. Ciprofloxacin should be stopped if the course is not already completed.

FAMILY PLANNING

Females: Avoid in pregnancy. Treatment should be stopped at least 3 months before trying to conceive. Avoid in breastfeeding.

Males: For advice on paternal exposure, please discuss with secondary care.

VACCINATIONS

Check Department of Health Green Book guidance and if not covered, discuss with secondary care

BACK-UP INFORMATION AND ADVICE

Contact Details	Oxford University Hospitals NHS Foundation Trust	
Rheumatology	Rheumatology Helpline (Adult and Paediatric) Adult - Option 1 (Monday to Friday 8am - 2pm, answerphone service) Paediatric - Option 2 (Monday to Friday, answerphone service) Closed on weekends and bank holidays Rheumatology Registrar/Consultant on call Registrar on site Monday to Friday 9am-8pm Weekends and bank holidays 9am-5pm	Tel: 01865 737656 Email: Adult – rheumatology.noc@nhs.net Paediatric - cnspaedrheumatology@ouh.nhs.uk OUH switchboard number: 0300 304 7777, ask for Rheumatology on call
Medicines Information	Tel: 01865 221505 (Monday to Friday 9am - 5pm) Email: Medicines.information@ouh.nhs.uk	

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