Oxford University Hospitals NHS
NHS Trust

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Clinical Commissioning Group

METHOTREXATE FOR USE IN OCULAR INFLAMMATION (OPHTHALMOLOGY) Adults and Paediatrics
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for methotrexate therapy in ocular inflammation. 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 Responsibilities

Shared care assumes communication between the specialist, GP 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.

Specialist

- Complete pre-treatment assessment (detailed below)
- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care
- Ensure the patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly
- Provide copy of patient information leaflet and drug monitoring card where appropriate
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient throughout treatment
- Patients will be followed up by telephone call from the clinic pharmacist approx. 4 weeks after starting treatment to confirm they are tolerating the medicine, 2 week blood test has been completed and whether there are any other issues.

GP

- Prescribe medication once the dose is stable or shared care is agreed
- Ensure all monitoring is completed in accordance to the specific shared care protocol (listed under on-going monitoring).
- Check and record results then advise the specialist of any deteriorations or abnormal results
- Notify the specialist to any changes in patients condition, any adverse drug reactions or failure to attend tests

Patient

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Attend for blood tests and monitoring when required
- Ensure monitoring card is kept up to date and is brought to all appointments
- 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.

Supporting Information
DMARDS such as methotrexate are commonly used in ocular inflammation
Methotrexate may be used alone or in combination with other immunomodulatory drugs e.g. tacrolimus, prednisolone or with biologics such as adalimumab.

Methotrexate is used as a second line therapy for those patients who require > 7.5mg prednisolone/day to control disease, require frequent high dose steroids due to frequently relapsing disease or those with severe disease on presentation.

The commonest indication is in children suffering from persistent sight-threatening uveitis

Prescribing information

Prescriptions must state the form, strength, dose and directions in full.
The use of 'as directed' in prescribing must be avoided
Doses must be taken on the same day each week
Patient must be supplied with the NPSA Patient-held blood monitoring and dosage record booklet and the manufacturers Patient Information Leaflet by the clinic when they are first prescribed methotrexate. If it is being used in an unlicensed indication this must be explained to patient.

<u>Oral methotrexate</u>
Only 2.5mg tablets should be prescribed and dispensed to avoid potentially fatal errors.
Oral solutions available as specials as per BSPAR guidance. Tablets do disperse in water.

<u>Parenteral methotrexate</u>
Consider using methotrexate by s/c administration only on the advice of a specialist for:
o Patients with GI side effects despite regular folic acid 5 mg, 6 days a week.
o Non-responders to oral therapy after an 8 - 12 week trial in order to improve drug bioavailability.
Parenteral methotrexate can:
o Improve the patients quality of life and satisfaction with treatment
o Ensure the maximum bioavailability
o Reduce symptomatic side effects for some patients, thus increases in the therapeutic dose are better tolerated
o Extend the time that disease is controlled before expensive anti-TNF therapies need to be introduced.

<u>Subcutaneous Methotrexate</u>
As agreed by APCO only Metoject® subcutaneous methotrexate preparations should be used within Oxfordshire. All prescribing of methotrexate subcutaneous should be via brand name.
Metoject® is not licensed for use in uveitis however it's use is well established
Metoject® is a single use pre-filled auto-injector pen (this replaced the pre-filled syringe presentation and has a different administration technique). It is available in 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg and 25 mg pens. Only these standard doses should be prescribed by GPs. Other strengths are difficult to obtain in the community.
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 relative / carer to do this for them. The patient will be counselled by the OEH team, most commonly by the specialist pharmacist
After 2 to 3 months of s/c injection the specialist will re-assess if the treatment is of benefit and whether it should be continued.

Disposal of sharps

Cytotoxic sharps boxes (purple) 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.

Contraindications and Precautions

Contraindication	**Action**
Pregnancy	It is essential that both female and male patients of child bearing age should use effective and reliable contraception whilst on methotrexate and for at least 3-6 months after stopping it. Patients planning on becoming pregnant or who think they are pregnant should be seen by the specialist.
Breast feeding	Do not use
Significant renal disease	Do not use if GFR less than 10ml/min
Untreated folate deficiency, leucopenia, thrombocytopenia or other pre existing blood dyscrasias.	Do not use.
Chronic liver disease and alcoholism	Relative contraindications
Severe COPD	Do not use
Immunodeficiency	Do not use
Suspected local or systemic infection	Treat infection vigorously. Continue methotrexate unless symptoms significant.
Ascites or pleural effusion	Can accumulate in these fluids and subsequently return to circulation causing myelosuppresion
Precautions	**Action**
Elective surgery	Methotrexate can be continued (caution for early detection of infection and complications).
Renal impairment	Reduce the dose (avoid if GFR <30 ml/min).
Chickenpox/shingles	Stop methotrexate if proven infection. For those with exposure to chickenpox or shingles and no history of infection/vaccination, passive immunisation with VZIG should be carried out.

Dosage

Indication	**Dose**
Adults	Initial dose of 7.5 mg **once a week**, adjusted according to response to a normal maintenance dose of 15mg – 20mg and a maximum of 25 mg once a week depending on disease severity. Can be given orally or subcutaneously

Children	Dose by mouth, s/c injection or IM injection should initially be 10-15mg /m2 **once weekly** increased if necessary to a maximum of 25mg /m2. (The BNFC should be referred to for rough guide to Body Surface Area for different aged children).

Folic acid should be co-prescribed to reduces the risk of hepatotoxicity and gastrointestinal side effects: 5mg once weekly is usually sufficient for both adults and paediatrics.
To aid monitoring folic acid usage, prescribe a quantity for the same duration of supply as methotrexate (e.g. four weeks).
To aid memory, some departments advise patients to take Methotrexate on Mondays and Folic acid on Fridays

Time to Response
Methotrexate can take between 6 weeks to 3 months to have a full effect.

Pre-Treatment Assessment
Height
Weight
BP
Baseline FBC, U+E, LFT if nil results available in previous 3 months
Pregnancy test (where applicable)
Chest XRay (adult patients)
Varicella zoster serology in children to determine immune status to chickenpox. Consider vaccine if susceptible and if methotrexate can be delayed.
Hepatitis B/C screening (if risky behaviours identified or if there is any LFT abnormality)
HIV screening (if risky behaviours identified)

Ongoing Monitoring
FBC, U+E, LFTs 2 weeks after starting treatment then
FBC, U+E, LFTs monthly for 3 months then
FBC, U+E, LFTs every 2 months to continue

May be extended further to 3 monthly if results are stable beyond 2 years on therapy

Increase frequency of monitoring if patient at risk of toxicity

FBC, U+E, LFTs should be repeated 2 weeks after any dose change then revert to previous monitoring schedule.

Where applicable: Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported)

Actions to be taken

Side Effects	**Action**
WBC <3.5 x 109/l	Adults: Perform a differential and increase frequency of monitoring. Paediatric: Withhold and discuss with specialist
Neutrophils <1.6 x 109/l	Withhold and discuss with specialist. Bone marrow suppression can occur abruptly. May present as a fever and sore throat
Platelets <140 x 109/l	Withhold and discuss with specialist. Bone marrow suppression can occur abruptly.

Unexplained eosinophilia >0.5 x 10/L	Withhold and discuss with specialist.
MCV >105	Check folate, B12 and TFT, and treat if appropriate. If WBC normal repeat in 4 weeks. Stop methotrexate and seek advice.
Creatinine increase >30% over 12 months and/or calculated GFR < 60ml/min	Withhold until discussed with specialist team.
Adult liver function 2 - 3 fold rise in ALT >3 fold rise in ALT or ALT/AST > 100U/L	Reduce the dose by 2.5 mg and repeat in 1 - 2 weeks. LFTs can return to normal after stopping for 2 weeks. Withhold until discussed with specialist.
Albumin <30g/l	Withhold until discussed with specialist
Paediatric liver function ALT or AST >120	Withhold until discussed with specialist. 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 injection)
Nausea and/or vomiting	Usually improves over time For adults 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. □ A short-term anti-emetic. For children consider: Increase folic acid to 1-5mg, 3 days a week. Maximum increase to 5mg 6 days a week (omitting the day methotrexate is taken). Anti-emetic can be prescribed such as cyclizine or ondansetron If unable to tolerate refer back to specialist for review.
Hair loss	Usually mild, rarely significant. Reversible on stopping drug.
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) or reduced exercise tolerance	Methotrexate pneumonitis may occur. Withhold treatment, arrange chest X-ray and discuss urgently with consultant. Pneumonitis is very rare in paediatric practice. Discuss with paediatric rheumatologist if an atypical presentation or persists > 2 weeks without preceding infection.
Abnormal bruising	Withhold until FBC result available
Sore throat or other unusual infection	Sore throat or other unusual infection Susceptible to opportunistic infections such as viral wart, TB and pneumocystitis.
Cervical dysplasia	Regular cervical smears
Diarrhoea	Consider reducing dose
Fever, chills	Withhold until FBC result available

In addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance..

- 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 (this depends on speciality so follow advice of specialist) but take as normal the following week.
- Folinic acid (given as calcium folinate) should be used for methotrexate induced myelosuppression, severe mucositis or methotrexate overdoses

Notable Drug Interactions (Refer to BNF and SPC)

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.
Immunisation with Live vaccines	Patients receiving methotrexate must NOT receive immunisation with LIVE vaccines (BCG, oral typhoid, oral cholera, measles, mumps, rubella, yellow fever, Sabin polio, Varicella/ Chickenpox, Rotavirus and Japanese Encephalitis). Inactivated polio is available although suboptimal response may be seen.

	Continue with standard vaccination strategy for any patient with IBD and Paediatric Rheumatology (check latest guidance) – H1N1, pneumococcal polysaccharide vaccine, HPV according to national guidance, hepatitis B for selected patients. Seasonal influenza vaccination is recommended. **Do not use** Fluenz Tetra® (nasal flu vaccine) as it is a live vaccine. Continue with standard vaccination strategy for any patient with IBD and Paediatric Rheumatology (check latest guidance) – H1N1, pneumococcal polysaccharide vaccine, HPV according to national guidance, hepatitis B for selected patients.
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' advice7. 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.

Back-up Information and Advice

Name, job title, department	Contact Details (phone/email)
Clare Faulkner Specialist Pharmacist-Ocular Inflammation Service	Service email: oeh.uveitis@nhs.net 01865 741166 bleep 8314

References

1. BNF 76, Sept 2018-Mar 2019

2. EMC, https://www.medicines.org.uk/emc/ Summary of Product Characteristic (SPC) for metoject [20/02/2019]

3. Ledingham J et Al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology*, Volume 56, Issue 6, 1 June 2017, Pages 865–868 [Accessed 20/02/2019]

4. Appendix A In: British Medical Association and Royal Pharmaceutical Society of Great Britain (2019). British National Formulary 76th Edition. BMJ Group and RSP Publishing, London.

5.. A clinical handbook of adult immunosuppressive therapy for ocular inflammatory diseases. University Hospitals Bristol NHS foundation Trust and Moorfields Eye Hospital NHS foundation Trust version 2 March 2018.

6. Scottish Uveitis National Managed Clinical Network Treatment Guidelines 2010 https://www.sun.scot.nhs.uk/Documents/uveitis%20treatment%20guideline%20sep%2020101revised%20.pdf [Accessed 20/02/2019]
7. NPSA, Patient Safety Alert no.13. Improving compliance with oral methotrexate guidelines, June 2006.
8. EMC, https://www.medicines.org.uk/emc/ Summary of Product Characteristic (SPC) for methotrexate 2.5mg tablets [20/02/2019]