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British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR); (Feb, 2017) recommends harmonisation of monitoring schedules, for all DMARDs that require laboratory monitoring. These should follow the same frequency of testing.

PROTOCOL FOR THE ADMINISTRATION OF METHOTREXATE – INFORMATION FOR GENERAL PRACTITIONERS

BACKGROUND FOR USE

Methotrexate is a disease modifying anti rheumatic drug (DMARD) of proven benefit in the treatment of rheumatic diseases in particular rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, SLE, polymyositis and vasculitis. Methotrexate is often used in combination with other DMARDs to achieve disease remission. Methotrexate should only be initiated by the Rheumatologist. The drug can be administered orally or by subcutaneous injection.

DOSAGE REGIME

Methotrexate is given **ONCE WEEKLY.** Our usual starting dose is 10- 12.5mg weekly. The therapeutic range is between 7.5 – 25mg weekly. If maximum oral dose is not effective or causes intolerance parenteral route of administration will be considered. Time to response is 6 – 12 weeks. Folic acid is prescribed routinely at a dose of 5 – 10mg weekly to be taken 2 days after methotrexate. Folic acid can be given more frequently but not on the day of Methotrexate. Folic acid reduces the risk of hepatotoxicity and gastrointestinal side effects and improves compliance. Methotrexate should be prescribed in multiples of 2.5mg tablets. All patients should have an NPSA shared care booklet, in which blood results and dose are documented.

PRE TREATMENT ASSESSMENT BY RHEUMATOLOGIST

- FBC, LFTS, U&Es, EGFR, ESR and CRP.
- Chest X-ray (unless done within last 6 months).

- Consider lung function test in patients with risk factors such as smoking or pre-existing lung conditions.

MONITORING:

- FBC, Creatinine, Calculated GFR, ALT, AST ; two weekly for six weeks then, once on stable dose, monthly for three months.
- Thereafter, FBC, Creatinine, Calculated GFR, ALT, AST and Albumin, at least every 12 weeks.
- More frequent monitoring is appropriate in patients at higher risk of toxicity
- Combination therapy of Methotrexate and Leflunomide require monitoring to be extended for a longer term. **– (extend monthly monitoring beyond 6 months)**
- If possible blood test should be taken at the trough level i.e. on the morning before taking the Methotrexate, as transaminase increase 2 x normal is common within 2 days of drug administration

  Please note that in addition to absolute values for haematological and biochemical indices a rapid fall/rise or a consistent downward/upwards trend in any value should prompt caution and extra vigilance.

SIDE EFFECTS	ACTIONS
WBC <3.5 X 10^9/l	Withhold drug; repeat WBC in 1/52, if normal, continue, otherwise discuss with Rheumatology Department
Neutrophils <1.7 x10^9/l	Withhold until discussed with rheumatology Department
Platelets <140 x 10^9/l	Withhold until discussed with Rheumatology Department
Liver function 2-3 fold rise in ALT >3 fold rise in ALT	Reduce the dose by 2.5mg and repeat in 2 weeks Withhold until discussed with Rheumatology team
MCV > 105 – 110 fl MCV > 110 fl	Check folate, TFT, B12 and treat if appropriate. If WCC normal repeat in 4 weeks and continue drug Stop MTX and seek advice
Renal impairment	MTX toxicity can be increased as excreted renally. Caution in patients with co-morbidities. Withhold if worsening renal function
Nausea	Ensure patient is on folic acid, consider increase of folic acid. If nausea, severe, increase folic acid to 5mg d days per week, omitting day MTX is taken. Split MTX dose over one evening and the next morning. An anti-emetic can be prescribed.
Mouth ulcers	May respond to an increase in Folic acid, as above

Rash or severe ulceration	Urgent FBC for WCC. Withhold until discussed with Rheumatologist. Look for alternative causes. Re- challenge with smaller dose once symptoms settle.
Menstrual dysfunction/Amenorrhoea	May occur during treatment and for a short time following cessation
Otherwise unexplained dyspnoea/cough	Pneumonitis may occur. Withhold drug and discuss urgently with Rheumatology Team. Urgent CXR
Severe sore throat, abnormal bruising, nose bleed	Immediate FBC and withhold until result of FBC available.

CONTRAINDICATIONS AND PRECAUTIONS

Conception, pregnancy and breastfeeding	For men and women, contraceptive advice should be given, as pregnancy should be prevented for a minimum of 3 months after discontinuation of treatment. Breastfeeding is contra-indicated
Vaccination with LIVE vaccines	Patients receiving Methotrexate must NOT receive live vaccines
NSAIDs	Can continue if taken regularly and monitored. Avoid over the counter NSAIDs/aspirin
Trimethoprim/Co-trimoxazole	Avoid, can cause bone marrow depression

- **FLU AND PNEUMOCOCOCCAL VACCINES ARE RECOMMENDED FOR PATIENTS ON IMMUNOSUPRESSIVE THERAPY**

REFERENCE:

http://www.rheumatology.org.uk/about_bsr/press_releases/bsr_publishes_updated_guideline_nonbiologic_dmards.aspx

https://academic.oup.com/rheumatology/article/3053478/BSR-and-BHPR-guideline-for-the-prescription-and