Methotrexate - Crohn's Disease - Full Clinical Guideline

Reference No: CG-T/2024/114

Introduction

Crohn's disease is a chronic relapsing and remitting inflammatory condition of the intestinal tract. Corticosteroids are generally the treatment of choice for achieving remission. Immunomodulatory drugs can be useful in the management of patient's refractory to, or dependent on corticosteroid treatment. The thiopurine agents, azathioprine and mercaptopurine are considered first line immunomodulatory drugs used for Crohn's disease, but some patients fail these treatments due to lack of response, intolerance, or serious side effects such as leucopoenia.

Methotrexate (MTX) is a dihydrofolate reductase inhibitor with cytotoxic and anti-inflammatory effects. MTX is a useful second line immunomodulatory drug that may be used to induce and maintain remission in Crohn's disease.

Purpose and Scope

To provide guidance on the management and monitoring of patients being treated with MTX. This is a cytotoxic agent and therefore should be given with caution and under the guidance of a consultant gastroenterologist.

Indications

- Patients with steroid dependent/refractory Crohn's disease who have failed treatment with a thiopurine agent.
- MTX may provide a therapeutic effect more rapidly (4-6 weeks) than the thiopurine agents (8-12 weeks), and this may be desirable in certain cases.
- Methotrexate orally can be co-administered with anti-TNF drugs especially infliximab to reduce loss of response secondary to anti infliximab antibody formation.
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Contraindications

- **Pregnancy*:*** MTX is both abortifacient and teratogenic and pregnancy should be avoided for at least three months following last exposure in a potential parent of either sex.
- ***Breast feeding****:* MTX is excreted in milk.
- **Active infection and immunodeficiency syndromes.**

Cautions

MTX should be used with caution, or alternative treatments considered, in patients with blood disorders, liver disease, and significant lung disease. Other folate antagonist drugs such as trimethoprim, sulphonamides and phenytoin, and renal impairment (MTX is excreted via the kidneys), can potentiate the toxic effects of MTX.

Side effects and toxicities

- **Bone marrow suppression** (up to 1 %)

- **Liver toxicity:** liver fibrosis or cirrhosis may develop with long term MTX use (3 % with cumulative MTX dose of 4 g). It is more likely to occur in those with underlying liver disease; for this reason use of MTX should be carefully considered in patients already at risk of liver disease (*eg* alcohol excess, metabolic syndrome). Risk of liver fibrosis is reduced when lower doses (≤ 20 mg) are given once weekly. Pre treatment liver biopsy is not required in patients without risk factors for liver disease, but a biopsy to assess for fibrosis may be considered when the cumulative dose reaches 4 g (3.5 to 5 years if maintenance dose is 15-20 mg), if treatment is to continue. Liver chemistry should be monitored regularly, and abnormalities may be transient.

- **Hypersensitivity pneumonitis:** may develop in up to 2 % and should be suspected if cough and dyspnoea develop whilst on treatment.

- **Gastrointestinal side effects** such as nausea, diarrhoea and stomatitis can occur early on in treatment, and may be relieved by co-prescription of folic acid. Other folate antagonist drugs, such as trimethoprim, sulphonamides, and phenytoin, should be avoided.

Administration

- MTX is usually initially administered as a **once weekly** intramuscular or subcutaneous injection 25mg for between ten and sixteen weeks.
- If the patient has responded following this induction regimen, MTX is usually given orally, preferably at a lower dose such as 15 mg **once weekly**. This oral dose may be increased to 20 or 25 mg once weekly if response is lost at the lower dose.
- Folic acid 5mg once weekly, two or three days after the MTX dose, should also be given, and may reduce gastrointestinal side effects.

There are no current recommendations in the literature as to how long treatment with MTX may be continued. If treatment for several years is planned, the patient should be further warned of potential side effects and the need for further monitoring techniques such as a liver biopsy.

Monitoring therapy

- Patients should be warned to be vigilant for symptoms of infection.
- Patients should be provided with a NPSA blood monitoring and dosage **record book** to facilitate communication of blood test results and drug dosage changes. **This book should be carried by the patient whenever they visit the doctor, nurse or pharmacist.**
- Baseline FBC, U&E and LFT, along with CXR and pulmonary function tests including gas transfer factor should be obtained prior to treatment.
- FBC, U&E and LFT should be monitored fortnightly for the first 6 weeks, then at 3 months, then 3 monthly thereafter.
- If the maintenance dose is increased, blood tests should be temporarily monitored on a fortnightly basis again, until it is clear that values are stable.

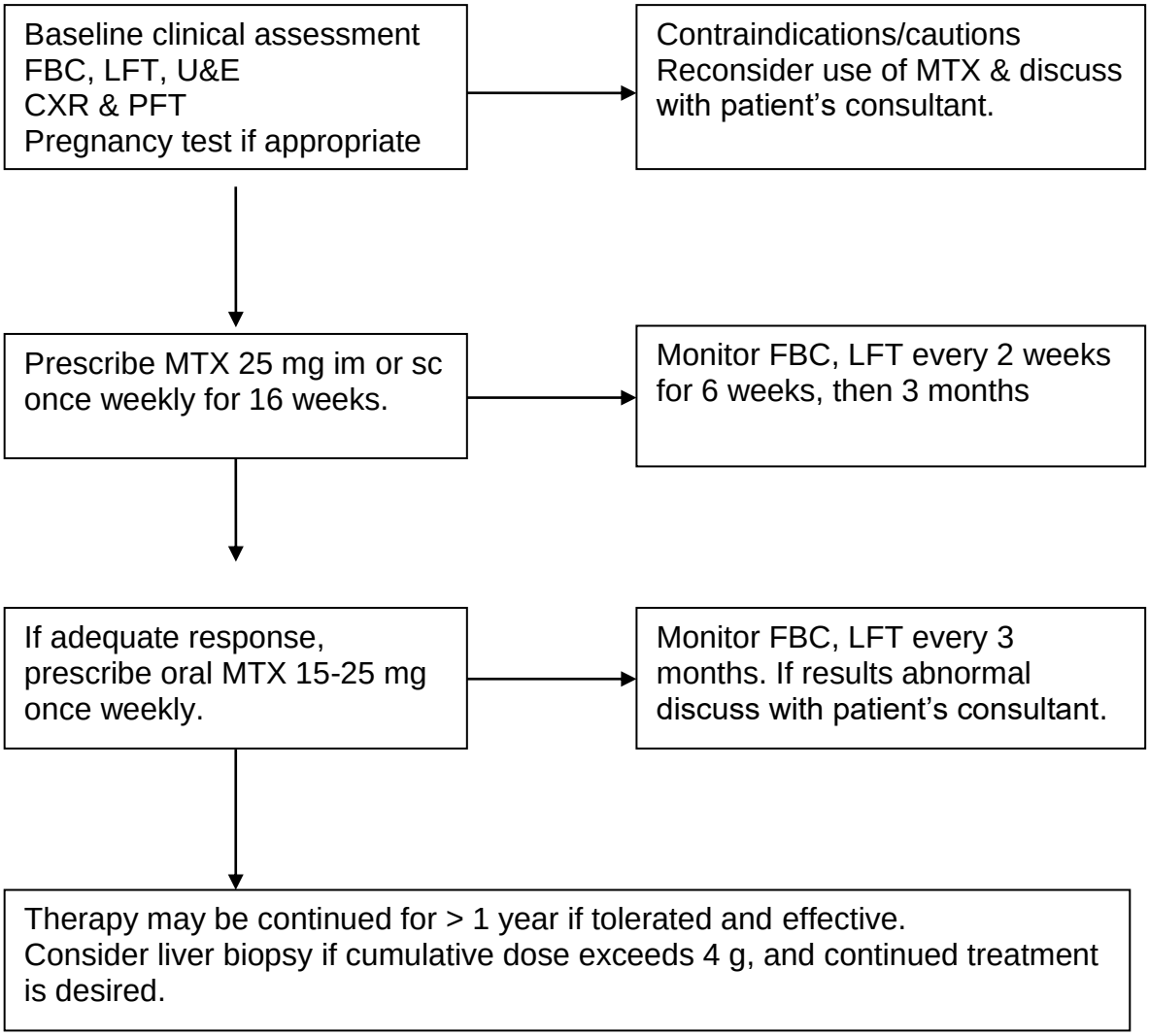
Withhold treatment and discuss with the patient's consultant under the following circumstances:

- Total white cell counts $\leq 3 \times 10^9$/l or neutrophil count $\leq 2.0 \times 10^9$/l or platelet count $\leq 150 \times 10^9$/l.
- ALT $>$ twice upper limit of normal range.
  (Under these circumstances it may be reasonable to repeat the blood test on a weekly basis, and re-challenge with MTX when the value has returned to normal).
- Symptoms suggestive of active infection such as fever, headache, sore throat, or rash.
- New onset cough or dyspnoea.

References

Hawthorne AB. Methotrexate: a useful alternative in Crohn's disease? Gut 2001;**49**:9-10.
Carter MJ, Lobo A *et al*. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;**53** (Suppl V):v1-v16.
Travis SPL, Stange EF *et* al. European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. Gut 2006 **55**(Suppl I): i16-i35.
Zhang J et al Impact of Biologic Agents with and Without Concomitant Methotrexate and at Reduced Doses in Older Rheumatoid Arthritis Patients Arthritis Care & Research 2015; **67: 624**–632

USE OF METHOTREXATE IN CROHN'S DISEASE FLOWCHART



Documentation Controls

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