LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE: METHOTREXATE in DERMATOLOGY and RESPIRATORY

General Principles

Shared Care Responsibilities:

In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 70, September 2015 – March 2016, pg.4)

Aims:

(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between the Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from members of the Arden and GEM commissioning Support Unit – Lincolnshire Prescribing & Medicines Optimisation Team.

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Principles of shared care

The General Medical Council published their Good Practice in Prescribing and Managing Medicines and which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

Good practice recommendation 35.

- Decisions about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

Good practice recommendation 36.

- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

Good practice recommendation 37.

- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

Good practice recommendation 38.

- If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required

Good practice recommendation 39.

- In both cases, you will be responsible for any prescription you sign.

Good practice recommendation 40.

- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required

Good practice recommendation 41

- If you share responsibility for a patient's care with a colleague, you must be competent to exercise your share of clinical responsibility.

You should:

a) Keep yourself informed about the medicines that are to be prescribed for the patient
b) Be able to recognise serious and frequently occurring adverse side effects
c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them
d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient's condition

Good practice recommendation 42

- In proposing a shared care arrangement, specialists may advise the patient's general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from authoritative guidance or recommended treatments and provide both the general practitioner and the patient with sufficient information to permit the safe management of the patient's condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient's care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Drug Details

Approved Name: **Methotrexate**
Brand Name: Non-proprietary
Form and Strength: 2.5mg tablets (only 2.5mg tablets are to be prescribed).

Specialist Responsibilities

The specialist secondary/tertiary care service will:
1. Send a letter to the GP requesting that the GP participates in shared care. As part of the communication the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef
2. Carry out base line checks of FBC, U&E' including creatinine and LFTs, and P3NP (Dermatology only). Folate & Serum B12 levels in elderly patients > 70 years not required for dermatology patients. Folate & Serum B12 levels not routinely checked for respiratory patients.
3. Conduct a baseline chest x-ray (if not done within last 6 months). Include Pulmonary Function test in base line checks for selected patients at specialist's discretion. All respiratory patients should have had a recent spirometry reading within last 3 months. It is the responsibility of the specialist to ensure this is checked if there is not record of there one being done within last 3 months.
4. Decide whether a liver biopsy is appropriate and carry out if indicated.
5. Carry out hepatitis, HIV and Varicella Zoster serology.
6. Initiate and stabilise methotrexate therapy
7. Ensure that the patient receives supplies of methotrexate (and folic acid if required) from the hospital or prescribed from the hospital on FP10HP until the GP formally agrees to share care.
8. Provide patient with Methotrexate patient treatment information leaflet.
9. Provide patient with NPSA patient-held monitoring and dosage record book and record all results in this book.
10. Undertake monitoring at appropriate intervals until dose stabilised and GP has agreed to undertake routine monitoring.
11. Recommend dose and timing of any concomitant folic acid therapy.

12. Periodically review the patient's clinical condition and communicate promptly to the GP any changes in dose or monitoring requirements.
13. Advise the GP on when to adjust dose, stop treatment or consult with specialist. dosage alterations where appropriate.
14. Be available to give advice to the GP and ensure that clear backup arrangements exist for GPs to obtain advice and support. (See contact details)

GP Responsibilities

The GP will:
1. Notify the consultant in writing, without undue delay, if they agree to share care.
2. Monitor the patients overall health and wellbeing.
3. Monitor the patient for adverse drug reactions and remain vigilant to the risk of potential drug interactions.
4. Prescribe methotrexate and folic acid therapy as recommended by the hospital specialist.
5. Carry out monitoring tests according to guidelines specified in the monitoring section and record all results in the patient held record book.
6. Act promptly on the results of the blood tests and adjust or stop the dose if appropriate.
7. Ensure methotrexate is included on the electronic patient record in order to minimise the chances of prescribing other drugs that would interact with methotrexate.
8. Report adverse events to the specialist service

If in doubt STOP the treatment and contact the Specialist – within 7 days.

Referral Criteria

1. Patients will have received at least 3 months of methotrexate therapy on hospital prescription.
2. Patients will have been stabilised on a suitable dose of methotrexate. During this time it may be more convenient for the patient to have blood tests conducted at the GP surgery, but the responsibility for ensuring that the monitoring is done and the interpretation of the results remains with the specialist until the GP has agreed to shared care.
3. The specialist will have carried out an assessment of efficacy.

Licensed Indications

Moderate to severe psoriasis unresponsive to topical conventional therapy.

Unlicensed indications –

Recalcitrant eczema, lymphomatoid papulosis mycosis fungoids and as a steroid sparing agent in immunobullous diseases, sarcoidosis and dermatomyositis.
Interstitial lung diseases, sarcoidosis , pulmonary vasculitis and asthma.

Recommended Dosage and Administration

METHOTREXATE should be administered **ONCE A WEEK** on the same day of the week.

Dermatology

Oral methotrexate 2.5mg as a test dose then 10mg once weekly increased according to response in steps of 2.5mg – 5mg at intervals of at least 4 weeks, usual dose 7.5 -25mg once weekly to a maximum weekly dose of 30mg.
Stop treatment if inadequate response after 3 months at the optimum dose.

Folic acid 5mg daily is also given on six days of the week when methotrexate is not taken to improve patient tolerance, prevent folate deficiency and reduce toxicity.
Folic acid must never be taken on the same day as methotrexate.

Respiratory

Respiratory indications general – initial dose 5mg weekly adjusted to 7.5mg to 25mg weekly depending on response

Folic acid 5mg daily is also given on six days of the week when methotrexate is not taken to improve patient tolerance, prevent folate deficiency and reduce toxicity.
Folic acid must never be taken on the same day as methotrexate..

Background Pharmacology

Methotrexate is a competitive inhibitor of dihydrofolate reductase and thus interferes in the process of DNA synthesis and cell replication.
It is used in the treatment of autoimmune diseases as a disease modifying agent (DMARD)

Preparations Available

Methotrexate is available as tablets containing 2.5mg and 10mg of methotrexate. Attention should be paid to the strength of methotrexate tablets and the frequency of dosing, and patients should be reminded of the need to check the dose and strength of the tablets with each prescription.
To avoid confusion and reduce the risk to patients, only 2.5mg tablets should be prescribed.

Adverse Effects

Common:-

Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea, ulcerative stomatitis (oral ulceration), rarely gastrointestinal ulceration). Alopecia (usually minor) Troublesome nausea can be treated with an anti-emetic (e.g. prochlorperazine)

Less common:-

Hypersensitivity reactions (fever, rigors, rash)
Bone marrow suppression (leucopoenia**, thrombocytopenia**, anaemia)

Rare but significant:-

Hepatotoxicity (liver cirrhosis reported) **patients should only drink minimal amounts of alcohol.** Avoid methotrexate if pre-existing liver disease.
Pulmonary toxicity (interstitial pneumonitis often associated with eosinophilia, rarely pulmonary fibrosis). This is not dose related and presents with dry cough, dyspnoea and often fever. **This requires immediate cessation of treatment and reporting to a specialist.**

Please refer to monitoring section for further details on monitoring and management of adverse effects.

Further details are provided below on some of the common adverse effects associated with methotrexate therapy. The current edition of the BSR/BHPR guideline for DMARDS provides further information on the adverse effects of methotrexate.

Hepatotoxicity

Liver fibrosis is related to the presence of psoriasis, concomitant and past alcohol consumption and (to a lesser extent) the cumulative dose 1.5g of methotrexate.

Role of P3NP. Serum Procollagen peptide 3-amino terminal peptide (PN3P) can be helpful in identifying those patients at risk of liver fibrosis. A recent study suggests that the patients with repeated normal levels ofP3NP are very unlikely to have significant liver damage from fibrosis/cirrhosis and that the follow-up liver biopsies may only be offered to patients with persistently abnormal levels of P3NP over 4.2ng/ml. However 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.
Role of liver biopsies. Current studies in patients with RA suggest that liver biopsies are not cost effective for at least the first 10 years of methotrexate use in patients with normal liver function values. Clinically serious liver disease (CSLD) is rarely seen in RA patients receiving low dose methotrexate and routine liver biopsies are therefore not recommended and should only be carried out at the discretion of the treating rheumatologist.
Liver biopsies are not routinely required for respiratory patients.
In dermatology patients with psoriasis, a liver biopsy should be considered after every 1.5g unless the P3NP remains normal in which case the risk of liver fibrosis is very low.

Haematological: Bone marrow toxicity.
Macrocytic indices without anaemia are common and do not require action. A 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 this occurs, follow the guidelines outlined in this document.

Reproductive effects: Methotrexate is a potent teratogen and abortifacient. Reversible oligospermia may occur.

Pulmonary toxicity:
Pulmonary toxicity occurs with a frequency of 1; 108 patient years compared with 1:35 patient years for hepatotoxicity and 1:58 patient years for neutropenia. Methotrexate pneumonitis (MP) is a rare idiosyncratic hypersensitivity reaction. It is most frequently but not exclusively seen within the first year of treatment. Many studies suggest that the incidence of MP is much higher in patients with pre-existing lung disease.

Central Nervous System: Headaches, drowsiness, dizziness and blurred vision.

Other:
Hair loss (usually mild, rarely significant), fatigue, abnormal bruising, sore throat, rash, oral ulceration, photophobia.
Abnormal bruising/sore throat necessitate withholding of therapy until a FBC is available.
Macrocytosis (MCV>105fl) will necessitate a check of B12 and folate status and treatment if low.

Drug Interactions

Clinically significant drug interactions (refer to BNF for full list)
Trimethoprim & Co-trimoxazole - Antifolate effect of methotrexate is increased and greatly increases risk of marrow aplasia. **Concurrent use should be avoided**.
NSAIDs. Excretion of methotrexate probably reduced – monitor for signs of toxicity. Patients should be advised to avoid self medication with over the counter aspirin or ibuprofen. Discuss with rheumatologist before commencing patient on newly prescribed NSAIDs.
Neomycin - monitor efficacy – possible reduced absorption of methotrexate.
Ciprofloxacin – monitor for signs/symptoms of toxicity – excretion of methotrexate possibly reduced.
Doxycycline/tetracycline, sulfonamides – increased risk of toxicity**.**
Penicillins – increased risk of toxicity
Clozapine – avoid methotrexate as increased risk of agranulocytosis.
Ciclosporin – increased risk of toxicity
Leflunomide – increased risk of toxicity
Antimalarials – antifolate effect of methotrexate increased by pyrimethamine.
Cytotoxics – increased risk of pulmonary toxicity
Probenacid – increased risk of toxicity.
Retinoids - increased risk of toxicity.
Anaesthetics – antifoalate effect of methotrexate increased by nitrous oxide, avoid concomitant use.

For full list of drug interactions please refer to appendix 1 of the BNF.

Contraindications and cautions in use.

Contra-indications

Hypersensitivity to methotrexate and any of the excipients.
Liver impairment any abnormality of Liver function tests (LFTs) before therapy or during therapy if LFTs do not normalise after 2 weeks)
Moderate to severe renal impairment.
Pregnancy –female patients must be advised not to conceive whilst receiving methotrexate. A reliable form of contraception should be used by men and women whilst on methotrexate and for at least 6 months after discontinuing it. Discontinue methotrexate and refer immediately if a patient or partner discovers they are pregnant whilst taking methotrexate.
Breast feeding –women being treated with methotrexate should not breastfeed.
Active infection –chronic and recurrent infections especially respiratory or urinary tract, TB, HIV or other immunodeficiency syndromes.
Pre-existing blood disorders such as bone marrow hypoplasia, leucopoenia, thrombocytopenia or significant anaemia.
Untreated folate deficiency
History of alcohol abuse or liver cirrhosis
Ascites, significant pleural effusion
Ulcers of the oral cavity and known active gastrointestinal ulcer disease.

Immunization:

Live vaccinations should not be administered whilst taking methotrexate. Patients should avoid all live vaccines such as oral polio, oral typhoid, MMR, BCG and yellow fever. Contact hospital specialist for advice on any vaccinations required.
Inactivated polio is available although a sub-optimal response may be seen.
Annual flu vaccination is recommended.

In patients taking methotrexate exposed to chicken pox or shingles, passive immunization should be carried out using VZIG. The Herpes Zoster immunoglobulin's can be obtained from Health protection Agency. Tel.No 020 8200 6868

Cautions in use

Hepatic impairment

Methotrexate should be used with caution in patients with a history of or current liver disease.

Alcohol consumption

Alcohol consumption should be well within national guidelines and should be in the region of 4-6 units a week.

Dermatology patients are advised to avoid alcohol completely as there is an increased risk of liver fibrosis in those patients.

Risk factors for hepatoxicity

Along with excessive alcohol consumption obesity and diabetes increase the likelihood of methotrexate induced liver damage.

Unpasteurised foods

Patients should be given advice to avoid unpasteurised milk or soft cheese and to be aware of normal hygiene conditions in the handling of food particularly if they are also taking steroids and or one o the biologic therapies such as adalimumab, etanercept and infliximab.

Renal impairment

Acute prophyrias

Blood disorders – extreme caution should be taken if used when patient has pre-existing blood disorder (see contraindications).

Peptic ulceration

Ulcerative colitis

Ulcerative stomatitis

Diarrhoea

Photosensitivity – psoriasis lesions aggravated by UV radiation (skin ulceration reported)

Risk of accumulation in pleural effusion or ascites, which leads to increased risk of systemic toxicity – drain before treatment.

Monitoring

Routine monitoring -Blood tests should be taken on the day before methotrexate is taken – NEVER on the day of methotrexate therapy

Baseline:

FBC, U&E, Creatinine, LFTs, Chest X-ray (unless chest x-ray done in previous 6 months).

P3NP levels (dermatology patients)

Pulmonary function tests, liver biopsies and hepatitis serology should be considered in selected patients.

Hepatitis, HIV and Varicella Zoster serology for all dermatology patients.

Folate and serum B12 levels in the elderly>70yrs (not required for dermatology patients)

Follow-up

FBC (including ESR) U& E's and LFTs every 2 weeks until the dose of methotrexate and monitoring results have been stable for 6 weeks. Thereafter monthly until the dose and disease have been stable for 1 year. Thereafter the monitoring may be reduced in frequency, based on clinical judgement with due consideration for risk factors including age, co-morbidity, renal impairment etc when monthly monitoring should continue.

P3NP every 3 months for dermatology patients.

Ask patient about rash, oral ulceration, sore throat or unexplained dyspnoea or cough at each visit.

Treatment should be stopped and advice from the supervising specialist sought if:

- Rash or oral ulceration develops
- WBC falls below 3.5 x 10^9/l
- Neutrophils fall below 2.0 x 10^9/l
- Platelets fall below 150 x 10^9/l
- AST or ALT shows greater than a two-fold increase
- Albumin unexplained fall (in absence of active disease)
- Significant deterioration in renal function
- MCV>105fl. Withhold treatment and check serum B12, folate and TFT and discuss with specialist team if necessary.
- Patient should be advised to report the following
- Any signs and symptoms suggestive of infection as this may be a marker of bone marrow suppression I.e. Sore throat, fever, chills, unexplained bruising or bleeding.
- Any signs suggestive of liver toxicity such as severe nausea & vomiting, abdominal discomfort and dark urine.
- Signs suggestive of respiratory effects e.g. new or increasing dyspnoeas or persistent dry cough or fever
- Any signs suggestive of a hypersensitivity reaction e.g. rigors, fever, rash.
- Mouth or throat ulceration
- Whites of the eyes become yellow or patient develops severe skin itching
- Significant reduction (20%) in renal function

A rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Remember: if in doubt STOP the methotrexate and contact the specialist (within 7 days).

Indication of Likely Cost of Therapy in Primary Care

10mg once weekly 28 day cost £1.07 (assuming 2.5mg tablets)
20mg once weekly 28 day cost £2.14 (assuming 2.5mg tablets)

Information Given to the Patient

Dermatology patients
British Association of Dermatologists (BAD) has produced an information sheet for patients on the use of methotrexate which is available at:
http://www.bad.org.uk/shared/get-file.ashx?id+106&itemtype+document

Contact Details

Dermatology department
Dermatology Nurses
Lincoln (01522) 573712
Pilgrim (01205) 446111

Dermatology Secretaries Lincoln (01522) 573412 and 573 680
Dermatology Secretary Pilgrim (01205) 446436 and 446165
Dermatology Secretary Grantham (0476) 565232
Respiratory Department
Respiratory Secretaries Lincoln (01522) 573417 and 573226

References

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