LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE: METHOTREXATE Unlicensed use in the management of sarcoidosis.

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 74, September 2017 – March 2018, pg.5)

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 guideline in this series are available from members of the Optum Health System Support (HSS), Medicines Management and Optimisation (MMO) Team.

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Principles of shared care

NHS England published guidance - Responsibility for prescribing between Primary, Secondary and Tertiary care – January 2018.

Extracts from guidance highlighting the key recommendations:
(Numbering kept from original document, for reference)

1.0 Introduction

1.1 Shared Care Prescribing guidelines are local policies to enable General Practitioners to accept responsibility for the prescribing and monitoring of medicines/ treatments in primary care in agreement with the initiating service.

1.4 Where possible shared care should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared care policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER (AMBER 1 for Lincolnshire) through the traffic light system.

… However it should be remembered that the provision of shared care prescribing guidelines does not necessarily mean that the GP has to agree to accept clinical and legal responsibility for prescribing; that they should only do so if they feel clinically confident in managing that condition.

2.3 Reasonable predictable clinical situation

2.3.1 Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stale or predictable.

2.4 Agreement of shared care between consultant and GP

2.4.1 Referral to the GP should only take place once the GP has agreed in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that the supply arrangements have been finalised. The secondary/ tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be informed to obtain further prescriptions from the GP.

2.7 Clear definition of responsibility

2.7.1 The areas of care for which each clinician has responsibility should be clearly defined.

2.8 Clinical responsibility

2.8.1 Clinical responsibility for prescribing is held by the person signing the prescription who must also ensure adequate monitoring.

2.9 Communication network & emergency support

2.9.1 Telephone details and (if appropriate) secure email addresses of both parties should be exchanged and recorded. This will enable the practice to access timely advice, guidance and information if problems arise, and will also enable secondary care clinicians to easily contact the GP if necessary. This should include out of hours contact numbers, how to access the on-call duty doctor. Patients and their carers should also be provided with contact details for support and help if required both in and out of hours.

2.9.2 People who are being treated on the advice of a secondary care team, but are no longer being seen in that setting, may still need a review should problems arise. The appropriate level of care or advice should be available from the secondary care team in a timely manner without necessarily requiring a new referral.

6.0 Monitoring

6.0.1 All appropriate monitoring arrangements must be fulfilled. The person delivering that aspect of the shared care agreement should ensure that the resources to do this are in place in the clinical setting in which they are delivered.

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
2. Carry out base line checks of FBC, U&E's including creatinine and LFTs. Including folate and serum B12 levels in the elderly>70yrs, CRP and ESR.
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.
4. Decide whether a liver biopsy is appropriate and carry out if indicated.
5. Carry out hepatitis, HIV and varicella Zoster serology at the discretion of the lead specialist.
6. Initiate and stabilise methotrexate therapy
7. Ensure that the patient receives supplies of methotrexate 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 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.
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. Check with the specialist before prescribing and administering vaccines. Avoid immunisation with live vaccines. (see page 6)
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.

9. **Stop Methotrexate if patient has suspected or active infection**, **whether or not they are receiving treatment with antibiotics. Treatment should only be recommenced once patient clear of infection.**
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.

Unlicensed indications

Sarcoidosis

Recommended Dosage and Administration

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

Respiratory indications

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

For further information on adverse effects please refer to the online BNF which can be accessed via https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via: www.medicines.org.uk

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 PIIINP. Serum Procollagen peptide 111amino terminal peptide (PN111P) can be helpful in identifying those patients at risk of liver fibrosis. A recent study suggests that the patients with repeated normal levels of PIINP 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 PIINP 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.

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

For detailed information on drug interactions, please refer to the online BNF which can be accessed via https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via: www.medicines.org.uk
Below is a summary of some of the key interactions.

Live vaccines
Avoid immunisation with live vaccines. BCG vaccine, influenza (live), MMR (live), rotavirus, typhoid (oral), varicella –zoster, yellow fever (live) increases risk of generalised, potentially life threatening infection.

Co-trimoxazole or trimethoprim
Avoid concomitant use. Can cause severe bone marrow suppression

Other antibacterials
Other antibacterials such as tetracyclines, penicillins or ciprofloxacin may increase methotrexate toxicity. It is recommended that when patients require a short course of antibiotics, methotrexate should be withheld for the duration of the course and restarted on the usual day. For antibiotics courses that exceed two weeks duration contact specialist for advice.

NSAIDS
Excretion of methotrexate can be reduced by non-steroidal anti-inflammatory drugs (NSAIDs) with possible increased toxicity. Patients should be advised against self-medicating with over the counter NSAIDS.

Contraindications and cautions in use.

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via: www.medicines.org.uk

Contra-indications

Methotrexate use is contra-indicated in:
Significant impaired hepatic function/ alcoholism, liver disease.
Moderate to severe renal impairment eGFR <30ml/min/1.73m^2
Serious, acute or chronic infections such as tuberculosis, HIV
Immunodeficiency syndromes
Ulcers of the oral cavity and known active gastro intestinal ulcer disease.

Stop Methotrexate in all cases of active or suspected infection.
Severe haematological impairment or profound deterioration. – in particular severe anaemia, leucopenia or thrombocytopenia.
Untreated folate deficiency
Significant pleural effusion
Previous history of methotrexate lung disease
Known hypersensitivity to methotrexate or any of the excipients in formulation used.
Ascites
Pregnancy/planned pregnancy within 3-6 months of treatment (men & women)
Breast feeding
Live vaccines are contraindicated during methotrexate treatment.

Cautions in use

Alcohol consumption

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

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

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 of the biologic therapies such as adalimumab, etanercept and infliximab.

Risk factors for hepatoxicity

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

Pregnancy/Breast feeding

Pregnancy

Female patients receiving treatment with methotrexate or the female partners of male patients receiving methotrexate therapy must be advised not to conceive whilst they or their partner are receiving methotrexate therapy.
A reliable form of contraception should be used by both men and women who are prescribed methotrexate and this should be continued for at least 3 months after discontinuing methotrexate therapy.
If a pregnancy occurs in either the female patient or their female partner (if the patient is male) discontinue methotrexate therapy immediately and contact the specialist service for advice.

Breast feeding

Women being treated with methotrexate should not breastfeed

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)

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

Folate and serum B12 levels in the elderly>70yrs

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, then monthly for 3 months and then every 3 months. 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.

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 any symptoms indicating liver toxicity e.g. Nausea and vomiting, abdominal discomfort, dark urine, signs of jaundice. Severe skin itching.
- Patient should be advised to report any respiratory effects e.g. new or increasing dyspnoea or persistent dry cough or fever (with no obvious cause – suspected pneumonitis.
- Patient should be advised to report any signs which may indicate blood disorders e.g. persistent or severe sore throat, abnormal/ unexplained bruising or bleeding, oral ulceration
- Patient should report any potential signs of an infection

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 (Drug Tariff April 2019)

2.5mg tablets £1.77 for 28 tablets
10mg once weekly 28 day cost £1.01 (assuming 2.5mg tablets)
20mg once weekly 28 day cost £2.02 (assuming 2.5mg tablets)

Information Given to the Patient

Pre-treatment, patient information leaflet.
Patient-held, monitoring and dosage record.

Contact Details

Respiratory Team ULHT:
First contact the respiratory secretaries
Lincoln (01522) 573417 and 573226

References

1. BNF 76 September 2018 - March 2019 and https://bnf.nice.org.uk/
2. British Society Rheumatology (BSR) and British health professionals in rheumatology (BHPR) Guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008
3. British Society Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) Non - Biologic disease-modifying anti-rheumatic drug (DMARD) Guidelines. Rheumatology Updated 2016.
4. Quick reference guideline for monitoring of disease modifying anti-rheumatic drug (DMARD) therapy. Updated November 2009.
5. Cambridgeshire Joint Prescribing Group Methotrexate Shared Care Guideline
6. Guys and St Thomas' NHS Trust Shared care Guideline methotrexate, (oral and subcutaneous) in adult patients with rheumatoid arthritis.
7. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders. Ann Rheum Dis 2009; 68; 1086-1093.
8. Summary of products characteristics (SPC) accessed from medicines.org. Matrex 2.5mg tablets. Pfizer. Last updated 2nd October 2014.
Additional reference October 2018
9. The Sheffield Area Prescribing Group. Shared care guideline for methotrexate in adults. Date approved May 2018.
10. Shared Care Guideline Methotrexate. Cambridgeshire and Peterborough Clinical Commissioning Group. Approved February 2018. Due for review February 2020.

Author(s)

Original August 2016 (update of dermatology protocol to include respiratory indication.
Dr Z. Pogson – Consultant Respiratory Physician

C.M Johnson – Interface Lead Pharmacist NHS Lincolnshire
Revised March 2019: C.M Johnson – Support Service Pharmacist, Optum HSS, MMO team.

In consultation with the following ULHT respiratory specialists
Dr Z. Pogson
Dr H.Saman
Dr A. Buls
Dr B. Asuquo
Dr K. Scheele
Dr S. Matusiewicz
Dr C. Soden

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