THE BARNSLEY, BASSETLAW & ROTHERHAM

Shared Care Protocol
For
Myasthenia Gravis or Chronic Inflammatory Demyelinating Polyradiculopathy in Adults

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Approved by: Barnsley Area Prescribing Committee

Doncaster and Bassetlaw Area Prescribing Committee **(for Bassetlaw only – document does not apply to Doncaster)**

Rotherham Medicines Management Committee

Version 1

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Shared Care Protocol for the prescribing of medicines used to treat Myasthenia Gravis or Chronic Inflammatory Demyelinating Polyradiculoneuropathy in adults

Statement of Purpose

This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of patients initiated on treatment for Myasthenia Gravis or Chronic Inflammatory Demyelinating Polyradiculoneuropathy by the Sheffield Teaching Hospitals NHS Trust Neurologists, where this is appropriate and in the patients' best interests.

This guideline covers the pharmacological management only, which is only one aspect of the care pathway.

Users should be aware that this document is guidance on the management of a condition, not a commissioning arrangement.

Background

Myasthenia gravis (MG) is a chronic autoimmune disorder of the post-synaptic membrane at the neuromuscular junction in skeletal muscle. Elevated serum levels of antibodies against the acetylcholine receptor or muscle-specific tyrosine kinase are usually present. Treatments include anticholinesterases and immunosuppresants.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is a chronic autoimmune disorder affecting the peripheral nerve. Immunotherapy is the mainstay of treatment.

This shared care protocol includes three immunosuppressant medications considered suitable for shared care for management of these conditions. Use of these agents would only be expected to be initiated by neurology specialists when first line treatments have been either unsuccessful or considered to confer an unacceptably high risk of complications.

Treatments for these conditions that are successfully tolerated will usually be prolonged, often for many years and may be lifelong. The patient will be under long term follow up with the consultant neurologist.

The medicines listed below are not licensed for the treatment of neurological conditions. Primary care will only be asked will only be requested to take over prescribing of a particular medicine where this is recognised as clinically appropriate use, e.g. published national/international guideline, trial data or recognised as established use. References to support prescribing in these settings are provided

Medicines included in this shared care document

Azathioprine, Mycophenolate Mofetil, Methotrexate

Responsibilities of specialist clinician

- Diagnosis and assessment, decision to initiate medication, ensuring there are no interactions with concurrent therapy or disease states at the time of the initial consultation and subsequent reviews.
- Undertake pregnancy testing at baseline prior to treatment initiation where applicable.
- Where applicable; to explain to patient (and partner if applicable) the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy.
- Ensure patient is fully informed of potential benefits, side effects of treatment, and that the medicine is being used off-label; this should be documented
- To provide patient / carer with contact details for support and help if required; both in and out of hours
- To initiate treatments for MG & CIDP as appropriate
- Undertake baseline testing, as specified in individual medicine summaries, prior to the initiation of medication (see Appendix 1).
- To undertake prescribing, side effect monitoring & blood testing until the patient is well established on treatment without complications for 6 months. Blood tests will be arranged by the specialist, with the patient able to have phlebotomy at a facility near to them as local arrangements allow, e.g. local acute trust or GP practice, however interpretation the of results remains with the specialist during initial 6 months.
- To contact patient's GP to request prescribing and monitoring under shared care and send a link to or copy of the shared care guideline. (see Appendix 2 for template letter)
- To advise the GP regarding continuation of treatment, including the likely duration of treatment.
- To discuss any concerns with the GP regarding the patient's therapy
- The patient to remain under the specialists' care

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- Confirm the agreement and acceptance of the shared care prescribing arrangement and that supply arrangements have been finalised (see Appendix 2 for template letter). Or to contact the requesting specialists if there are concerns in joining in shared care arrangements
- To report any serious adverse reaction to the appropriate bodies e.g. MHRA and the referring specialist

- To continue to prescribe for the patient as advised by the specialist after minimum initial 6-month period by specialist.
- Ensure monitoring as indicated in monitoring section (see Appendix 1)
- To flag any abnormal results on monitoring blood tests in a timely manner in order for the consultant to advise on management
- To inform the specialist if the patient discontinues treatment for any reason
- To inform the specialist if the patient becomes pregnant while on treatment, see individual medicine summaries as treatment may be contraindicated in pregnancy.
- Check drug interactions with any new medication started or any new conditions diagnosed. Contact the specialist team if possible interactions found and discuss with Consultant Neurologist if necessary.
- To seek the advice of the specialist if any concerns with the patient's therapy
- To conduct an annual medication review or more frequent if required. In the event that the GP is not able to prescribe, or where the SCP is agreed but the specialist is still prescribing certain items e.g. Hospital only product; the GP will provide the specialist with full details of existing therapy promptly by secure method on request.
- For medication supplied from another provider prescribers are advised to follow recommendations for Recording Specialist Issued Drugs on Clinical Practice Systems

Responsibilities of Patients or Carers

- To be fully involved in, and in agreement with, the decision to move to shared care
- To attend hospital and primary care clinic appointments and blood tests and to bring monitoring information e.g.: booklet (if required). Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the primary care prescriber or specialist should the clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or primary care prescriber whilst taking the prescribed medication
- To read the product information given to them
- To take the medication for their condition as prescribed
- Inform the specialist, primary care prescriber or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.

Indication

Drug treatment - indications and recommended treatment regimes

In general, when the decision to treat is made, these medications should be used in the following order:

- First Line: Azathioprine
- Second Line: Mycophenolate
- Third Line: Methotrexate

Further explanation/rationale is provided below:

Treatment of Myasthenia Gravis and Chronic Inflammatory Demyelinating Polyradiculoneuropathy in patients who relapse on a dose of steroid which the specialist considers is likely to cause long-term side effects*, or who are intolerant to or not responding to first-line treatment with agents such as steroids.

**2015 ABN Myasthenia Gravis guidelines state doses above 15-20mg prednisolone on alternate days as being probably too high for long-term use and cite a target maintenance dose of 7-8mg on alternate days.[1]*

Usually, the decision to start treatment with one of these agents occurs once a patient with MG or CIDP relapses despite a dose of corticosteroid considered too high for safe long-term use or, in CIDP, also if intravenous immunoglobulin fails to adequately control symptoms or is contraindicated. In some cases, treatment with one of these agents may be started at an earlier time-point, for example, if the clinician considers that there is a patient-specific factor than renders long-term steroids (or immunoglobulin in the case of CIDP) more risky or less likely to achieve disease control than usual.

Azathioprine and mycophenolate are considered essentially equivalent in terms of efficacy although there is slightly stronger evidence to support the use of azathioprine in myasthenia (a single, small clinical trial)[2], which is why azathioprine is considered the first-line steroid-sparing agent in this condition. Also, Azathioprine is currently (Oct. 2021), more than 4 times less expensive than Mycophenolate. However, drug interactions and tolerability can be problematic, which means that mycophenolate may be prescribed in preference in certain cases. Methotrexate is generally considered a third-line option for patients that do not respond to, are intolerant of, or have contraindications to azathioprine and mycophenolate.

None of these agents is licensed for use in these neurological conditions, however they are recognised in published treatment guidelines as follows:

Azathioprine & Mycophenolate use in Myasthenia Gravis is recognised by the Association of British Neurologists[1], acknowledged by BMJ Best Practice Guidance[3] and supported by other published data[4,5,6]

Methotrexate use in Myasthenia Gravis is also recognised by the Association of British Neurologists[1] and supported by other published data[4,5,6]

Azathioprine, Mycophenolate & Methotrexate are treatment options included in guidance for the treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy issued by the European Federation of Neurological Societies/Peripheral Nerve Society[7]. BMJ have also issued Best Practice Guidance for this condition which includes these options[8].

Medicine Summaries

Azathioprine

BNF available at: https://doi.org/10.18578/BNF.584089745

SmPC available at: https://www.medicines.org.uk/emc/product/3823/smpc

Dose

The consultant neurologist will confirm the dosage at the point prescribing is transferred to the GP.

Myasthenia Gravis & Chronic Inflammatory Demyelinating Polyradiculoneuropathy
50 mg orally once daily initially, increase by 50 mg/day increments once weekly to a maintenance dose of 2-3 mg/kg/day (however see renal impairment dose adjustment below).

This dose recommendation is based on BMJ Best Practice Myasthenia Gravis guidelines and adapted for uniformity across these conditions according to experience in routine clinical practice at STHFT

Dose Tapering - Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Once patient is stabilised for a sufficient time (usually years) tapering by 25-50 mg/day every 3-6 months may be considered, but this decision should be made on a case-by-case basis. The consultant neurologist would determine dose tapering. It is their responsibility to inform the GP of any changes.

Renal Impairment
A lower dose must be used if there is renal impairment[9]

CrCl <20mL/min – 75% of usual dose
CrCl <10mL/min – 50% of usual dose

Monitoring
See Appendix 1

Contraindications
The details below are not a complete list and the BNF and the SmPC remain authoritative

- Hypersensitivity to azathioprine or mercaptopurine
- Homozygous Thiopurine S-methyltransferase (TPMT) deficiency
- Lesch-Nyhan syndrome
- Severe hepatic impairment
- Breastfeeding
- NUDT15 variant homozygotes.
  - The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans

Side Effects & Recommended Actions
The details below are not a complete list and the BNF and the SmPC remain authoritative

Report any suspected adverse reactions to the MHRA, using the yellow card system. https://yellowcard.mhra.gov.uk/

- Hypersensitivity reactions including malaise, fever, vomiting, diarrhoea, rash, dizziness, rigors, myalgia, hypotension, arthralgia & interstitial nephritis.
- Pancreatitis. Bone marrow toxicity (anaemia, leukopaenia, thrombocytopaenia) - patients should be advised to report unexplained bruising, bleeding, or severe sore throat.
- Alopecia.
- Increased risk of some cancers (skin and haematological).
- Opportunistic infections (potentially fatal if associated with neutropaenia)

Recommended actions for adverse events

Adverse event	**Action**
Hypersensitivity, pancreatitis	Stop azathioprine treatment and contact neurology by phone or email
Bruising, bleeding	Check FBC, clotting screen, LFTs, alcohol history If unexplained – Stop azathioprine treatment and contact neurology by phone or email
Malaise, flu-like symptoms	Contact neurology for advice
Itching	Check for other causes to confirm this is drug induced: Is this a pre-existing symptom, complications of disease, steroid effects, etc. Consider seeking neurology advice on dose reduction and ongoing review
Rash	Check for other causes to confirm this is drug induced: Is this a pre-existing symptom, complications of disease, steroid effects, etc. Mild – Consider contacting neurology for advice on dose reduction and ongoing review Severe – Stop azathioprine treatment and contact neurology by phone or email
Alopecia	Check FBC and LFTs Mild – Contact neurology for advice on dose reduction and ongoing review Severe – Stop azathioprine treatment and contact neurology by phone or email
Oral ulcers, stomatitis	Check WBC Check for candida & treat accordingly Mild - mouthwash and good dental hygiene Severe – Stop azathioprine treatment and contact neurology by phone or email
Diarrhoea	Check for other causes Mild - Treat symptomatically and/or Consider contacting neurology for advice on dose reduction and ongoing review Severe – Stop azathioprine treatment and contact neurology by phone or email

Interactions

The details below are not a complete list and the BNF and the SmPC remain authoritative

Vaccines

- Live vaccines must be avoided until at least 3 months after the end of treatment with azathioprine. Examples of live vaccines include oral polio, oral typhoid, MMR, BCG, yellow fever, varicella zoster – for full details check the latest SPC – check the relevant chapter of the green book and SmPC.
- Inactivated vaccines – there may be reduced response – check the relevant chapter of the green book and SmPC prior to administration.
- If possible, give vaccines as appropriate before initiating treatment.

Febuxostat may decrease the metabolism of azathioprine. Concomitant administration of both should be avoided.

Filgotinib is expected to increase the risk of immunosuppression. Concomitant administration of both should be avoided.

Allopurinol – This blocks azathioprine metabolism. Concomitant administration of allopurinol and azathioprine may result in fatal toxicity: reduce azathioprine dose to one quarter (25%) of usual dose and contact specialist for advice on ongoing management.

Warfarin – anticoagulant effect reduced by azathioprine – monitor

Aminosalicylates (sulfasalazine, mesalazine, olsalazine, etc) and co-trimoxazole may enhance bone marrow toxicity – monitor

ACE inhibitors (enalapril, lisinopril, perindopril, ramipril etc) are predicted to increase the risk of anaemia and/or leucopenia. - monitor

Milk/Dairy products - These should be avoided at the time the dose is taken owing to the presence of xanthine oxidase which may reduce the plasma concentration of 6-mercaptopurine (the active metabolite of azathioprine)

Additional Information

Stop use during active infection

In the event of a patient developing an acute infection requiring antibiotic treatment, check FBC and CRP and withhold azathioprine for the duration of antibiotic treatment.

UV Protection

Advise patients to avoid exposure to sunlight and UV light with protective clothing and a high protection sunscreen. Encourage OTC vitamin D supplementation, as per national advice.

Pregnancy

Use of azathioprine in pregnancy is considered relatively safe, however a full discussion must be undertaken with the patient to inform of the risks/benefits re continuing treatment and achieve a shared treatment decision.

Up to date healthcare professional information is available from UK Teratology Information Service (UKTIS) https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-AZATHIOPRINE-OR-MERCAPTOPURINE-IN-PREGNANCY/

Patient information is available from Best Use of Medicines in Pregnancy (BUMPs https://www.medicinesinpregnancy.org/Medicine--pregnancy/Azathioprinemercaptopurine/

Mycophenolate Mofetil

BNF at: https://doi.org/10.18578/BNF.976548500

SmPC available at: https://www.medicines.org.uk/emc/product/1103/smpc

Dose

The consultant neurologist will confirm the dosage at the point prescribing is transferred to the GP.

These dose recommendations are based on BMJ Best Practice Myasthenia Gravis & BMJ Best Practice Chronic Inflammatory Demyelinating Polyradiculopathy guidelines and adapted for uniformity across these conditions according to experience in routine clinical practice at STHFT.

Myasthenia Gravis

The usual starting dose is 500mg bd for at least 2 weeks, then increased to 1g bd.

The appropriate rate will be determined individually by the consultant neurologist depending on the severity of the symptoms and the tolerability.

The usual initial maintenance dose in Myasthenia Gravis is 1g bd.

The maintenance dose may be increased to 1.5 g bd depending on patient-specific factors and clinical response. The usual maximum dose is 1.5g bd.

If successfully tolerated the treatment is ongoing (generally lifelong). The patient will be under long term follow up with the consultant neurologist. Sometimes it is possible to reduce the dose after a period of prolonged stability (years). This decision should be made by the consultant neurologist in consultation with the patient on a case-by-case basis. Many patients stay on the same dose long-term.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

The usual starting dose is 500mg bd for at least 2 weeks, then increased to 1g bd.

The maintenance dose may be increased to 1.5 g bd depending on patient-specific factors and clinical response. The usual maximum dose is 1.5g bd.

Once patient is stabilised for a sufficient time (usually years) tapering by 500 mg/day every 3-6 months may be considered, depending on clinical picture, on a case-by-case basis. The consultant neurologist will determine dose tapering. It is their responsibility to inform the GP of any changes.

Monitoring

See Appendix 1

Contraindications

The details below are not a complete list and the BNF and the SmPC remain authoritative

- Hypersensitivity to mycophenolate mofetil or mycophenolic acid or to any of the product excipients

- Women of childbearing potential who are not using highly effective contraception. A pregnancy test **must** be undertaken prior to commencement to rule out unintended use in pregnancy.
- Women who are breastfeeding.
- Pregnancy prevention measures must be in place for both female and male patients, see additional information
- Uncontrolled infection
- Significant renal, liver or bone marrow failure

Side Effects & Recommended Actions

The details below are not a complete list and the BNF and the SmPC remain authoritative

Report any suspected adverse reactions to the MHRA, using the yellow card system. https://yellowcard.mhra.gov.uk/

Gastrointestinal upset is the most common side effect – e.g. diarrhoea, abdominal cramps, nausea and vomiting.

Others include but are not limited to bacterial & viral infections, bone marrow failure, anaemia, leucopenia, neoplasms, headache, hypertension, dyspnoea, oedema & pyrexia.

Teratogenicity – effective contraception required during treatment (for both female & male patients) and for 6 weeks before & after discontinuation of treatment. See contra-indications above and Additional Information below

Recommended actions for adverse events

Adverse event	Action
New Onset Hypertension Worsening hypertension Hypertension that is not responding to current antihypertensive treatment	Stop treatment, contact neurology department
Bruising/bleeding	Check FBC, clotting screen, LFTs, alcohol history If unexplained – Stop mycophenolate treatment and contact neurology by phone or email
Diarrhoea	Check for other causes Mild - Treat symptomatically and/or Consider contacting neurology for advice on dose reduction and ongoing review Severe – Stop mycophenolate treatment and contact neurology by phone or email
Rash	Check for other causes to confirm this is drug induced: Is this a pre-existing symptom, complications of disease, steroid effects, etc. Mild – Consider contacting neurology for advice on dose reduction and ongoing review Severe – Stop mycophenolate treatment and contact neurology by phone or email

Interactions

The details below are not a complete list and the BNF and the SmPC remain authoritative

Vaccines

- Live vaccines must be avoided until at least 3 months after the end of treatment with Mycophenolate. Examples of live vaccines include oral polio, oral typhoid, MMR, BCG, yellow fever, varicella zoster – for full details check the latest SPC – check the relevant chapter of the green book and SmPC. , e.g. rubella, BCG, small pox, yellow fever, etc
- Inactivated vaccines – there may be reduced response – check the relevant chapter of the green book and SmPC prior to administration.
- If possible, give vaccines as appropriate before initiating treatment.

Medicinal products that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics) have the potential to reduce the efficacy of mycophenolate mofetil *(see additional information re antibiotics).*

Antacids (such as magnesium and aluminium hydroxides) and Proton Pump Inhibitors – decrease absorption of mycophenolate. H2 receptor antagonists do not appear to do have this effect[10].
Probenecid – may prevent renal excretion and increase mycophenolate levels
Aciclovir/ganciclovir may increase mycophenolate levels
Rifampicin – may reduce levels of active metabolite but also increase risk of toxicity.

Additional Information

Stop use during active infection

In the event of a patient developing an acute infection requiring antibiotic treatment, check FBC and CRP and withhold mycophenolate for the duration of antibiotic treatment.

Pregnancy prevention

Discontinue 6 weeks prior to conception – effective contraception is needed during this time. Please see contraindications above and info below.

The MHRA have issued two safety updates regarding preventing use in pregnancy[11,12] these include the following recommendations:

- Physicians should ensure that women and men taking mycophenolate mofetil and mycophenolic acid understand: the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy
- Mycophenolate mofetil or mycophenolic acid treatment should only be initiated in women of child bearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy
- Mycophenolate mofetil or mycophenolic acid should only be given to women of childbearing potential who are using highly effective contraception
- Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment
- Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products

- Discuss with male patients planning to have children the implications of both immunosuppression and the effect of prescribed medications on the pregnancy
- Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose

UV Protection

Advise patients to avoid exposure to sunlight and UV light with protective clothing and a high protection sunscreen. Encourage OTC vitamin D supplementation, as per national advice.

Methotrexate

(oral formulation only)

BNF available at: https://doi.org/10.18578/BNF.680195013

SmPC available at: https://www.medicines.org.uk/emc/product/1376/smpc

Dose

Methotrexate is taken ONCE WEEKLY. The prescription must specify the day of the week the dose is to be taken / administered.

The consultant neurologist will confirm the dosage at the point prescribing is transferred to the GP.

Myasthenia Gravis
It is usually given at a dose of 5–15 mg once weekly.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy
7.5 to 15 mg once weekly on the same day of each week for 8-12 months

Doses for either condition will be adjusted by specialist according to patient factors such as age or weight.

Monitoring

See Appendix 1

Contraindications

The details below are not a complete list and the BNF and the SmPC remain authoritative

- Significantly impaired hepatic function, liver disease; alcohol consumption above recommended limits
- Pregnancy/planned pregnancy within 3-6 months of treatment (men & women), breast feeding;
- Pre-existing blood dyscrasias;
- Significantly impaired renal function (eGFR <30/mL/min/1.73m^2);

- Previous methotrexate induced lung disease;
- Known allergic hypersensitivity to methotrexate or other excipients;
- Serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes, ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- Live vaccines must be avoided during treatment with methotrexate, see Additional Information section below.

Side Effects & Recommended Actions

The details below are not a complete list and the BNF and the SmPC remain authoritative

Report any suspected adverse reactions to the MHRA, using the yellow card system. https://yellowcard.mhra.gov.uk/

- Haematological – neutropenia, thrombocytopenia, macrocytosis, rarely aplastic anaemia.
- Mucocutaneous – mouth ulcers, alopecia, rash
- GI – nausea, diarrhoea
- Hepatic fibrosis – risk factors include alcohol intake above recommended safe limits, psoriasis, obesity and previous liver disease
- Pulmonary – rare acute severe pneumonitis, pulmonary fibrosis
- Suppression of ovarian and testicular function (thought to be reversible)
- Infections – opportunistic infections may occur. Infections can require early and vigorous treatment. Patients advised to stop methotrexate until infection resolved.
- Headaches, depression, irritability

Recommended actions for adverse events

Adverse event	Action
Bruising, bleeding	Check FBC, clotting screen, LFTs, alcohol history If unexplained – Stop methotrexate treatment and contact neurology by phone or email
Malaise, flu-like symptoms	Contact neurology for advice
Itching	Check for other causes to confirm this is drug induced: Is this a pre-existing symptom, complications of disease, vasculitis, steroid effects, etc. Reduce dose - consider seeking neurology advice on dose reduction and ongoing review
Rash	Check for other causes to confirm this is drug induced: Is this a pre-existing symptom, complications of disease, vasculitis, steroid effects, etc. Mild – Reduce dose - consider seeking neurology advice on dose reduction and ongoing review Severe – Stop methotrexate treatment and contact neurology by phone or email
Alopecia	Reduce dose, stop if severe and seek neurology advice
Oral ulcers, stomatitis	Check WBC Check for candida & treat accordingly Mild - mouthwash and good dental hygiene Severe – Stop methotrexate treatment and contact neurology by phone or email
Nausea, anorexia, vomiting, taste disturbance	Advise to take at night Consider anti-emetic, split dose Severe – stop and contact neurology by phone or email

Diarrhoea	Check for other causes Mild - Treat symptomatically and/or Consider contacting neurology for advice on dose reduction and ongoing review Severe – Stop methotrexate treatment and contact neurology by phone or email
New or increasing dyspnoea or persistent cough	Exclude infection and cardiac failure Stop and contact neurology by phone or email
Headache	Check for other causes Mild – try analgesia and reduce dose - consider seeking neurology advice on dose reduction and ongoing review Severe – stop methotrexate treatment and contact neurology by phone or email

Interactions

The details below are not a complete list and the BNF and the SmPC remain authoritative

Methotrexate interacts with a significant number of other medicines. It is essential to check for interactions using appropriate reference sources (e.g. BNF, SmPC, Green Book) when prescribing any new medication.

Vaccines

- Live vaccines must be avoided until at least 3 months after the end of treatment with Methotrexate. Examples of live vaccines include oral polio, oral typhoid, MMR, BCG, yellow fever, varicella zoster – for full details check the latest SPC – check the relevant chapter of the green book and SmPC. , e.g. rubella, BCG, small pox, yellow fever, etc
- Inactivated vaccines – there may be reduced response – check the relevant chapter of the green book and SmPC prior to administration.
- If possible, give vaccines as appropriate before initiating treatment.

Antibacterials

- **PATIENTS SHOULD NEVER RECEIVE TRIMETHOPRIM OR CO-TRIMOXAZOLE WHILST ON METHOTREXATE** due to risk of significant bone marrow suppression. If this is discovered to have occurred, stop methotrexate and urgently check FBC – methotrexate can be restarted 1 week after stopping trimethoprim or cotrimoxazole if FBC normal.
- Penicillins reduce methotrexate excretion and should be used with caution.
- Other antibacterials may interact with methotrexate, including neomycin, ciprofloxacin, doxycycline and tetracycline

Probenecid - is contraindicated due to reduction in excretion
NSAIDS - may reduce methotrexate excretion & increase risk of nephrotoxicity
Proton Pump Inhibitors – can reduce methotrexate excretion – caution in renal impairment

Additional Information

Stop use during active infection

In the event of a patient developing an infection requiring antibiotic treatment, check FBC and CRP and withhold methotrexate for the duration of antibiotic treatment.

Pregnancy prevention

Methotrexate is teratogenic and use in pregnancy is contraindicated

Patients of either gender should use adequate contraception during treatment and wait for at least 6 months after discontinuation of methotrexate before trying to conceive.

Men and Conception

There is a theoretical risk of sperm mutation in males, therefore methotrexate is not recommended to be used during conception. Contraceptives should be used for at least 6 months after cessation of methotrexate.

In men who wish to conceive with their partner while on treatment, there is limited data to support decision making. The most up to date recommendations should be sought, e.g. from SmPC and UK Teratology Information Service (UKTIS). Careful discussion and shared decision making with patients who are in this situation, should be undertaken by the neurologist, taking into account disease severity and alternative treatment options.

Breast Feeding

Methotrexate is contraindicated during breast feeding.

Folic Acid – co-prescription

Co-prescription of folic acid for patients taking methotrexate significantly reduces the risk of side effects and blood test abnormalities.

Folic acid should be prescribed at a dose of 5mg once weekly, usually 48 hours after the methotrexate dose unless otherwise directed by secondary care; the dose is increased if patients experience methotrexate related side effects or has folate deficiency

Folic acid **SHOULD NOT** be taken on the same day that the patient takes methotrexate. This is to avoid the possibility of the folic acid adversely affecting the absorption of methotrexate.[13]

Re-Referral guidelines

The patient will remain under long-term follow-up with the consultant neurologist. The consultant neurologist is contactable for any issues that may occur once GP has taken over prescribing.

Prescribing information

Azathioprine, Mycophenolate Mofetil and Methotrexate can be prescribed generically for neurology conditions.

Methotrexate is administered ONCE weekly. The prescription must specify the day of the week the dose is to be taken / administered.

Contacts for Support, education and information

Advice is available from the consultant neurologist in charge of the patient. Contact as follows for the respective CCG commissioned services

Contact Details	Telephone number	Email
Consultant Neurologist Dr E Hobson	0114 2261049	esther.hobson2@nhs.net
Lead Neurosciences Pharmacist (STHFT) Natasha Hoyle	0114 2713225	natasha.hoyle@nhs.net

STH intranet website: http://nww.sth.nhs.uk/nhs/NeuroScience/Neurology/

Equality and Diversity

No relevant considerations

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Acknowledgment

South West Yorkshire APC Shared Care documents for Azathioprine, Mycophenolate and Methotrexate were used in the development of this Shared Care Protocol

- Azathioprine - https://www.swyapc.org/wp-content/uploads/2021/05/FINAL-Azathioprine-SCG-Final-approved-Sept-2020.pdf (last accessed 08 Jul 2021)
- Mycophenolate Mofetil - https://www.swyapc.org/wp-content/uploads/2015/06/Mycophenolate-SCG-FINAL-Approved-June-2015.pdf (last accessed 08 Jul 2021)
- Methotrexate - https://www.swyapc.org/wp-content/uploads/2015/09/Methotrexate-SCG-FINAL-Sept15.pdf (last accessed 08 Jul 2021)

Shared Care Protocol for the prescribing of medicines used to treat Myasthenia Gravis or Chronic Inflammatory Demyelinating Polyradiculoneuropathy in adults

Appendix 1
Azathioprine, Mycophenolate Mofetil and Methotrexate Monitoring Requirements

Baseline

All baseline monitoring to be undertaken by specialist

Test	Azathioprine	Mycophenolate Mofetil	Methotrexate
Height	✓	✓	✓
Weight	✓	✓	✓
FBC	✓	✓	✓
U&Es	✓	✓	✓
LFTs	✓	✓	✓
Blood Borne Virus Screen (Hepatitis B, Hep C & HIV)	✓	✓	✓
Varicella Zoster Virus Antibody	✓	✓	✓
Thiopurine methyltransferase assay	✓		
Lipids		✓	
Cervical Screening	✓		
Pregnancy		✓ if applicable see additional information for Mycophenolate Mofetil	✓ if applicable see additional information for Methotrexate
BP		✓	✓
Chest X Ray			✓
Lung Function (if indicated)			✓
HRCT if TLCO <70% or clinical concern			✓
TB Quantiferon	✓	✓	✓

Maintenance

Maintenance monitoring initially by specialist until care is shared with GP

The Hospital Specialist must confirm to the GP which stages of the maintenance monitoring have already been completed at the point when prescribing and monitoring are transferred to the GP.

GP then to continue monitoring as per tables overleaf.

Cont'd on next page

Appendix 1 cont'd

Maintenance cont'd

Test	Azathioprine	Mycophenolate Mofetil	Methotrexate
FBC	✓	✓	✓
U&Es	✓	✓	✓
LFTs	✓	✓	✓
BP		✓	
Respiratory assessments if any clinical concerns			✓
Skin examination	✓ Periodically only		

Frequency of Maintenance Monitoring[1]

Timeline once on stable dose	**Frequency**
From achievement of stable dose for 6 weeks	Every 2 weeks
From 6 weeks to 18 weeks	Every 4 weeks
From 18 weeks	Every 12 weeks
Timeline following a change in dose	
From achievement of stable dose for 6 weeks	Every 2 weeks
From 6 weeks	Revert to previous monitoring schedule

The hospital specialist should be informed if there is any increase in urea, creatinine or liver enzymes, or decrease in white cell count, haemoglobin, platelet or neutrophil count outside the normal range. It is the responsibility of the hospital specialist to advise on actions required e.g. more frequent monitoring, dose reduction, cessation of medication on a case-by-case basis. Recommended actions are shown overleaf:

Cont'd on next page

Appendix 1 cont'd

Actions in response to monitoring

Investigation	Action
WBC <3.5 x10^9/L Neutrophils < 1.6 x10^9/L Platelets < 150 x10^9/L	Stop treatment, contact neurology department.
MCV above 105 fL	Check TFT, B12 and folate, alcohol history
Hb fall >1g in 4 weeks or below 10g	Check for increased disease activity Ask about NSAID use and symptoms of GI blood loss or dyspepsia and stop NSAIDS if implicated. Check MCV and iron studies Consider endoscopy
Deranged liver function tests (ALT or AST) Greater than normal and less than 3x upper limit of laboratory reference range	Repeat bloods every 2 weeks Ask patient about viral/bacterial infections Check that it is not due to another drug or alcohol Consider contacting neurology for advice for advice on dose reduction
Greater than or equal to 3x upper limit of laboratory reference range	Stop treatment, contact neurology department.
Unexplained reduction in albumin <30g/L	Contact neurology for advice
Unexplained eosinophilia >0.5 x10^9/L	Contact neurology for advice
Deterioration of U&E from baseline	Consider contacting neurology for advice for advice on potential dose reduction
Additional specific to Azathioprine	
Skin examination	Stop if clinical concern, contact neurology for advice
Additional specific to Mycophenolate Mofetil	
New Onset Hypertension Worsening hypertension Hypertension that is not responding to current antihypertensive treatment	Stop treatment, contact neurology department
Additional specific to Methotrexate	
eGFR <40/mL/min/1.73m^2	Stop methotrexate, contact neurology for advice
eGFR <50/mL/min/1.73m^2	Recheck in 2 to 3 weeks, contact neurology for advice if level remains below 50/mL/min/1.73m^2
New cough/breathlessness or other respiratory concerns.	Contact neurology for advice

Appendix 1 References

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Shared Care Protocol for the prescribing of medicines used to treat Myasthenia Gravis or Chronic Inflammatory Demyelinating Polyradiculoneuropathy in adults

Appendix 2
Template letter to GPs with GP Acceptance slip

Dear Dr

Our mutual patient has Myasthenia Gravis/Chronic Inflammatory Demyelinating Neuropathy (delete as appropriate) and has been started on treatment with azathioprine/mycophenolate/methotrexate (delete as appropriate). This is because (please add explanation)

The Shared Care protocol is attached to this letter.

As part of shared care arrangements please can you undertake monitoring as specified in Appendix 1 of this Shared Care Protocol and also monitor adherence, response and side effects to therapy every [insert frequency]. Please will you also undertake to prescribe for this patient?

Please note: The prescriber is responsible for monitoring the patient on the medication being prescribed

Please acknowledge you would be happy to take on shared care by completing and returning the slip below to above address or by secure email to [specify email address]

Please do not hesitate to contact us if you have any concerns, or wish to discuss things further.

Yours sincerely
Electronically checked by

Insert Clinician Name
Insert Clinician's Title

Re:

IMPORTANT REMINDER

The prescriber is responsible
for monitoring the patient on the medication being prescribed

_____*please tear here, return to address or email* _____

RE: …… DOB: …… ……. NHS:……..
Address: ……..

I AGREE to take on shared care of this patient (delete/score through as appropriate)

I DO NOT AGREE to take on shared care of this patient (delete/score through as appropriate)

Signed ……

GP Practice……

Date……