Oxford University Hospitals NHS
NHS Trust

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Clinical Commissioning Group

MYCOPHENOLATE MOFETIL FOR USE IN DERMATOLOGY, LIVER, NEUROLOGY, RESPIRATORY, GASTROENTEROLOGY and RENAL
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for mycophenolate mofetil therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF

Shared Care Protocol – Responsibilities

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Unless otherwise stated in the protocol, the responsibilities are as follows:

Specialist

- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care
- Ensure the patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly
- Provide copy of patient information leaflet and drug monitoring card where appropriate
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient throughout treatment

GP

- Prescribe medication once the dose is stable or shared care is agreed
- Ensure all monitoring is completed in accordance to the specific shared care protocol.
- Check and record results then advise the specialist of any deteriorations or abnormal results
- Notify the specialist to any changes in patients condition, any adverse drug reactions or failure to attend tests

Patient

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Attend for blood tests and monitoring when required
- Ensure monitoring card is kept up to date and is brought to all appointments
- Report any side effects to the GP or a member of the specialist team

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BACKGROUND

Mycophenolate mofetil is an immunosuppressive drug. It is often referred to as a “steroid sparing agent” or “immunomodulator.” Mycophenolate mofetil (MMF) should only be initiated on the recommendation of a specialist. Its uses in this protocol are limited to those mentioned below.

Dermatology

- Used for immunobullous skin diseases, systemic vasculitis and systemic lupus erythematosus (off label indications).

Gastroenterology

- Used to induce and maintain remission in ulcerative colitis and Crohn’s disease.
- It is used in patients who require continuous or repeated courses of corticosteroids and who have failed to respond to, or are intolerant of, other immunomodulator drugs like azathioprine, mercaptopurine and methotrexate.
- Like all immunomodulators used in IBD it is unlicensed for this indication.

Hepatology

- MMF is used either alone or with steroid as a long term treatment of patients with autoimmune liver disease (unlicensed indication).
- This is initiated if the patient is unable to tolerate azathioprine - which is first line for autoimmune liver disease.
- MMF is also used as one of up to three immunosuppressive agents post liver transplant (licensed indication).

Respiratory

- MMF is used in conjunction with prednisolone is a therapeutic option in the interstitial lung diseases, especially those associated with connective tissue disorders or vasculitis
- MMF is used 2nd line, when first choice disease modifying agents, azathioprine or cyclophosphomide, are not controlling the disease or side effects of these agents are intolerable.

Neurology

- MMF is used as second-line therapy for a range of neurological disorders including myasthenia gravis, inflammatory myopathies and neuropathies, CNS vasculitis and other immune-mediated central and peripheral nervous system diseases (unlicensed indications).

Renal

- Used for systemic lupus erythematosus and systemic vasculitis and occasionally for patients with nephritis
- Use is unlicensed in these conditions.

- Use in kidney and pancreas transplant patients is not covered by this protocol as supply and monitoring is undertaken by Oxford Transplant Centre.

Ophthalmology and Rheumatology

See separate Shared Care Protocols

DOSAGE

INDICATION	DOSE
Dermatology	MMF is given orally at a starting dose of 500mg once or twice daily, increasing by 500mg weekly until optimum or maximum tolerated dose is reached. Typical dose is 1-2g daily in divided doses up to maximum dose of 3g per day.
Gastroenterology	The dose of MMF used in IBD is usually between 250mg twice daily and 1g twice daily.
Hepatology	The dose of MMF used in liver patients is usually between 1 - 1.5g twice daily.
Respiratory	Starting dose is 500mg daily for the first week, 500mg twice daily for the second week and increased gradually by 500mg each week until the optimum or maximum tolerated dose is reached. Typical dose is 1 – 2g daily in two divided doses. In severe or resistant cases, a maximum of 3g daily in two divided doses may be used.
Neurology	The starting dose is 500mg once daily, increasing after a week to 500mg twice daily. Thereafter, if there are no adverse effects, the usual maintenance dose is 1g twice daily (maximum dose 1.5g twice daily)
Renal	The dose of MMF used in renal disease is usually between 250mg twice daily and 1.5g twice daily.

PRESCRIBING ADVICE

- The therapeutic benefit will often be seen after 3 months of therapy.
- The tablets or capsules should be swallowed whole and not crushed or broken, with or after food.
- ‘flu vaccination is recommended
- Supply patient with a PIL when first prescribed

PREPARATIONS AVAILABLE

- 250mg and 500mg tablets and capsules
- 1g/5ml oral suspension.
- There is no clinical difference in generic or branded preparations of MMF. It should therefore be prescribed **generically**.

PRE-TREATMENT ASSESMENT

FBC, including platelets and differential, U&E's, LFT's, CRP and urinalysis. Chest X-ray. A pregnancy test must also be carried out for those who are of child bearing age. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended[5]. The second test should be done 8–10 days after the first one and immediately before starting MMF.

ONGOING MONITORING

FBC weekly for 6 weeks, thereafter monthly (or when stable consider 3 monthly under specialist recommendation). The monitoring of FBC must also be undertaken 2 and 4 weeks after each dose increase. LFTs, U&Es and CRP must be carried out monthly.

Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported)[5].

Side Effects	**Action**
WBC < 3.5 X 10^ 9/l	Withhold until discussed with specialist team. Please note that lupus patients and those on steroids often have lymphopenia so often have a normal neutrophil count but total WCC might be low.
Neutrophils < 2.0 X 10 ^ 9/l	Withhold until discussed with specialist team.
Platelets < 150 X 10 ^ 9/l	Withhold until discussed with specialist team.
Alk Phos, ALT, AST > 2x rise from upper limit of reference range	Withhold until discussed with specialist team.
GFR< 20mls/min	the maximum dose of MMF is 1g BD
MCV > 105	Check B12, folate and TFT. If low start appropriate supplementation. Check alcohol status
Sterile haematuria / UTI	Withhold until discussed with specialist team.
Rash	Withhold until symptoms clear. Consider re-challenging at a lower dose. If rash recurs stop MMF and discuss with specialist team
Oral Ulceration	Treat oral ulceration and check FBC. Only stop if

	neutrophil count is low.
Hypersensitivity reactions	Fever, malaise, rash, vomiting, muscle/bone pain, dizziness. Stop MMF
Nausea, vomiting, diarrhoea	Administer tablets after meals to reduce nausea. An anti-emetic or dose reduction may help. If symptoms persist stop MMF
Abnormal bruising or sore throat	Withhold until FBC result available
Malignancy	Discuss with specialist team.

Please note that in addition to absolute values for haematological indices a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance. NB. Some liver patients with cirrhosis will have pre-existing pancytopenia and lupus patients may have leucopenia because of lymphopenia.

CONTRAINDICATIONS AND PRECAUTIONS

Pregnancy and breastfeeding	Avoid in pregnancy or those trying to conceive. Exercise extreme caution when MMF is used in patients with childbearing potential and in breast feeding mothers. Only be given to women of childbearing potential who are using highly effective contraception Female patients who can become pregnant must use at least one reliable form of contraception before, during and for 6 weeks after stopping treatment. Two forms of contraception are preferred but no longer mandatory[6]. Avoid in breast feeding.
Family Planning	For male patients, EMA now recommends that either the male patient or his female partner use reliable contraception during mycophenolate treatment and for at least 90 days after stopping treatment.
Vaccination with LIVE vaccines	Patients receiving MMF must NOT receive immunization with LIVE vaccines. Inactivated polio is available although sub-optimal response may be seen.
Chicken pox /Shingles	Patients suffering from chickenpox or active skin lesions in shingles withhold MMF and inform specialist team. Exposure to chickenpox or shingles passive immunization

	should be carried out using VZIG
Alcohol	Limit alcohol intake to 14 units per week
Localised or systemic infections	Withhold MMF if patient has a serious infection, including hepatitis B and C and a history of tuberculosis. Patients being treated with MMF are at increased risk for opportunistic infections, fatal infections and sepsis. These infections are often related to a high total immunosuppressive burden and may lead to serious and fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.
HGPRT Defeciency	MMF is an inosine monophosphate dehydrogenase (IMPDH) inhibitor and should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
Sunlight/UV exposure	Patients receiving MMF are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Give general advice to minimise risk of skin cancer i.e. patients should wear protective clothing and use a sunscreen with a high protection factor.
NSAIDS	May be used unless GFR is low.

DRUG INTERACTIONS (refer also to BNF and SPC)

- Antacids and oral magnesium supplements reduce MMF absorption and if required should be separated from MMF by 2-3 hours
- MMF may reduce the effectiveness of oral contraception
- Cholestyramine: may decrease the absorption and bioavailability of MMF by 40%.
- Oral iron may reduce absorption
- Metronidazole and norfloxacin may reduce bioavailability.
- Plasma concentration of active metabolites of MMF are reduced by rifampicin.
- Ciclosporin A – Ciclosporin A pharmacokinetics are unaffected by MMF however, if concomitant ciclosporin treatment is stopped, an increase in plasma concentration of MMF of upto 30% is to be expected.
- Aciclovir – MMF increases plasma concentration of aciclovir. Plasma concentration of inactive metabolite of MMF increased.
- Clozapine – can lead to agranulocytosis
- Phenytoin– reduced absorption of antiepileptic

CONTACTS

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