Shared care guideline

Mycophenolate mofetil (MMF) – Guidelines for its use in multisystem autoimmune diseases

Executive summary

- This shared care guideline outlines the responsibility of primary and secondary care clinicians in managing mycophenolate in rheumatic diseases.
- Mycophenolate mofetil (MMF) is an immunosuppressant drug used particularly in patients with active systemic lupus erythematosus (SLE) (especially with nephritis), myositis, inflammatory lung disease and vasculitis.
- Ongoing monitoring is required – Monthly FBC, electrolytes and creatinine, LFTs, ESR
- The responsibilities of the hospital specialist, GP and patient for this shared care guideline can be found within this document (see section 11 below.)

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. 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. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here.

1. Scope

Prescribing and monitoring of mycophenolate mofetil (MMF) by GPs & hospital consultants.

2. Aim

This shared care guideline outlines the responsibility of primary and secondary care clinicians in managing mycophenolate in rheumatic diseases.

3. Introduction

Mycophenolate mofetil (MMF) is an immunosuppressant drug used particularly in patients with active SLE (especially with nephritis), myositis, inflammatory lung disease and vasculitis.

4. Abbreviations

BNF	British National Formulary
CCG	clinical commissioning group
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
FBC	full blood count
GP	general practitioner
LFT	liver function test
MMF	mycophenolate mofetil
MMT	
SLE	systemic lupus erythematosus
SPC	summary of product characteristics
U&E	urea and electrolytes
VZIG	varicella zoster immunoglobulin

5. Dose and administration

- Typical dose 1-2g daily, maximum dose 3g daily
- Dosage advised by hospital specialist but typically a gradual increase in dosage eg
    - Week 1: 500mg **once** daily. Check FBC. If tolerated -
    - Week 2: 500mg **twice** daily. Check FBC, U&E. If tolerated -
    - Week 3: 1g morning, 500mg evening. Check FBC. If tolerated -
    - From 4 weeks: 1g **twice** daily
- Time to response 6-12 weeks

Further information can be found in the Summary of Product Characteristics (SPC):
http://www.medicines.org.uk/emc/medicine/1679

6. Adverse effects

Very common (≥ 1 in 10)
Common (≥ 1 in 100 and < 1 in 10)
Uncommon (≥ 1 in 1000 and < 1 in 100)
Rare (≥ 1 in 10000 and < 1 in 1000)

System organ class		**Adverse drug reactions**
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common	-
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leukocytosis
Metabolism and nutrition disorders	Very common	-
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Very common	-
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia
Nervous system disorders	Very common	-
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Very common	-
	Common	Tachycardia
Vascular disorders	Very common	-

	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	-
	Common	Skin hypertrophy, rash, acne, alopecia,
Musculoskeletal and connective tissue disorders	Very common	-
	Common	Arthralgia
Renal and urinary disorders	Very common	-
	Common	Renal impairment
General disorders and administration site conditions	Very common	-
	Common	Oedema, pyrexia, chills, pain, malaise, asthenia,
Investigations	Very common	-
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

Further information can be found in the SPC: http://www.medicines.org.uk/emc/medicine/1679

7. Cautions

- Contraindicated in pregnancy/ breastfeeding
- Avoid in infections
- Reduced dose if significant renal impairment
- Risk of lymphoma and skin cancer (total sunblock in summer)
- Active serious gastro-intestinal disease (risk of haemorrhage, ulceration and perforation)
- Risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants
- Elderly (increased risk of infection, gastro-intestinal haemorrhage and pulmonary oedema);
- Measure serum immunoglobulin levels if recurrent infections develop, and consider bronchiectasis or pulmonary fibrosis if persistent respiratory symptoms such as cough and dyspnoea develop.

- **MHRA/CHM advice: Mycophenolate mofetil, mycophenolic acid: updated contraception advice for male patients (February 2018):** Available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, however mycophenolate mofetil and mycophenolic acid are genotoxic and a risk cannot be fully excluded.

Further information can be found in the SPC: http://www.medicines.org.uk/emc/medicine/1679

8. Contraindications

- Hypersensitivity to mycophenolate mofetil or mycophenolic acid.
- Pregnancy & breastfeeding –
    - Contraception is essential during treatment and for at least three months after discontinuing MMF. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity.
    - It is recommended that men who are planning to have children stop MMF for at least three months prior to trying for a pregnancy with their partner.
- Women of childbearing potential should use at least 1 method of effective contraception before and during treatment, and for 6 weeks after discontinuation—2 methods of effective contraception are preferred. It is recommended that male patients or their female partner use effective contraception during treatment and for 90 days after discontinuation.

- Patients receiving MMF must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen. Annual flu vaccination is recommended. In patients receiving MMF exposed to chickenpox or shingles passive immunization should be carried out using VZIG.

Further information can be found in the SPC: http://www.medicines.org.uk/emc/medicine/1679

9. Interactions

Notable drug interactions (refer to BNF and SPC) include:

- Antacids: Containing aluminium and magnesium hydroxide cause a decrease in the absorption of MMF by 33% and bioavailability by 17%
- Cholestyramine: may decrease the absorption of MMF and bio-availability by 40%
- Probenecid: Prevents renal tubular secretion and causes an increase in plasma concentration of MMF
- Aciclovir: and other antivirals: Causes increase in the concentration of both MMF and acyclovir which increases risk of haematological toxicity. However, the increase is significant only in renal impairment.
- Rifampicin – plasma concentration of active metabolite of MMF reduced by rifampicin.
- Patients receiving MMF must not receive immunization with live vaccines due to the increased risk of generalised infection (possibly life-threatening)

Further information can be found in the SPC (http://www.medicines.org.uk/emc/medicine/1679).

10. Monitoring standards and actions to take in the event of abnormal test results/ symptoms

	Whose responsibility	Action
Pre-treatment	Hospital rheumatology team	Assess renal function (mycophenolate 95% excreted via the kidneys) • BP • Creatinine/ electrolytes, including eGFR • FBC, LFTs, varicella status • Chest x-ray • Baseline ESR • 'In women of childbearing potential where there is a possibility of pregnancy two pregnancy tests 8-10 days apart are recommended'
Initiation to stabilisation	Hospital rheumatology team (or GP if in agreement)	• Weekly FBC for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops). • Fortnightly electrolytes and creatinine, and LFTs until dose has been stable for four weeks.
On-going monitoring once stable	GP	• Monthly FBC, electrolytes and creatinine, LFTs, ESR
All blood results to be recorded in patient-held record book		

Side effect	Action by GP
Gastrointestinal intolerance	Split total daily dose into multiple daily doses eg 1g BD to 500mg QDS
WBC < 3.5x10^9/L	**Stop mycophenolate and inform rheumatologist or rheumatology practitioner:** telephone 01223 217398 or 216774 If unsure, or progressive abnormal trend, please telephone above numbers for advice
Neutrophils < 1.5x10^9/L	
Platelets < 150x10^9/L	
Abdominal pain, nausea, diarrhoea, weight loss	
Pruritus, rash (very rarely Stevens-Johnson syndrome)	
Breathlessness (new or increased)	
Oral ulceration/ sore throat/ abnormal bruising	Discuss with hospital team eg on-call trainee or specialist nurse.
Abnormal LFTs **>2 fold rise in aspartate transaminase (AST), alanine transaminase (ALT) (from upper limit of reference range)**	Discuss with hospital consultant or specialist nurse.
Abnormal LFTs **> 4 fold rise in AST, ALT(from upper limit of reference range)**	**Stop mycophenolate** and discuss with hospital consultant or specialist nurse immediately.

11. Shared care responsibilities

a. Hospital specialist:

- Undertake pre-treatment assessment, monitoring & follow up as described in Section 10.
- Exclude pregnancy
- Provide advice to patient on use of MMF, side effects and cautions (including contraception and pregnancy)
- Prescribe MMF until dose stabilised.
- Inform the GP of the dose of MMF to be prescribed once stable.
- Send a letter to the GP requesting shared care for the patient.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- To provide any advice to the patient/carer when requested.

b. General practitioner:

- Undertake prescribing (once dose stabilised), monitoring & follow up as described in Section 10.
- Prescribe MMF at the dose recommended by the hospital specialist.
- Agreement to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.

c. Patient or parent/ carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP. This includes any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.

- Follow advice on contraception and inform specialist and GP immediately if pregnancy is suspected - See Section 8: Contraindications

12. Contact numbers for advice and support

Rheumatology Department Decisions to alter or discontinue treatment are usually discussed via the Rheumatology Helpline on 01223 217398. The on-call rheumatology specialist registrar (SpR) may also be contacted via the Addenbrooke's Contact Centre.		
Specialist	**Post**	**Telephone**
Jill Bloxham; Julie Isaacson; Tracey Nash Teresa Del Sordo	Rheumatology Practitioners CTD Nurse	01223 254933 01223 274544
Dr Gavin Clunie	Consultant Rheumatologist	01223 216774
Dr Frances Hall	Consultant Rheumatologist	01223 256883
Dr Deepak Jadon	Consultant Rheumatologist	01223 217716
Dr Natasha Jordan	Consultant Rheumatologist	01223 256883
Dr Mark Lillicrap	Consultant Rheumatologist	01223 217716
Dr Anshuman Malaviya	Consultant Rheumatologist	01223 217716
Dr Andra Negoescu	Consultant Rheumatologist	01223 216774
Dr Kenneth Poole	Consultant Rheumatologist	01223 216774
Dr Nick Shenker	Consultant Rheumatologist	01223 256883

Vasculitis and lupus		
Professor David Jayne	Professor in Nephrology & Vasculitis	01223 336816
Dr Lisa Willcocks	Consultant in Nephrology	01223 274885
Dr Rachel Jones	Consultant in Nephrology	01223 254637
Dr Natasha Jordan	Rheumatology Consultant	01223 586796
Dr Frances hall	Rheumatology Consultant	01223 586796
Stella Burns	Lead Specialist Vasculitis Sister	01223 217259
Jane Hollis	Lupus Nurse Specialist	01223 217050
Teresa Del Sordo	Connective Tissue Disease Nurse specialist	01223 596441
Donna Goymer	Behcets specialist nurse	01223 586835

Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

Disclaimer

It is **your** responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Document management

Document ratification and history	
Approved by:	Cambridge University Hospitals NHS Foundation Trust Joint drug and therapeutics committee (JDTC)
Date approved:	16 October 2018
Approved by:	Cambridgeshire and Peterborough Joint Prescribing Group (CPJPG)
Date approved:	18 September 2018
Date placed on CPJPG website:	26 October 2018
Review date:	October 2020

Obsolete date:	January 2021
Supersedes which document?	Version 4, June 2016
Authors:	Dr Gavin Clunie, Consultant Rheumatologist Dr Nicholas Shenker, Consultant Rheumatologist Rachel Berry, Deputy Clinical Pharmacy Services Manager
Owning provider trust:	Cambridge University Hospitals NHS Foundation Trust
File name:	SCG mycophenolate mofetil (MMF) Version5 October 2018.doc
Version number:	5
Unique reference no:	JPG180918
CUH Document ID:	24397

The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics (http://www.medicines.org.uk/emc/medicine/1679).