Mycophenolate Mofetil in the Management of Immune-Related Adverse Effects (irAEs)

A guide for members on the prescribing and monitoring of Mycophenolate Mofetil when used in the management of irAEs because of treatment immune-checkpoint inhibitors.

British Oncology Pharmacy Association in Collaboration with The Immuno-Oncology Clinical Network

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1. Introduction

- Mycophenolate mofetil is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which in turn causes the inhibition of the *de novo* pathway of guanosine nucleotide synthesis. T- and B-lymphocyte proliferation is dependent on this pathway so mycophenolate mofetil is a potent inhibitor of lymphocyte proliferation. Mycophenolate mofetil has been used since the early 1990s for acute allograft rejection. Off licence it has been used as a steroid sparing agent for the treatment of rheumatic diseases and to treat immune-related adverse events (irAEs) from treatment with checkpoint inhibitors, most commonly IR-hepatitis

- The ESMO guidelines suggest the use of mycophenolate as a steroid sparing agent in immune mediated hepatitis, interstitial lung disease, rheumatological toxicity, neuromuscular toxicity and myocarditis. There are published case reports of mycophenolate mofetil use in these conditions. Also use for steroid refractory disease

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate Mycophenolate Mofetil. It is not a clinical guideline, but a consensus view of current use of Mycophenolate Mofetil when used for irAEs. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance processes.

2. Prescribing and Monitoring Advice

2.1 Contraindications

- Hypersensitivity to Mycophenolate Mofetil.
- Hypersensitivity to any of the excipients
- Pregnancy or breastfeeding

2.2 Precautions

- Immunisations - Avoid live immunisations.
- Avoid if previous hepatitis B or C infection, or recurrent shingles
- Marked renal failure (eGFR below 25 mL/min)
- Due to the increased risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high sun protection factor
- Localised or systemic infection
- Very frail or elderly patients (increased risk of certain ADRs)
- Patients with suspected lymphoproliferative disorder
- Patients with unexplained anaemia, leukopenia or thrombocytopenia
- Active gastrointestinal disease
- Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.
- Increased severity of COVID –19 may occur. In these circumstances the advice is to dose reduce or discontinue the use of mycophenolate
- Avoid in patients with a rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)

- Hypogammaglobulinaemia can occur in patients receiving mycophenolate in combination with other immunosuppressants. In patients with recurrent infections serum immunoglobulins should be measured.
- There have been reports of bronchiectasis in patients receiving mycophenolate in combination with other immunosuppressants. Monitor for cough and dyspnoea
- Patients should report any signs of infection, unexplained bruising, bleeding, or any other manifestation of bone marrow suppression

2.3 Pregnancy Advice

- Before starting Mycophenolate mofetil treatment, people of childbearing potential should have a negative pregnancy test.
- Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended.
- A second test should be done 8-10 days after the first one and immediately before starting Mycophenolate mofetil, unless exceptional circumstances exist whereby a delay in the initiation of treatment would cause harm to the patient and the prescriber is satisfied that a single test is adequate to rule out pregnancy.
- Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Refer to MHRA Drug Safety Update for more detail.

2.4 Pre-treatment assessment

Baseline investigations including:

- Full blood count (FBC)
- Urea and electrolytes (U&E), including creatinine and creatinine clearance (CrCl)
- Liver function tests (LFTs): Bilirubin, Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and albumin. It may be helpful to request BOTH ALT and AST initially to determine nature of transaminitis if immune-related hepatitis is suspected.
- Clotting profile
- Height and weight
- Blood pressure
- Screening for viral infections as per local policy, e.g. HIV and hepatitis B and C, varicella zoster, Epstein Barr virus, cytomegalovirus
- Screening for lung disease, including tuberculosis, should be undertaken at clinician discretion on a case by case basis
- Provide or request appropriate vaccination prior to treatment initiation, if possible, according to local arrangements (e.g. pneumococcal, shingles, influenza, COVID-19)

Other considerations at baseline:

- Review current medication (e.g. statins, antibiotics, antifungals)
- Consider MRI/USS liver to exclude progressive disease/thromboembolism and evaluation of inflammation if immune-related hepatitis is suspected

2.5 Pharmaceutical form

- Mycophenolate mofetil is available as 250mg capsules, 500mg tablets and 1g/5ml powder for oral suspension, and a 500mg powder for concentrate for solution for infusion.
- Brands include Cellcept® and Myfenax®; generics are available and may be more cost effective.

- Mycophenolic acid is available as gastro-resistant capsules 180 mg and 360 mg tablets
- Mycophenolic acid 720 mg is approximately equivalent to Mycophenolate mofetil 1 g but unnecessary switching should be avoided, due to pharmacokinetic differences. Mycophenolic acid should usually be reserved for patients who do not tolerate mycophenolate mofetil.

2.6 Dosage

- For IrAEs, initiate Mycophenolate mofetil at 500mg BD, then escalate to 1g BD after 3-5 days if tolerated
- In certain cases Mycophenolate mofetil can be increased in 250mg increments to 1.25g BD or 1.5g BD
- Maximum 1.5g BD
- The maximum dose in severe renal impairment (<25ml/min) is 1g twice a day
- No dosage adjustments are needed for patients with severe hepatic impairment
- If IV treatment is being considered it is recommended to seek specialist advice.

2.7 Method of administration

- Mycophenolate mofetil orally can be taken with or without food, although it causes less gastric irritation if given with a meal.
- If a dose is missed it should be taken as soon as remembered, then dosing resumed at the usual times. However, a double dose should not be taken to make up for a missed dose.
- Capsules and tablets should not be opened, crushed, or chewed, to avoid inhalation or direct contact with skin or mucus membranes of the active substance. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.
- IV administration:
    - IV infusion only. Do not administer by rapid or bolus IV injection
    - Reconstitute each 500mg vial with 14mls glucose 5%. Gently shake the vials. Then, further dilute the contents of the 2 vials in 140ml of glucose 5%. Infuse over 2 hours.

2.8 Other monitoring

<u>Initial Monitoring</u>

- FBC, LFTs and U&Es should be monitored regularly
- When used in IR-hepatitis consider the following recommendations:
- Monitor LFTs and INR every 3 days and review patient twice weekly
- If LFT improving, check LFTs weekly
- Consider weaning corticosteroids if improving
- After corticosteroids stopped, continue Mycophenolate mofetil for at least 2 weeks.
- Consider weaning the dose of mycophenolate before stopping.
- Refer to specialty teams (e.g. hepatologist, cardiologist, rheumatologist, etc.) for further advice if no improvement on Mycophenolate mofetil.

Other considerations

- Patients aged 70-79 years old could be eligible for the shingles vaccine (herpes zoster). For patients taking Mycophenolate mofetil 1g/day or more, or lower doses together with prednisolone ≥7.5 mg / day, a non-live vaccine should be used. Specialist input may be required.
- Annual influenza vaccinations are recommended.
- COVID-19 vaccination as per national schedule.
- Patients aged 70-79 years old could be eligible for the RSV vaccine.

2.9 Adverse effects

- These are the most common adverse effects.
- This is not an exhaustive list. See SmPC for further details.

System	**Adverse Effects** (very common or common)
Gastrointestinal disorders:	Nausea and vomiting, abdominal cramps, constipation, diarrhoea, dyspepsia, GI ulceration, bleeding and perforation, suspected pancreatitis
Metabolism and nutrition disorders	Hypercholesterolemia, hypophosphatemia, acidosis, hyperglycaemia, hyperkalaemia, hyperlipidaemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hyperuricaemia, gout, weight decrease
Skin disorders:	Skin hypertrophy, acne, alopecia, rash
Blood disorders	Anaemia and leucopoenia, leucocytosis, pancytopenia, thrombocytopenia
Infection and Infestations	Bacterial and viral infections, fungal infections
Nervous system disorders	Headache, dizziness, hypertonia, paraesthesia, somnolence, convulsions
Psychiatric disorders	Confusion, depression, insomnia, anxiety
Cardiac disorders	tachycardia
Vascular disorders	Hypertension, hypotension, venous thrombosis, vasodilatation
Respiratory disorders	Cough, dyspnoea, pleural effusion. Pulmonary fibrosis is very rare
Renal and urinary disorders	Haematuria, renal impairment and increase in blood creatinine
Hepatobiliary disorders	Rise in ALP, LDH, transaminases, hepatitis, hyperbilirubinemia
Musculoskeletal disorders	Arthralgia and muscle weakness
Other:	Oedema, asthenia, pyrexia Suspicion of malignancy

2.10 Drug interactions

- The table below lists the most common interactions but is not exhaustive. The SmPC and other drug interactions resources should be further consulted.

Drug	Interaction
Aciclovir / ganciclovir / valaciclovir / valganciclovir	possible increased plasma concentration of antiviral and mycophenolate metabolite, especially in patients with renal impairment; possible increased risk of haematological toxicity
Antacids and proton pump inhibitors	reduced absorption of mycophenolate
Further immunosuppression e.g. azathioprine, ciclosporin, sirolimus	increased risk of bone marrow suppression
Cholestyramine / colesevelam	reduced absorption of mycophenolate
Ciclosporin	reduced mycophenolate exposure
Isavuconazole	possible increased risk of mycophenolate adverse effects due to increased exposure to mycophenolate or its metabolite
Telmisartan	may reduce mycophenolate exposure
Live vaccines	Increased risk of generalised infection.
Rifampicin	decreased plasma concentration of mycophenolate
Sevelamer	reduced mycophenolate exposure; separate administration by 1-3 hours

2.11 Advice to patients

- Patients receiving mycophenolate mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow failure.
- During a serious infection (requiring antibiotics) mycophenolate mofetil should be temporarily discontinued until the patient has recovered from the infection.
- Patients should be advised to tell anyone who prescribes a new medicine that they are taking mycophenolate. Patients should ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- Patients have a small increased risk of skin cancers so should be advised to wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin.
- Mycophenolate mofetil may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.
- All patients should use at least one form of effective contraception (2 forms of contraception preferred), and to take a pregnancy test if they think they could be pregnant. Patients should inform

their oncology team immediately if they or their partners become pregnant or are planning a pregnancy.

- Patient should not donate blood during treatment or for 6 weeks after stopping, and not to donate semen during treatment or for 90 days after stopping.
- Patients should avoid contact with people with chicken pox or shingles and report any such contact urgently to their oncology team.
- Mycophenolate is teratogenic and should not be handled by pregnant women
- Capsules and tablets should not be opened, crushed or chewed
- Some medications can affect the way mycophenolate works, or mycophenolate can affect the way some other medications work. Patients should inform a doctor if they are taking any of the following:
    - Antibiotics, anti-fungals or anti-virals
    - Antacids or treatments for stomach ulcers
    - Medications that can suppress your immune system such as azathioprine
    - Cholestyramine used to lower your cholesterol
    - Phosphate binders for patients with kidney failure

3. Appendix 1 Example Patient Information Leaflet

What is Mycophenolate Mofetil?

Mycophenolate Mofetil is an immunosuppressant. It reduces the strength of your immune system to treat autoimmune conditions.

It has also been found to be useful for some side-effects that can occur when patients are given immunotherapy to treat cancer. In this case the immune system has become active against one part of the body (e.g. the liver), and Mycophenolate Mofetil supresses the immune system to prevent damage to that area of your body.

How do I take Mycophenolate Mofetil?

The dose of Mycophenolate Mofetil usually starts at 500mg twice a day, increased gradually according to your response to the medication to achieve the most effective dose to treat your condition. It works slowly and can take up to several weeks to take full effect. If there is no improvement after a few months your doctor may consider stopping the medication.

The tablets or capsules should be taken twice a day with, or soon after food (it may cause irritation if taken on an empty stomach). Swallow the tablets or capsules whole. Do not chew or crush the tablets and do not open the capsules before swallowing. Taking with food and drink has no effect on your treatment with Mycophenolate Mofetil.

Try to take your doses at the same times of day each day, as this will help you to remember to take them. If you do forget to take a dose, take it as soon as you remember (unless it is nearly time for your next dose, in which case leave out the missed dose). Do not take two doses together to make up for a forgotten dose.

Do not take Mycophenolate Mofetil if you:

- are allergic to Mycophenolate Mofetil, mycophenolic acid or any of its excipients
- are pregnant or breast feeding

Discuss with your doctor:

- if you suffer from Lesch-Nyhan or Kelley-Seegmiller syndrome
- if you suffer from an active serious digestive system disease

Drug monitoring

Mycophenolate Mofetil can affect your blood cells, kidneys and your liver. Your doctor will periodically carry out blood tests to ensure your new medication is not causing you any problems. How often you need to have bloods tests done will depend on the condition you are being treated for. Initially you may need to have a bloods test twice a week, but this is likely to be less frequently as time passes.

How long will I need to take Mycophenolate Mofetil for?

Every patient is different, and how long you need treatment with Mycophenolate Mofetil for will depend on how well controlled the immunotherapy side effect is. In the majority of cases, you will only need to take it for a few months. However, there are some patients who will need to remain on Mycophenolate Mofetil longer term.

Does Mycophenolate Mofetil have any side-effects?

Most medicines cause side-effects. The manufacturer's leaflet contains a list of the known side-effects for this medicine. Everyone reacts differently to medicines. You may have some side-effects or none at all. There are several possible side effects that you may notice.

Side effects include:

- Feeling sick (nausea)
- Being sick (vomiting)
- Diarrhoea
- Tummy (abdominal) pain
- Reversible hair loss
- Sensitivity to sunlight
- Increased risk to infection: if you develop 'flu-like' symptoms, cough, sore throat, or a high temperature contact your oncology team immediately.

If you encounter someone with chickenpox or shingles, or if you develop either of these you need to contact your doctor immediately.

It is important to tell your doctor if you develop any new symptoms after starting Mycophenolate Mofetil.

Can I still be vaccinated?

Some vaccines contain a live form of the virus. These are called live vaccines, and you cannot have a live vaccine whilst you are on Mycophenolate Mofetil.

Please take to your doctor if you are not sure about this.

Is it safe to be in the sun?

Mycophenolate Mofetil reduces your body's defence mechanism. Because of this, there is an increased risk of skin cancer. Limit the amount of time you spend in the sunlight and avoid exposure to ultraviolet light such as tanning machines. Where protective clothing and use a sunscreen with a high sun protective factor (SPF).

Is it safe to become pregnant while I am taking Mycophenolate Mofetil?

You may have already had these conversations with your oncology team before starting immunotherapy. It is important that you do not plan a pregnancy if you are on Mycophenolate Mofetil and should use effective contraception if sexually active.

If you are a woman who could become pregnant you must use at least one form of effective contraception before you start taking Mycophenolate Mofetil (two is preferred), during the entire treatment with Mycophenolate Mofetil and for 6 weeks after you stop taking Mycophenolate Mofetil.

The evidence does not indicate an increased risk of malformations and miscarriages if the father takes Mycophenolate Mofetil. However, a risk cannot be completely excluded. As a precaution you or your female partner are recommended to use at least one form of reliable contraception during treatment and for 90 days after you stop taking Mycophenolate Mofetil.

Can I take other medicines whilst I am taking Mycophenolate Mofetil?

You should always check with your oncology team or pharmacist if you are started on any new medicines, including anything you may buy over the counter or herbal remedies. This is because Mycophenolate Mofetil can affect the way some other medicines work. Also, other medicines can affect the way Mycophenolate Mofetil works.

Supply of Mycophenolate Mofetil

You must not stop taking Mycophenolate Mofetil unless advised to do so by your hospital team. Mycophenolate Mofetil will be prescribed from the hospital team when you start taking it, and it is important you make sure you don't run out of Mycophenolate Mofetil.

In some hospitals, the hospital team will ask your GP to prescribe further supply. The hospital team will support and advise your GP when needed. Your hospital team will discuss this with you when you start treatment with Mycophenolate Mofetil.

Who can I contact for further information?

If you have any queries about your Mycophenolate Mofetil the best people to speak to are the oncology team who you are under, team of specialists who have prescribed the Mycophenolate Mofetil for you or an oncology pharmacist.

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5. Acknowledgements

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6. Document control

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