Mycophenolate Mofetil (MMF)

SCG: For Interstitial Lung Disease (ILD)

The following guidelines are designed to provide information relating to mycophenolate mofetil and to outline the responsibilities of the primary and secondary care teams in the prescribing of mycophenolate mofetil.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

Introduction:

Mycophenolate mofetil is an immunosuppressant which acts by inhibiting the synthesis of guanosine nucleotides in T and B lymphocytes. It is rapidly converted to the active metabolite mycophenolic acid by plasma esterases.

Mycophenolate mofetil is licensed for the treatment of acute rejection in transplant patients. However, there are case series of patients with interstitial lung disease (ILD), in particular those patients with associated autoimmune diseases, who have benefited from mycophenolate mofetil therapy.

At Papworth Hospital NHS Foundation Trust, mycophenolate mofetil will be used for patients with ILD related to connective tissue diseases and in those with idiopathic interstitial pneumonias who are intolerant or have not responded to therapeutic trials of other immunosuppressants (especially azathioprine). The recommendation to start treatment will be made by the hospital specialist consultant only.

RESPONSIBILITIES and ROLES

Specialist responsibilities- Interstitial Lung Disease (ILD) team:

1. Identify patients who would potentially benefit from mycophenolate mofetil therapy.
2. Initially prescribe and stabilise the patient on the treatment regimen and monitor lung function.
3. Send a letter to the GP requesting shared care for this patient.
4. Provide routine clinic follow-up on a regular basis.
5. Monitor efficacy of the treatment and side effects. Advise GP on review, duration or discontinuation of treatment where necessary.
6. Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
7. To inspect patient held results booklet at each outpatient attendance and advise on action to be taken in the event of abnormal blood results.
8. Provide access to back up and support facilities.
9. Evaluate any adverse events reported by the GP. (All potential adverse events should be reported to the CSM).
10. Educate patients in knowledge of drug therapy to maximise compliance and be aware of when to seek medical attention.
11. Inform GP of patients who do not attend clinic appointments.
General Practitioner’s responsibilities:

1. Prescribe mycophenolate mofetil once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital.
2. Monitor patient’s overall health and well being.
3. Check for possible drug interactions when newly prescribing or stopping concurrent medication.
4. Report any suspected adverse events to the ILD team. (All potential adverse events need to be reported).
5. Monitor blood results (FBC and LFTs) weekly for first month after initiation by the ILD team and with any increase in dose. Once stabilised, two monthly FBC and LFTs can be performed (See ‘Monitoring’ section).
6. Should gastrointestinal side effects occur, please ensure the patient is taking the tablet with food.

Patient’s role:

1. Notify any adverse events to GP and ILD team.
2. Notify use or intended use of over the counter (OTC) and herbal medications.
3. Report any sore throat, infection, fever, unexplained bruising or bleeding to GP and ILD team. This should have been discussed with you at the commencement of this treatment by either the Specialist Nurse or ILD Consultant.
4. Minimise exposure to sunlight and UV light by wearing protective clothing and using a sunscreen with a high protection factor.
5. Keep alcohol intake to a minimum.

BACK-UP ADVICE AND SUPPORT

- Papworth Hospital Main Switchboard 01480 830541
- Pharmacy Medicines Information Service 01480 364179 (Mon-Fri 9-5)
- Pharmacy Medicines Helpline 01480 364739 (Answerphone)
- Interstitial Lung Disease Physicians: Dr Parfrey and Dr Simler via 01480 364530 (ILD secretaries)
- Interstitial Lung Disease Nurse Specialist: Emma Harris 01480 364184 or via switchboard (blp 109)

Out of hours support Chest Medical Unit junior doctor on call
You can also contact the service by email on: ILD.secretary@papworth.nhs.uk
SUPPORTING INFORMATION

Licensed indications:

- Mycophenolate mofetil is currently licensed for the prophylaxis of acute transplant rejection in conjunction with ciclosporin and oral corticosteroids in patients receiving renal, cardiac or hepatic transplants.

Therapeutic Use for Interstitial Lung Disease:

- It is being increasingly recognised that mycophenolate mofetil may be a useful agent in patients who have multi-system disease e.g. autoimmune disease such as SLE, systemic sclerosis, polymyositis and Rheumatoid Arthritis, associated with lung fibrosis. Mycophenolate mofetil may be prescribed as part of combined therapy usually with prednisolone. It may be used when therapeutic trials of other immunosuppressant agents have been unsuccessful.

Dosage and Administration:

Dosing in ILD:

As advised by hospital specialist but typically a gradual increase in dosage:

- Week 1: 500mg once daily    Check FBC and LFTs
- Week 2: 500mg twice daily    Check FBC and LFTs
- Week 3: 500mg in morning and 1g in evening    Check FBC and LFTs
- To remain on this dose until next clinic review within next 2 weeks
- Check response and tolerability at clinic visit and increase to 1g twice daily

NOTE: Under NO circumstances should the active metabolite (mycophenolic acid) (Brand name Myfortic®) be prescribed due to pharmacokinetic differences in dosage equivalence.

Contraindications and precautions:

- Hypersensitivity to mycophenolate mofetil or mycophenolic acid (the active metabolite of mycophenolate).
- Pregnancy and breast feeding. Contraception is essential.
- Avoid in Hepatitis B/C and herpes simplex/shingles.
- Reduce the dose in the presence of significant renal impairment.

Side Effects:

All immunosuppressive agents are powerful and potentially toxic drugs, and therefore adverse events may be observed. Any adverse effects detected should be reported directly to the ILD team. All potential adverse effects should be reported to the CSM.

Gastrointestinal symptoms are the most commonly associated side effect of drug treatment with mycophenolate. Such symptoms frequently settle without the need for treatment discontinuation. Bone marrow suppression is less frequent than with azathioprine. The following is a summary of the commonest adverse reactions reported with mycophenolate mofetil:
- **Gastrointestinal** Nausea, vomiting, diarrhoea, abdominal pain
- **Haematological** Leucopenia, anaemia, thrombocytopenia

Immunosuppressed patients are more susceptible to infection (bacterial, viral, fungal and protozoal) and malignancy, especially lymphomas caused by oncogenic viruses and skin tumours.

The above list of adverse events is not exhaustive but does cover the most frequently reported events. A more comprehensive list can be found in the mycophenolate mofetil (Cellcept®) Summary of Product Characteristics (see www.emc.medicines.org.uk).

**Monitoring:**

**Pretreatment assessment:**
- Renal function (Creatinine and electrolytes, and Creatinine clearance if concerned about renal impairment) as mycophenolate mofetil is 95% excreted via the kidneys.
- Blood pressure
- FBC, LFTs and lipids.

**Monitoring:**
- FBC and LFTs are required every week for first 4 weeks of treatment, twice monthly for second and third months of treatment, then every month during the first year of therapy. This is to monitor for evidence of neutropenia, bone marrow suppression and deranged liver function tests.

**Action to take in event of abnormal test results/symptoms:**

<table>
<thead>
<tr>
<th>Blood test results</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (WCC) &lt; 4.0 x 10^9/L</td>
<td>Contact ILD team</td>
</tr>
<tr>
<td>Neutrophils &lt; 2.0 x 10^9/L</td>
<td>Contact ILD team</td>
</tr>
<tr>
<td>Neutrophils &lt; 1.5 x 10^9/L</td>
<td><strong>Stop treatment</strong> and contact ILD team</td>
</tr>
<tr>
<td>Lymphocytes &lt; 0.5 x 10^9/L</td>
<td>Contact ILD team</td>
</tr>
<tr>
<td>Platelets &lt;150</td>
<td><strong>Stop treatment</strong> and contact ILD team</td>
</tr>
<tr>
<td>ALT/AST &gt; twice upper limit of normal</td>
<td><strong>Stop treatment</strong> and contact ILD team</td>
</tr>
</tbody>
</table>

**Symptoms**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Action</th>
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<tbody>
<tr>
<td>Oral ulceration/stomatitis</td>
<td><strong>Stop treatment</strong> and contact ILD team</td>
</tr>
<tr>
<td>Persistent or severe sore throat</td>
<td>Take FBC (<strong>stop treatment if abnormal</strong>) and contact ILD team</td>
</tr>
<tr>
<td>Severe or persistent infection</td>
<td><strong>Stop treatment</strong> and take FBC and contact ILD team</td>
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**Drug Interactions:** (This list is not exhaustive)
- **Live Vaccines** Should be avoided in immunocompromised individuals. The influenza vaccination may be of value and will be discussed with patients on an individual basis.
- **Azathioprine** Should not be given concurrently.
- **Antacids** With magnesium and aluminium hydroxides, a decrease in the absorption of mycophenolate mofetil may occur.
• **Colestyramine** A decrease in the absorption of mycophenolate mofetil may occur with concurrent administration.

• **Proton pump inhibitors** may cause a decrease in mycophenolate levels.

• **Probenecid** Prevents renal tubular secretion and hence causes an increase in mycophenolic acid plasma concentrations with concurrent administration.

• **Antibacterials** Co-amoxiclav, metronidazole, norfloxacin, ciprofloxacin each may reduce blood levels of mycophenolate mofetil through interference of enterohepatic recirculation.

• **Rifampicin** Causes a decrease of mycophenolic acid levels.

### Co-prescribing of NSAIDs

Be aware that any patients who co-administer a non steroidal anti-inflammatory drug (NSAID) are at greater risk of low platelet count, increased bleeding and/or bruising.

For advice on mycophenolate interactions or co-prescribing please do not hesitate to contact the pharmacy Medicines Information Dept (see page 2).

### Cost:

- **Drug Tariff July 2011** £28.40 for 50 capsules (generic formulation)
- Approximate cost per month for 500mg BD dose: £30.00.

### References:

- **Cellcept® Summary Product Characteristics, Roche Medical Information Department – revised 27th October 2009, accessed website (www.emc.medicines.org.uk) on 22/07/2011**
- **Chest 2006; 130:30-36 Swigris JJ et al: Mycophenolate Mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease**
- **Am J Gastroenterol 2000; 95:3674-75 Treiber G. Mycophenolate mofetil for therapy-resistant interstitial lung disease associated with ulcerative colitis**
- **Medical Hypotheses 2001; 57:701-02 Altschuler EL. Consideration of mycophenolate mofetil for idiopathic pulmonary fibrosis**
- **www.Pneumotox.com**