Cardiff & Vale (C&V) UHB Corporate Medicines Management Group (c MMG)

SHARED CARE

Drug: MYCOPHENOLATE MOFETIL/SODIUM Protocol number: CV 15

Indication: RENAL, PANCREAS OR COMBINED RENAL PANCREAS TRANSPLANTATION IN ADULTS

General guidance

This protocol sets out details for the shared care of patients taking **mycophenolate mofetil/sodium** and should be read in conjunction with the General Guidelines for Shared Care. Sharing of care requires communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **The doctor who prescribes the medication legally assumes responsibility for the drug and the consequences of its use.** The prescriber has a duty to keep themselves informed about the medicines they prescribe, their appropriateness, effectiveness and cost. They should also keep up to date with the relevant guidance on the use of the medicines and on the management of the patient's condition.

Background

Drug therapy in transplantation is complicated and patients require regular assessment to monitor the progress of the transplant and to monitor for drug side effects. Anti-rejection agents must be continued for the duration of the life of the transplant but both the number of agents and doses prescribed are greater in the first year post surgery, especially in the first three months when the risk of acute rejection is greatest. After 12 months, the risk of acute rejection is lower but drugs are still required to prevent acute and, equally importantly, chronic rejection processes.

Most new transplant patients will be discharged from hospital on a combination of three anti-rejection drugs:

- Calcinuerin inhibitor (ciclosporin or tacrolimus)
- Anti-proliferative agent (azathioprine or mycophenolate mofetil)
- Corticosteroids (prednisolone)

Mycophenolate mofetil is a relatively new anti-rejection agent but is widely prescribed. When given as part of a triple therapy regimen as described above produces significant benefits in terms of patient survival, reduction in the number of transplants lost through acute rejection and reduction in acute rejection episodes.

Mycophenolate mofetil is a newer, more potent anti-proliferative agent when compared to azathioprine. It has a different mechanism of action from azathioprine but, like azathioprine, is a pro-drug. Mycophenolate mofetil is converted in vivo to the active agent, mycophenolic acid. The higher potency means that at 12 months post surgery, transplant organ survival rates and incidence of acute rejection episodes are improved in comparison with azathioprine.

The vast majority of patients referred for shared care will have been on mycophenolate mofetil as part of their primary immunosuppression post transplantation. However, it is possible that a patient switches to mycophenolate mofetil at a later date from the initial anti-rejection agents prescribed for them:

- Not tolerating existing drugs
- Experiencing acute rejection episodes or chronic rejection problems which require an escalation of immunosuppression – this is termed "rescue therapy"

In both instances, it will most likely be a switch from the other anti-proliferative agent, azathioprine.

Mycophenolate sodium is a newer, enteric coated formulation of mycophenolic acid which has demonstrated similar efficacy to mycophenolate mofetil. Mycophenolate sodium is converted in vivo to the active component, mycophenolic acid.

The transplant unit does not currently have many patients prescribed mycophenolate sodium. It is not yet being used in place of the other anti-proliferative agents as part of the primary immunosuppression post transplantation.

The sole indication at present is as a switch from mycophenolate mofetil in patients who are experiencing significant gastrointestinal intolerance. These patients may not even be able to take low doses of mycophenolate mofetil. Individual patients may benefit from a change to the different formulation in terms of a reduction in severity of these side effects. Consequently, they may also be able to tolerate a higher dose, exposing them to more mycophenolic acid which may have the advantage of enhancing anti-rejection efficacy. Individual patients will be considered for mycophenolate sodium shared care referral after an evaluation by the transplant unit of the benefits of a switch from mycophenolate mofetil.

Responsibilities

A. Consultant responsibilities

1. When treatment is **initiated** send Shared Care request form with Shared Care Protocol to GP.
2. Baseline and continued monitoring of biochemical and haematological parameters and clinical parameters for mycophenolate mofetil/sodium.
3. When a GP positive response to SC has been received and patient has been stabilised send a letter to GP "handing over" the Shared Care of the patient to the GP.
4. The patient will be informed to contact their GP immediately if any of the following occur: diarrhoea, rash, mouth ulcers, bruises, itching, bleeding, fever, sore throat, jaundice or other infection.
5. Advise female patients to consult with Transplant team if considering pregnancy.
6. Monitoring of clinical response, side effects and check any alteration in patient's medication.

7. When patient is established on a stable dose of mycophenolate mofetil/sodium (this can vary between four and twelve weeks post transplant) send shared care agreement request to GP.
8. Respond to any request from GP to review the patient due to adverse effects of therapy.
9. Advise the GP on continuing or stopping mycophenolate mofetil/sodium therapy following medical review of the patient and associated drug therapy.
10. Notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.

B. General practitioner responsibilities

1. Within one week of receipt return the completed Shared Care request form to indicate whether or not willing to undertake Shared Care.
2. Prescribe mycophenolate mofetil/sodium as part of the shared care agreement.
3. Monitor the general health of the patient.
4. Seek advice from the consultant on any aspect of patient care which is of concern e.g. unexplained fever.
5. Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
6. Recommend that patient receives pneumococcal vaccination and annual influenza vaccination.
7. To act on advice provided by the Consultant if patient does not attend for appropriate monitoring.

C. Patient responsibilities

1. Consent to treatment with mycophenolate mofetil/sodium.
2. Attend regular appointments with specialist centre and GP.
3. Report any side effects to the specialist or GP whilst taking mycophenolate mofetil/sodium.

Dosage Regimen

The initial dose of **mycophenolate mofetil** (which would be started on day of transplant surgery) is usually 1g twice a day. This can be adjusted, usually in response to one of the two factors described below, so the optimum dose will be determined individually for each patient:

- Dose reduced because mycophenolate mofetil not tolerated, e.g. bone marrow suppression or gastrointestinal side effects. The most common dose adjustment is to reduce to 500mg twice a day. 750mg or 250mg twice a day are less frequently prescribed.
- Dose reduced to minimise long term complications, once transplanted organ well established and risk of acute rejection has diminished.

The initial dose of **mycophenolate sodium** if used as primary immunosuppression at time of transplantation is usually 720mg twice a day. Patients switching from mycophenolate mofetil because of gastrointestinal intolerance are likely to start on a

smaller dose, for example 360mg twice a day. Doses can be adjusted, usually in response to one of the three factors described below, so the optimum dose will be determined individually for each patient:

- Dose reduced because mycophenolate sodium not tolerated, e.g. bone marrow suppression or gastrointestinal side effects.
- Dose reduced to minimise long term complications, once transplanted organ well established and risk of acute rejection has diminished.
- Dose increased because gastrointestinal side effects reduced since converting from mycophenolate mofetil.

Monitoring

During treatment

Regular clinical assessment of the patient will be carried out by the transplant unit and mycophenolate mofetil/sodium dosage adjustments may occur.

Regular monitoring is crucial for the overall management of transplant patients. It will aid detection of side effects due to drugs such as mycophenolate mofetil for which the following are routinely checked:

- Full blood count
- Liver function tests
- Creatinine and electrolytes

Each of these parameters will checked up to three times a week in the early post transplant phase. For a stable, long term patient this frequency reduces gradually but will always be a minimum of every 3 months.

Patients will be issued with a monitoring booklet to record results of these investigations.

When they attend transplant clinic, patients will be asked if any alterations have been made to their medication.

GPs should seek advice from Hospital Transplant team where the following blood test results (unrelated to mycophenolate mofetil/sodium monitoring) are present.

WBC	$< 4x10^9$/L * and/or
Neutrophils count	$<1.5x\ 10^9$/L*
Platelets	$< 150 \times 10^9$/L*
Or 3 successive falls within the normal range	
AST/ALT	> 2-fold rise (from upper limit of reference range)

Adverse effects

The spectrum of side effects with mycophenolate mofetil/sodium is broadly similar to that of azathioprine. For example, the principal adverse effects are on the bone marrow and the gut. When compared to the less potent anti-proliferative drug, azathioprine, incidence of these side effects is generally higher with mycophenolate mofetil/sodium.

Haematological:

- Bone marrow suppression can manifest as leucopenia, thrombocytopenia or anaemia. Pancytopenia is rare. Haematological effects are reversible and often dose related. They will resolve with temporary cessation of mycophenolate mofetil/sodium therapy or, if the effects on blood counts are less severe, a dose reduction. In either case, an escalation in the monitoring frequency will be needed until the blood results have improved.

Gastrointestinal:

- Nausea, vomiting, anorexia, abdominal pain, diarrhoea and dyspepsia can occur with mycophenolate mofetil/sodium. These adverse events can be dose related so will resolve with temporary cessation of therapy or a dose reduction. Peptic ulcer disease and gastric bleeds are less common but more severe gut side effects.

Other side effects include:

- Hepatotoxicity, including hepatitis and jaundice
- Rash
- Alopecia

Mycophenolate mofetil/sodium is immunosuppressive and as such predisposes to infection. Chickenpox and measles in non-immune patients of all age groups can be particularly serious and such patients may require passive immunisation after contact. The hospital should be consulted.

Varicella-zoster infections must be treated with systemic antiviral therapy and herpes simplex infections may require topical or systemic antiviral therapy.

According to level of risk for the individual patient, prophylaxis may be required for between 3 and 6 months against cytomegalovirus (with valganciclovir), pneumocystis carinii pneumonia (with cotrimoxazole) or tuberculosis (with isoniazid).

Fever should be fully investigated with: -

- Blood culture
- Full blood count
- Urine culture
- Throat swab
- Full clinical examination to elicit the cause.

Fever may also be a sign of rejection.

Interactions

Some interactions lead to reduced levels of mycophenolate mofetil/sodium in the blood which reduces drug efficacy and increases risk of rejection:

- Reduced mycophenolate mofetil/sodium absorption (magnesium and aluminium containing antacids)
- Reduced bioavailability by interfering with enterohepatic recycling of mycophenolate mofetil/sodium (cholestyramine and other bile salt binding agents, ciclosporin)

Antiviral drugs such as aciclovir and valganciclovir will compete for the same route of renal tubular secretion into the urine as mycophenolate mofetil/sodium. So co-administration can increase blood levels of both drugs, especially in the presence of renal impairment. However, these changes to the pharmacokinetics of both drugs are rarely clinically significant.

If there are concerns about prescribing a drug for a transplant patient on mycophenolate mofetil/sodium, the transplant unit should be contacted and the transplant doctor/nurse/pharmacist will be able to offer advice.

Special recommendations

Live vaccines must be avoided in all transplant patients.

There is an increased risk of skin cancer in transplant patients. They should be advised to take appropriate steps to protect themselves against the harmful effects of sunlight, to be vigilant for changes to their skin and to report these changes to the transplant unit.

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