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

SHARED CARE

Drug: AZATHIOPRINE **Protocol number: CV 04**

Indication: LIVER TRANSPLANTATION IN ADULTS

General guidance

This protocol sets out details for the shared care of patients taking **azathioprine** 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.

A. Consultant responsibilities

1. Send the shared care request with shared care protocol to GP when the patient's care has reverted from the tertiary centre, e.g. Birmingham, to the Cardiff and Vale UHB consultant.
2. Continued monitoring of biochemical and haematological parameters and clinical parameters for azathioprine.
3. Ensure patient is aware of benefits and risks of taking azathioprine.
4. The patient will be informed to contact their GP immediately if any of the following occur: diarrhoea, rash, mouth ulcers, bruises, itching, bleeding, sore throat or jaundice.
5. Advise patient to contact GP immediately, if he/she develops fever or other evidence of infection, for clinical assessment and blood tests. (FBC and CRP)
6. Advise female patients to consult with Transplant team if considering pregnancy.
7. Monitoring of clinical response, side effects and check any alteration in patient's medication.
8. 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.

9. Respond to any request from GP to review the patient due to adverse effects of therapy.
10. Advise the GP on continuing or stopping azathioprine therapy following medical review of the patient and associated drug therapy. The Cardiff and Vale UHB consultant is responsible for ensuring that any advice by the tertiary centre (e.g. Birmingham) on continuing or stopping azathioprine is communicated to the GP practice.
11. 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 azathioprine 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. (FBC and CRP should be checked to assess if there is significant inflammatory response /possible severe infection)
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 azathioprine.
2. Attend regular appointments with specialist centre and GP.
3. Report any side effects to the specialist or GP whilst taking azathioprine

Dosage Regimen

The usual starting dose post liver transplantation is 1.5mg/kg as a single daily dose with food. This dose may be decreased over time

Monitoring by Hospital Team

<u>During treatment</u>

Post transplant

FBC should be performed at baseline and at weekly intervals during the first 2 months or as recommended by the specialist. This may be reduced later in therapy but will always be a minimum of every 3 months.

Liver function tests should be performed at baseline then monthly for the first two months, then at intervals of not longer than 3 monthly thereafter.

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

GPs should seek advice from specialist team where the following blood test results (unrelated to azathioprine monitoring) are present.

WBC	< $4x10^9$/L and/or
Neutrophils count	<1.5x 10^9/L or Lymphocyte count < 0.5 x 10^9/L
Platelets	< 150 x 10^9/L
Or 3 successive falls within the normal range	
AST/ALT	> 2-fold rise (from upper limit of reference range)

* **patients may continue treatment if WBC is 3.0 - 4.0 x 10^9/L if the neutrophil count is above 1.5 x 10^9/L**

Adverse effects

The principal adverse effects of azathioprine are on the bone marrow and the gut.

Haematological:

- Bone marrow suppression – leucopenia is most common followed by thrombocytopenia then anaemia. Pancytopenia is rare. Haematological effects are reversible and often dose related. They will resolve with temporary cessation of azathioprine 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 azathioprine. These adverse events can be dose related so will resolve with temporary cessation of therapy or a dose reduction.

Other side effects include:

- Hepatotoxicity, including dose related reversible cholestatic jaundice and, rarely hepatic veno-occlusive disease.
- Rash
- Alopecia
- Acute renal failure due to interstitial nephritis (very rare)
- Pancreatitis (very rare)
- Pneumonitis (very rare)

Azathioprine 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: -

- Full blood count
- Urine culture
- Throat swab
- Full clinical examination to elicit the cause.
- Blood Cultures (Secondary care)

Fever may also be a sign of rejection.

Interactions

- Allopurinol – azathioprine levels will be increased with increased toxicity unless the azathioprine dose is reduced significantly -avoid combination.
- The anticoagulant effect of warfarin may be reduced by azathioprine. Regular INR monitoring should be undertaken if both agents are used.
- Thiazide diuretics and furosemide have been observed to increase metabolism of azathioprine resulting in treatment failure.
- Angiotensin-converting enzyme inhibitors – increased risk of anaemia or leucopenia when given with azathioprine.
- Co-trimoxazole and trimethoprim increased risk of haematological toxicity when given with azathioprine.

If there are concerns about prescribing a drug for a transplant patient on azathioprine, the transplant unit/Gastroenterology team should be contacted for 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.

Contacts

029 20743618 Hepatology Specialist Nurse - answer machine

029 20744796 Elaine Healy – secretary to Dr Brijesh Srivastava

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