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

SHARED CARE

Drug: CICLOSPORIN **Protocol number: CV 06**

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

General guidance

This protocol sets out details for the shared care of patients taking **ciclosporin** 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)

Ciclosporin has been used in the transplantation field since the 1980s and 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.

The vast majority of patients referred for shared care will have been on ciclosporin as part of their primary immunosuppression post transplantation. However, it is possible that a patient switches to ciclosporin at a later date because they have not tolerated the initial anti-rejection agents prescribed for them. In this instance, it will most likely be a switch from the other calcinuerin inhibitor, tacrolimus.

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, clinical parameters and therapeutic drug monitoring for ciclosporin.
3. Initiate therapy following full discussion with the patient of benefits and risks.
4. Advise female patients to consult with Transplant team if considering pregnancy.
5. Monitoring of clinical response, side effects and check any alteration in patient's medication.
6. 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.
7. Respond to any request from GP to review the patient due to adverse effects of therapy.
8. Advise the GP on continuing or stopping ciclosporin therapy following medical review of the patient and associated drug therapy.
9. 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 ciclosporin 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. Seek advice from Transplant team if patient presents with unexplained fever.
8. To act on advice provided by the Consultant if patient does not attend for appropriate monitoring.

C. Patient responsibilities

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

Dosage Regimen

The initial dose (which would be started on day of transplant surgery) is usually 8mg/kg/day in 2 divided doses. This is adjusted according to blood levels and clinical response. There is significant inter-patient variation in factors such as absorption and metabolism of ciclosporin so the optimum dose will be determined individually for each patient.

Monitoring by Hospital team

<u>During treatment</u>

Regular measurement of trough (pre-dose) ciclosporin levels, alongside a clinical assessment of the patient, are necessary to allow further dosage adjustments to be made. Target therapeutic levels are higher in the early post transplant phase:

- 150 to 250ng/ml (first 3 to 6 months)
- 100 to 200ng/ml (thereafter)

The frequency of these measurements will depend on the clinical situation as indicated by the consultant requesting shared care. For example, drug levels will be checked more frequently during periods when levels have become sub-therapeutic or toxic or when the patient is required to take a drug that interacts with ciclosporin.

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

- Full blood count
- Creatinine and electrolytes
- Blood sugars
- Blood pressure
- Liver function tests

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 ciclosporin monitoring) occur.

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 principal adverse effect is nephrotoxicity, which can be difficult to differentiate from rejection, and any other cause of raised creatinine such as infection or obstruction.

Other important side effects include:

- Hypertension
- Hypercholesterolaemia
- Neurological complications such as tremor and paraesthesiae
- Hyperglycaemia
- Hyperkalaemia
- Hypomagnesaemia
- Hirsuitism
- Gingival hypertrophy
- Hepatic dysfunction
- Bone marrow suppression

Some ciclosporin side effects are related to elevated blood levels.

Ciclosporin 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

Ciclosporin (and the other calcinuerin inhibitor, tacrolimus) undergo hepatic metabolism via cytochrome P450 enzyme systems. Many drugs can inhibit (for example macrolide antibacterials and azole antifungals) or induce (for example rifamycin antibacterials) the activity of these enzymes. This can lead to, respectively, elevated ciclosporin levels (increasing risk of side effects such as nephrotoxicity) or reduced ciclosporin levels (increasing the risk of rejection).

Where possible, the co-prescription of additional, predictable nephrotoxic drugs alongside ciclosporin is avoided.

Grapefruit juice has constituents that inhibit ciclosporin metabolism so patients are advised to avoid it.

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

Special recommendations

Ciclosporin must always be prescribed by brand to avoid inadvertent brand switching

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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