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

SHARED CARE

Drug: TACROLIMUS Protocol number: CV 43

Indications: RENAL, PANCREAS OR COMBINED RENAL PANCREAS TRANSPLANTATION IN ADULTS.

LIVER TRANSPLANTATION IN ADULTS

General guidance

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

Tacrolimus is licensed for immunosuppression in kidney and liver transplantation and for the treatment of resistant rejection.

It is a macrolide immunosuppressant which suppresses T-cell activation, T-helper-cell-dependent B-cell proliferation, and the production of lymphokines such as interleukins –2 and –3. This mode of action is similar to that of ciclosporin but tacrolimus is more potent. Tacrolimus is never prescribed concurrently with ciclosporin.

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

Post renal transplant. Tacrolimus is typically prescribed as part of a triple therapy regimen with mycophenolate mofetil or azathioprine and prednisolone.

Post liver transplant. Tacrolimus is typically prescribed initially as part of a dual therapy regimen with prednisolne. Depending on the aetiology, prednisolone may be withdrawn after 3-4 months

Responsibilities

A. Consultant responsibilities

1. When treatment is **initiated** send the shared care request with shared care protocol to GP. For liver transplant patients send the shared care request with shared care protocol to GP when the patient's care has reverted to the Cardiff and Vale UHB consultant. The brand of tacrolimus required should be specified.
2. Baseline and continued monitoring of biochemical and haematological parameters, clinical parameters and therapeutic drug monitoring for tacrolimus.
3. Initiate therapy following full discussion with the patient of benefits and risks.
4. Monitoring of clinical response, side effects and check any alteration in patient's medication.
5. Advise female patients to consult with Transplant team if considering pregnancy.
6. When a GP positive response to SC has been received and patient is established on a stable dose of tacrolimus (this can vary between four and twelve weeks post transplant) send a letter to GP "handing over" the Shared Care of the patient to 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 tacrolimus therapy following medical review of the patient and associated drug therapy. For liver transplant patients the Cardiff and Vale UHB consultant is responsible for ensuring that any advice by the tertiary centre (e.g. Birmingham) on continuing or stopping tacrolimus is communicated to the GP practice.
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 tacrolimus as part of the shared care agreement.
3. Monitor the general health of the patient.
3. Seek advice from the consultant on any aspect of patient care which is of concern. e.g. unexplained fever
4. Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
5. Recommend that patient receives pneumococcal vaccination and annual influenza vaccination**.**
6. Suspected non-compliance with immunosuppression is serious and can lead to loss of the graft-refer to the specialist urgently
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 tacrolimus.
2. Attend regular appointments with specialist centre and GP.
3. Report any side effects to the specialist or GP whilst taking tacrolimus.

Dosage Regimen

Post transplant (renal and liver)

The initial dose (which would be started on day of transplant surgery) is usually between 0.1 and 0.2mg/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 tacrolimus so the optimum dose will be determined individually for each patient in hospital by monitoring blood levels of tacrolimus and plasma creatinine.

Preparations available: Prograf 500 micrograms, 1mg and 5mg capsules and Advagraf 500micrograms, 1mg and 5mg capsules.

Prograf and Advagraf are not interchangeable without careful therapeutic monitoring. Substitution should be made only under close supervision of a transplant specialist.

Tacrolimus should be taken on an empty stomach, either one hour before or two hours after a meal.

Monitoring

<u>During treatment</u>

The target blood level for an individual patient will depend on the time since transplant, the history of rejection and side effects.

Post liver transplant
The risk of rejection diminishes with time and, after six weeks, the dose can usually be reduced in the transplant clinic to target trough blood levels of about 5 ng/ml for long-term maintenance

Post renal transplant Regular measurement of trough (pre-dose) tacrolimus 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:

- 10 to 15ng/ml (first 3 to 6 months)
- 5 to 10ng/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 tacrolimus.

Regular monitoring is crucial for the overall management of transplant patients. It will aid detection of side effects due to drugs such as tacrolimus 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 tacrolimus 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 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. Occasionally this can induce hyperkalaemia or hypertension. In renal transplantation, nephrotoxicity must be distinguished from rejection, urinary tract infection, ureteric obstruction and vascular thrombosis.

Other important side effects include:

- Hypertension
- Hypercholesterolaemia
- Neurological complications such as tremor and paraesthesiae
- Hyperglycaemia
- Hyperkalaemia
- Hypomagnesaemia

- Hepatic dysfunction
- Bone marrow suppression

Some tacrolimus side effects are related to elevated blood levels.

The spectrum of side effects with tacrolimus is very similar to that of ciclosporin but there are differences in the frequency of specific adverse events between the two agents. Tacrolimus is probably more diabetogenic and more neurotoxic but probably less likely to increase blood pressure or lipids and certainly less likely to cause hirsuitism and gingival hypertrophy.

Tacrolimus 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

Tacrolimus (and the other calcinuerin inhibitor, ciclosporin) 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 tacrolimus levels (increasing risk of side effects such as nephrotoxicity) or reduced tacrolimus levels (increasing the risk of rejection).

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

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

The overwhelming majority of interactions with calcinuerin inhibitors are common to both ciclosporin and tacrolimus.

If there are concerns about prescribing a drug for a transplant patient on tacrolimus, 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.

Neurological disturbances - patients should not drive or operate dangerous machinery if they have significant disturbance.

Infections - should be promptly investigated and treated when suspected.

Pregnancy/Contraception. Patients planning to become pregnant should be referred to the specialist at the earliest opportunity.

Breast feeding. Patients should not breast feed whilst receiving tacrolimus.

Reviewed February 2014 **Date of next review February 2017**