

SHARED CARE

Drug: TACROLIMUS Protocol number: CV 43

Indication: 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.

Post liver transplant. Tacrolimus is typically prescribed initially as part of a dual therapy regimen with prednisolone. Depending on the aetiology, prednisolone may be withdrawn by the Transplant team after 3-4 months. Patients may also be on Azathioprine or MMF in addition to Tacrolimus to prevent graft rejection.

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. **The brand of tacrolimus required should be specified.**

2. Continued monitoring of biochemical and haematological parameters, clinical parameters and therapeutic drug monitoring for tacrolimus.
3. Ensure patient is aware of benefits and risks associated with tacrolimus therapy.
4. Monitoring of clinical response, side effects and check any alteration in patient's medication.
5. Advise female patients to consult with specialist if considering pregnancy.
6. 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)
7. 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
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 tacrolimus 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 tacrolimus is communicated to the GP practice.
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 tacrolimus 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. Suspected non-compliance with immunosuppression is serious and can lead to loss of the graft-refer to the specialist urgently
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 tacrolimus.
2. Attend regular appointments with specialist and GP.
3. Report any side effects to the specialist or GP whilst taking tacrolimus.

Dosage Regimen

Post transplant

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:

Oral tacrolimus preparations should be prescribed and dispensed **by brand name only** to minimise the risk of inadvertent switching between products which has been associated with reports of toxicity and graft rejection.

- *Adoport, Prograf , Capexion, Tacni and Vivadex are immediate –release capsules that are taken twice daily, once in the morning and once in the evening.*
- *Modigraf granules are used to prepare an immediate-release oral suspension which is taken twice daily, once in the morning and once in the evening.*
- *Advagraf is a prolonged –release capsule that is taken once daily in the morning.*

Switching between tacrolimus brands requires careful supervision and therapeutic monitoring by an appropriate transplant specialist.

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

Monitoring in secondary care

During treatment

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

Post 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. The optimum trough level of tacrolimus may vary from patient to patient as some patients may require more immunosuppression and some less. The transplant team would make a decision about the optimum level required.

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
- Liver function tests
- Blood cultures

Each of these parameters will be 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.

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

GPs should seek advice from secondary care 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* 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 10⁹/L if the neutrophil count is above 1.5 x 10⁹/L

Adverse effects

Nephrotoxicity is a partly dose dependent side effect. Occasionally this can induce hyperkalaemia or hypertension. Other important side effects include:

- Hypertension
- Hypercholesterolaemia
- Neurological complications such as tremor and paraesthesiae- are the most common side effects but are only occasionally severe enough to warrant dose reduction.
- Hyperglycaemia is seen in some patients and may require treatment with oral agents or insulin.
- 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 hirsutism 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: -

- 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

Tacrolimus (and the other calcineurin 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).

Examples of drugs which alter tacrolimus plasma concentrations (this list is not exhaustive)

Increase levels	Cimetidine, diltiazem, erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole, nifedipine, omeprazole, voriconazole, atazanavir, nelfinavir, ritonavir, saquinavir, felodipine
Decrease levels	Caspofungin, rifampicin, phenytoin, phenobarbitone, St John's Wort.

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

Nephrotoxicity	Neurotoxicity	Hyperglycaemia	Hyperkalaemia
Aminoglycosides, amphotericin B, co-trimoxazole, NSAIDs, vancomycin.	Aciclovir, ganciclovir	Corticosteroids	Potassium-sparing diuretics, potassium supplementms.

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

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

If there are concerns about prescribing a drug for a transplant patient on tacrolimus, secondary care should be contacted. It is essential to inform the specialist prior to any interacting drugs being prescribed so that tacrolimus blood levels can be monitored. Inappropriate co-prescribing could lead to graft loss or serious toxicity.

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- 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.

Contraception- tacrolimus may inhibit the metabolism of steroid based contraceptives; barrier methods are recommended.

Contacts

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