Health and Social Care Board

Interface Pharmacist Network
Specialist Medicines

Tacrolimus

Post Solid Organ Transplant Shared Care Guideline

Using a printed guideline? Always check you are using the most up to date version. See www.ipnsm.hscni.net

Specialist Details	Patient Identifier
Name: _____	
Location: _____	
Tel: _____	Date: _____

Introduction

There are a number of oral tacrolimus products available. Recent MHRA/CHM advice recommends all oral tacrolimus products should be prescribed and dispensed by brand name only, to minimise any risk of inadvertent switching between products which has been associated with reports of toxicity and graft rejection.
The two main brands use in Northern Ireland transplant units are Prograf® and Advagraf®. Prograf is an immediate release formulation that is taken twice a day; Advagraf is a prolonged release formulation that is taken once daily in the morning. Prograf® and Advagraf® are not interchangeable without careful therapeutic monitoring. Substitution should be made only under close supervision of a transplant specialist.

Licensed indication: immunosuppression post organ transplant.

- **Post renal transplant**: tacrolimus may be prescribed as monotherapy but is typically prescribed as part of a dual or triple therapy regimen with mycophenolate mofetil or azathioprine or sirolimus, and prednisolone. The dose and number of drugs are gradually tapered depending on the occurrence or likelihood of rejection, nephrotoxicity or other drug effects. Tacrolimus is never prescribed concurrently with ciclosporin.
- **Adult dosage and administration.** The dose will be adjusted by the specialist according to individual requirements and trough tacrolimus levels. Target trough levels decline as time from transplant increases. Maintenance doses vary between patients though typically a range of 1 - 4mg twice daily (Prograf®) is common in adults at three months post transplant
- **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 Depending on the aetiology, prednisolone may be withdrawn after 3 - 4 months.
- **Adult dosage and administration.** The dose will be adjusted to individual requirements and will be titrated in the early stages post-transplant to achieve a trough level of approximately 10 nanograms/ml. The dose will then be adjusted depending on time post transplant and according to clinical need, typically to achieve a level between 4 – 8 nanograms/ml.

Preparations used in Northern Ireland transplant units:

- Prograf® 500 micrograms, 1mg and 5mg capsules. Prograf® is an immediate release formulation that must be taken twice a day: once in the morning and once in the evening. Caution: a number of immediate release preparations are available.
- Advagraf® 500micrograms, 1mg, 3mg and 5mg capsules. Advagraf® is a prolonged-release formulation that must be taken once a day in the morning.

Prograf® and Advagraf® are not interchangeable without careful therapeutic monitoring.
Substitution should be made only under close supervision of a transplant specialist.
Capsules should be taken on an empty stomach at least one hour before, or two hours, after a meal.

Hospital Specialist Responsibilities

- Agree shared care with the patient's GP, **specifying the brand of tacrolimus required.**
- Send a copy of this guideline to the GP.
- Provide patient/carer with relevant information on use, side effects and the need for monitoring of medication
- Baseline tests and ongoing safety monitoring:
  - FBC
  - LFT
  - U&E
  - Urinalysis
  - Lipids
  - Blood glucose
  - Blood pressure
  - Trough tacrolimus level
- Drug monitoring and any tacrolimus dose adjustments.
- Investigate, as appropriate, where symptoms suggest viral or fungal infections or possible tumours.
- Provide any other information or advice for the GP if required.

GP Responsibilities

- Prescribe tacrolimus as either Prograf® or Advagraf® as specified by the specialist.
- Monitor patient's overall health and wellbeing.
- The Liver Unit may occasionally request levels or tests to be repeated at the GP practice but will provide specific advice on this and the process to follow.
- Identify and report adverse drug reactions to the initiating specialist and the usual bodies (e.g. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia.) - see BNF or Green Book.
- Passive immunization using Varicella immunoglobulin (VZIG) should be considered in non-immune patients if exposed to chickenpox or shingles. Contact Regional Virus Laboratory, Royal Group of Hospitals, for advice if exposure is suspected.
- **Suspected non-compliance** with immunosuppression is serious and can lead to loss of the graft - refer to the specialist urgently.

Adverse Effects, Precautions and Contraindications

Nephrotoxicity If a significant sustained reduction in GFR occurs consider referral to specialist.
Acute Kidney Injury (AKI): Transplant patients are at increased risk of developing AKI. ACEI, ARBs, and NSAIDs should be withheld in situations of hypotension/hypovolaemia (GAIN,2014)
Infection: immunosuppressants can increase susceptibility to infection.
Hypertension is frequently encountered. If treatment is required follow guidelines but do not use diltiazem, nicardipine, verapamil, nifedipine or felodipine as they may increase plasma tacrolimus levels. Refer if hypertension remains uncontrolled.
Episodes of diarrhoea: blood levels of tacrolimus may significantly change during diarrhoea episodes; extra monitoring of tacrolimus levels is recommended**.**
Cardiomyopathy has been reported in children given tacrolimus after transplantation. The specialist will advise on any relevant management required.
Blood disorders; Leucopenia, anaemia, thrombocytopenia, pancytpopenia, pure red cell aplasia, neutropenia, and leucocytosis have been reported are most likely to be discovered at outpatient appointments. GPs should be alert to any oral ulceration / sore throat, unexplained rash or abnormal bruising or bleeding.
Headache, tremor, insomnia, blurred vision: Refer to specialist if persistent or severe.
Alopecia occurs in around 10% of patients - refer back to the specialist.
Hyperglycaemia. The development of post transplant diabetes mellitus is common; the risk of occurrence is most common with tacrolimus.
Hepatic dysfunction and **hyperlipidaemia** are screened for at outpatient appointments. Statin therapy is recommended for hyperlipidaemic patients.

Adverse Effects, Precautions and Contraindications (continued)

Cancer risk Patients receiving long-term immunosuppressive drugs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised. Adherence to population screening programmes is particularly important in this population.
Pregnancy / Contraception. Patients discovered or planning to become pregnant should be referred to the specialist at the earliest opportunity. Initially post-transplant, barrier contraception is the preferred method of contraception, but at a later stage the combined oral contraceptive is a suitable option for transplant recipients. Intra-uterine devices are not suitable for this group of patients.
Breastfeeding: Patients should not breastfeed whilst receiving tacrolimus.
Vaccines. Live vaccines should be avoided, except on the advice of initiating specialist.

Common Drug Interactions

The interactions listed below relate to tacrolimus. Consideration should be given to the other agents used as part of a regime.
Tacrolimus is metabolised by cytochrome P450 and interacts with many drugs that are metabolised by this group of liver enzymes.
The following drugs should not be initiated by GP unless discussed with specialist:
Antibiotics: erythromycin and clarithromycin increase tacrolimus levels; rifampicin decreases tacrolimus level.
Anti-epileptics: carbamazepine, phenobarbital and phenytoin decrease tacrolimus levels.
Antifungals: fluconazole; itraconazole, posaconazole and voriconazole increase tacrolimus levels.
Anti-obesity drugs: orlistat decreases tacrolimus levels.
Antiretrovirals: some may increase tacrolimus levels.
Calcium-channel blockers: diltiazem, nicardpine, felodipine, nifedipine and verapamil increase tacrolimus levels
Grapefruit and grapefruit juice: Patients should avoid as this can cause an increase in tacrolimus levels.

Potassium-sparing diuretics, Potassium salts, Aldosterone antagonists e.g. spironolactone and eplerenone may exacerbate tacrolimus-induced hyperkalaemia and should only be initiated with regular monitoring of U&Es.

Ranolazine: increases tacrolimus levels**.**
St John's Wort is known to decrease tacrolimus levels. Herbal medicines may have an effect on drug levels. Avoid concomitant use.

Communication

Renal Units

Altnagelvin Hospital: Renal Unit	028 7161 1162
Antrim Hospital: Renal Unit	028 9442 4894 or 028 9442 4472
Belfast City Hospital: Renal Unit	028 9504 0719
Daisy Hill Hospital: Renal Unit	028 3083 5036
Omagh hospital and primary care complex (OHPCC): Renal Unit	028 8283 3350
Royal Belfast Hospital for Sick Children: Dialysis Unit	028 9063 6621
Ulster Hospital: Renal Unit	028 9056 4839

Liver Unit

Royal Victoria Hospital	028 9063 3182

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC or the BNF

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