

Tacrolimus (non-transplant indications)

Ophthalmology shared care guideline

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	Date: _____

Introduction

MHRA/CHM advice

“Oral tacrolimus products: prescribe and dispense by brand name only, to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity” (June 2012).

To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only and should not be prescribed generically. Switching between tacrolimus brands requires careful supervision and therapeutic monitoring by an appropriate specialist.

Unlicensed indication: Inflammatory eye disease.

Adult dosage and administration

- The dose will be adjusted by the specialist according to individual requirements and trough tacrolimus levels.
- The patient will be commenced on a dose of 30 – 80 micrograms/kg per day in two divided doses. The dose is then titrated to achieve the desired response (the trough level required to prevent ocular inflammation without toxicity is considered to be between 5 and 10 nanograms/ml).

Maintenance doses vary between patients though typically a range of 1 – 4 mg twice daily is common in adults.

Capsules should be taken on an empty stomach at least one hour before, or two hours, after a meal.

Available as:

- **Twice daily immediate release preparations:** Adoport[®], Prograf[®], Capexion[®], Tacni[®], and Vivadex[®] are immediate-release capsules that are taken twice daily, once in the morning and once in the evening. Common strengths include 500 micrograms, 1 mg and 5 mg capsules.
- 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. Strengths include 200 microgram and 1 mg sachets.
- **Once daily modified release preparation:** Advagraf[®] and Envarsus[®] are prolonged-release products that are taken once daily in the morning. Advagraf[®] is available as 500 micrograms, 1 mg, 3 mg and 5 mg capsules. Envarsus[®] is available as 0.75 mg, 1 mg and 4 mg tablets.

Tacrolimus must be prescribed by brand name only and should not be prescribed generically.

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with tacrolimus.
- Agree shared care with the patient's GP. **Specify the brand of tacrolimus required.** Caution: a number of brands are available.
- Provide the patient/carer with relevant (preferably written) information on use, side effects and need for monitoring of medication.
- Provide shared care monitoring book if required.
- Undertake baseline tests as indicated in monitoring table.
- Review results of safety monitoring and request additional tests as required.
- Perform trough drug levels and adjust dose if required (ensure time of last dose is written on request form).
- Monitor disease response to treatment and need to continue therapy.
- Continue to review patient at specified intervals sending a written summary to the GP whenever the patient is reviewed.
- Provide any other information or advice for the GP if required.

Monitoring table		Hospital specialist	GP		Hospital specialist
Test	Indication	Pre-treatment baseline	During treatment		Annual review
			Until on stable dose for 6 weeks	Thereafter	
FBC	Baseline assessment, dose adjustment disease activity scoring	✓	Every 2 weeks	Every month *	As part of annual review or as clinically indicated
LFTs					
U&Es, eGFR					
Blood pressure					
Blood glucose					
Lipids	Detection of adverse reactions	✓	Every 6 months		
Height & weight	Baseline assessment	✓	Not routinely required		If clinically indicated
Urinalysis	To assess for renal disease (proteinuria) or infection				
Chest x-ray	Baseline respiratory assessment and TB screening				
PFTs, TB screening if indicated					
ECG					
Trough tacrolimus level	Dose adjustment	If clinically indicated	If requested by specialist		
Ask about oral ulceration/sore throat, unexplained rash or unusual bruising/bleeding		✓	At every consultation		✓

If a further DMARD is added as combination therapy, or the dose is increased, the initial starting schedule should be reinstated. There may be clinical circumstances where the frequency of monitoring may vary and this should be specified by the initiating specialist

* Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis

GP responsibilities

- Prescribe tacrolimus **as brand specified** by the specialist. Caution: a number of brands are available.
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Prevent ongoing prescription if patient is not compliant with monitoring.
- Any blood sampling for determination of a tacrolimus trough level (if requested) should be taken just prior to the next dose (approx. 12 hours after last dose of immediate release product or approx. 24 hours after last dose of modified release product). The time of sample and of last dose should be recorded on the request form.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by 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 eg. 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, duty virologist 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals.
- Ask about oral ulceration/sore throat; unexplained rash or unusual bruising at every consultation.

Withhold tacrolimus and contact specialist if:

- WCC < 3.5 x 10⁹/L
- Neutrophils < 1.6 x 10⁹/L
- Unexplained eosinophilia >0.5 x 10⁹/L
- Platelets < 140 x 10⁹/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 – 3 x ULN, continue tacrolimus, repeat bloods and seek specialist advice). Minor elevations of AST/ALT are common.
- If renal impairment develops
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough

Normal reference range may vary slightly between labs.

Results should be recorded in the patient's shared care monitoring record booklet (where in use)

Please note: An unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

Contraindicated in hypersensitivity to tacrolimus or other macrolides.

Nephrotoxicity. If a significant sustained reduction in eGFR occurs, consider referral to specialist.

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.

Blood disorders: leucopenia, anaemia, thrombocytopenia, pancytopenia, pure red cell aplasia, neutropenia, and leucocytosis have been reported. GPs should be alert to any oral ulceration, sore throat, unexplained rash or abnormal bruising or bleeding.

Electrolyte disturbances: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, hyperuricaemia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia and other electrolyte abnormalities have been reported.

Caution should be exercised in patients with risk factors for **QT prolongation**, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities.

Headache, tremor, insomnia: refer to specialist if persistent or severe.

Alopecia occurs in around 10% of patients - refer back to the specialist.

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: women of childbearing potential receiving tacrolimus should be advised to use effective contraception. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity without discontinuing tacrolimus.

Breastfeeding. Women being treated with tacrolimus should seek specialist advice.

Live vaccines: Consult the Green Book and take additional advice from initiating specialist if required.

Common drug interactions

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, voriconazole and miconazole oral gel increase tacrolimus levels.

Anti-obesity drugs: orlistat decreases tacrolimus levels.

Antiretrovirals: some may increase tacrolimus levels.

Calcium-channel blockers: diltiazem, nicardipine, felodipine, nifedipine and verapamil increase tacrolimus levels.

Ciclosporin: avoid concomitant use.

Dabigatran: tacrolimus possibly increases plasma concentration of dabigatran, avoid concomitant use.

Grapefruit and grapefruit juice: patients should avoid as this can cause an increase in tacrolimus levels.

NSAIDs (and other medicines with nephrotoxic effects): possible increased risk of nephrotoxicity.

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.

Primidone: plasma concentration of tacrolimus reduced by primidone.

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.

Trimethoprim: possible increased risk of nephrotoxicity when tacrolimus given with trimethoprim

Communication

For any queries relating to this patient's treatment with tacrolimus, please contact the specialist named at the top of this document.

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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