Health and Social Care

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

Interface Pharmacist Network
Specialist Medicines

Tacrolimus (non-transplant indications)

Paediatric and Adolescent 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" (Nov 2017).
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.

Note: liquid formulations are currently only available generically as unlicensed specials; with Tacrolimus 5mg/5ml (PCCA Ltd.) being the liquid formulation of choice in Northern Ireland.
Patients should be maintained on the same liquid product (the same formulation, strength and manufacturer) that they have been started on. Switching between tacrolimus brands (or specials manufacturers) requires careful supervision and therapeutic monitoring by an appropriate specialist.

Unlicensed indications include: nephrotic syndrome.

Paediatric dosage and administration

Nephrotic syndrome: Initially 150 micrograms/kg (to a maximum of 5mg) Twice Daily. The dose is then titrated to achieve the desired response (the trough level required is usually considered to be between 5 and 8 nanograms/ml. Maintenance dose is individualised depending on clinical situation.

The dose will be adjusted by the specialist according to individual requirements and trough tacrolimus levels.

Available as:
The Department of Health Northern Ireland has produced an Agreed List of the most common liquid medicines in Paediatrics in Northern Ireland in order to reduce the likelihood of errors across the interface and therefore enhance patient safety. https://niformulary.hscni.net/wpfd_file/hsc-agreed-list-of-paediatric-liquid-medicines/

Oral liquid formulations:
- Tacrolimus 5mg/5ml (PCCA Ltd.) This is the liquid formulation of choice.

Twice daily immediate release preparations (if these preparations are used, they should be prescribed by brand name only and should not be prescribed generically):
- 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. Capsules should be taken on an empty stomach at least one hour before, or two hours after a meal.
- 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.

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with tacrolimus.
- Agree shared care with the patient's GP. Specify the formulation and brand of tacrolimus required. If oral liquid formulation is required specify **Tacrolimus 5mg/5ml (PCCA Ltd.) is the oral liquid of choice. The manufacturer must be specified**
- Caution: a number of formulations and brands are available.
- Advise GP on dose of tacrolimus to be prescribed.
- Varicella Zoster immune status: if non-immune, consider immunisation prior to starting treatment.
- Provide the patient/carer with relevant (preferably written) information on use, side effects and need for monitoring of medication. Counsel thoroughly on the importance of receiving the same brand or liquid formulation by the same specials manufacturer
- 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.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered.
- Report any adverse drug reactions to the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.

<table>
<tr><th colspan="2">Monitoring table</th><th>Hospital specialist</th><th>GP</th><th>Hospital specialist</th></tr>
<tr><th>Test</th><th>Indication</th><td>Pre-treatment baseline</td><td>During treatment</td><td>At review</td></tr>
<tr><td>FBC
LFTs
U&Es, eGFR
Blood pressure
Blood glucose
Bone Profile
Magnesium</td><td>Baseline assessment, dose adjustment disease activity scoring</td><td>✓</td><td>Not routinely required; unless requested by specialist; or clinically indicated</td><td>Monitor until stable dose achieved; Thereafter as part of review or as clinically indicated</td></tr>
<tr><td>Height & weight</td><td>Baseline assessment</td><td rowspan="2">✓</td><td rowspan="3">Not routinely required</td><td rowspan="3">If clinically indicated</td></tr>
<tr><td>Urinalysis</td><td>To assess for renal disease (proteinuria) or infection</td></tr>
<tr><td>Chest x-ray
PFTs, TB screening if indicated</td><td>Baseline respiratory assessment and TB screening</td><td rowspan="2">If clinically indicated</td></tr>
<tr><td>ECG</td><td>Baseline cardiology assessment</td><td></td><td></td></tr>
<tr><td>Trough tacrolimus level</td><td>Dose adjustment</td><td></td><td>If requested by specialist</td><td>At least weekly until stable dose in target range and then at least 3 monthly thereafter</td></tr>
<tr><td colspan="2">Ask about oral ulceration/sore throat, unexplained rash or unusual bruising/bleeding</td><td>✓</td><td>At every consultation</td><td>✓</td></tr>
</table>

GP responsibilities

- Prescribe tacrolimus **as formulation and brand /liquid specials manufacturer specified** by the specialist. Caution: a number of brands are available. Refer to specialist if unsure of brand/liquid specials manufacturer.
- Arrange monitoring if requested by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests, if indicated.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- 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 the initiating specialist. Note the live formulation (eg. Fluenz Tetra®) must not be used.
- Check patient has received pneumococcal vaccine according to BNF or Green Book schedule.
- Provide COVID 19 vaccination as appropriate as per local arrangements and Green Book.
- Ask about oral ulceration/sore throat; unexplained rash or unusual bruising at every consultation.

Contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- **Unexplained** eosinophilia >0.5 x 10^9/L
- Platelets < 120 x 10^9/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 (not always appropriate to stop but may need dose adjustment)
- Unexplained fall in serum albumin
- Post-exposure prophylaxis consideration
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough

Normal reference range may vary slightly between labs.
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, pancytpopenia, 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:

Increased risk of nephrotoxicity: NSAIDs, antivirals (acyclovir, ganciclovir, valaciclovir, valganciclovir), aminoglycoside antibiotics (amikacin, gentamicin, tobramycin, vancomycin), bacitracin, capreomycin, carboplatin, cephalosporin antibiotics (eg cefaclor, cefalexin), ciclosporin, cidofovir, cisplatin, colistimethate, foscarnet, ifosfamide, inotersen, methotrexate, neomycin, oxaliplatin, pemetrexed, penicillamine, pentamidine, polymyxin b, streptomycin, streptozocin, tenofovir, trimethoprim, zidovudine, zoledronate.

Increased risk of hyperkalaemia: aliskiren, ACE inhibitors or angiotensin-II receptor antagonists, ciclosporin, heparin and LMWHs, darbepoetin, potassium-sparing diuretics (e.g. amiloride, triamterene), potassium salts, aldosterone antagonists (e.g. spironolactone, potassium canrenoate, eplerenone) epoetin, potassium aminobenzoate, tolvaptan. Hyperkalaemia is particularly notable when ACE inhibitors or angiotensin-II receptor antagonists are given with spironolactone or eplerenone.

Increased levels of tacrolimus: amiodarone, aprepitant, atazanavir, berotralstat, ceritinib, chloramphenicol, ciclosporin, macrolide antibiotics (e.g. clarithromycin, erthromycin), cobicistat, crizotinib, darunavir, calcium channel blockers (e.g. diltiazem, nicardipine, verapamil), dronedarone, antifungals (e.g. fluconazole, isavuconazole, itraconazole, ketoconazole, miconazole oral gel, posaconazole, voriconazole), fosamprenavir, grazoprevir, idelalisib, imatinib, ivacaftor, larotrectinib, letermovir, lomitapide, lopinavir, lorlatinib, netupitant, nilotinib, nirmatrelvir, palbociclib, pibrentasvir with glecaprevir, ranolazine, ribociclib, ritonavir, rucaparib, tigecycline, tipranavir, tucatinib.

Decreased levels of tacrolimus: apalutamide, bosentan, brigatinib, carbamazepine, doravirine, efavirenz, enzalutamide, fosphenytoin, lumacaftor, mitotane, nevirapine, phenobarbital, phenytoin, pitolisant, primidone, rifampicin, sirolimus, st john's wort.

Increased risk of immunosuppression: JAK inhibitors (baricitinib, filgotinib), dexrazoxane

Effect on other medicines (avoid): dabigatran, mifamurtide, tofacitinib.

Other:

- Tacrolimus potentially increases the risk of serotonin syndrome when given with venlafaxine.
- Sarilumab potentially affects the exposure to tacrolimus. Manufacturer advises monitor and adjust dose.
- Grapefruit and grapefruit juice: patients should avoid as this can cause an increase in tacrolimus levels. This may also apply with Seville orange, pomelo and pomegranate.
- Herbal medicines may have an effect on drug levels

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 at www.medicines.org.uk or the BNF

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