NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for use of Tacrolimus in adult solid organ transplant patients
Monitoring level Amber 1 - perform higher level of monitoring e.g. 6 monthly review

Generic and Proprietary/Brand Name
Tacrolimus – brand names Prograf®, Advagraf®, Adoport®, Capexion®, Modigraf®, Envarsus®,Tacni®, Vivadex®
Indications for shared care
Post adult solid organ transplant. Shared-care will only be considered appropriate at least three months post-transplant and only when the immunosuppression regimen is stable, co-morbid conditions are being treated and there is no longer a need for the patients to be seen as frequently in clinic.

Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document**
Prescribing • Review patient in clinic • Inform the patient of side effects and long term monitoring before initiating treatment. • Prescribe tacrolimus for at least three months until the immunosuppression regimen is stable, co-morbid conditions are being treated and there is no longer a need for the patients to be seen as frequently in clinic. • Inform the GP when tacrolimus is initiated. When the patient is near completing a satisfactory initiation period, the physician will write to the GP to request they take over prescribing. • Inform the patient/carers of the arrangements being made to share care with their GP, including information on who will be monitoring each aspect of therapy. • Inform the GP of the results taken at each clinic visit. Any action required will be taken by the physician and information on any changes to medication will be given in the accompanying letter. **Initial and ongoing monitoring** The following tests are taken at each appointment, depending on clinical need: • Urea & electrolytes (inc. calcium & phosphate) • Full blood count • Mid-stream urine (for Culture & Sensitivities) • Whole blood, trough tacrolimus level (once initiated) • Liver function tests • Blood pressure • Blood glucose • Lipid screening for total cholesterol	**Prescribing** • Prescribe tacrolimus once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital • If the GP has concerns over the prescribing of tacrolimus, they will contact the physician as soon as possible. • Identify adverse effects and treat or report to physician where appropriate. • Alert transplant unit to any identified non compliance with immunosuppressants • Avoid drug interactions • Avoid live vaccines **It is vital that doses are not changed without first consulting the physician.** **Monitoring** • Identify adverse effects and treat or report to physician where appropriate • If a patient presents with a likely infection an urgent FBC and urea & electrolytes should be taken (see section on indication for referral back to specialist) • Alert the specialist to any identified non compliance with immunosuppressants **Carry out tests as requested in writing by the specialist**

Patient Information

- Capsules should generally be administered on an empty stomach or at least 1 hour before, or 2 to 3 hours after a meal, to achieve maximal absorption.
- On clinic days the morning dose should be omitted until after the blood is sampled.
- Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
- Please refer to Patient Information Leaflets for Prograf®, Advagraf®, Adoport®, Modigraf®, Envarsus®, Tacni®, Vivadex® and Capexion®, available at **http://www.medicines.org.uk/emc/**

Specialist Contact Details

- Dr. Andrews, Consultant Nephrologist, NNUH via secretary on 01603 286659
- Dr. Karim, Consultant Nephrologist, NNUH via secretary on 01603 288930
- Langley Ward, NNUH on 01603 289974

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Before 2004 tacrolimus occasionally replaced ciclosporin in the drug regimen to augment high dose corticosteroid infusions in treating acute rejection episodes. It was also used *de novo* in regimens for recipients of non-heart beating donors.

Tacrolimus is *never* used in combination with ciclosporin.

Licensed use and agreed local off-label use

Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

Criteria for Patient Selection

For adult patients who have undergone a solid organ transplant.

Addenbrooke's Hospital (primary transplant centre) tailor their immunosuppression regimen to their estimate of the 'immunological risk' of the transplant. Tacrolimus is given to patients at intermediate and high immunological risk and those with delayed graft function (dose and duration according to Addenbrooke's protocols) unless contraindicated. Patient care is transferred to the NNUH three months post transplant. Within the NNUH, tacrolimus is used in accordance with Addenbrooke's protocols.

Patients may also be changed from ciclosporin to tacrolimus if they experience a rejection episode or develop side effects.

Latest NICE guidance https://www.nice.org.uk/guidance/ta481 states the circumstances under which tacrolimus may be used under recommendation 1.2 and further guidance under 3.8-3.13.

Form and strength of preparation

The formulations of Tacrolimus available include:

- Prograf® normal release formulation - 0.5mg, 1mg and 5mg hard capsules.
- Adoport® normal release formulation - 0.5mg, 1mg and 5mg hard capsules.
- Capexion® normal release formulation - 0.5mg, 1mg and 5mg hard capsules.
- Tacni® normal release formulation - 0.5mg, 1mg and 5mg hard capsules.
- Vivadex® normal release formulation - 0.5mg, 1mg and 5mg hard capsules.
- Advagraf modified release capsules - 0.5mg, 1mg and 5mg prolonged-release hard capsules (a minority of patients take the modified release capsules).
- Envarsus® modified-release tablets -750 micrograms, 1mg, 4 mg
- Modigraf® sugar-free granules – 0.2mg and 1mg

It is imperative that tacrolimus is prescribed by brand name, in order to avoid confusion, due to the associated risk of either toxicity or rejection should the patient receive the wrong formulation. Different brands of Tacrolimus are not interchangeable.

Side Effects and Management

Link to BNF

Link to SPC

Drug Interactions

Link to BNF

Link to SPC

Many drugs, including tacrolimus, are metabolised via the microsomal cytochrome P450 enzyme system in the liver. Some drugs have the effect of inhibiting P450 thereby increasing available tacrolimus in the blood to potentially toxic levels. Others induce the enzyme promoting the degradation of tacrolimus to sub therapeutic levels. Tacrolimus itself initially inhibits the P450 system but ultimately acts as P450 inducer. It may therefore alter the effects of other drugs which share the P450 metabolic pathway.

Drugs which may *increase* tacrolimus levels:

Ketoconazole	Fluconazole	Itraconazole, Posaconazole	Voriconazole
Diltiazem	Nifedipine	Nicardipine	Verapamil
Erythromycin	Clarithromycin	Clotrimazole	Protease inhibitors
Bromocriptine	Cimetidine	Danazol	Dapsone
Nefazodone	Omeprazole	Tamoxifen	Amiodarone
Chloramphenicol	Ceritinib	Ciclosporin	Dronedarone
Antivrals			
Grapefruit juice can increase tacrolimus levels and should therefore be avoided.			

Drugs which may *decrease* tacrolimus levels:

Carbamazepine	Phenytoin	Fosphenytoin
Primidone	Phenobarbital	St. John's Wort
Isoniazid	Rifampicin	Metamizole
Sirolimus		

Other interactions:

- Tacrolimus has been shown to increase the blood level of phenytoin
- Tacrolimus potentially increases the risk of serotonin syndrome when given with venlafaxine.
- Nephrotoxic drugs (e.g. cephalosporins, NSAIDS, aminoglycosides, trimethoprim, co-trimoxazole, colistimethate, zoledronic acid) can increase the nephrotoxicity if tacrolimus and should be used with extreme caution.
- Neurotoxic drugs (e.g. Aciclovir, ganciclovir, norfloxacin and ciprofloxacin) can increase the neurotoxicity of tacrolimus.
- Potassium-sparing agents (e.g. ACEIs, ARBs, aldosterone antagonists, darbo/epoetin, heparin/LMWH –especially with NSAIDs) may exacerbate tacrolimus-induced hyperkalaemia and should only be initiated with regular monitoring of U&E's.
- Tacrolimus is extensively bound to plasma proteins. Possible interactions with other drugs known to have high affinity to plasma proteins (e.g. NSAIDS, oral anticoagulants and oral anti-diabetics) should be considered.
- Vaccines may be less effective in immunocompromised patients. Live Vaccines should be avoided.

It is essential to inform the transplant unit if one of the interacting drugs is being newly prescribed, or stopped, so the tacrolimus blood levels can be monitored.

Cautions and Contraindications

Link to BNF

Link to SPC

- **Hypersensitivity** to tacrolimus (or to any of the excipients) and other macrolides.
- **Pregnancy** is contra-indicated by the manufacturers of Prograf®.
- Patients discovered or planning to become pregnant should be started on folic acid 400micrograms daily and referred to their physician at the earliest opportunity.
- The manufacturers of tacrolimus advise that the **combined oral contraceptive** (COC) should not be used with tacrolimus. This is due to a theoretical risk that the COC is less effective when taken concurrently with tacrolimus. There have been no reported problems of this in clinical practice and therefore thel physicians continue to recommend the COC as a viable method of birth control in patients on tacrolimus.
- Extra monitoring of tacrolimus concentrations is recommended during episodes of **diarrhoea**.
- The **combined administration of ciclosporin and tacrolimus should be avoided** and care should be taken when administering tacrolimus to patients who have previously received ciclosporin.
- **Breast feeding** should be avoided during therapy.
- Increased **susceptibility to infection** and the possible **development of lymphoma and other malignancies**, particularly of the skin, may result from immunosuppression.
- **Exposure to sunlight and UV light** should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Initiation of therapy and ongoing dose regimen

Initiation by Consultant at the Norfolk and Norwich University Hospital or Addenbrooke's Hospital.

Initial dose:
The initial dose of tacrolimus is titrated to achieve the desired trough blood level. The level required to prevent rejection without causing toxicity is considered to be between 5 and 15 nanograms/ml.

Physicians will generally try to obtain blood levels between 10-15 nanograms/ml in the early post-transplant period.

Doses required to achieve this level vary between patients, though typically a total daily dose range of 2mg to 8mg is common in adults;
i.e. 1mg to 4mg twice daily of normal release capsules;
2mg to 8mg once daily of prolonged-release capsules

Maintenance dose:
Dose adjustment during post-transplant period:
Tacrolimus doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments to give lower maintenance blood levels of approximately 5-10 nanograms/ml

Administration Information

- It is recommended that the oral daily dose in normal-release capsules be administered in two divided doses (e.g. morning and evening).

- Capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant. The capsules should be swallowed with fluid (preferably water).
- Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption.
- On clinic days the morning dose should be omitted until after the blood is sampled.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

Long term.

Baseline assessment and ongoing monitoring – by Specialist

Baseline monitoring:

- Urea & electrolytes (inc. calcium & phosphate)
- Liver function tests
- Mid-stream urine (for Culture & Sensitivities)
- Blood pressure
- Full blood count
- Blood glucose
- Lipid screening

Continued specialist monitoring:
The following tests are taken at each appointment, depending on clinical need:

- Urea & electrolytes (inc. calcium & phosphate)
- Full blood count
- Mid-stream urine (for Culture & Sensitivities)
- Whole blood, trough tacrolimus level
- Liver function tests
- Blood pressure
- Blood glucose
- Lipid screening for total cholesterol

Interim tests may be required between clinic visits. If this is the case the specialist will write to the GP stating which test is to be taken and at what time. The specialist will provide the patient directly with an ICE form to receive phlebotomy from their nearest service.

GP / Community Team or other Primary Care monitoring responsibilities

- Identify adverse effects and treat or report to physician where appropriate
- If a patient presents with a likely infection an urgent FBC and urea & electrolytes should be taken (see section on indication for referral back to specialist)
- Alert the specialist to any identified non compliance with immunosuppressants

Carry out tests as requested in writing by the specialist

Consultant / Specialist prescribing responsibilities

- Review patient in clinic
- Inform the patient of side effects and long term monitoring before initiating treatment.
- Prescribe tacrolimus for at least three months until the immunosuppression regimen is stable, co-morbid conditions are being treated and there is no longer a need for the patients to be seen as frequently in clinic.
- Inform the GP when tacrolimus is initiated. When the patient is near completing a satisfactory initiation period, the physician will write to the GP to request they take over prescribing.

- Inform the patient/carers of the arrangements being made to share care with their GP, including information on who will be monitoring each aspect of therapy.
- Inform the GP of the results taken at each clinic visit. Any action required will be taken by the physician and information on any changes to medication will be given in the accompanying letter.

GP prescribing responsibilities

- Prescribe tacrolimus once the patient has been stabilised on therapy and side effects have been excluded as far as possible by the hospital
- If the GP has concerns over the prescribing of tacrolimus, they will contact the physician as soon as possible.
- Identify adverse effects and treat or report to physician where appropriate.
- Alert transplant unit to any identified non compliance with immunosuppressants
- Avoid drug interactions
- Avoid live vaccines

It is vital that doses are not changed without first consulting the physician.

Indications for referral back to Specialist

- Neutropenia (white cell count <4 * 10^9/L, neutrophils <1.3 * 10^9/L
- Significant decline in renal function
- Hypertension BP>130/80mmHg
- Concerns by GP or patient

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Document history:

Version	Date	Author / Editor	Status	Comment
1.	Sept 2007	Dr Mahzuz Karim, Consultant in Nephrology, Hannah Waller, Specialist Clinical Pharmacist Renal	Superseded	Due for review Sept 2009

		Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist		
2.	Nov 2009	Dr Mahzuz Karim, Consultant in Nephrology, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Due for review Nov 2011
3.	Sept 2012	Dr Mahzuz Karim, Consultant in Nephrology, Claire O'Dwyer, Specialist Clinical Pharmacist Renal Medicine, NNUH / Fiona Marshall TAG Lead Pharmacist	Superseded	Adoport®, Capexion®, Tacni®, Vivadex® added to list of generic options. Patients must **not** be swapped between brands, once initiated. Approved by the TAG on 6th September 2012.
4.	Oct – Nov 2014	Dr Mahzuz Karim, Consultant in Nephrology, NNUH / Fiona Marshall TAG Lead Pharmacist, NEL CSU Anglia	Superseded	Updated into current TAG template format. Clinical content reviewed by the NNUH. Entry regarding timetable for repatriation of prescribing responsibility added to Additional information. **November 2014:** The TAG recommended adding under the specialist monitoring section "The specialist will provide the patient directly with an ICE form to receive phlebotomy from their nearest service".
5.	May 2016	As for 4.	Current	Continued need reviewed by the TAG – repatriation not complete and homecare services not yet established. Use to be extended by another year – revisit May 2017. Envarsus® and Modigraf® products added.
6.	Nov 2017	As for 4.	Current	Continued need reviewed by the TAG – repatriation not complete. Use to be extended by another 6 months – revisit May 2018. Link to current NICE guidance updated. Interactions section updated in line with BNF.
7.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended

				for a year from meeting due to covid pressures
8.0	Feb 2024	Jen Carroll, TAG Lead Technician	FINAL	Content not reviewed. Existing SCA transferred to new template ready for publication on KNoW. References to 'renal transplant' amended to 'solid organ transplant' For TAG approval