NHS LINCOLNSHIRE in association with
UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE:
Tacrolimus for Maintenance of Immunosuppression after Kidney Transplantation in Adults
This protocol cover the use of the brands Prograf®, Adoport® which are immediate release formulations administered twice daily

General Principles

Shared Care Responsibilities:
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 70, September 2015 - March 2016, pg.4)

Aims:
(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between the Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and , if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from members of the Arden and GEM commissioning Support Unit – Lincolnshire Prescribing & Medicines Optimisation Team.

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Principles of shared care

The General Medical Council published their Good Practice in Prescribing and Managing Medicines and which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

Good practice recommendation 35.

- Decisions about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

Good practice recommendation 36.

- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

Good practice recommendation 37.

- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

Good practice recommendation 38.

- If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required

Good practice recommendation 39.

- In both cases, you will be responsible for any prescription you sign.

Good practice recommendation 40.

- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required

Good practice recommendation 41

- If you share responsibility for a patient's care with a colleague, you must be competent to exercise your share of clinical responsibility.

You should:

a) Keep yourself informed about the medicines that are to be prescribed for the patient
b) Be able to recognise serious and frequently occurring adverse side effects
c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them
d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient's condition

Good practice recommendation 42

- In proposing a shared care arrangement, specialists may advise the patient's general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from authoritative guidance or recommended treatments and provide both the general practitioner and the patient with sufficient information to permit the safe management of the patient's condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient's care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Drug Details

Approved Name: Tacrolimus
Brand Name: Prograf®, Adoport®
Form and Strength: Capsules 500micrograms, 1mg and 5mg
There are now six different formulations of tacrolimus:
This shared care protocol only covers the use of two oral formulations Prograf and Adoport which are immediate release formulations for twice daily administration. The Leicester and Lincoln renal services use Prograf for those patients with older transplants and Adoport for patients with more recent transplants.
Only a transplant consultant can approve any changes in the brand/formulation that is to be prescribed.
All tacrolimus products must be prescribed by brand.
The Medicines Healthcare Regulatory Agency (MHRA and the Commission on Human Medicines (CHM). Have issued advice in June 2012 that all oral tacrolimus products 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.
Switching between products requires careful therapeutic monitoring. Substitution should only be made under the supervision of a transplant specialist.

Specialist Responsibilities

The specialist secondary/tertiary care service will:

All patients eligible for treatment under this protocol will have received their renal transplant at least six months ago and will now be transferred to the care of the Lincoln based renal services.

1. Send a letter to the GP notifying them of the changes to the ongoing care of the patient and asking them if they are willing to accept share care, and confirm that they will continue to provide regular prescriptions for tacrolimus.

Either enclosed a copy of the shared care protocol or the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef.

2. Ensure that the patient receives supplies of tacrolimus until the GP formally agrees to share care, except in those circumstances where the patient already receives these medications from the GP under a prior arrangement.
3. Measure biochemistry including tacrolimus levels, U&Es and Full Blood counts in line with local and national guidelines/protocols.
4. Titrate of the dose of tacrolimus as necessary to the optimum level according to blood results and local/national guidelines.
5. Advise the GP when the dose should be changed.
6. Provide patient with treatment information leaflet.
7. Communicate promptly any changes in monitoring and modification of tacrolimus dose to the GP.
8. Communicate promptly any changes in test results to the GP.
9. Periodically (at six-monthly intervals in clinic) review the patient's clinical condition.
10. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
11. Follow up any adverse drug reactions reported by the GP and report back to the GP.
12. Advise the GP on related issues such as drug interactions.
13. Respond to issues raised by the GP after the care of the patient has been transferred.

GP Responsibilities

The GP will:

1. Notify the consultant in writing, within two weeks, if they agree to share care.
2. Provide repeat prescriptions after achievement of a stable dose regime according to recommendations by the Nephrology department, Lincoln County Hospital.
3. Monitor the patients overall health and wellbeing.
4. Ensure advice is sought from the secondary care clinician if there is any significant change in the patient's physical health status.
5. Monitor the patient for adverse drug reactions and abnormalities and remain vigilant to the risk of potential drug interaction, and raise these issues with the secondary care clinician if necessary.
6. Carry out any investigations that are communicated and deemed appropriate.
7. Change the dose or stop treatment in line with instructions from the secondary care clinician.
8. Consult promptly with the specialist when test results are abnormal or when patient defaults from blood test appointments undertaken by primary care.

Referral Criteria

1. Patients will have been stabilized on their immunosuppressants, and other specialist medications.
2. Patients will have received their renal transplant at least six months ago and their ongoing supervision and care will have been transferred to the Lincoln based renal services.
3. The specialist will have carried out an assessment of efficacy.

Licensed Indications

Tacrolimus is licensed for the maintenance of immunosupression following kidney transplantation in adults.

Recommended Dosage and Administration

Tacrolimus (Adoport®)

Starting dose: 200-300micrograms/kg/day in two divided doses altered according to drug levels

Maintenance dose: Tacrolimus level aimed for is 5 to 8 nanograms/ml at 1 year post kidney transplant. The dose required to maintain that level shows a large inter-individual variation from 500micrograms twice daily to 9mg twice daily. The most common dose seen is 2mg twice daily. Drug levels will be measured and dose alterations will be carried out by secondary care

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As time progresses post transplant, the final Tacrolimus target levels may be decreased to 4 to 6 nanograms/ml at the discretion of the renal transplant specialist.

Background Pharmacology

Tacrolimus specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell transduction pathways.

Tacrolimus inhibits the formation of cytotoxic lymphocytes which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines.

Preparations Available

500micrograms, 1mg and 5mg capsules of tacrolimus (Prograf® (Adoport®).

Adverse Effects

There are a large number of adverse effects associated with tacrolimus. For full details please refer to current edition of the BNF or the product SPC.
Common or very common: acne, alopecia, anaemia, anorexia, anxiety, arthralgia, ascites, bile-duct abnormalities, bloating, blood disorders, cholestatis, confusion, constipation, depression, diarrhoea, dizziness, dyspepsia, dyspnoea, electrolyte disturbances, flatulence, gastrointestinal inflammation, ulceration and perforation, haemorrhage, headache, hepatic dysfunction, hyperglycaemia, hyperkalaemia, hypertension,hyperuricaemia, hypokalaemia, impaired hearing, ischaemic events, jaundice, leucopenia,mood-changes,muscle cramp, nausea, oedema, pancytopenia, paraesthia, parenchymal lung disorders, peripheral neuropathy, photophobia, leural effusion, psychosis, renal failure, renal impairment, renal tubular necrosis, seizures, sleep disturbances, sweating, tachycardia, thrombocytopenia, thromboembolic events, tinnitus, tremor, urinary abnormalities, visual disturbances, vomiting, weight change.
Uncommon: amnesia, arrhythmia, cardiac arrest, cardiomyopathy, cataract, cerebrovascular accident, coagulation disorders, coma, dermatitis, dysmenorrhoea, encephalopathy, gastro-intestinal reflux disease, heart failure, hypertonia, hypoglycaemia, influenza like symptoms, palpitation, pancreatitis, paralysis, paralytic ileus, peritonitis, photosensitivity, respiratory failure, speech disorder.
Rare: blindness, dehydration, hirsuitism, pericardial effusion, posterior reversible encephalopathy syndrome, respiratory distress syndrome, thrombotic thrombocytopenic purpura, toxic epidermal necrolysis.
Very rare: haemorrhagic cystitis, myasthenia, Stevens Johnson Syndrome.
Frequency not known : agranulocytosis, haemolytic anaemia, pure red cell aplasia.

Drug Interactions

Tacrolimus is implicated in a large number of drug interactions. For complete list please refer to BNF or the product SPC.
Those listed below are indicated by the BNF as being clinically significant.
a) Analgesics possibly increased risk of nephrotoxicity when tacrolimus given with Non Steroidal Anti-Inflammatory Drugs (NSAIDs).
b) Antibacterials plasma levels of tacrolimus increased by erythromycin, clarithromycin, chloramphenicol, telithromycin. Plasma levels decreased with rifabutin, rifampicin. Possible risk of nephrotoxicity if given with aminoglycosides and vancomycin.
c) Avoid concomitant use with dabigatran possibly increases plasma levels of dabigatran.
d) Avoid concomitant use with St Johns Wort – decreases levels of tacrolimus.
e)Antiepileptics - Phenobarbital, fosphenytoin , phenytoin and primidone reduce tacrolimus plasma levels also tacrolimus can increase fosphenytoin and phenytoin levels.
f) Antifungals – Increased tacrolimus levels with fluconazole, itraconazole, ketoconazole,posaconazole,voriconazole. And possibly increased by miconazole. Plasma levels of tacrolimus possibly reduced by caspofungin and possible risk of nephrotoxicity with amphotericin.
g) Antipsychotics avoid use of tacrolimus with droperidol due to risk of ventricular arrhythmias.

h) Antivirals risk of nephrotoxicity with acyclovir,ganiciclovir, valaciclovir or valganciclovir, also effects on tacrolimus levels dependent on which antiviral isused.//9 see BNF for details)
i) Calcium channel blockers -increased levels of tacrolimus with felodipine,nicardipine,verapamil,diltiazem and nifedipine.
j) tacrolimus increases plasma levels of ciclosporin with increased risk of nephrotoxicity recommend avoid concomitant use.
k) Diuretics increase risk of hyperkalaemia if tacrolimus given with potassium sparing diuretics and aldosterone antagonists.
l) Grapefruit juice – increases plasma levels of tacrolimus.
m) Potassium salts give increased risk of hyperkalaemia.
n) Live attenuated vaccines should not be used
o)cytotoxics possibly increases plasma concentration with afatinib – manufacturer advises separating administration of tacrolimus by 6-12 hours. Cqaution in use with crizotinib and increases plasma concentration with imatinib.
p) Ranolozine plasma levels of tacrolimus increased.

Precautions and Contraindications

Precautions

During maintenance phase extra monitoring of tacrolimus levels and kidney function are recommended during diarrhoea episodes.
Exposure to sunlight and UV light should be minimised by wearing protective clothing and using sun screen with a high protection factor because of the potential risk of malignant skin changes.
CSM issued warning on risk of cardiomyopathy in children. Patients should be monitored by echocardiography for hypertrophic changes and dose reduction or discontinuation should be considered if these occur.
May increase blood pressure therefore regular monitoring is recommended.
Increased risk of infections
Increased incidence lymphoproliferative disorders
Increased risk of malignancies
Increased risk of neurotocicity
May cause QT interval prolongation

Contraindications

Hypersensitivity to macrolides. Pregnancy (non-hormonal methods of contraception should be used) , breast feeding, avoid concurrent administration with ciclosporin.
Hypersensitivity to tacrolimus.or any of the excipients
As Prograf contains lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
The printing ink used to mark Prograf capsules 0.5 mg and 1 mg contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using Prograf
As Adoport contains lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
Pregnancy - exclude pregnancy before starting treatment. Avoid use unless potential benefit outweighs risk- risk of premature delivery, intra-uterine growth restriction and hyperkalaemia, toxicity – in animal studies.
Breast feeding – avoid as present in breast milk.

Monitoring

Tacrolimus Levels, Full blood counts, U and Es and Liver Function Tests every 6 months or more frequently. Monitoring remains the responsibility of the secondary care service although some testing may be devolved to the primary care setting.

Treatment should be reviewed and advice from the supervising specialist sought if:

-there is deterioration in the clinical condition and/or the patient experiences major side-effects.

-serum creatinine levels rise by >20% in 3 months.

Indication of Likely Cost of Therapy in Primary Care

January 2016

Tacrolimus (Prograf®) 500 micrograms:	£61.88 for 50 capsules
Tacrolimus (Prograf®) 1mg:	£80.28 for 50 capsules
Tacrolimus (Prograf®) 5mg:	£296.58 for 50 capsules
Tacrolimus (Adoport®) 500 micrograms:	£42.92 for 50 capsules
Tacrolimus (Adoport®) 1mg:	£55.69 for 50 capsules
Tacrolimus (Adoport®) 5mg:	£205.74 for 50 capsules

Information Given to the Patient

Patient information leaflet available with each container of tacrolimus (Prograf®, Adoport®)

Contact Details

Lincoln Renal Unit: 01522 573961

Caroline Taylor: 01522 573598
Renal Pharmacist
County Hospital

References

1. BNF 67 September 2015 - March 2016.
2. SPCs for Prograf® Astellas, eMC . Last updated 02.10.15.
3. SPC Adoport Sandoz limited.. last updated 7.09.11.
4. Drug Tariff January 2016

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