University Hospital of North Staffordshire NHS
NHS Trust

NHS
Stoke on Trent

North Staffordshire Combined Healthcare NHS
NHS Trust

NHS
North Staffordshire

Effective Shared Care Agreement for the prevention and treatment of **rejection following renal transplantation**

Prograf® (Tacrolimus capsules)

These forms (1 and 2) are to be completed by both the Consultant initiating the therapy and the GP who is continuing care. A copy of the completed form should be retained by the GP and a copy should be returned to the Consultant, for filing in the patient's notes.

Form 1: - Consultant Copy*

Patient Name: **NHS Number:**

Date of Birth: **Telephone Number:**

Address:

(Or attach Addressograph label)

Patients Signature: **Date:**

And / or on behalf of the patient

Carer's Name: **Telephone Number:**

Address:

Carer's Signature: **Date:**

And:

Consultant Name: **Directorate:**

Address:

Telephone Number: **Fax Number:** **Email:**

Signature: **Date:**

And:

GP Name:

Address:

Telephone Number: **Fax Number:** **Email:**

Signature: **Date:**

Approved by Area Prescribing Committee on: 02/12/2009 Version: v1
Review date: 02/12/2011

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Form 2: - GP Copy*

Patient Name: **NHS Number:**

Date of Birth: **Telephone Number:**

Address:

(Or attach Addressograph label)

Patients Signature: **Date:**

And / or on behalf of the patient

Carer's Name: **Telephone Number:**

Address:

Carer's Signature: **Date:**

And:

Consultant Name: **Directorate:**

Address:

Telephone Number: **Fax Number:** **Email:**

Signature: **Date:**

And:

GP Name:

Address:

Telephone Number: **Fax Number:** **Email:**

Signature: **Date:**

Effective Shared Care Agreement for the prevention and treatment of: -

rejection following renal transplantation

This shared care agreement outlines the ways in which the responsibilities for managing the prescribing of Prograf® for the prevention and treatment of rejection following renal transplantation will be shared between the specialist and general practitioner (GP). If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition will remain with the specialist. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practical.**

Sharing of care assumes communication between the specialist, GP and patient / carer. The intention to share care should be explained to the patient / carer by the doctor initiating treatment. It is important that patients / carers are consulted about treatment and are in agreement with it. Patients who have undergone a renal transplant are usually under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

Specialist responsibilities
Initiation
1 Perform initial baseline tests. These include FBC, LFT's, U&E's, creatinine clearance, lipids, BP, ECG, coagulation values and monitoring for diabetes.
2 Initiate treatment with Prograf®.
3 Discuss the benefits, side effects of treatment and warning signs that need to be reported with the patient.
4 Check for possible drug interactions with tacrolimus and avoid prescribing interacting drugs.
5 Assess likelihood of compliance.
6 Ask the GP whether he or she is willing to participate in shared care and explain the intention to share care with the patient/ carer.
7 Record results of baseline tests and monitor in accordance with local protocol.
8 Clearly state that the Prograf® brand of tacrolimus should be prescribed.
9 Prescribe medication until care is transferred to GP.
Follow-up assessments
9 Review immunosuppressant therapy including tacrolimus levels.
10 Titrate the dose if necessary to establish patient on a safe / effective dose.
11 Monitor patients Creatinine / eGFR at required intervals
12 Monitor patients LFT's, U&E's, blood pressure, blood glucose and lipids as required.
13 Check for side effects and report adverse events to the CSM and GP where appropriate
Support to GP
14 Provide copy of effective shared care agreement and supporting information.
15 Promptly communicate with GP, advising of blood test results if requested, any dosage adjustments required and when to refer the patient back to specialist care.
16 Advise when and how to adjust the dose/ stop treatment or consult the specialist.
17 Inform GP if patient does not attend specialist appointments.
18 Have a mechanism in place to receive rapid referral of a patient from the GP in event of deteriorating clinical condition.
19 Ensure clear backup arrangements exist for GPs to obtain advice and support
20 Advise the GP when the patient should receive the pneumococcal vaccine.

General Practitioner responsibilities
1 Reply to the request for shared care as soon as practical.
2 Ensure prescribe by brand; prescribe Prograf® as directed by the specialist.
3 Contact the specialist if you suspect the patient is not complying with their medication.
4 Adjust the dose as advised by the specialist.
5 Check for possible drug interactions when prescribing new medication and avoid prescribing interacting drugs.
6 Ensure the patient understands which warning symptoms to report.
7 Treat hypertension as advised by the specialist.
8 Recommend that female patients attend for a cervical smear annually.
9 Recommend the patient receives an influenza vaccine yearly and pneumococcal vaccine as required.
10 Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
11 Refer the patient to the specialist if his/ her condition deteriorates.
12 Report any suspected adverse events to specialist team and any severe adverse events to CSM.
13 Stop treatment on advice of specialist.

Patient's role	
1	Consent to treatment with Prograf®.
2	Take medication according to doctors' instructions.
3	Attend follow up and other appointments.
4	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
5	Know which brand of tacrolimus they are taking and question any differences in the supply received.
6	Share any concerns in relation to treatment or their condition.
7	Inform specialist if you feel you are having problems taking your medication or have stopped taking it.
8	Inform specialist or GP of any other medication being taken, including over-the-counter products.
9	Do not take any herbal remedies without checking with the specialist
10	Alert physician prior to any vaccine administration that you are taking tacrolimus.
11	Female patients should ensure that their GP offers them a cervical smear annually.
12	Ensure that you receive the influenza vaccine annually from your GP.
13	Take adequate precautions to avoid exposure to ultraviolet light i.e. wear sunscreen / protective clothing.
14	Report signs of hyperglycaemia (increased thirst, frequent urination, tiredness, increased susceptibility to infections such as thrush) to the specialist or GP.
15	Report any adverse effects or warning symptoms to the specialist or GP.

SUPPORTING INFORMATION FOR PROGRAF® (TACROLIMUS) EFFECTIVE SHARED CARE AGREEMENT

This information should be read in conjunction with the Summary of Product Characteristics for Prograf® (Tacrolimus) available from www.medicines.org.uk

Licensed indications

Prograf® (Tacrolimus) is licensed for use in renal transplantation for prevention and treatment of allograft rejection.

Dosage and Administration

Prograf® dosing should be based primarily on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. Oral Prograf® should commence at 0.20 -0.30 mg/kg/day administered as two divided doses (morning and evening). Administration should commence within 24 hours after the completion of surgery. Capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water) on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption.

There is a prolonged release formulation of tacrolimus (Advagraf®) available. Inadvertent, unintentional or unsupervised switching of immediate- or prolonged-release formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under or over immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. **Therefore prescribing should be by brand and should not differ to that recommended by the specialist.**

Contraindications

Patients with a known hypersensitivity to tacrolimus or other macrolides or any excipients.

Tacrolimus should not be given to breast-feeding mothers. In addition it should be reserved during pregnancy for individuals where no more suitable alternative treatment is available. Patients attempting to conceive should discuss this with their specialist.

Therapeutic Use

- Refer to NICE technology appraisal guidance 85 (September 2004) – Immunosuppressive therapy for renal transplantation in adults, available from **www.nice.org.uk**
- Midland Therapeutic Review Advisory Committee (MTRAC). Verdict & Summary: - Tacrolimus (Prograf®), Jan 1997.

Monitoring

Several immunoassays are available for determining tacrolimus concentrations in whole blood. In current clinical practice, whole blood levels are monitored using immunoassay methods. Blood trough levels should be taken approximately 12 hours post dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose

adjustment, changes in regimen or following concomitant administration of substances which may alter tacrolimus whole blood concentrations. Prograf® has a low clearance; adjustments to the dosage regimen may take several days before changes in blood levels are apparent. It is necessary to consider the clinical condition of the patient when interpreting whole blood tacrolimus levels.

At UHNS whole blood trough levels of tacrolimus will be checked by the hospital. For the first three months post-transplant, a level of 10-15 nanograms /ml is aimed for, and this is reduced to 5-8 nanograms /ml for the maintenance phase. Levels may be individualised for patients.

Monitoring of renal function is essential; deterioration may necessitate a reduction in dosage. Monitoring of liver function and serum potassium is advised. Lipids and blood pressure should also be monitored as required, with appropriate treatment of hypertension commenced if necessary. Please refer if control is problematic. The patient should also be advised to report the signs of hyperglycaemia.

Side Effects

Very common (≥1/10): tremor, headache, diarrhoea, nausea, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, hypertension, insomnia.

Common (≥1/100, <1/10): ischaemic coronary artery disorders, tachycardia, anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal, seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, impaired writing, nervous system disorders, blurred vision, photophobia, eye disorders, tinnitus, dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations, gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms, renal failure, acute renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms, pruritus, rash, alopecias, acne, increased sweating, arthralgia, muscle cramps, pain in limb, back pain, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, decreased appetite, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities, primary graft dysfunction, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders, asthenic conditions, febrile disorders, oedema, pain and discomfort, increased blood alkaline phosphatase, increased weight, disturbed body temperature perception, hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis, anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders.

Uncommon (≥1/1000, <1/100): ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations, coagulopathies, abnormal coagulation and bleeding analyses, pancytopenia, neutropenia, coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia, cataract, hypoacusis, respiratory failures, respiratory tract disorders, asthma, paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastrooesophageal reflux disease, impaired gastric emptying, anuria, haemolytic uraemic syndrome, dermatitis, photosensitivity, joint disorders, dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia, infarction, deep limb venous thrombosis, shock, multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, increased blood lactate dehydrogenase, decreased weight, dysmenorrhoea and uterine bleeding, psychotic disorder.

Rare (≥1/10,000, <1/1000): pericardial effusion, thrombotic thrombocytopenic purpura, hypoprothrombinaemia, hypertonia, blindness, deafness neurosensory, acute respiratory distress syndrome, subileus, pancreatic pseudocyst, toxic epidermal necrolysis (Lyell's syndrome), hirsutism, thirst, fall, chest tightness, decreased mobility, ulcer, hepatic artery thrombosis, venoocclusive liver disease.

Very rare (<1/10,000): abnormal echocardiogram, myasthenia, impaired hearing, nephropathy, cystitis haemorrhagic, Stevens Johnson syndrome, increased fat tissue, hepatic failure, bile duct stenosis.

Patients receiving tacrolimus, as with other potent immunosuppressive agents, are frequently at increased risk for infections (viral, bacterial, fungal, protozoal).

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Patients should be advised to avoid excess ultraviolet light exposure or limit it by wearing protective clothing and using a sunscreen with a high protection factor and the use of live attenuated vaccines should be avoided.

Drug Interactions

Drugs may either increase or decrease plasma or whole blood tacrolimus levels usually by inhibition or induction of enzymes involved in tacrolimus metabolism, particularly CYP3A4.

Drugs that decrease tacrolimus levels:
Carbamazepine, phenytoin, rifampicin, St John's Wort, sevelamer, phenobarbital, maintenance doses of corticosteroids, prednisolone/ methylprednisolone (high dose), metamizole, isoniazid, caspofungin, sirolimus.

Drugs that increase tacrolimus levels:
Macrolides, ketoconazole, fluconazole, itraconazole, voriconazole, diltiazem, nicardipine, verapamil, metoclopramide, ethinylestradiol, danazol, prednisolone/ methylprednisolone (high dose), protease inhibitors, imatinib, chloramphenicol, telithromycin, quinupristin/ dalfopristin, posaconazole, miconazole, clotrimazole, nifedipine, omeprazole, lansoprazole, pantoprazole and nefazodone, bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, felodipine, metronidazole.

Grapefruit juice has been reported to increase tacrolimus levels and should therefore be avoided.

Care should be taken with other drugs that exhibit nephrotoxic synergy:
Aminoglycosides, amphotericin B, vancomycin, trimethoprim (+ sulfamethoxazole), NSAIDs, gyrase inhibitors, aciclovir, ganciclovir, ciclosporin.

Care is required for concomitant use of potassium sparing diuretics, potassium supplements, ARBs as tacrolimus treatment may be associated with hyperkalaemia or may increase pre-existing hyperkalaemia.

Care should be taken with aciclovir and ganciclovir as they may cause neurotoxicity when used with tacrolimus.

Tacrolimus may increase plasma concentration of phenytoin, ciclosporin, pentobarbital, phenazone and mycophenolic acid.

Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have a high affinity for plasma proteins should be considered (e.g. NSAIDs, oral anticoagulants or oral antidiabetics).

Tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure; care should be exercised when deciding upon contraceptive measures.

Combined use with ciclosporin is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin.

Primary Care Costs (emims July 2009)

Prograf® capsules
0.5mg £63.13 / 50 capsules
1mg £81.90 / 50 capsules £163.78 / 100 capsules
5mg £302.56 / 50 capsules

References

Joint Formulary Committee. British National Formulary. 57th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2009

Summary of Product Characteristics – Prograf® 0.5mg, 1mg, 5mg Hard Capsules. Astellas. Last revised 26th May 2009. Accessed via www.medicines.org.uk

Baxter, K. Stockley's Drug Interactions. Pharmaceutical Press 2009. Accessed via www.medicinescomplete.com

BACK-UP ADVICE AND SUPPORT

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