PREVENTION OF REJECTION IN ADULT PATIENTS WITH RENAL TRANSPLANTATION

SIROLIMUS

This shared care guideline sets out details for the sharing of care of patients prescribed **SIROLIMUS** for prevention of **REJECTION OF RENAL TRANSPLANTATION IN ADULT PATIENTS**. These guidelines provide additional limited information necessary to aid in the treatment of patients with **SIROLIMUS**. As with all shared care guidelines they highlight significant prescribing issues but should be used in conjunction with the ABPI summary of product characteristics (SPC/Data sheet) and ***do not*** replace them.

INTRODUCTION/BACKGROUND INFORMATION

Immunosuppression is essential in preventing the rejection of allograft organs in hepatic and renal transplantation. However the greatest risks to life after renal transplantation are the adverse effects of long-term immunosuppression.

Sirolimus inhibits both B and T cell activation leading to suppression of immune and rejection responses.

The pharmacological action appears to differ to that of tacrolimus and ciclosporin.

INDICATIONS FOR THE PURPOSES OF THIS GUIDELINE

- Immunosuppression in cases of ciclosporin or tacrolimus nephrotoxicity
- Primary immunosuppression in kidney allograft recipients with low to medium immunological risk.

DOSAGE AND ADMINISTRATION

Doses may be administered as an oral liquid or tablet. Sirolimus should be taken at the same time each day in relation to food.

After 2-3 months of standard immunosuppression therapy sirolimus may be added. Initial dosing should commence orally at a daily dose of 6mg loading dose followed by 2mg once daily dose. Over the following 2-3 months the dose is then individualised by aiming to obtain a sirolimus drug trough level of 4-12 ng/mL. During this time concurrent ciclosporin doses should be tapered to obtain a trough drug level of 150-400 ng/mL

In the maintenance phase, ciclosporin is progressively discontinued over 4-8 weeks and sirolimus dose increased to give a drug trough level of 12-20 ng/mL. Concurrent dosing with corticosteroids is required at this stage.

Sirolimus is often swapped directly instead of ciclosporin or tacrolimus in cases where there is evidence of nephrotoxicity i.e., no tapering of the ciclosporin dose.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or excipients
- Pregnancy (exclude before starting—if contraception needed non-hormonal methods should be used).
- Breastfeeding.

PRECAUTIONS

- Monitor renal function if given in combination with ciclosporin.
- Dose increases may be required in patients from African-American background.
- Hepatic impairment – close monitoring of drug trough levels recommended.

Interactions (see below)

Very common > [1 in 10] > Common > [1 in 100] > Uncommon > [1 in 1000] > Rare > [1 in 10000] > Very rare

SIDE EFFECTS

Very common:

Lymphocele, peripheral oedema, abdominal pain, diarrhoea, anaemia; thrombocytopenia, anaemia, hypercholesterolemia, hypertriglyceridemia, hypokalaemia; increased lactate dehydrogenase, arthralgia, acne, urinary tract infection, peripheral oedema.

Common:

Sepsis, abnormal healing; fever; oedema; fungal, viral, and bacterial infections, tachycardia, venous thromboembolism, stomatitis, leucopenia; neutropenia; thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, abnormal liver function tests, bone necrosis, epistaxis; pneumonia; pneumonitis, skin cancer, rash, pyelonephritis; proteinuria.

Uncommon:

Pancreatitis, lymphoma/post transplant lymphoproliferative disorder; pancytopenia, pulmonary haemorrhage, pericardial effusion, pulmonary embolism, nephritic syndrome

Rare:

Lymphoedema, hypersensitivity reactions, including anaphylactic/ anaphylactoid reactions, angioedema, and hypersensitivity vasculitis.

Increased risk of malignancies including lymphoma, skin and other tumours appear to be linked to degree and duration of immunosuppression. The incidence is similar to that of other immunosuppressive agents or therapies.

MONITORING

Secondary care

Monitoring of sirolimus therapy is the responsibility of secondary care. Those parameters, which will normally be monitored include:

- Blood levels of sirolimus.
- Electrolytes, creatinine & urea.
- Full blood count and coagulation values.
- Liver function tests.

Primary care

The monitoring of cholesterol level may be shared with the GP by agreement. Monitoring of cholesterol is recommended every 6 months.

REFER TO THE SPECIALIST TEAM IF:

Side effect	Action
Hypercholesterolaemia	Discuss with specialist
Cardiomyopathy	Refer to specialist
Neurological symptoms	Refer to specialist
Signs of blood dyscrasia	Refer to specialist

COMMON/SIGNIFICANT DRUG INTERACTIONS

Increased levels of sirolimus

- Inhibitors of CYP3A4 (such as diltiazem, verapamil, ketoconazole, miconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) decrease the metabolism of sirolimus and increase sirolimus levels.
- Weak inhibitors of CYP3A4 (e.g. nicardipine; clotrimazole, fluconazole; troleandomycin; bromocriptine, cimetidine, danazol, atazanavir, lopinavir).
- Sirolimus plasma concentration increased by ciclosporin.

Decreased levels of sirolimus

- Inducers of CYP3A4 (such as rifampin or rifabutin) increase the metabolism of sirolimus and decrease the sirolimus levels.
- Weak inducers of CYP3A4: (e.g. St. John's Wort, (*Hypericum perforatum*); carbamazepine, phenobarbital, phenytoin).
- Grapefruit juice affects CYP3A4 mediated metabolism and should therefore be avoided.
- Pharmacokinetic interactions may be observed with gastrointestinal prokinetic agents such as cisapride and metoclopramide.

Other drug interactions

- Live vaccinations (oral polio, measles, mumps, rubella, BCG, oral typhoid, yellow fever) should not be administered whilst taking ciclosporin. Attenuated vaccines may be less effective.

NOTES

- Tablets should be protected from light.
- Oral solution should be kept in the fridge 2-8C but if necessary may be kept at room temperature for up to 24 hours.
- Oral solution should be mixed with at least 60 ml water or orange juice in a glass or plastic container immediately before taking; refill container with at least 120 ml and drink immediately (to ensure total dose). Do not mix with any other liquids.
- Patients require counselling on the potential risk of skin malignancy from exposure to UV light, including: not using sunbeds and covering exposed skin with clothes or sunscreen with SPF of at least 25.

PRODUCT INFORMATION

SIrolimus (Rapamune®)

Tablets 1 mg, 30-tab pack = £90.00; 2 mg, 30-tab pack = £180.00

Oral solution 1 mg/mL, net price 60 mL = £169.00.

REFERENCES

- Summary of Product Characteristics: accessed via www.emc.medicines.org.uk January 2008
- BNF 55 March 2008
- NICE guidance 85 - Immunosuppressive therapy for renal transplantation in adults September 2004 - http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11544

AUTHORS

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AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

These are suggested ways in which the responsibilities for the management of patients that are prescribed **SIROLIMUS** for the **PREVENTION OF RENAL TRANSPLANT REJECTION** can be shared between the specialist and the general practitioners. GPs are **invited** to participate. If the GP is not confident to undertake these roles, then 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 practical.**
Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them.
The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Specialist responsibilities:

- ❑ Prescribing the drug is retained for 3 months or until the patient's condition/dose is stabilised and the GP agrees to take over responsibility for prescribing.
- ❑ Provide the patient or patient's parents/guardians/carers with suitable written and verbal information about the drug prior to starting medication and discuss the benefits and side effects of treatment.
- ❑ Monitoring of blood level of **sirolimus** and other monitoring described in the Shared Care Guideline will normally be the responsibility of secondary care and will normally include creatinine levels.
- ❑ Prompt communication of test results and any treatment changes in therapy at least 3 monthly and whenever a significant change in monitoring parameters occurs or ANY change in drug therapy.
- ❑ Ensure monitoring of cholesterol every 6 months or as agreed with the GP.
- ❑ As appropriate, liaison with other members of the multidisciplinary team e.g. renal pharmacist, transplant nurse.
- ❑ Ask the GP whether they are willing to participate in shared care.
- ❑ Specify review dates at clinically relevant time intervals for both the GP and the consultant.
- ❑ Provide the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required relating to this drug.
- ❑ Reporting adverse events to the CSM.

General Practitioner responsibilities:

- ❑ Reply to request for shared care as soon as practical.
- ❑ Prescribing of **sirolimus** after communication with the specialist regarding the need for treatment.
- ❑ Undertake monitoring of cholesterol 6 monthly as agreed with the specialist and outlined in the shared care guideline (unless carried out in the renal clinic).
- ❑ Prompt referral to a specialist if there is a change in the patient's status.
- ❑ Reporting to and seeking advice from a specialist on any aspect of patient care which is of concern to the GP and may affect treatment.
- ❑ Reporting adverse events to specialist and CSM.
- ❑ Immediate referral in the case of a severe adverse event or as per shared care guideline.

Patient responsibilities:

- ❑ Take **sirolimus** as prescribed
- ❑ Report any adverse effects to their GP and/or specialist regarding their treatment.
- ❑ Ensure that they have a clear understanding of their treatment
- ❑ Ensure they attend for monitoring requirements as per shared care guideline.
- ❑ Aware of the necessity of attendance for monitoring.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No:	E-mail address
Dr R D'Souza	(01392) 402587	Richard.DSouza@rdeft.nhs.uk
Dr C Bingham	(01392) 406366	Coralie.Bingham@rdeft.nhs.uk
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Shared Care Agreement Letter - Consultant Request

To: Dr.....

Practice Address: .....

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Patient Name:
Hospital number:
Date of birth:
Address:

DIAGNOSED CONDITION: **.....**

I recommend treatment with the following drug: **.....**

I am requesting your agreement to sharing the care of this patient according to the Devon Primary Care Trust North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Signed:	
Consultant name:	
Department:	
Contact telephone number:	
Date:	

GP RESPONSE

I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: ..... Date: .....

GP name: ..... *Delete as appropriate