Conversion from Calcineurin Inhibitors to Sirolimus in Renal Transplantation UHL Renal Guideline.

Trust Ref: C37/2010

1. Introduction

Chronic allograft nephropathy (CAN) is the major cause of renal allograft failure and loss. Prolonged use of calcineurin inhibitors (CNI) has been implicated in the pathogenesis of CAN and trial data suggests that CNI dose reduction or withdrawal can slow the rate of renal function decline in patients with CAN.

In order to maintain adequate immunosuppression, CNI withdrawal must be accompanied by introduction of alternative immunosuppressive agents. The options are either sirolimus or mycophenolic acid (MPA). Study data supports the use of both of these agents but there are no data that directly compares of MPA- and sirolimus-based treatment regimens following CNI withdrawal in patients with CAN. It is therefore not possible at this time to recommend one approach over the other. Treatment decisions in this situation should be made on an individual patient basis and must be discussed with the supervising consultant.

Data indicates that conversion to sirolimus in patients with significant renal impairment (i.e. serum creatinine > 220µmol/L; eGFR <40mls/min) or significant proteinuria (> 800mg/day; PCR > 80mg/mmol) is unlikely to prevent ongoing allograft failure. Therefore,conversion should be undertaken before significant renal impairment develops. Sirolimus conversion has been associated with significant increases in proteinuria. Therefore patients with heavy proteinuria (>1g/day) should probably not be considered suitable for conversion to sirolimus.

2. Scope

This guideline is aimed at medical, nursing and pharmacy staff responsible for the care of patients with renal transplants.

3. Recommendations, Standards and Procedural Statements

3.1 If patient proteinuric, start ACEi/ARB prior to conversion and titrate dose to maximum tolerated.

3.2 Conversion procedure

Day 0

Reduce CNI dose by 50%; Start sirolimus 2 to 3 mg/day

(**NB** If overlap with ciclosporin, sirolimus should be taken 4 hours after ciclosporin; if overlap with tacrolimus, sirolimus can be taken at the same time)

If patient also taking MPA, reduce dose to maximum of 1.5g/day of mycophenolate mofetil or 1.08g/day of mycophenolate sodium.

Maintain same prednisolone dose.

Measure trough sirolimus level at day 7.

Day 7 to 10

When target trough sirolimus level achieved (8 to 12 ng/ml), CNI is discontinued.

Prolonged treatment overlap periods (ie > 2 weeks) should be avoided.

3.3 Monitoring

Baseline biochemistry ,haematology profile and urine PCR.

Weekly biochemistry and haematology during conversion period

Weekly trough sirolimus levels until stable.

Blood lipids at least every 3 months for the first 6 months, then at least every 6 months

Urine protein/creatinine ratio at least every 3 months for the first 6 months, then at least every 6 months

Any significant decrease in eGFR during the conversion period needs to be discussed with the supervising consultant and investigated.

3.4 Adverse reactions

Anaemia. Minimise dose of other myelosuppressive drugs (eg MPA). Otherwise maintain sirolimus levels within target range, correct haematinic deficiencies, and administer erythropoeitin if Hb falls below 10g/dl.

Hyperlipidaemia. Dose dependent effect of sirolimus. Monitor as above and manage according to lipid protocol.

Pneumonitis. An interstitial pneumonitis (lymphocytic alveolitis) can develop. This generally resolves with withdrawal of sirolimus. Patients should be told to seek immediate advice from the transplant service if any respiratory symptoms (particularly dry cough and breathlessness) develop.

Patients on sirolimus who develop pneumonia are at increased risk of pnuemonitis

Proteinuria. As stated previously, some patients become increasingly proteinuric following conversion to sirolimus and some develop new onset proteinuria (in over 50% of patients in some studies) that may reach nephrotic levels. The long-term consequences of proteinuria in this setting are not clear but it is probably harmful. ACE inhibitors, ARBs and their combination should be used to manage this. If this approach results in control of proteinuria (to < 1g/day; PCR <100), sirolimus can be continued. If however, proteinuria either persists or increases, sirolimus should be discontinued. Discuss with consultant.

Wound healing

To avoid problems with wound healing - sirolimus should be reduced or discontinued prior to elective surgery and stopped in the event of emergency surgery. Patients should not receive sirolimus for 3 weeks following surgery. It may be appropriate to convert the patient to tacrolimus or ciclosporin and this should be discussed with a Consultant.

In low risk patients, sirolimus can be stopped and CNI introduced the same day. CNI and sirolimus level should be checked on day 3/4 (to allow the drug to reach steady state). Doses are adjusted to reach the target for the individual patient in consultation with the patients Consultant. In higher risk cases overlapping is recommended. Similarly, 3 weeks following surgery patients may be converted back to sirolimus – an overlap of CNI and sirolimus is generally recommended

4. Education and Training

All new staff working in this area will be directed to list of guidelines related to renal transplantation.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead

Renal transplant outcomes	NHS BT data	annually	Transplant nephrologists

6. Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidance documents

7. Supporting Documents and Key References

1. Diekmann F, Campistol JM. Conversion from calcineurin inhibitors to sirolimus in chronic allograft nephropathy: benefits and risks. Nephrol Dial Transplant. 2006 Mar;21(3):562-8

2. Kuypers DR. Benefit-risk assessment of sirolimus in renal transplantation. Drug Saf. 2005;28(2):153-81.

8. Key Words

Renal transplant, immunosuppression, sirolimus, mycophenolate, chronic allograft nephroapthy

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REVIEW RECORD

DATE	ISSUE NUMBER	REVIEWED BY	DESCRIPTION OF CHANGES (IF ANY)
12.12.12	1	Carr, Topham	No changes
31.10.16	2	Carr, Topham,Malik	Updated to new template
28.10.19	3	Topham	No changes
28.04.23	4	MMartinez JJesús-Silva	Changes in sirolimus start dosing and monitoring requirements