Immunosuppression Therapy Following Kidney Transplant UHL Renal Transplant Guideline

University Hospitals of Leicester NHS
NHS Trust

Trust Reference
C232/2016

RRCV CMG
Nephrology Service

1. Introduction

The standard renal transplant immunosuppression protocol at UHL comprises triple drug therapy involving; a calcineurin inhibitor (CNI) (Tacrolimus, Adoport®), an antiproliferative agent (Mycophenolate Sodium) and corticosteroids (Prednisolone).

2. Scope

This guideline is to help medical, nursing pharmacy staff managing medicines for patients undergoing renal transplantation.

3. Recommendations, Standards and Procedural Statements

3.1 Standard maintenance therapy

The table below summarises the dosing schedule for each individual immunosuppression agent:

<table>
<tr><th>Mycophenolate sodium</th><th>Tacrolimus* (Adoport®)</th><th>Prednisolone
(plain 5 mg tablets)</th></tr>
<tr><td rowspan="2">360 mg twice daily

*Sometimes dose reductions are necessary if mycophenolate is poorly tolerated (e.g. gastrointestinal side effects persist despite dose adjustments) or in case of bone marrow toxicity.</td><td>Starting dose: 0.1 mg/Kg/day in 2 divided doses (= 0.05 mg/Kg bd)

Subsequent doses to be adjusted depending on tacrolimus trough levels:

MONTH — TACROLIMUS TARGET LEVEL
0 – 6 — 8 ng/mL
6 - 12 — 4-6 ng/mL</td><td>Steroid dose reduction schedule

WEEK — DOSE
1 and 2 — 20 mg once daily
3 and 4 — 15 mg once daily
5 and 6 — 10 mg once daily
7 to 12 — 5 mg once daily</td></tr>
<tr><td colspan="2">*long acting preperations/other twice daily preparations: aim for same level</td></tr>
</table>

Most renal transplant patients will follow the above regimen. Immunosuppression therapy should be tailored to the individual depending on clinical need and tolerance. Patients at higher immunological risk may require higher target immunosuppression levels and changes from the standard regimen will be decided by a consultant transplant surgeon/nephrologist/transplant pharmacist.

3.2 Corticosteroid Dosing

Current evidence shows that acute rejection is more frequent in steroid-sparing strategies, but with no effect on mortality or graft loss. Steroid-sparing and withdrawal strategies showed benefits in reducing antihypertensive drug need, serum cholesterol, antihyperlipidaemic drug need, post-transplant diabetes mellitus (PTDM) requiring treatment and cataracts. Steroid avoidance did not alter serum cholesterol, but was associated with less frequent PTDM requiring treatment. Cardiovascular events were reduced with steroid avoidance.

After 3 months, kidney transplant recipients should follow the steroid withdrawal regimen described below.

MONTH	PREDNISOLONE DOSE
3	4 mg once daily
4	3 mg once daily
5	2 mg once daily
6	1 mg once daily
7	Stop - taper completed

Kidney transplant recipients with one or more of the following criteria should remain on 5 mg of prednisolone for at least the first 12 months after renal transplantation:

- One or more episodes of acute rejection
- HLA mismatch > 1-1-1
- All ABOi and HLAi kidney transplant recipients
- Those patients on a single immunosuppression agent in addition to steroids

3.3 Other Immunosuppressant agents

3.3.1 Ciclosporin

Some patients will require treatment with Ciclosporin (Neoral®) as an alternative to Tacrolimus within the standard immunosuppressive regime of CNI/Pred/MPA with IL2 induction.

Initial dose of oral ciclosporin (Neoral®): 5 to 7.5 mg/kg every 12 hours. Subsequent doses to be adjusted depending on ciclosporin trough levels.

TIME AFTER TRANSPLANT	CICLOSPORIN TARGET LEVEL RANGE
1 to 3 months	150-300 mmol/L
4 to 6 months	100-200 mmol/L
After 6 months	50-100 mmol/L

Approximately one third of the oral dose can be given as a slow intravenous infusion in sodium chloride 0.9% or dextrose 5% over 2-6 hours if patient is nil by mouth.

3.3.2 Sirolimus

Used as an alternative to CNI inhibitor for immunosuppression and occasionally in patients with IFTA or CNI toxicity.

Sirolimus must not be given in women planning pregnancy or in patients with a healing wound or planned elective surgery.

Sirolimus should be stopped at least 4 weeks prior to elective surgery and patient converted to CNI. If surgery is performed as an emergency conversion to CNI should be considered post-operatively. This must be discussed with a Consultant - see UHL guideline: **Transplant: Sirolimus conversion in the renal transplant recipient Trust Ref: C37/2010**

<u>Sirolimus maintenance target trough levels:</u>
Target range 5-15ng/ml depending on whether patient is taking other immunosuppressant medications. For patients receiving Prednisolone + MPA, the target range is 5-10ng/ml.

Target level should be tailored to the individual depending on clinical need and tolerance. Changes from the standard regimen will be decided in consultation with a consultant transplant surgeon/nephrologist/transplant pharmacist.

***CAUTION* SEEK ADVICE FROM RENAL PHARMACY ABOUT INTERACTIONS WITH IMMUNOSUPPRESSION MEDICINES. Sirolimus, tacrolimus and ciclosporin are extensively metabolised by the CYP3A4 isozyme** in the intestinal wall and liver. **Inhibitors of CYP3A4** (such as ketoconazole, voriconazole, itraconazole, or clarithromycin) decrease their metabolism and **increase** tacrolimus, sirolimus and ciclosporin **levels**. **Inducers of CYP3A4** (such as rifampin) increase their metabolism and **decrease** tacrolimus, sirolimus and ciclosporin **levels**. Co- administration of tacrolimus, sirolimus and ciclosporin with strong inhibitors of CYP3A4 or inducers of CYP3A4 is not recommended. This is not a comprehensive list, for more information about interactions, contact a specialist pharmacist for advice.

3.4 Adjuvant treatments:

3.4.1 Co-trimoxazole (oral) 480mg once daily.

Prophylactic agent administered for the first 6 months post-transplant against Pneumocystis jiroveci pneumonia. Patients allergic to co-trimoxazole or its constituents (trimethoprim and sulphonamides) will receive 750 mg twice a day of atovaquone (oral suspension 750mg in 5 mL).

3.4.2 Lansoprazole (oral) 15 mg once daily.

Post-op gastric protection. Continue existing therapy with proton pump inhibitor (PPI) or histamine$_2$ blocker. PPI treatment should be reviewed periodically and discontinued (if appropriate) three months after kidney transplantation.

3.4.3 Aspirin (oral) 75 mg once daily.

Administered as prophylaxis against renal vein thrombosis in the first 12 weeks post-transplant. Aspirin therapy is usually continued for secondary prophylaxis of CVD.

3.4.4 Valganciclovir (oral).

Valganciclovir is administered in high risk patients (CMV D+ve to CMV R-ve) for the first six months post-transplant as prophylaxis against cytomegalovirus (CMV) infection. Doses are adjusted according to the patient's renal function. Prophylaxis is also indicated in CMV positive KTRs treated with lymphocyte depleting antibodies (e.g. ATG, alemtuzumab) – see UHL guideline **Prophylaxis and Management of CMV in the Renal Transplant Patient Trust Ref: C123/2016**

3.4.5 Nystatin 100,000 units/mL 1mL four times a day (oral/topical)

Prophylaxis against oral and oesophageal infections due to Candida species. To be continued for 1 month after transplantation.

4. Education and Training

All new transplant medical, nursing and pharmacy staff must read this document.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead

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

8. Key Words

Transplant, Immunosuppression, maintenance

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DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT			
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REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
18May2016		SueCarr/Maria Martinez	Updated to new template
18 June 2019		Maria Martinez	Added links to relevant UHL guidelines, amended interaction section, minor changes to wording for clarification. Removed pamidronate (no longer used), extended valganciclovir prophylaxis to 6 months, updated aspirin dosing.
20/07/2020		Mr Bagul/Dr Topham/M Martinez	Added oral candidiasis prophylaxis and swapped ranitidine for lansoprazole in view of on-going H2 antagonist global stock unavailability
09/11/2020		Mr Bagul/Dr Topham/M Martinez	Updated Mycophenolate sodium as first line MPA agent as approved by the transplant MDT
08/06/2023		Mr Bagul	Note: Single dose/other Tacrolimus (ratified MDT 5/06/2023)

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