Trust Clinical Policy

Directorates of Renal Transplant, Nephrology and Pharmacy

Protocol for immunosuppression following renal transplantation

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Document History

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1.0 Introduction

This protocol provides a framework to assist staff in the prescribing and monitoring of immunosuppression following renal transplantation to adults on the Sir Peter Medawar Renal Transplant Unit at the Royal Liverpool University Hospital (RLUH). It represents the consultant transplant surgeons and nephrologists’ consensus view and represents the best evidence-based practice. It is not intended to replace individual clinicians’ judgement in specific cases.

1.1 Equality and diversity

The Trust is committed to an environment that promotes equality and embraces diversity in its performance as an employer and service provider. It will adhere to legal and performance requirements and will mainstream equality and diversity principles through its policies, procedures and processes. This policy should be implemented with due regard to this commitment.

To ensure that the implementation of this policy does not have an adverse impact in response to the requirements of the Race Relations (Amendment Act), the Disability Discrimination Act 2005, and the Equality Act 2006 this policy has been screened for relevance during the policy development process and a full impact assessment conducted where necessary prior to consultation. The Trust will take remedial action when necessary to address any unexpected or unwarranted disparities and monitor practice to ensure that this policy is fairly implemented.

This policy and procedure can be made available in alternative formats on request including large print, Braille, moon, audio, and different languages. To arrange this please refer to the Trust translation and interpretation policy in the first instance.

The Trust will endeavour to make reasonable adjustments to accommodate any employee/patient with particular equality and diversity requirements in implementing this policy and procedure. This may include accessibility of meeting/appointment venues, providing translation, arranging an interpreter to attend appointments/meetings, extending policy timeframes to enable translation to be undertaken, or assistance with formulating any written statements.

2.0 Objective

The objective of this policy is to ensure that all relevant staff understand the agreed choices of immunosuppression, including prophylactic anti-infectives, when an adult patient is initially transplanted at the RLUH.
3.0 Scope of the protocol

This policy applies to all adult patients receiving a cadaveric (heart-beating (HBD) or non-heart beating (NHBD)) or live-donor (LRD) kidney at the RLUH, except highly-sensitised or non-ABO blood-group compatible patients, for whom a separate protocol exists.

4.0 Protocol

The protocol is divided into five areas:
4.1 The “standard” transplant
4.2 The transplant where there are graft factors
4.3 The “non-standard” patient
4.4 The management of acute rejection
4.5 Use of prophylactic anti-infective agents

The brand names “Prograf”, “CellCept”, “Myfortic”, “Neoral” and “Sandimmun” are the only names allowed to be used in the RLUH. Generic names for these medicines presents the risk of the wrong formulation being prescribed or dispensed in primary care.

LRD = Live related donation
HBD = Heart-beating cadaveric donors
NHBD = Non-heart-beating cadaveric donors
PRA = panel-reactive antibodies

4.1 The “standard” transplant
- All LRD with negative cross-match and not-sensitised (PRA < 20%)
- HBD cadaveric transplants without graft factors
- No “2 DR” mismatch

Induction:
0.5-1g IV methylprednisolone in theatre, with
Basiliximab (Simulect) 20mg IV on day 0 and day 4

Maintenance:
Prograf to 8-12 mcg/L for 3 months, then 5-8mcg/L thereafter, with
CellCept 1500-2000mg daily (OR Myfortic 1080-1440mg daily if CellCept not tolerated).
4.2 Transplants with graft factors
- Extended criteria HBD cadaveric transplants (>60yrs, or >50yrs with two or more of hypertension, creatinine >135micromol/L, or cerebrovascular accident as cause of death
- All NHBD cadaveric transplants
- Delayed graft function (haemodialysis required within first 24 hours post-operatively unless for hyperkalaemia, less than 10% fall in serum creatinine) or anticipation of above

**Induction:**
0.5-1g IV methylprednisolone in theatre, with Alemtuzumab (MabCampath) 30mg SC on day 0 and day 1 (Unlicensed use; approved by Trust Medicines Management Group but requires patient consent)

**Maintenance:**
Prograf to 5-8mcg/L, with CellCept 1000mg daily (OR Myfortic 720mg daily if CellCept not tolerated)

4.3 The “non-standard” risk patient
- All patients with 2 DR mismatch
- All patients with PRA >20%
- Second transplant where first transplant had early graft loss due to acute rejection

**Induction:**
0.5-1g IV methylprednisolone in theatre, with Alemtuzumab (MabCampath) 30mg SC on day 0 and day 1 (Unlicensed use; approved by Trust Medicines Management Group but requires patient consent)

**Maintenance:**
Prograf to 8-12 mcg/L for 6 months, then 5-8mcg/L thereafter, with CellCept 1000mg daily (OR Myfortic 720mg daily if CellCept not tolerated)
4.4 Treatment of acute rejection episodes

4.4.1 Acute cellular rejection
Methylprednisolone 0.5-1g IV for 3 days
Partial response (creatinine falls but still more than 20% over baseline on day 5): oral prednisolone 100mg reducing to 20mg over 8 days. If steroid resistant rejection; no response or worsening of renal function; then consider ATG

4.4.2 Acute vascular rejection
Antithymocyte globulin (ATG) (Thymoglobuline) 1.5-3mg/kg through a central line (unlicensed dose and frequency), (following IV chlorphenamine 10mg and oral paracetamol 1g, and IV steroid if not already on a steroid). The patient is redosed when CD3 count rises to 50/μL (0.050x10^9/L) to cover a 14 day period. Prograf and CellCept/Myfortic are stopped on initiation of ATG and restarted on day 10; oral prednisolone 20mg daily is started on initiation.

4.4.3 Antibody-mediated rejection (diagnosed on C4D/DSA)
Plasma exchange plus IV immunoglobulin 0.5g/kg daily for 5 days, and then according to response. Dalteparin at therapeutic dose can be used if evidence of high resistive index (>95 on Doppler scan) or biopsy proven thrombotic arteritis. Rituximab is an option if C4D staining/DSA confirm the diagnosis.

4.5 Prophylaxis of infections

4.5.1 Fungal infections
Nystatin 100,000u/mL x 1mL QDS for 5 weeks IF HAD ATG/MabCampath

4.5.2 Pneumocystis carinii pneumonia

4.5.3 Cytomegalovirus prophylaxis
CMV status of potential recipients is to be tested for every six months. CMV negative patients are asked if they would accept a kidney from a CMV-positive donor. After transplant, valganciclovir is prescribed as below.
Donor(D)/Recipient(R) combinations:
D-ve/R-ve Not required
D-ve/R+ve Not required
D+ve/R+ve Not required unless received ATG
D+ve/R-ve Required for 3 months for all patients
Contraindication for (or declining of) valganciclovir prophylaxis must be documented in the case-notes and an appropriate CMV surveillance programme (weekly PCR and warnings to report to ward if febrile) instituted. Female patients should be warned to avoid pregnancy or use in lactation.

Patients receiving valganciclovir should be monitored daily (weekly after discharge) for:
- ADRs (especially blood dyscrasias)
- that the dose is still correct for their creatinine clearance
- signs of any possible infection (fever, rising creatinine, etc)
PCR viral load testing is not necessary in prophylaxis unless breakthrough infection is suspected.

<table>
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<tr>
<th>Creatinine clearance</th>
<th>Prophylactic valganciclovir dose (If possible, take with food)</th>
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<tr>
<td>&gt;59 mL/min</td>
<td>900mg OD (two tablets)</td>
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<tr>
<td>40-59 mL/min</td>
<td>450mg OD (one tablet)</td>
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<tr>
<td>25-39 mL/min</td>
<td>450mg on alternate days</td>
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<tr>
<td>10-24 mL/min</td>
<td>450mg twice a week</td>
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<tr>
<td>&lt;10 mL/min</td>
<td>Not recommended; pharmacy will advise on syrup formulation doses</td>
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5.0 Roles & Responsibilities

5.1 Clinical Director of Renal Transplant
The Clinical Director of Renal Transplant is required to ensure that the policy is implemented and updated if required.

5.2 Other staff
Other Consultant Surgeons and Nephrologists are required to follow this protocol, and document, with reasons, deviations from it. Clinic nurses are required to monitor creatinine clearances of patients on valganciclovir. Pharmacists are required to ensure that the protocol is maintained and followed.
6.0 References


7.0 Training & Resources
The major change in this policy is the use of MabCampath with is cheaper than basiliximab and subject to the approval of the MMG. Training and briefing will be provided to ward staff. The use of valganciclovir prophylactically has been shown to be cheaper than the costs of monitoring for and treating CMV.

8.0 Monitoring and Audit
The protocol and patient outcomes will be subject to regular audit through the UK Renal Registry. In addition, aspects of the protocol will be subjects for audit by medical and pharmacy staff.

8.1 Recording and Monitoring of Equality & Diversity
The Trust understands the business case for equality and diversity and will make sure that this is translated into practice. Accordingly, this protocol will be monitored to ensure its effectiveness.

Monitoring information will be collated, analysed and published on an annual basis as part of our Single Equality and Human Rights scheme. The monitoring will cover all strands of equality legislation and will meet statutory employment duties under race, gender and disability. Where adverse impact is identified through the monitoring process the Trust will investigate and take corrective action to mitigate and prevent any negative impact.

The information collected for monitoring and reporting purposes will be treated as confidential and it will not be used for any other purpose.
Appendix: administration of antithymocyte globulin and alemtuzumab

Antithymocyte globulin (ATG) Protocol

1. **Indications:** Steroid resistant Rejection
   Acute Vascular Rejection

2. **Precautions**
   - All patients should have CXR before commencing treatment. If fluid overloaded patient requires treatment, mostly with dialysis.
   - ATG to be given only after review of patient by senior member of staff.

3. ATG should be administered via a central venous line

4. A doctor should be available on the ward during test dose and first dose.

5. **Test Dose:**
   - ATG 5mg (IV)in 100mls of 0.9% saline IV over 1 hour into a central line
   - Watch for signs of anaphylaxis – swelling of the lips, tongue and pharynx, bronchi spasms, hypotension
   - Minor reactions such as fever, rigors and rashes are not contraindication to commencing the therapeutic dose
   - **If anaphylaxis happens the following steps are to be taken:**
     1. Call senior medical cover
     2. Ensure airway is patent
     3. Lay the patient flat (BP)
     4. Give 100% O₂
     5. Give adrenalin 0.5-1mg (1/1000) im, repeat every 10 minutes if necessary

6. **First Dose:**
   - If the patient tolerates the test dose then therapeutic dose should be administered.
   - *Give chlorphenamine 10mg, and hydrocortisone 100 mg IV*
   - 1ˢᵗ dose – 1.5-3mg/kg in 50-100mls of 0.9% saline or 5% dextrose given IV into a central line over 8-12 hours.
   - Subsequent doses can be given over 4-6 hours
   - Further ATG doses can be given if:
     a. CD3 count >50cells/ml (0.05x10⁹/L)
     b. Neutrophil count > 2.0x10⁹/L
     c. Platelet count >75x10⁹/L
   - Duration of treatment – 14 days
   - Prograf/CellCept/Myfortic to be stopped at the start of treatment and resumed on day 10
   - Prednisolone 20mg started at the start and continued afterwards
Appendix: Alemtuzumab (MabCampath) Protocol

Alemtuzumab is potent anti CD52 antibody. When used as an induction agent in high immunological risk kidney transplant recipients, it reduced the incidence of acute rejection, and graft loss. It also allowed the avoidance of steroids and reduced calcineurin inhibitor doses. Cytokine release syndrome associated with the IV injection is not seen in the SC administration. (This is an unlicensed use; approved by Trust Medicines Management Group but requires patient consent)

1. Indications:
   - Non standard immunological risk –
     - 2DR MM
     - PRA >20%
     - Patient lost 1st graft due to AR within short period
   - Patient with graft issues
     - Extended criteria donors
     - NHBD

2. Consultant Surgeon on call makes the decision regarding Campath

3. Chlorphenamine 10mg, hydrocortisone 100mg to be given IV 30 minutes prior to alemtuzumab

4. 1st dose given subcutaneously in theatre after induction : 30mg.

5. 2nd dose given on 1st post operative day
   Chlorphenamine, hydrocortisone and paracetamol are given IV 30 minutes before the 2nd dose.