PROTOCOL FOR IMMUNOSUPPRESSION FOLLOWING RENAL TRANSPLANTATION
Cardiff Transplant Unit
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Background
The purpose of immunosuppression following organ transplantation is to reduce the immune reaction of the host against the implanted graft. Immunosuppressive drugs have come a long way since the 1980’s and have contributed to the excellent graft survival seen today. Reassuringly, there has been a definite and continuous improvement in graft survival over the last 20 years despite the transplantation of more marginal grafts into often higher risk recipients.

Unfortunately, all immunosuppressive regimens are non-specific and therefore associated with significant side-effects as a consequence of impaired immunosurveillance and reduced host responses to infection. Successful outcomes following transplantation are always a balance between avoidance of rejection and unacceptable increased susceptibility to infection. The intensity of immunosuppression required by individual recipients is variable, but at present there are no recognised means of determining and monitoring this. It is hoped that more sophisticated characterisation of relevant biomarkers, as well as further studies of host immunity, might allow individualisation of immunosuppression in the future.

The following factors are taken into account when considering the immunological risk of a specific transplant:

- HLA mismatch (DR>B>A)
- Presence of historic or current HLA donor specific antibodies
- Ischaemic injury, prolonged cold ischaemic time
- Younger recipient and older donor age
- Ethnicity, those of black Afro-Caribbean descent are at increased risk

The evidence that informs the choice of immunosuppression is based on open label studies, randomised controlled trials, and retrospective analyses. The Collaborative Transplant Study (CTS, www.ctstransplant.org) was initiated in 1982 in recognition of the need to collect comprehensive long term data related to transplantation. With the support of more than 400 transplant centres (including Cardiff) in 42 countries, more than 500,000 data sets for all solid organ transplants have been collected, and this resource therefore provides the most comprehensive repository for retrospective analyses. For example, the significance of factors listed above to increase immunological risk has been confirmed, and a positive effect for the use of either IL-2 receptor blockade or ATG induction on the rate of rejection and graft survival in immunologically higher risk recipients (1).

**Choice of Induction Agent**

Transplant immunosuppression is divided in two phases: induction and maintenance. Two agents are licensed for induction treatment – rabbit anti-thymocyte globulin (rATG, Thymoglobulin®) and an anti-interleukin 2 receptor monoclonal antibody, basiliximab (Simulect®). In addition, there have been a number of studies demonstrating efficacy of the anti-CD52 monoclonal antibody alemtuzumab (Campath®). However, the use of alemtuzumab as an induction agent remains unlicensed.

There are numerous trials and subsequent meta-analyses comparing different induction regimens (2), and a comprehensive review is provided by UpToDate.

Considering the local approach to induction treatment, historically the Cardiff Transplant Unit has used different immunosuppressive protocols for transplants performed after circulatory death (DCD), those following brain death (DBD) and those from living donors. rATG was introduced as the induction agent for DCD and pancreas transplants in Cardiff in 2004. The use of polyclonal ATG preparations has been reported to be associated with an increased likelihood of the development of post-transplant lymphoproliferative disorder (PTLD). However, this association is not seen with rATG to a cumulative dose of 6mg/kg, as used locally (3, 4).

The recent large 3C study (5) randomised recipients to either alemtuzumab-based induction treatment (followed by low-dose tacrolimus and mycophenolate without steroids), or basiliximab-based induction treatment (followed by standard-dose tacrolimus, mycophenolate and prednisolone). The primary outcome of biopsy-proven acute rejection within the first 6 months was significantly improved in the alemtuzumab group (7% vs 16% who received basiliximab) but there was no impact on graft or patient survival at 6 months. There was no difference in number of serious or opportunistic infections between the two groups, but there was an increase in BK infections in those who received alemtuzumab...
(total viraemia or biopsy proven BK nephropathy, 8% vs 4%). Analysis of the UNOS database has not shown an increased incidence of PTLD following alemtuzumab induction, compared to basiliximab or rATG (6), and there is accumulating evidence to support its use in the paediatric population (7).

The Cardiff Transplant Unit was the second highest recruiting unit to the 3C study. The resulting familiarity with alemtuzumab has led to increased use over the last two to three years, particularly for living donor transplants.

A number of UK transplant units use tacrolimus monotherapy after alemtuzumab induction; however this requires a higher dose of tacrolimus, which might impact on graft function. The addition of mycophenolate allows for a lower dose, without an increase in rejection episodes.

The current recommendations are based on the success of the Cardiff DCD program using rATG induction, and the results of the 3C study, with acknowledgement of the CTS data and other trials reported in the literature. These recommendations also serve to clarify some changes that have already been implemented on an individual patient basis.

It should be emphasised that optimal outcomes are not down to a single immunosuppressive drug, or even to a specific drug combination. Holistic management, including immunosuppression, but also attention to fluid balance, blood pressure, infection control and psychological support, ultimately defines outcomes. Intensive and scrupulous monitoring of patients in the early phase cannot be overemphasised.

It should be stressed that this guidance is indicative. Recipients are individuals and donor characteristics are variable. Deviation from this policy is not unexpected, but the specific grounds for this should be recorded.

**DCD kidney transplants**

**Induction immunosuppression**

T cell depletion with rATG at the time of transplantation is recommended for three reasons:

1. **Delayed Graft Function (DGF)** is likely (80% of such grafts locally, especially if the donor is older than 60 years and the Cold Ischaemic Time is >12 hours). This may be prolonged by full dose tacrolimus, and the use of a T cell depleting antibody allows reduction or omission without an increase in rejection. When DGF is prolonged, the risk of this being due to rejection is extremely low (local data), and transplant biopsy can safely be deferred for three weeks following transplantation.

2. **Ischaemia-reperfusion injury** increases the immunogenicity of the graft, and more intense induction treatment is required to minimise the risk of acute rejection.

3. Experiments in animals exposed to ischaemic insult have shown less tubular damage and less vascular inflammation in rATG treated animals.
rATG is contraindicated in the following circumstances (consider basiliximab as below):

- WCC <2 X 10⁹/L
- Platelets <75 X 10⁹/L
- Systolic hypotension <90 mmHg

**Administration**

**Caution:** Close supervision is required. In patients with fluid overload, rATG may rarely cause pulmonary oedema due to an increase in vascular permeability. The patient must be reviewed by a member of medical staff prior to the infusion, and appropriately counselled about potential side effects, notably a reaction at the time of infusion (fever, rigors, rash, hypotension).

- rATG is given via a central line for 5 days at a daily dose of 1.25 mg/kg (rounded to the closest 25 mg).
- The maximum individual daily dose is 125mg.
- rATG is diluted in 250ml sodium chloride 0.9% and given over 6 hours for the first two doses, then over 4 hours thereafter if the first doses are well tolerated.
- The first dose is given in theatre during implantation.
- Pre-treatment is given prior to each dose to prevent an infusion reaction:
  - Chlorphenamine 10mg slow IV bolus.
  - Hydrocortisone 100mg slow IV bolus (may be omitted for third and subsequent doses if no adverse reaction to first and second infusions).
- The CD3 count is monitored daily.
- Although the results are not used to guide dosing for induction, they will be used to analyse whether the number of doses might be reduced in future immunosuppression protocols.

- An infusion reaction is **not** in itself a contraindication to continuing treatment, but infusion rate may need adjustment.
- The dose of rATG used for induction is lower than that used for the treatment of rejection. The treatment of rejection is detailed below in appendix 1.
- Prophylaxis against infection – please see below.

**Maintenance immunosuppression**

- Tacrolimus (Adoport® brand)
- Mycophenolate Mofetil (MMF)
- Prednisolone

**Tacrolimus:** 0.05 mg/kg/day divided in two equal doses (maximum 2mg bd), starting on day 0 and aiming for a trough level of 3 – 5µg/L during the course of treatment with rATG. NB. This is half the standard prescription dose. Maintenance of a lower target range in the presence of prolonged DGF after completion of rATG is at Consultant discretion.
The use of rATG induction allows initial omission of tacrolimus if there are particular concerns about DGF. Once independent renal function is established, the target dose range is increased to 5 – 8 µg/L for the first three months.

**MMF:** Initial dose 750 mg BD starting on day 0. Monitoring of therapeutic level is usually not required. The dose is not modified unless there is leucopaenia/neutropaenia (see appendix 2) or significant GI intolerance (see appendix 3 which includes consideration of a switch to mycophenolate sodium – MPS).

**Prednisolone:** Prednisolone is used to reduce the inevitable graft inflammation that accompanies two ischaemic insults. Methylprednisolone 500mg IV is given prior to graft reperfusion followed by an initial maintenance dose of 20 mg/day orally for 4 weeks. From then onwards this dose is reduced by 5 mgs every 2 weeks so the patient is steroid free after 10 weeks. The rationale for early steroid withdrawal is based on studies showing an increased risk of rejection with late withdrawal. If there has been acute rejection in the first 3 months, prednisolone is increased as below (appendix 1) and continued for at least one year following the rejection episode.

**DBD and Living Donor kidney transplants**

**Induction immunosuppression**

The alemtuzumab formulation used as an induction agent in transplantation (Campath®) is an unlicenced medicine and only available via a Patient Access Scheme. It is a humanised monoclonal antibody directed at the cell surface glycoprotein CD52 expressed on both T and B lymphocytes. Rapid and profound lymphocyte depletion occurs following administration of alemtuzumab, reducing the risk of rejection.

**Alemtuzumab is relatively contraindicated in the following situations (consider basiliximab as below):**

- Recipient history of chronic viral infection, ie HBV, HCV or HIV, HPV or previous graft loss to BKV (see discussion below).
- Recipient or donor history of malignancy (excluding basal cell carcinoma).
- Recipient with hereditary nephritis and deafness, i.e. Alport’s syndrome (anecdotal case reports of pulmonary haemorrhage).
**Administration**
Alemtuzumab is produced as a 30mg/ml concentrate for SC injection, and given as a single dose prior to surgery on the day of transplantation. Alemtuzumab should be prepared for injection using standard aseptic technique, and may be given on the ward or in theatre. The injection is given into either the flank or thigh.

- Pre-treatment is given to prevent injection related reactions:
  - Chlorphenamine 10mg slow IV bolus.
  - Hydrocortisone 100mg slow IV bolus.
  - Paracetamol 1g PO.

**Pregnant women should not prepare or administer alemtuzumab.**

Please note: severe and occasionally life threatening systemic reactions have been reported following administration of alemtuzumab (more details can be found in the Summary of product characteristics, SmPC, at www.medicines.org.uk). Full resuscitation facilities should be available.

Mild to moderate acute adverse reactions are common and related to cytokine release, including headache, flushing, pruritus, tachycardia, hypotension, rigors, fever, dyspnoea, rash, nausea and vomiting. Caution should be used in patients with a history of ischaemic heart disease and those receiving anti-hypertensives. These reactions are less common with SC administration compared to IV.

All patients require regular observations during and after the administration of alemtuzumab.

Injection site reactions are common, and usually respond within 24 hours to chlorphenamine 4 mg PO and paracetamol 1g PO, which may need to be repeated.

Alemtuzumab inevitably causes profound and long-lasting lymphopaenia, and may cause other cytopenias. The development of autoimmunity, especially thyroid disease, is well-recognised following the treatment of multiple sclerosis with alemtuzumab. This is thought to be due to rapid B cell repopulation in the relative absence of T cell regulatory mechanisms that promote immune tolerance (8), but interestingly has been reported only rarely following the use of alemtuzumab in the context of solid organ transplantation (9). Testing of thyroid function is only indicated if there is clinical suspicion of over- or under-activity.

**Maintenance immunosuppression**
The standard long term maintenance immunosuppression consists of:
- Tacrolimus (Adoport® brand)
- Mycophenolate Mofetil (MMF)
- No prednisolone (unless prescribed pre-transplant)
Tacrolimus: Initial daily dose 0.1 mg/kg divided in two equal doses (maximum 4mg BD), aiming for a level of 5 – 8 µg/L. In the event of DGF, a lower dose of tacrolimus may be considered.

MMF: Initial dose 500 mg BD starting on day 0. Monitoring of therapeutic level is usually not required. The dose is not modified unless there is leucopaenia/neutropaenia (see appendix 2) or significant GI intolerance (see appendix 3 which includes consideration of a switch to mycophenolate sodium – MPS).

Following the initial dose of methylprednisolone in theatre (500 mg IV), no steroids are used for maintenance unless rejection has occurred (see management of rejection - appendix 1).

**Tacrolimus monitoring**

Tacrolimus has a narrow therapeutic window and must be prescribed by brand name (Adoport® for all new transplant patients). Blood levels can be affected by drug interactions, with the most common culprits listed below. The trough blood level of tacrolimus is measured on an EDTA sample taken before the morning dose (which is then given, do not wait for the result). Any dose adjustment is made from the evening dose. Levels for tacrolimus are sent on Monday, Wednesday and Friday for in-patients in the early post-transplant period (Saturday levels need to be pre-arranged), and on the day of out-patient clinic attendances (the laboratory assay is run every weekday). If the levels are within the desired range usually no modification is required. If in doubt about interpretation of result, or how to change the dose in response to high or low levels, please discuss with Consultant or renal pharmacist.

Always investigate causes of unexpected disruptions to tacrolimus levels before making any dose adjustments. For example, a high level due to patient taking the morning dose before their blood test or a low level due to patient admitting to regularly missing tacrolimus doses will not require a dose change.

Tacrolimus levels will not correct immediately following a dose change so avoid frequent adjustments. For example, a dose change based on abnormal levels may not lead to correction into the target range on a repeat blood test taken within 48 hours.

Interpretation of result (unless immediately post-transplant with delayed graft function, in which case low levels are desirable):

- **5 – 8µg/L. Just right**
  - In target range, continue current dose.
  - A change of dose is not usually needed if the level is intermittently up to 10µg/L. Particularly when reviewing long term recipients, consideration of the overall trend is important.
• **<5 µg/L. Too low**
  o Assess adherence (particularly in outpatients).
  o Confirm concomitant medications for hepatic enzyme CYP3A4 inducers, eg St John’s Wort (present in herbal remedies), carbamazepine, rifampicin.
  o Increase dose if appropriate.
  o Arrange repeat level in 3 – 5 days.

• **8 - 15µg/L. Too high**
  o Ask patient about timing of preceding dose and any intercurrent illness (especially diarrhoea, may increase absorption).
  o Confirm concomitant medications for hepatic enzyme CYP3A4 inhibitors eg clarithromycin, diltiazem, azole anti-fungals.
  o Check for dietary changes (grapefruit juice increases bioavailability of tacrolimus).
  o Assess trend in levels and consistency of results (an occasional level between 8 and 10µg/L does not usually warrant a change in dose).
  o Reduce dose if appropriate.
    ▪ For in-patients, a greater reduction in the evening dose on the first day can be considered, and may achieve the target level sooner.
  o Arrange repeat level in 3 – 5 days.

• **>15µg/L. Very high – usually due to patient having taken the morning dose before blood test**
  o As above, in addition if the level is a true trough level:
  o Omit one or more doses and reduce maintenance dose.
  o Arrange repeat level in 1 – 2 days.

**Special circumstances**

1. **Immunosuppression for the elderly (>70 years) or frail**
   Consider omission of T cell depleting antibody and use of basiliximab, or omission of antibody induction entirely. Although this avoids intense immunosuppression at the time of transplant, this benefit should be weighed against the subsequent need for higher doses of maintenance immunosuppression.

Basiliximab is administered prior to the transplant (day 0) and on day 4, as 20 mg IV. No premedication is needed.

Maintenance immunosuppression following basiliximab consists of: tacrolimus (Adoport® brand), 0.1mg/kg divided in two equal doses, MMF 1g BD and prednisolone 20mg OD for 4 weeks, thereafter reducing by 5mg/fortnight to stop 10 weeks post-transplant (unless the recipient was taking long term prednisolone prior to transplantation). If the primary cause of renal failure is glomerulonephritis, consider continuing prednisolone 5mg OD.
Alternatively, following rATG induction, consider dual treatment with tacrolimus and MMF or tacrolimus and prednisolone from the time of transplant; and following alemtuzumab induction, consider monotherapy with tacrolimus.

2. **Indications for long term steroid maintenance**

Long-term maintenance with steroids is required for certain patients, notably:

- Those already taking maintenance steroid treatment prior to transplantation.
  - Double dose for three days post-operatively.
- Following a rejection episode (other than borderline) – prednisolone should be continued for at least one year (see below).
- Glomerulonephritis as primary renal disease (discuss with Consultant Nephrologist).

3. **Second (or subsequent) transplant**

Consideration should be given to duration and intensity of prior immunosuppression (eg previous induction treatment, previous treatments for acute rejection, cumulative dose of rATG), cause of graft loss and sensitisation. Use of T cell depleting antibodies is not generally contraindicated, and may be preferred as these patients are frequently sensitised to both HLA and non-HLA antigens (10).

A second course of basiliximab should be used cautiously. There is a risk of a severe hypersensitivity reaction on re-exposure, in particular if immunosuppression has been withdrawn (11).

Historically, re-transplanted recipients in Cardiff have received long term maintenance treatment with prednisolone. However, recent evidence indicates that following T cell depletion, steroids can safely be minimised in this group, with subsequent avoidance of the consequences of steroid treatment (12).

If the recipient has previously taken tacrolimus, this can be used to guide dose rather than weight.

4. **Chronic viral infection**

rATG is relatively contraindicated when there is recipient history of chronic viral infection, for example HBV (other than HBCAb positivity alone), HCV or HIV. In these patients, basiliximab is the preferred induction agent unless there is a compelling reason to use rATG.

If the recipient has lost a previous graft to BK nephropathy, or has a history of florid HPV infection, consider basiliximab, although as noted above this will require higher maintenance immunosuppression.

There is a paucity of data relating to re-transplantation following PTLD. Most cases in the literature have reported a successful outcome, with the majority having received rATG...
induction. Although intuitively avoidance of T cell depletion at induction might be preferable, as above this comes at the cost of higher maintenance immunosuppression.

5. Recipient with an existing solid organ transplant

Recipients of a functioning SOT will already be taking long-term maintenance immunosuppression. They generally do not require induction treatment due to the increased risk of infection, particularly following T cell depletion. They may however require augmentation of their baseline immunosuppression.

6. Other immunosuppressants

Recipients may be taking an immunosuppressant drug other than those that form part of the current regimen.

i. Ciclosporin. The first developed calcineurin inhibitor, now superseded by tacrolimus. Most patients taking ciclosporin will be longstanding recipients.

ii. Azathioprine. An anti-proliferative. Most patients taking azathioprine will be longstanding recipients, or transplanted as children. May be used as an alternative to MMF/MPS for patients with intolerable side effects (Consultant decision, see also appendix 3). The usual dose is 1.5 - 2mg/kg. TPMT levels need to be checked (patients with low levels of activity are at risk of increased myelosuppression and dose should be halved). The result takes 10 – 14 days to be reported. If azathioprine is started before the TPMT result is available, a starting dose of 1mg/kg should be used. NB significant interaction with allopurinol increasing the risk of azathioprine induced bone marrow suppression – a dose of 0.5mg/kg should be used.

iii. Sirolimus (Rapamune®). Sirolimus is an mTOR (mammalian Target of Rapamycin) inhibitor. Recipients may have been switched from tacrolimus due to intolerance or malignancy, to minimise potential tacrolimus nephrotoxicity or as part of the 3C trial. Sirolimus has a long half life so therapeutic drug levels are not achieved quickly and it takes 7 – 14 days reach steady state. When switching from tacrolimus to sirolimus, continue the tacrolimus until therapeutic sirolimus levels are achieved. Like tacrolimus, sirolimus also has a narrow therapeutic window and requires monitoring of trough levels, but is only taken once daily. When prescribing, the brand name should be specified. Drug interactions are similar to CNIs. The usual starting dose is 3mg OD (2mg if <60kg), with a usual target plasma level of 6 – 12µg/L.

iv. Once daily tacrolimus (eg Advagraf®, Envarsus®). Recipients may have been switched to a once daily formulation for a number of indications, including: very high or very low BD dose requirement with significantly variable or persistently high levels, neurological side effects or life style (shift work). Discuss with consultant nephrologist or renal pharmacist before switching to once a day tacrolimus formulations.
7. HLA identical related living donor
The risk of rejection is very low, consider omitting antibody induction.

8. Black Afro-Caribbean recipients
A higher dose of tacrolimus may be required (due to the prevalence of genetic polymorphisms that result in more rapid metabolism of tacrolimus). Discuss appropriate dose with renal pharmacist and transplant Consultants.

Prophylaxis against infection

Non-specific
Chlorhexidine mouthwash 10ml QDS for duration of rATG induction.

Oral candida
Nystatin suspension 1ml QDS for duration of rATG induction, and continued for up to 2 weeks following completion of course.

Cytomegalovirus (CMV)
Valganciclovir: Patients with negative CMV status receiving a positive organ, and any patient with positive status should receive 3 months prophylaxis with valganciclovir. The dose is adjusted according to creatinine clearance.

<table>
<thead>
<tr>
<th>Creatinine clearance, ml/min (Cockroft and Gault formula)</th>
<th>Valganciclovir dose (prophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 (including dialysis dependency)</td>
<td>450mg twice weekly</td>
</tr>
<tr>
<td>25 - 39</td>
<td>450mg alternate days</td>
</tr>
<tr>
<td>40 - 59</td>
<td>450mg OD</td>
</tr>
<tr>
<td>&gt;60</td>
<td>900mg OD</td>
</tr>
</tbody>
</table>

Link for Cockroft-Gault calculator:
https://www.medcalc.com/creatinine-clearance-cockroft-gault-equation

The detailed recommendations for CMV surveillance post-prophylaxis and treatment of CMV disease are described in a separate protocol.

Pneumocystis jirovecii pneumonia (PCP)
Co-Trimoxazole: 480 mg OD for 6 months, re-prescribed for a further 6 months following treatment of rejection with methylprednisolone or rATG (see appendix 1). Second line (only for those with known allergy to cotrimoxazole): Dapsone 100mg OD. Third line: Atovoquone 750mg BD or monthly nebulised Pentamidine.
**Tuberculosis (TB)**
Transplant recipients with a history of TB infection or with a high risk of TB exposure (eg previously lived in a TB endemic area) should be prescribed TB prophylaxis for 6 months post-transplant with Isoniazid 300mg OD. Pyridoxine 10mg OD can also be prescribed in selected patients (eg malnutrition) to prevent isoniazid related peripheral neuropathy.

**Hepatitis B**
If there are donor or recipient factors indicating a risk of HBV infection (discuss with virology), the transplant recipient can be prescribed HBV prophylaxis for 6 months post-transplant with Lamivudine – dose adjusted according to renal function.

<table>
<thead>
<tr>
<th>Creatinine clearance, ml/min (Cockroft and Gault formula)</th>
<th>Lamivudine dose (using 100mg tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>25mg OD</td>
</tr>
<tr>
<td>25 - 50</td>
<td>50mg OD</td>
</tr>
<tr>
<td>&gt;50</td>
<td>100mg OD</td>
</tr>
</tbody>
</table>

**Concomitant medication**

**Pre-existing**
B-blockers: Should always be continued throughout the peri-operative period and long term if required.

ACE inhibitors/ARBs: Usually stopped in the peri-operative period due to their confounding effect on interpretation of serum creatinine. If the patient receives them to optimise left ventricular function they can be continued with caution, with careful monitoring of serum potassium.

Other anti-hypertensive drugs: Usually stopped peri-operatively, may be re-introduced if hypertensive post-transplant.

Lipid lowering drugs: Usually stopped peri-operatively but should be restarted on discharge. Consider statin dose reduction due to potential interaction with tacrolimus, which increases risk of statin induced muscle toxicity.

Alfacalcidol: usually stopped unless prior parathyroidectomy.

Cinacalcet: usually stopped, but may need restarting if hypercalcaemia develops.

ESA: usually stopped, low threshold for restarting if anaemia persists due to DGF.

**New**
No routine prescription of omeprazole or nifedipine (in contrast to previous protocols). If taking PPI on admission, review need to continue.
Aspirin, 75mg OD: prevention of renal vein thrombosis and cardiovascular protection.

Ranitidine, 150mg BD: stop on discharge unless prescribed steroids.

Simvastatin, 20mg ON: if not already taking a statin consider starting on discharge unless there is a contra-indication.
# Summary

**Peri-operative induction immunosuppression**

**DCD**
- Methylprednisolone 500mg IV
- rATG 1.25mg/kg IV X 5 days (max 125mg/day) over 4 to 6hrs
  - premedication with hydrocortisone and chlorphenamine

**Maintenance**
- Tacrolimus (Adoport®) starting at 0.05mg/kg/day in two divided doses
  *Consider omitting if DGF is anticipated until independent kidney function resumes*
  - Target level 3 – 5 µg/L during rATG, 5-8 µg/L for the long term
- Mycophenolate Mofetil 750mg BD
- Prednisolone 20 mg OD, wean by 5mg/fortnight from 4 weeks post-transplant to stop at 10 weeks (see exceptions)

**DBD/Living donors**
- Methylprednisolone 500mg IV
- Alemtuzumab 30mg SC
  - premedication with chlorphenamine, hydrocortisone and paracetamol

**Maintenance**
- Tacrolimus (Adoport®) 0.1mg/kg/day in two divided doses
  - Target level 5 – 8 µg/L for the long term
- Mycophenolate Mofetil 500mg BD

**Alternative regimen if T cell depletion not used or contra indicated**
- Methylprednisolone 500mg IV
- Basiliximab 20mg iv days 0 and 4

**Maintenance**
- Tacrolimus (Adoport®)
  - Target level 6 – 9µg/L for three months, 5 – 8µg/L long term
- Mycophenolate mofetil 1000mg BD
- Prednisolone 20 mg OD, wean by 5mg/fortnight from 4 weeks post-transplant to stop at 10 weeks (see exceptions)
APPENDIX 1

Guidance for the treatment of rejection
All treatment for rejection will be approved by the Consultant Nephrologist or Surgeon responsible for the care of the patient.

Cellular Rejection

1. Methylprednisolone

The standard first-line treatment for cellular rejection (Banff 1A or 1B, no evidence of vascular or antibody mediated rejection) is a pulse of intravenous steroid.

| Prescribe: | Methylprednisolone 500 mg IV daily for three days. |
| This should be diluted in 50 ml of either 0.9% saline or 5% glucose and given over 30 minutes |

Methylprednisolone can be given through either a peripheral or a central line. Oral steroids should be discontinued for the duration of IV treatment.

2. Increase baseline immunosuppression

Prednisolone. Following intravenous pulse, start 20mg daily for 2 – 4 weeks, then reduce by 5mg/fortnight to maintenance dose of 5mg. Withdrawal may be considered after one year.

Anti-proliferative agent. Some recipients (usually those transplanted as children) may be taking azathioprine. Change to mycophenolate (MMF 1g BD or MPS 720mg BD). If already taking MMF or MPS, optimize dose.

CNI. Optimise dose of tacrolimus to target range. Consider switching ciclosporin to tacrolimus.

mTOR inhibitor. Consider switching sirolimus to tacrolimus.

3. Anti-thymocyte globulin (rATG)

The standard treatment for rejection refractory to methylprednisolone is rATG, at a higher dose than that used for induction.

*Extreme caution should be taken when considering the use of rATG as treatment for rejection in elderly patients, or those with any active infection.*

Indications

1. Steroid resistant rejection - defined as incomplete or no response to three day pulse of Methylprednisolone (see above) or relapse of/ongoing rejection within one week of steroid pulse.

2. First line treatment for severe rejection (Banff 2A or 2B, or vascular involvement).

3. rATG in combination with antibody removal in cases of mixed ACR/AMR.
4. Third rejection episode within the first three months (this occurs rarely).

**Administration**

*Caution:* close supervision is required. In patients with fluid overload, rATG may rarely cause pulmonary oedema due to an increase in vascular permeability. The patient must be reviewed by a member of medical staff prior to the infusion, and appropriately counselled about potential side effects, notably a reaction at the time of infusion (fever, rigors, rash, hypotension).

- rATG is given via a central line for 7 days at a daily dose of 2mg/kg (rounded to the closest 25 mg).
  - If rATG was also given as induction treatment, consider a shorter course of 3 days.
- The maximum individual daily dose is 200mg.
- rATG is diluted in 250ml sodium chloride 0.9% and given over 6 hours for the first two doses, then over 4 hours thereafter if the first doses are well tolerated.
- Pre-treatment is given prior to each dose to prevent an infusion reaction:
  - Chlorphenamine 10mg slow IV bolus
  - Hydrocortisone 100mg slow IV bolus (if the first two doses are well tolerated, this may not be needed for subsequent infusions)
- The CD3 count is monitored daily, and in contrast to the use of rATG as an induction agent the dose is dependent on the CD3 count (see below).
- An infusion reaction is **not** a contraindication to continuing treatment, but infusion rate may need adjustment.

**Other immunosuppression during ATG treatment**

- **When ATG is started for treatment for rejection for 7 days ALL other immunosuppression is suspended** (take care to explain this to the patient, particularly if they are self medicating).
- In those circumstances when the decision has been made for ATG to be given for only 3 days (eg it has already been used for induction) there is no need to stop tacrolimus.
- Tacrolimus is usually restarted two days prior to completion of the course of treatment, to allow establishment of a therapeutic level. Mycophenolate has a rapid onset of action and is restarted when the course is complete.
- An increase in baseline immunosuppression is indicated following completion of the course of rATG (unless contra-indicated by an individual patient’s clinical circumstances), for example – by adding or increasing steroids, optimizing the doses of MMF and tacrolimus dose as above.
**Other precautions**

- *The patient should be nursed in a side room* and have maximum one visitor. Contact with small children (germ factories) should be avoided if possible.

- The first dose should ideally not be given out of hours.

- During the first two doses the patient is likely to experience a cytokine release syndrome manifested as pyrexia, rigors, mild hypotension and flu-like symptoms. This is not an automatic reason to stop the rATG, but the patient should be warned about these potential symptoms during counselling prior to consent to treatment.

- Paracetamol may be given for the pyrexia.

- If the symptoms are more severe or prolonged, further doses of hydrocortisone and/or chlorpheniramine can be given and the IV infusion of ATG slowed (over 8 hours).

- Infusion reactions are unusual following the third and subsequent doses.

- Treatment dose rATG causes profound immunosuppression, and a full clinical examination should be performed daily, to include the abdomen, chest, throat, tonsils and ears, looking for any sites of infection.

- If pyrexia persists or appears after the third day **all possible sites** including the central line should be cultured.

**Monitoring of rATG treatment**

*Please note: in contrast to induction, monitoring of absolute CD3 count is used to guide dose.*

Monitor:

1. Absolute CD3 count:

   **Daily** Mon-Fri, if unavailable and on weekends the previous CD3 and total lymphocyte counts will be used for dosing.

   The request needs a separate form from other blood tests, and requires a separate EDTA sample.

   The dose of rATG is titrated after the first dose according to the absolute CD3 count:

<table>
<thead>
<tr>
<th>CD3 Count</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 8/μl (10000/ml)</td>
<td>No dose is given</td>
</tr>
<tr>
<td>Between 8-40/μl (8000-40000/ml)</td>
<td>Half dose is given (i.e 1 mg/kg)</td>
</tr>
<tr>
<td>Greater than 40/μl (40000/ml)</td>
<td>Full dose is given</td>
</tr>
</tbody>
</table>

   **NOTE:** When dose is omitted due to low CD3 count this day counts towards the total number of days of ATG administration.

2. Platelets and haemoglobin will fall almost universally due to the presence of antibodies directed against platelet or red cell antigens in the polyclonal preparation.
Unless there is overt bleeding, this is not usually a reason for dose modification. Particular caution should be used if platelets fall below 50 x 10^9/l.

**Prophylactic medication**

Continue or start:

- Paracetamol 1g QDS PRN for pyrexia.
- Chlorexidine mouthwash 10ml QDS for the duration of treatment with rATG.
- Candida prophylaxis for up to 2 weeks following the completion of treatment with rATG.
  - Nystatin suspension 1ml QDS
- CMV prophylaxis for 3 months (see also Unit CMV guidelines):
  - Valganciclovir (dosed according to Creatinine Clearance, see above).
- *Pneumocystic jirovecii* prophylaxis for 6 months:
  - Co-Trimoxazole 480mg OD.
  - Second line (if known allergy to co-trimoxazole) - Dapsone 100mg OD or Atavoquone 750mg BD.

**Long term monitoring/follow-up**

Although often effective, treatment dose rATG is profoundly immunosuppressive, with the inherent hazards that this brings. It should only be given to appropriate selected patients who fulfil the required indications. Susceptibility to infection is increased both during administration and in the longer term, with the risk of subsequent development of PTLD being related to the cumulative dose. This risk is justified by the potential of a severe rejection episode to destroy or severely damage the graft. *Extreme caution should be exercised about using ATG in elderly patients or patients with active infection.*

**Active Antibody Mediated Rejection (AMR)**

Active AMR occurs in two settings. Early post-transplant, typically presenting in recipients with HLA sensitization and acute graft dysfunction, and later, smoldering, active AMR in patients with *de novo* or persistent donor specific antibodies (DSA). The latter scenario may also occur following minimization of immunosuppression. More florid late rejection may develop in the context of non-adherence, when there are often features of both cellular and antibody mediated rejection. Early AMR can often be reversed by the treatment described below, aimed at removing DSA. Later active AMR tends to be more resistant to treatment, and has been highlighted as a major focus for future clinical trials of novel agents designed to prevent progression to chronicity.

**Plasmapheresis**

Plasmapheresis should be used to treat biopsy proven active AMR caused by HLA DSA. The biopsy will show features of active microvascular inflammation, including peritubular capillaritis and glomerulitis, both of which may show deposition of C4d.
A 7 – 10 day course of 5 – 7 sessions of plasmapheresis is usually performed, with DSA levels sent prior to commencement and after 3 – 4 treatments to assess response. Plasmapheresis is usually performed on alternate days (to allow re-equilibration of IgG between the extravascular and intravascular compartments, and hence improve the efficiency of removal of total body IgG), except in cases of very severe early active AMR where it can be performed daily. The double or single filtration system can be used.

Each plasmapheresis session is followed by Intravenous Immunoglobulin (IVIG), 100 mg/kg until the final treatment, following which 1g/kg is given. In cases of severe early AMR a large dose of IVIG (2g/kg divided in two days) could be considered following the first exchange, with the aim of more rapid modulation of the antibody response.

Please also see separate departmental protocol for plasmapheresis.

Methylprednisolone (3 doses of 500mg IV) is usually given, as steroids cause plasma cell apoptosis. rATG (3 doses according to CD3 count) should be considered in mixed severe active AMR/ACR in addition to antibody removal.

Rituximab (1g, IV) may be given following completion of the course of plasmapheresis.

**Chronic Antibody Mediated Rejection**

Features of chronic AMR include transplant glomerulopathy, peritubular capillary basement membrane multilamination and accelerated arteriosclerosis, and are the consequence of long term exposure to DSA. Management should be focused on optimization of maintenance immunosuppression and tight blood pressure control, including blockade of the renin-angiotensin system. There is no evidence to support an additional role for antibody removal, unless the biopsy also shows active AMR superimposed on more chronic changes, in which case treatment of the active component as above may be considered.
APPENDIX 2

Management of Neutropaenia

Neutropaenia occurs in 20 – 50% recipients, typically around 3 months post-transplant, and is usually of rapid onset. The risk for these patients is an increased susceptibility to bacterial infections. A number of drugs are implicated in the development of neutropaenia, in particular MMF (and MPS), but myelotoxicity is also recognised with cotrimoxazole and valganciclovir. Tacrolimus impacts on enterohepatic recycling of MPA, resulting in increased exposure to MPA and hence greater potential for myelosuppression. Induction therapy with rATG or alemtuzumab has been reported to be associated with an increased risk of neutropaenia. Local experience has also implicated the use of rituximab. Neutropaenia is usually isolated and not associated with other cytopaenias. Lymphopaenia is a feature of induction with alemtuzumab and does not usually require intervention.

Neutropaenia may also occur consequent to viral infections (especially CMV), or overwhelming bacterial infections (which would be suspected from the clinical presentation).

Action

- Assess for indicators of CMV infection – constitutionally unwell, fever, dyspnoea, abnormal LFT’s. Check for time frame (CMV infection most likely at 6 weeks post transplant and 2 to 3 weeks post prophylaxis cessation).
- Send EDTA blood sample for CMV PCR.
- Advise patient of increased risk of infection – to seek medical advice early if unwell or febrile.

If neutrophil count > 1.5 but < 2

- Repeat FBC weekly until neutrophil count > 2.

If neutrophil count < 1.5 but > 0.5

- Consider halving the dose of MMF/MPS.
- Repeat FBC weekly until neutrophil count > 2.

If neutrophil count < 0.5

- As above.
- Consider stopping MMF/MPS. In pancreas or HLAi transplants, due to the increased rejection risk, consider first using a Granulocyte Colony Stimulating Factor (GCSF), eg Filgrastim.
*CAUTION*

*An interruption in treatment for more than 6 days is associated with an increased risk of rejection*

- Consider GCSF (eg 3 doses of Filgrastim 30 million units given daily or alternate days). This will increase neutrophil count, and is not associated with an increased risk of rejection.

- Repeat FBC twice weekly until neutrophil count > 0.5, then weekly until neutrophil count > 2.

- If neutropaenia persists after cessation of the antiproliferative agent and GCSF treatment, consider stopping valganciclovir (provided CMV PCR is negative) and /or cotrimoxazole.
APPENDIX 3

Management of gastrointestinal side effects for patients taking mycophenolate mofetil/sodium

Both mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) are pro-drugs, converted in vivo to the active drug mycophenolic acid (MPA). Gastrointestinal intolerance (especially diarrhoea and nausea) is reported in around 20% of patients taking MMF/MPS and in extreme cases necessitates discontinuation of treatment. It is important to recognise that gastrointestinal side effects with MMF/MPS are dose related and will often improve with a dose reduction – however this must be balanced against the potential to increase the risk of graft rejection by reducing the patient’s exposure to mycophenolic acid. These concerns are particularly relevant when the dose of MMF is less than 500mg BD (or 360mg BD for MPS).

MMF is always first line therapy based on extensive local clinical experience and drug acquisition cost. MPS is an enteric coated formulation but there is no clear evidence to demonstrate that it has a better tolerability profile than MMF. However individual patents may benefit from a switch to the alternative formulation, if they are experiencing clinically significant diarrhoea for example. In general, this strategy is indicated after the patient’s symptoms have not responded to an MMF dose reduction to 500mg BD and should be undertaken on a trial basis. If a month of MPS treatment doesn’t produce a clinically significant improvement, the patient should be switched back to MMF and alternative prescribing options considered (for example further reduction in MMF dose or switch to azathioprine).

In a small number of selected patients where there is a need to maintain a high exposure to mycophenolic acid, a switch to MPS can be considered before reducing the dose of MMF to 500mg BD. In such cases, again on a trial basis, MMF 1g BD and 750mg BD are approximately equivalent to MPS 720mg BD and 540mg BD respectively.

Before changing the MMF regimen rule out other causes of acute or chronic gastrointestinal upset and establish the onset of symptoms in relation to the MMF start date. Side effects such as diarrhoea generally appear in the early stages of treatment so if the patient has already been on the drug for 6 months with no problems, it is unlikely that new onset complications such as diarrhoea or nausea will be MMF related.

A simple algorithm for managing gastrointestinal side effects with MPA drugs is described below.
Patient with clinically significant MMF-related gastrointestinal intolerance

Current dose 1g BD
Reduce dose to 750mg BD
No improvement in 4 weeks?
Reduce dose to 500mg BD
No improvement in 4 weeks?

Current dose 750mg BD
Reduce dose to 500mg BD
No improvement in 4 weeks?

Current dose 500mg BD
Reduce dose to 500mg BD
No improvement in 4 weeks?

Switch to MPS 360mg BD
No improvement in 4 weeks?

Prescribing options
(Dependent on severity of side effects balanced against risk of graft rejection):
• Switch back to MMF 500mg BD?
• Switch back to MMF but reduce dose to 250mg BD?
• Stop MMF/MPS?
• Switch to azathioprine (generally less GI tolerability problems than MMF/MPS – discuss dose regimen with consultant nephrologist or senior renal pharmacist)?
• Reduce MPS dose to 180mg BD?
References


11. Simulect - product monograph


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