Use of Daclizumab in Preventing Delayed Graft Function in Non-heart Beating Donor Kidney Transplantation in Newcastle upon Tyne*

Introduction: Use of marginal kidneys, such as from non-heart beating donors (NHBD), offers the opportunity to compensate for the growing discrepancy for demand for kidneys and their availability from brain-stem dead donors. Such kidneys are prone to delayed graft function (DGF), which can be prolonged by nephrotoxic drugs including calcineurin inhibitors. This study aims to determine whether use of daclizumab (DZB) induction and delayed introduction of tacrolimus (TAC) can reduce the incidence of DGF without increasing the incidence of acute rejection.

Methods: Randomised controlled trial with two groups: (A) DZB with TAC delayed until serum creatinine < 350µmol/l (4.0 mg/l) or biopsy-proven acute rejection; (B) introduction of TAC immediately post-transplant. Both groups also received mycophenolate mofetil and prednisolone. Machine perfusion and viability assessment based on flow characteristics and perfusate enzyme levels was used for all kidneys.

Results: Immediate function in 53% of DZB and 13% of TAC group (p=0.02). Acute rejection in 22% of DZB group and 39% of TAC group (p=NS). Groups well matched demographically, although higher recipient cardiovascular risk score was observed in DZB group (5 vs. 3, p=0.01).

Conclusion: Use of DZB with delayed introduction of TAC reduces the incidence of DGF in NHBD kidney transplantation, without increasing the incidence of acute rejection. This strategy may be beneficial in kidney transplantation from other forms of marginal donors.

Key words: NHBD, kidney, transplantation, daclizumab, basiliximab, IL-2 receptor antibody, delayed graft function, rejection

Schlüsselwörter: NHBD, Niere, Transplantation, Daclizumab, Basiliximab, IL-2-Rezeptor-Antikörper, verzögerte Transplantatfunktion, Abstoßung

Introduction

The greatest problem facing clinicians in transplantation today is the growing discrepancy between the increasing demand for organs and their decreasing availability from brain-stem dead donors(1-3). A solution to this problem is to expand the pool of potential donors by the use of organs from marginal donors, such as older donors, donors with previously unacceptable co-morbidity or non-heart beating donors (NHBD).

Kidney transplantation from non-heart beating donors is now an accepted therapy with established programmes in numerous centres, including ours. These have been shown to have similar long-term function(4) and identical graft and patient survival to kidneys from traditional heart-beating brain-stem dead donors(5), but experience higher rates of primary non-function (PNF) and delayed graft function (DGF) (6). Prolonged DGF has deleterious effects in the form of increased hospital stay, with a probable increased risk of hospital-acquired infection, and the morbidity associated with continuing dialysis requirement and renal biopsies. The increased incidence of PNF and increased incidence and duration of DGF can also deter transplant units from using NHBD kidneys, increasing waiting times for potential recipients.

The increased incidence of PNF and DGF are mainly due to acute tubular necrosis caused by the primary warm ischaemic injury that inevitably occurs in NHBD transplantation, but other effects of the ischaemia-reperfusion injury include endothelial injury with leakage and sequestration of pro-inflammatory mediators within the graft, increasing alloreactivity and therefore predisposing to acute rejection. Following transplantation, further insults to the already injured graft, such as dehydration or the use of nephrotoxic drugs, are likely to prolong the duration of delayed graft function, and care is therefore taken to avoid such insults.

The calcineurin inhibitors form a class of drugs which are nephrotoxic but hitherto often considered unavoidable in kidney transplantation. They cause constriction of the glomerular arterioles, increasing intra-renal resistance and inhibiting effective reperfusion of the graft following transplantation (7-9). Calcineurin-inhibitor reduction or avoidance could therefore be expected to reduce delayed graft function, but possibly at an unacceptable cost of increased incidence and severity of acute rejection.

Monoclonal (OKT3) and polyclonal (ATG and ALG) anti-T cell antibodies are often used in the prevention and treatment of acute rejection, especially in the United States. They may reduce the deleterious effects of DGF(10, 11) but are associated with significant short and long-term side effects(12-14) which we feel precludes their routine use. Basiliximab (Simulect™; Novartis, Surrey, UK) and daclizumab (Zenapax™; Roche, Herts., UK) are newer monoclonal antibodies directed against the CD-25 subunit of the IL-2 receptor on T cells, and thus inhibit the clonal expansion of T cells, antibody formation and cell-mediated immune responses. They have been shown to reduce the incidence of acute rejection when used as induction therapy with a calcineurin-inhibitor based immuno-suppressive regime without causing the side effects of cytokine release syndrome and post-transplant lymphopro-

Abbreviations

ATG anti-thymocyte globulin 
ATN acute tubular necrosis 
DGF delayed graft function 
DZB daclizumab 
IL-2 interleukin-2 
IL-2R interleukin-2 receptor 
NHBD non-heart beating donor 
PNF primary non-function 
TAC tacrolimus
liferative disorder that are associated with OKT3, ATG and ALG(15).

We hypothesised that use of induction therapy with an anti-IL-2 receptor antibody (daclizumab) could allow delaying the use of a calcineurin-inhibitor until DGF has resolved, and therefore aimed to determine whether such a strategy could reduce the incidence and duration of DGF without increasing the incidence of acute rejection.

Methods

A prospective, randomised, two-arm controlled trial to evaluate daclizumab, as part of a calcineurin sparing regimen to reduce the incidence and duration of delayed graft function in recipients of NHBD kidneys. The aim of the study was to demonstrate an improvement in graft immediate function rates from 5% to 40%.

The primary endpoint was the duration of delayed graft function (DGF), which was defined as the time from transplantation to the last session of haemodialysis or last peritoneal dialysis exchange, but excluding a single session of dialysis within 24 hours of the transplant operation performed solely to treat a high serum potassium level. Secondary endpoints were considered to be the creatinine clearance at the end of the three month post transplant study period (Cockcroft-Gault estimation); as well as the incidence and severity of acute rejection episodes.

The study formed part of a two-centre trial, but machine perfusion was only performed in one of the two centres, and we are reporting only the machine-perfused group here.

Study Protocol

Recipients of first non-heart-beating (Maastricht Category II, III and IV) kidneys were included in the trial. Exclusion criteria were pregnancy, previous transplant recipients and patients designated to receive ATG or OKT3 administration by local protocol. Patients designated to receive a non-heart-beating kidney graft were, after appropriate consent (operative procedure and clinical trial), allocated to a treatment arm. Randomisation was performed using an open, predesignated balanced block of four sequence; this ensured equal distribution between the treatment and control groups.

Kidneys were retrieved from controlled and uncontrolled NHBD donors (Maastricht categories II and III) using a previously described protocol(6), using double-balloon triple-lumen aortic catheters, inserted via a cutdown onto the femoral artery, to cool the kidneys and perfuse with cold Marshall’s organ preservation solution while laparotomy and retrieval of the organs could be arranged. Following retrieval, kidneys were machine perfused for 3 to 4 hours and a viability assessment made based on flow characteristics and perfusate enzyme levels.

The two trial groups received immunosuppressants according to the following schedule. Group A received an induction dose of 2mg/kg of daclizumab (DZB) and methylprednisolone 500mg intravenously before graft implantation. Subsequent doses of 1mg/kg daclizumab were given at 14 day intervals. Tacrolimus (PrografTM; Fujisawa, Middlesex, UK) was instituted, at a dose of 0.1 mg/kg/bd, when either the recipient’s serum creatinine had fallen below 350 µmol/l (4.0 mg/dl) or if there was evidence of acute rejection on core biopsy.

Group B had a single induction dose of methyl-prednisolone 500mg and tacrolimus started the following morning. Background immunosuppression in both groups was with mycophenolate mofetil (CellCept™; Roche, Herts., UK) (2g a day) and prednisolone (20mg od). Dosing of tacrolimus in both groups was aimed at maintaining a trough level between 8-12 ng/l.

All patients with DGF or displaying altered graft function underwent core biopsy at intervals of between five and seven days. Acute rejection was treated with three boluses of methylprednisolone 500mg administered intravenously on consecutive days. Persistent (steroid-resistant) rejection and severe (Banff IIIB/ III) rejection was treated by a course of ATG therapy.

Ethics

Ethical approval for the study was sought and obtained from the Newcastle regional ethical committees. All patients were supplied with a detailed, plain-English information sheet about the study and invited to participate on the basis of informed consent.

Statistical Analysis

Normally distributed data are reported as means. Non-parametric data are reported as medians with ranges. Between group analysis was performed using an independent samples t-test or Mann-Whitney U test for continuous variables as appropriate. For categorical variables probability values were calculated using the Fisher’s exact test, depending on the expected cell size. All tests were interpreted at a significance level of 0.05 and all p-values reported are for two-sided alternative hypotheses. Patients with primary non-function of their graft were censored from the analysis.

Results

A total of 51 patients were recruited into the two-centre study, with 36 in the machine-perfused group reported here. All patients consented to randomisation.

The two groups were well matched demographically (Table 1), although the mean Newcastle cardiovascular risk score (Table 2) was higher in the DZB group (5 vs. 3, p=0.01, unpaired t test). There were differences in outcome between the two groups (Table 3) of which the only incidence of immediate function was statistically significant (53% vs. 13%, χ² test). This lead to a median delayed graft function time to zero in the DZB group; one elderly (74 yrs) recipient had an extended period of delayed graft function (28 days) which reduced the statistical significance of this finding (p=0.20, MWU).

There was a higher incidence of infective episodes in Group A (Figure 1). All these infections were mild or moderate severity requiring no escalation in overall level of care of the patient (readmission or critical care intervention). The incidence of acute rejection was 22% in the DZB group and 39% in the TAC group (p=NS). One recipient in each group required treatment with ATG for steroid resistant or vascular rejection. Both recipients were discharged with functioning grafts.
Discussion

The incidence of immediate function was higher than expected in both arms of the trial (53% vs. 16%), but the higher incidence in the DZB group supports our initial hypothesis that delayed introduction of calcineurin inhibitors would reduce the incidence and duration of DGF. That there was no significant difference in incidence or severity of acute rejection supports the contention that anti-IL-2R provide sufficient immunosuppression in combination with mycophenolate mofetil and prednisolone to safely delay the introduction of calcineurin-inhibitors in the immunosuppressive regime.

There was a significantly higher cardiovascular risk score in the DZB, reflecting factors shown to increase the duration of DGF (16), and so if the two groups had been better matched, the difference in DGF rates may have been even greater than that observed.

Kidneys from non-heart beating donors form one type of marginal kidneys, but other marginal kidneys such as those from older or hypertensive donors are also at higher risk of DGF than kidneys from optimal donors. As transplant centres make greater use of marginal kidneys, it will be increasingly important to adopt strategies to minimise DGF and PNF. Although many of the factors predisposing to PNF and DGF are predetermined and beyond the control of clinicians managing the recipients, delayed introduction of calcineurin-inhibitors can be seen from this study to be a feasible and safe method of reducing the risk of DGF, confirming the results of previous studies on the effect of use of anti-IL-2R antibodies and delayed calcineurin-inhibitors on graft function (17, 18).

References

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Tab. 3: Graft and recipient outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group A (DZB) (n=17)</th>
<th>Group B (Control) (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNF (censored)</td>
<td>12% (2/17)</td>
<td>16% (3/19)</td>
<td>NS</td>
</tr>
<tr>
<td>IF</td>
<td>53% (8/15)</td>
<td>13% (2/16)</td>
<td>0.02 (*)</td>
</tr>
<tr>
<td>Duration of DGF</td>
<td>0 days (0-28)</td>
<td>7.5 days (0-16)</td>
<td>0.20 (MW U)</td>
</tr>
<tr>
<td>Courses of MP</td>
<td>0.5</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Courses of ATG</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Transplant biopsies</td>
<td>21</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>23 days (13-98)</td>
<td>21 days (14-50)</td>
<td>NS</td>
</tr>
<tr>
<td>Cr Clearance</td>
<td>50</td>
<td>57</td>
<td>NS</td>
</tr>
</tbody>
</table>

5 Median (range); 6 Number of treatment courses of Methyl-prednisolone per patient; 7 Number of treatment courses of ATG per group; 8 Total number of biopsies per group; 9 Median (range); 10 At 3 months (Cockcroft-Gault estimation) (ml/min)

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![Fig. 1: Infective episodes per group during the study period](image-url)