Original Article

Improved efficacy of basiliximab over antilymphocyte globulin induction therapy in paediatric renal transplantation

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Abstract

Background. Basiliximab is a chimeric human/mouse monoclonal antibody directed against the alpha chain of the IL-2 receptor, CD25, which has been reported as successfully reducing rejection in adult renal transplant recipients. Reported clinical experience of basiliximab in paediatric renal transplantation is limited.

Methods. Using two intravenous doses on day 0 (pre-operatively) and day 4 with prednisolone and cyclosporin A (dual) maintenance immunosuppression in 42 children undergoing renal transplantation in our unit (SIM group), we have compared patient and graft outcome, rejection rates in the first 6 months, renal function and the incidence of Cytomegalovirus (CMV) infection with 42 consecutive children who previously received antilymphocyte globulin immunoprophylaxis with prednisolone, cyclosporin A and azathioprine (triple) maintenance immunosuppression (ALG group). The two groups were similar, including HLA mismatching, apart from age and size at transplantation (SIM = 10.3 ± 5.4 years vs ALG = 12.4 ± 4.2 years, \( P < 0.05 \)).

Results. One patient in the SIM group died from food inhalation with a functioning kidney and one patient in the ALG group from Pneumocystis pneumonia and post-transplant lymphoproliferative disorders with a rejecting graft. Both 1- and 2-year actuarial graft survivals were 93% for the SIM group and 86% for the ALG group (NS). Three grafts were lost in the SIM group—none from rejection (thrombosis 2, death 1)—and seven in the ALG group—three from rejection. Occurrence of biopsy documented rejection in the first 6 months after transplantation was 0.15 ± 0.22 for the SIM group and 0.35 ± 0.51 episodes per pt-month at risk for ALG treatment (\( P < 0.04 \)). Early rejection within 30 post-operative days occurred in only four SIM patients, three of whom had undergone retransplantation. Forty-seven per cent of rejection episodes occurred between days 30 and 44 in SIM treated patients. Switching to tacrolimus was similar in both groups; 24% of the SIM groups were prescribed triple therapy. Estimated glomerular filtration rate was 46.0 and 46.2 ml/min for SIM and ALG groups, respectively, six months after transplantation. Ten per cent of SIM and 19% of ALG treated patients developed clinically significant CMV infection (NS) but none of 16 (R+ ) SIM children had CMV infection compared with 8 out of 15 (R+ ) ALG patients (\( P < 0.01 \)).

Conclusions. Basiliximab immunoprophylaxis and dual therapy reduces rejection episodes in the first six months and maintains graft survival and function after paediatric renal transplantation. Seventy-six per cent of children receiving basiliximab immunoprophylaxis were successfully maintained on long-term dual immunosuppression. This immunosuppressive protocol reduces CMV disease in CMV+ recipients compared with ALG induction and triple therapy.

Keywords: ALG; basiliximab; paediatric renal transplantation

Introduction

Antibody induction therapy has been used in renal transplantation to increase the allograft survival rate. Antibodies used in the past include antilymphocyte globulin (ALG), antithymocyte globulin (ATG) or anti-CD3 monoclonal antibodies (e.g. OKT3). Recently, a chimeric monoclonal antibody that recognizes the \( \alpha \)-chain of the IL-2 receptor, CD25, has been used successfully in adult renal transplantation as induction therapy [1,2], as well as in liver, cardiac, pancreas and lung transplantation. A 32% reduction in acute rejection episodes and a 56% reduction in steroid resistant rejection requiring ATG/OKT3 antibody therapy in the first six months after transplantation were observed. In these studies, European patients were maintained on prednisolone and cyclosporin A

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(dual) immunosuppression [1] and American patients on prednisolone, cyclosporin A and azathioprine (triple) therapy [2]. Little data have been published on the use of basiliximab in paediatric renal transplantation [3,4], but some have been reported for liver transplantation [5,6].

Historically, since the introduction of cyclosporin A in renal transplantation in 1983, we have used antibody induction therapy routinely for all allografts subsequent to a clinical audit, which revealed significant rates of steroid resistant or vascular rejection after renal transplantation requiring treatment with ATG. Because of our concern over the long-term consequences of additional immunosuppression, particularly post-transplant lymphoproliferative disorders (PTLD) and other neoplasms, we chose to emulate the European basiliximab trial in adults by using it as induction therapy followed by cyclosporin A and prednisolone dual maintenance therapy.

**Subjects and methods**

Forty-two children have received basiliximab induction therapy (SIM group) for renal transplantation, using two intravenous doses, respectively (pre-operatively on day 0 and on day 4; 10 mg if recipient’s weight <35 kg, 20 mg if ≥35 kg), in our paediatric renal unit since April 1998, together with prednisolone (60 mg/m² per day weaning to 10 mg/m² on alternate days by 13 weeks post-transplant) and microemulsion Neoral cyclosporin A (150 mg/m² b.d. orally with doses adjusted to maintain 12-h trough levels at 200 µg/l (months 1–3), then 150 µg/l (months 4–6) and around 100 µg/l thereafter).

For comparison of our clinical practice, the casenotes of 42 children previously consecutively transplanted with ALG induction (ALG group) using 0.2 mg/kg daily on days 0–3 together with prednisolone, microemulsion Neoral cyclosporin A (doses as above) and azathioprine (60 mg/m² per day from day 0) beginning May 1996, were analysed. The aetiology of the end-stage renal failure was similar, as shown in Table 1.

Renal dysfunction was investigated by urine microscopy and culture, repeat plasma creatinine, ultrasonography where appropriate and kidney biopsy. Documented cellular rejection Banff grade 3 or 4.1 was treated with methylprednisolone (600 mg/m²×3 daily doses) in the first 6 weeks after transplant or oral prednisolone (3 mg/kg/day×3 daily doses) from 7 weeks onwards. Banff grade 4.1b rejection resulted in azathioprine being added to the patient’s dual maintenance immunosuppression in the SIM group. If further Banff grade 3 or 4.1 rejection occurred, a switch to tacrolimus (initially 0.1 mg/kg b.d.) was made. Grade 4.2 rejection was immediately treated by switching to tacrolimus and methylprednisolone as above. Ten days of ATG antibody treatment was given if the tacrolimus response failed or was inadequate. No patient in either group received prophylactic ganciclovir medication.

Patient demographics, height, weight, transplant type and allograft number, HLA-A, -B and DR mismatches at the time of transplantation were recorded. Plasma creatinine, patient height and estimated glomerular filtration rate (GFR; 40 × height/plasma creatinine) 6 months after transplantation were compared with or without correction for the patient’s body surface area (BSA). The total number of renal biopsies, as well as those showing rejection, their Banff grade and their timing after transplant, together with the number of treatment ATG courses by 6 months post-transplant were analysed. Cytomegalovirus (CMV) status of donor (D) and recipient (R) and prevalence of disease (fever and malaise, pneumonitis, hepatitis) post-transplant were assessed. Patient and actuarial graft survival, \( \chi^2 \) tests for distribution variables and unpaired, two-tailed Student’s t-test for differences of means were calculated using SPSS (v9) statistical software.

**Results**

The clinical demographic data are shown in Table 1. There were more living donor grafts in the SIM group (\( \chi^2 = 4.98, \ P > 0.05 \)), but the number of HLA

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**Table 1. Demographic characteristics of renal transplant recipients and their allografts according to protocol**

<table>
<thead>
<tr>
<th></th>
<th>SIM group</th>
<th>ALG group</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (M/F)</td>
<td>42 (23/19)</td>
<td>42 (25/17)</td>
<td>NS</td>
</tr>
<tr>
<td>Recipient ESRF diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital dysplasia</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Congenital obstructive uropathy/reflux</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Genetic disease</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>FSGS</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pre-emptive transplants (no.)</td>
<td>14</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Age at transplantation (years, mean±SD)</td>
<td>10.3±5.4</td>
<td>12.4±4.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recipient’s BSA at transplantation (m², mean±SD)</td>
<td>1.056±0.413</td>
<td>1.271±0.370</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Live cadaveric donors</td>
<td>19/23</td>
<td>11/31</td>
<td>NS</td>
</tr>
<tr>
<td>No. re-grafts</td>
<td>6</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age (years, mean±SD)</td>
<td>29±13.4</td>
<td>26±16.3</td>
<td>NS</td>
</tr>
<tr>
<td>HLA mismatches (mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-A</td>
<td>0.74±0.54</td>
<td>0.68±0.53</td>
<td>NS</td>
</tr>
<tr>
<td>HLA-B</td>
<td>0.90±0.53</td>
<td>0.8±0.61</td>
<td>NS</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>0.43±0.5</td>
<td>0.43±0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>
mismatches at transplantation were similar. There were differences in mean age (±SD) of the recipient (SIM group, 10.3 ± 5.4 vs ALG group 12.4 ± 4.2 years, \( P < 0.05 \)) and consequently their BSA at transplantation.

One patient in each group died; the boy treated with ALG died of *Pneumocystis* pneumonia following treatment for persistent rejection at 83 days after transplantation. At post mortem, PTLD was discovered in the lung. The basiliximab-treated child, who died at 16 days post-transplantation, had recurrence of focal segmental glomerulosclerosis (FSGS) for which he was undergoing plasma exchange and, following a renal biopsy and bleeding, he vomited, aspired and could not be resuscitated. At the time of his death, his transplant was functioning with a plasma creatinine of 119 \( \mu \text{mol/l} \). Actuarial allograft survival at both 1 and 2 years was 93% for the SIM group and 86% for the ALG group (NS). In the SIM group, three allografts were lost, two from technical/surgical thrombosis immediately post-operatively, and one in the patient who died. Seven kidneys were lost in the ALG group; four from thrombosis and three from rejection (including the patient who died). One girl lost two transplants, one each with ALG and basiliximab therapy, from surgical/technical graft thromboses associated with homocysteinaemia and venous anomalies of the abdomen.

The mean number of renal biopsies performed per patient in the first 6 months post-transplant for renal dysfunction was halved with basiliximab therapy and biopsy-proven acute rejection was similarly reduced. Fifty-five per cent of basiliximab-treated patients had no rejection, 26% had one episode and 19% had two or more episodes (range 2–5 episodes, Figure 1). This compares with 38% with no rejection, 14% with one rejection episode and 48% with recurrent rejection on renal biopsy (range 2–9 episodes) for those children induced with ALG, which is not significantly different.

Three out of four children treated with basiliximab who showed rejection before day 28 had cadaveric re-grafts (Figure 2) and the other child, his first cadaveric allograft. Nine out of 19 rejection episodes with basiliximab therapy occurred between 30 and 44 days after transplantation. There was no difference in acute rejection severity in the first rejection biopsy between the two protocols and the frequency of switching to tacrolimus-based immunosuppression. Azathioprine was added to the maintenance immunosuppression in only 24% of basiliximab-treated recipients.

Renal function 6 months post-transplantation, assessed by calculation of mean estimated GFR, \( \text{ml/min/1.73 m}^2 \) BSA was better at 69.1 ± 19 ml/min/1.73 m\(^2\) in the SIM group compared with 58.2 ± 21 ml/min/1.73 m\(^2\) for the ALG group (\( P < 0.04 \)). However, correcting for recipient’s body size, the absolute GFR 6 months after transplantation expressed as ml/min was no different (46.0 ± 46.2 ml/min for SIM and ALG groups, respectively). Stratification for the type of donor revealed no significant difference in renal function between the two protocols, despite more recurrent rejection being observed in the ALG group.

There were 4/42 cases of CMV disease in the SIM group and 8/42 cases in the ALG group (\( \chi^2 = 3.29, P > 0.05 \)). However, the prevalence of CMV disease in CMV\(^+\) combinations was significantly reduced with basiliximab and dual maintenance immunosuppression (Table 2, \( \chi^2 = 10.46, P < 0.01 \)); reactivation of recipient CMV infection was not observed. One SIM group D\(^-\)/R\(^-\) recipient had a primary infection. He was also simultaneously positive for Epstein-Barr virus by DNA PCR testing following tacrolimus, ATG and intravenous \( \gamma \)-globulin treatment for early persistent acute cellular and vascular rejection. In those receiving ALG immunophrophylaxis, reactivation was seen in 3/7 CMV\(^+\) recipients who were transplanted with CMV\(^+\) donors. None of the CMV\(^-\) ALG recipients developed CMV disease with CMV\(^+\) kidneys.

**Fig. 1.** The number of biopsy-confirmed rejection episodes observed in children within the first 6 months after renal transplantation for basiliximab (●) and ALG (○) immunophrophylaxis, according to the age of the recipient at transplantation.

**Fig. 2.** The timing of the first observed biopsy-confirmed acute rejection after renal transplantation in children receiving basiliximab (■) or ALG (□) induction.
Table 2. CMV disease after transplantation

<table>
<thead>
<tr>
<th>Group</th>
<th>D+/R−</th>
<th>D−/R−</th>
<th>D+/R+</th>
<th>D+/R+</th>
<th>I</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIM with disease</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>7</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ALG with disease</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

D, donor; R, recipient; +, CMV positive; −, CMV negative by serology.

*Between SIM and ALG for R+ combinations only.

Discussion

This report has assessed the clinical benefits of basiliximab immunoprophylaxis combined with dual maintenance immunosuppression over the use of ALG induction and long-term triple therapy in a single paediatric renal unit. It therefore extends the reported experience of this novel immunosuppressant in paediatric renal transplantation. Outcome measures, such as graft survival and function, the prevalence of acute rejection in the first 6 months after transplantation and CMV disease, greatly favoured basiliximab and dual therapy in children undergoing renal transplantation. Others, such as grade of acute rejection and early renal function, show no detriment. In this study, we arbitrarily analysed an equal number of consecutively transplanted children treated with ALG induction as a comparison group, with the hypothesis that the results obtained with basiliximab should not be worse. While this retrospective analysis in a single centre is not ideal, with the possible introduction of bias, the medical and surgical management of the two groups of patients by four clinicians and two surgeons did not differ in respect to matters other than immunosuppression prescribed. The two groups were well matched apart from recipient age and size (Table 1). These factors would tend to decrease allograft survival in the SIM group because of the increased risk of thrombosis and difficulties in stabilising cyclosporin exposure in young patients, but may produce better estimates of renal function based on a corrected body surface area. Mean calculated GFR based upon the recipient’s absolute BSA was no different at 6 months post-transplant. These weaknesses in our study design are fully recognized, but must be compared with the difficulties of organizing a prospective, randomized placebo-controlled trial in several paediatric renal transplantation centres.

Two large prospective placebo-controlled trials of basiliximab in 700 adult renal transplant patients have been published [1,2], which showed a significant decrease in rejection in the first year after transplantation. There was a 32% reduction in biopsy-confirmed acute rejection in the first 6 months (from 44% with placebo to 30% with basiliximab) and a 57% reduction in steroid-resistant rejection with the use of basiliximab in the European trial [1]. Kahan et al. [2] reported very similar results in the US study. Dual or triple maintenance therapy did not make any difference to rejection rates or 1-year allograft survival. Martins et al. [7] reported a 10% rejection rate in a small prospective open trial in adults comparing basiliximab with ATG (42% rejection rate) with triple immunotherapy, but this was not statistically different.

Our results may be interpreted as being disappointing when compared with rejection rates observed in the adult studies. Historically, rejection rates in paediatric renal transplants have been reported to be 44% in children treated with antibody induction (Minnesota ALG) and cyclosporin-based triple therapy [8]. North American Pediatric Renal Transplant Co-operative Study (NAPRTCS) data show 50% of paediatric renal transplant recipients experience rejection in the first year after transplantation [9]. There are few data about the use of basiliximab or daclizumab (an alternative humanized anti-CD25 monoclonal antibody) in paediatric renal transplantation, with reported rejection occurring in 16–50% of recipients [4,5]. Our data compare favourably with these results considering that lower cyclosporin doses and trough levels as well as long-term dual maintenance therapy were used. An international multicentre uncontrolled pharmacokinetic, tolerability and safety trial of basiliximab in children receiving de novo renal transplants has been carried out. The observed prevalence of acute biopsy-proven rejection episodes was 24% in the first 6 months (unpublished results, Offner et al.). In our unit (of whom only two patients were enrolled in the multicentre study), a reduced rate of rejection was observed compared with ALG induction. Most importantly, no kidney in the SIM group was lost through rejection, which contrasts with three allograft losses due to rejection in the ALG treatment group. One- and 2-year actuarial graft survivals were better in basiliximab-treated children, but not statistically significantly so. Our results also demonstrated that 76% of basiliximab-treated children were spared long-term triple immunosuppression.

Despite less long-term immunosuppression, the biopsy-documented rejection rate was halved with basiliximab in the first 6 months after transplantation with no difference in rejection severity recorded in the two groups, either with the first documented rejection grade or the mean of all episodes taken over the first 6 months (Table 3). Our results suggest basiliximab produces easier clinical management in young renal transplant recipients. Noticeably, rejection was recurrent in children older than 6 years treated with ALG and unusual in the basiliximab-treated group (Figure 1), all of whom were teenagers. Whether this reflects better inhibition of naive T-cell responses...
in very young children, which may be more dependent on IL-2, or whether basiliximab allows sufficient time to stabilize cyclosporin A therapy more adequately in young recipients, is unknown.

Early rejection was observed with basiliximab during the period when the antibody levels should have saturated lymphocyte IL-2Rs. This occurred in three re-transplanted children (all of whom had lost their previous graft soon after transplantation from thrombosis/rejection) and one other who had severe vascular rejection in his first cadaver graft. We cannot be sure he was not sensitized prior to transplantation as another paediatric renal unit had previously cared for him. However, we did not observe any post-transplant HLA antibody production.

While the lack of frequent rejection in the first 30 days after renal transplantation is advantageous with basiliximab immunoprophylaxis, we observed that 47% of the documented rejection episodes in the first 6 months after basiliximab induction occurred between days 30 and 44 (Figure 2). With the recommended dosing of basiliximab, saturating levels of the antibody above 2 μg/l should last 30–45 days post-transplant in children (unpublished results, Offner et al.) [4,10]. The observed timing of rejection in our SIM group corresponds to the period when basiliximab levels were expected to fall below IL-2R saturating concentrations, as reported by Kovarik et al. [11] in adults and the multicentre international trial in paediatric renal transplantation (unpublished results, Offner et al.), and is similar to that reported by Strehlau et al. [4]. Vester et al. [5] reported this might reflect the use of lower cyclosporin doses as well as IL-2R desaturation with basiliximab. Unlike Strehlau et al. [4], we did not observe lower trough cyclosporin levels at the time of rejection. Whether the common occurrence of rejection at 5–6 weeks after transplantation can be avoided with triple maintenance immunotherapy requires further study.

Introduction of tacrolimus for severe or steroid-resistant rejection was similar for the two groups of children but more ALG-treated children received ATG antibody as treatment for vascular rejection. Only 24% of basiliximab-treated patients had azathioprine prescribed, which was a benefit for the remaining 76% of patients.

Clinically significant CMV infection is common when large doses of steroids are used for treatment of rejection, particularly in the setting of a CMV positive donor organ or recipient being transplanted. Cytomegalovirus infection was not reported as being more common in adult renal transplant patients treated with basiliximab compared with placebo [1]. The number of children who developed fever and malaise or invasive CMV disease in our study was less overall, but not significantly so, in the SIM group, in keeping with the reduced rejection rates and need for high doses of steroids. This was particularly so when CMV + recipients were transplanted (Table 2, 0/16 SIM patients vs 8/15 ALG patients, P < 0.01). In contrast to this finding, none of the nine ALG-treated CMV– children had CMV infection when they received a CMV + kidney. These data illustrate a benefit for the majority of SIM patients as it removes the need for ganciclovir medication, either as treatment or prophylaxis.

The results using basiliximab induction with dual maintenance immunosuppression have improved the outcomes for paediatric renal transplant recipients in our unit. Less rejection, less CMV infection and less maintenance immunosuppression in the early post-transplant period are positively encouraging. These early results support our belief that basiliximab offers a marked clinical improvement over ALG induction in the initial clinical management of paediatric renal transplant recipients.

### References


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