Original Articles

Effect of steroid-free low concentration calcineurin inhibitor maintenance immunosuppression regimen on renal allograft histopathology and function

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Abstract

Background. The most common cause of late kidney transplant failure is insidiously progressive renal dysfunction associated with organ scarring and fibrosis. Advanced donor age, delayed graft function, calcineurin toxicity and repeated acute rejection episodes are risk factors for this pathophysiology.

Methods. We employed 3, 12 and 24 months surveillance renal biopsies, scored using the Chronic Allograft Damage Index (CADI), with periodic estimates of glomerular filtration rate (eGFR) to assess the effect of a steroid-free maintenance immunosuppression regimen on allograft histology and function. Ninety-one patients were induced with Alemtuzumab and then treated with mycophenolate sodium and low trough concentrations of tacrolimus.

Results. Fifty-six of 91 patients followed for 24 months showed no clinical rejection and in 16 more only minimal histological or borderline changes as defined by Banff criteria were observed. Histologically acute rejection was observed in 14 patients including two detected on surveillance biopsy. Five patients refused biopsies but showed stable eGFR for 24 months. Graft histopathology in the group with no rejection did not worsen. In contrast, nearly half the patients with acute rejection showed progression of CADI scores and a total of four grafts were lost over the 2 years. The 16 patients with borderline rejection changes exhibited stable glomerular filtration rate throughout, but 12.5% showed progression of CADI scores in the 12- to 24-month period.

Conclusions. Following Alemtuzumab induction and in conjunction with low-dose tacrolimus and mycophenolate, continuous steroid therapy was not required to prevent progressive injury or preservation of graft function in patients without biopsy-proven acute rejection. Scored surveillance renal biopsies provide a useful tool to monitor transplanted kidneys.

Keywords: graft survival; steroid free; surveillance biopsies

Introduction

Forty percent of renal allografts show progressive dysfunction starting months after transplantation and ultimately fail within a decade [1, 2]. More than 80% of renal transplant recipients with histologically proven graft scarring and fibrosis [3–5] experience progressive loss of renal function. Although the rate of rejection episodes has declined, severe, recurrent or late rejection episodes remain major risk factors for graft loss from progressive scarring [6–8]. This form of graft injury was designated chronic allograft nephropathy (CAN) [9]. Subsequently, the term interstitial fibrosis and tubular atrophy (IF/TA) helps to define the pathological changes that mark this destructive process [10].

Corticosteroids are used in transplant recipients to avoid acute rejection, interstitial fibrosis, glomerulosclerosis and reduce graft loss [11]. Steroids carry the risk of hypertension, post-transplant diabetes mellitus, hyperlipidemia, osteopenia, avascular bone necrosis and premature cataracts, and increase patient morbidity and mortality [12]. Consequently, transplant immunosuppression seeks to minimize or obviate the need for steroids. Calcineurin inhibitors (CNI) dramatically reduce early rejection episodes but can themselves cause both acute and chronic nephrotoxicity. The acute phase of renal injury may be accompanied by minimal histological changes and be reversed with a CNI dose reduction, whereas the chronic nephrotoxic phase is characterized by often irreversible histologic lesions especially arteriolar hylanosis [13, 14].

Assessing patients for progression of fibrosis, vascular sclerosis and tubular atrophy can be challenging. Comparing Chronic Allograft Damage Index (CADI) in sequential surveillance biopsies, however, has been found to be useful to evaluate progressive graft fibrosis [3, 15, 16]. We studied graft status using serial CADI-scored surveillance biopsies and repeated estimated glomerular filtration rate (eGFR) in consecutive patients maintained on corticosteroid-free low-dose CNI immunosuppression after Alemtuzumab induction.
Materials and methods

Study design

This retrospective analysis was approved by University of Buffalo Health Sciences Institutional Review Board. It involved all 91 renal allografts between September 2004 to August 2007, which employed this regimen.

Immunosuppressive regimen

Patients were induced with two doses of intravenous (IV) Alemtuzumab (Campath-1H Genzyme, Cambridge, MA). The first dose was given immediately prior to renal transplant (0.3 mg/kg, maximum dose 30 mg), followed by the second 24 h later (0.15 mg/kg, maximum dose 15 mg). Patients were premedicated with acetaminophen 650 mg orally, diphenhydramine 50 mg IV and methylprednisolone 500 mg IV prior to the first dose and 250 mg IV before the second dose of Alemtuzumab. Maintenance immunosuppression initiated on post-operative Day 2 consisted of tacrolimus (Astellas, Deerfield, IL), to achieve a trough concentration of 5–8 ng/mL, and mycophenolate sodium (Novartis, East Hanover, NJ) with a target dose of 720 mg twice daily.

Fifteen patients, separate from the 91 study patients, underwent renal transplantation from September 2004 to August 2007 but were not induced with Alemtuzumab. Our protocol excluded those receiving a kidney remotely, following another organ (heart, liver) (n = 2) and individuals undergoing the third or more renal transplant (n = 3). These five subjects received rabbit antilymphocyte globulin (Thymoglobulin; Sangstat, Fremont, CA). The remaining 10 subjects were induced with either Thymoglobulin (n = 9) or Simulect (n = 1) (basiliximab; Novartis) at the discretion of the on-call transplant team. These 10 patients included 5 males and 5 females, only one of whom had panel reactive antibody (PRA) >20%. The racial mix mirrored the larger group (Table 1).

Anti-infection prophylaxis

Valganciclovir (Roche, Nutley, NJ) was used for cytomegalovirus (CMV) prophylaxis if the donor was CMV antibody positive. For CMV-negative donors, Acyclovir (Abrexis, Schaumberg, IL) was prescribed for herpes simplex prophylaxis for 3 months. For pneumocystic carinii pneumonia prophylaxis if the donor was CMV antibody positive. For CMV-negative patients with sulfa allergy were administered aerosolized pentamidine monthly.

Follow-up

Patients were monitored daily while hospitalized. Subsequently, they were seen in the transplant clinic weekly for the first month, once or twice monthly for the next 2 months and monthly thereafter for 6 months with quarterly visits over the next 18 months. Glomerular filtration rate (GFR) was estimated using Modification of Diet in Renal Disease equation [17].

Table 1. Characteristics of the 91 patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Caucasian</th>
<th>African-American</th>
<th>Hispanic</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>63</td>
<td>28</td>
<td>63 (69.24%)</td>
<td>59 (64.83%)</td>
<td>24</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Mean recipient age</td>
<td>48.5 ± 10.2</td>
<td>56 (61.53%)</td>
<td>35 (38.47%)</td>
<td>45.38 ± 12</td>
<td>35 (38.47%)</td>
<td></td>
</tr>
</tbody>
</table>

Patients who underwent needle core biopsies at 3 months, 9–12 months and at 24 months. Histological changes were examined on 17 stained slides from each biopsy (11 hematoxylin–eosin, 3 PAS and 3 Gomori’s trichrome stains). The biopsy sample was judged adequate if at least five glomeruli and three arterioles were detected. CADI is a quantitative scoring system composed of six elements, each contributing up to 3 points to a total of 18 [9, 14, 16]. The components evaluated were (i) interstitial chronic inflammation, (ii) interstitial fibrosis, (iii) glomerular matrix expansion, (iv) glomerulosclerosis, (v) intimal proliferation of blood vessels and (vi) tubular atrophy. A zero score was assigned if the segment was normal or <10% of kidney parenchyma or glomeruli were affected. A score of '1' was assigned when 10–30% was abnormal; the sample was scored '2' if 30–60% of the tissue showed changes. Morphologic alterations affecting >60% of the component was assigned a score of '3'.

The renal allograft biopsies were scored independently by two pathologists. If the total CADI scores differed, a consensus reading was attained after the pathologists simultaneously reviewed the biopsy. Ten percent of the biopsies, chosen by the nephrologist, were de-identified and rescoring by the lead pathologist. Mean difference between the initial and second score was 0.45.

Patients were divided into two groups based upon biopsy results: (i) biopsies with cumulative CADI scores <4 and (ii) biopsies with CADI scores ≥4. Progression of graft injury was assessed based on the number of recipients who advanced from the low-CADI group to the high-CADI group at the next scheduled biopsy. This cutoff was chosen because Yilmaz et al. [16] showed that patients with CADI score ≥4 at 1 year were more likely to have graft failure at 3 years when compared to patients with CADI score <4. Immunofluorescence microscopy was performed on all specimens as a staining for complement degradation product C4d (ALPCO Diagnostics, Salem, NH). Biopsies showing tubulointerstitial inflammation and clinical and/or histopathologic suspicion of BK virus infection/viral cytopathic effect were stained with BK BioProbe (Enzo Life Sciences Inc., New York, NY). Both immunofluorescence and immunohistochemical stains were appropriately controlled. Electron microscopy was performed in all cases when the patient had a primary glomerulonephritis or significant proteinuria, and on any biopsy where glomerular abnormalities were noted on the light or immunofluorescence microscopy and could not be definitively explained using those techniques.

Clinical biopsies

Twelve patients experienced graft dysfunction manifested by a rise in serum creatinine >20% from baseline or new-onset proteinuria or hematuria. These patients had additional biopsies beyond the protocol. The protocol schedule was resumed if graft function improved or stabilized.

Table 2. Chronic Allograft Damage Index (CADI) scores at 3 and 12 months*

<table>
<thead>
<tr>
<th>CADI score</th>
<th>3 Months</th>
<th>12 Months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>54 (96.4%)</td>
<td>51 (91%)</td>
<td>0.43</td>
</tr>
<tr>
<td>≥ 4</td>
<td>2 (3.6%)</td>
<td>5 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with no episodes of acute rejection (n = 56).

Patients with borderline rejection (n = 16).

Table 3. CADI score in patients with three biopsies at 24 months (n = 34), who had no rejection*

<table>
<thead>
<tr>
<th>CADI score</th>
<th>3 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>32 (94.1%)</td>
<td>30 (88.2%)</td>
<td>30 (88.2%)</td>
<td>0.64</td>
</tr>
<tr>
<td>≥ 4</td>
<td>2 (5.9%)</td>
<td>4 (11.8%)</td>
<td>4 (11.8%)</td>
<td></td>
</tr>
</tbody>
</table>

* Differences between CADI scores at 3 and 12 months were assessed using chi-square.
**Delayed graft function**

Delayed graft function (DGF) was defined as the requirement for dialysis within 7 days after transplantation [18].

**Rejection**

Acute cellular rejection, acute antibody-mediated rejection and borderline changes were defined using the 2007 revision of the Banff classification [19].

**Statistical analysis**

Mean and SE values were calculated for all variables. The difference between means was calculated using chi-square test or Fisher exact test for categorical values and analysis of variance test and independent test for continuous variables. Reported P-values are two tailed and are considered statistically significant if $<0.05$. All analyses were performed using SPSS version 16.1 software (SPSS, Inc., Chicago, IL).

**Results**

Ninety-one patients were transplanted from September 2004 to August 2007 using this immunosuppression regimen. Demographics and clinical characteristics of the recipients and grafts are depicted in Table 1. Five of the 91 patients refused surveillance biopsies and developed no clinical indications for biopsy. All five had functioning grafts 24 months post-transplant. The average eGFR for this group at 24 months was 57.3 ± 3.5 mL/min.

Eighty-six patients had at least two biopsies. Of these 86 patients, 56 had no episodes of rejection, 16 had borderline or less histologic change [19] and 14 patients had clinical rejection. Eleven of the 14 who developed cellular rejection, 2 developed humoral rejection and 1 had evidence of both. The group of patients designated acute rejection included two who unexpectedly showed Banff Type Ia or more severe changes on scheduled biopsies.

Of the 56 patients with no evidence of rejection on the 3-month biopsy, only 3 (5.6%) progressed from a lower to a higher score on the second biopsy undertaken between 9 and 12 months post-transplant ($P = 0.43$) (Table 2). Thirty-four of 56 clinical rejection free patients underwent a third biopsy 2 years post-transplant. Of these individuals, 94% ($n = 32$) had CADI score of $\leq 4$ (Table 3) and showed no evidence of progression from the 9- to 12- to the 24-month biopsy. Of the remaining 22 patients, 12 refused, 3 died (2 cancer, 1 cardiac), 2 were lost to follow-up and 5 moved to another state (Figure 1). eGFRs were available from 16 of the surviving 19 patients at 24 months. Neither of the two grafts for which we did not have direct information was reported as failed to the United Network for Organ Sharing.

Sixteen patients (17.6%) had evidence of borderline or minimal rejection at 3 months or 12 months. These patients were managed by increase of both mycophenolate and tacrolimus to the upper limits of the protocol without the addition of corticosteroids. At 12 months, none progressed from low to a higher CADI score (Table 2). Eight of the 16 had biopsies at ~24 months and only one moved to a higher CADI score. All patients had functioning grafts at 24 months. The eight who did not have a third surveillance biopsy included six who refused and two who left the area.

Fourteen patients (16.3%) had at least one biopsy-proven acute rejection. Two of the cases were identified on
surveillance biopsy before any change in function was detected. Three of these lost their graft within 1 year. Of the 11 grafts that survived at least 1 year, 8 had initial CADI score of <4 but 6 progressed to a CADI score >4 on the 1-year biopsy. Of the six biopsies that showed worsened CADI scores, three showed persistent rejection and three other had newly discovered rejection. The other three patients had initial CADI scores >4 and the 1 year biopsies in this group showed no change. Another graft was lost between 1 and 2 years in the acute rejection group. Nine of the 10 patients with surviving grafts underwent 2-year biopsies (one refused). One biopsy exhibited improvement to the <4 from the >4 category. The CADI scores of the other eight with biopsies remained >4. Excluding the three individuals who died with functioning grafts, the four grafts lost in the patients with acute rejection were the only failures in the 91 subjects.

Five patients with no acute rejection showed evidence of calcineurin toxicity on the biopsy at 3 months and were managed by lowering the tacrolimus dose.

**Renal function studies**

Renal function was monitored at 3, 6, 9, 12 and 24 months using eGFR. The mean eGFR of patients with no clinical rejection remained stable through the 2 years (Table 4). In patients with borderline or less changes, the mean eGFR also remained stable >24 months. The mean eGFRs of patients with at least one episode of acute rejection are shown in Table 4. The mean eGFR of the 34 patients who underwent the 24-month biopsy was 53.7 ± 2.8 mL/min and did not differ (49.1 ± 3.5 mL/min) from the 16 patients with functioning grafts who did not undergo biopsy at 24 months.

**Discussion**

Newer immunosuppressive drugs have dramatically improved the short-term outcome of renal allografts. Acute rejection rates have declined to ~15–25% and 1-year graft survival rates have risen to >90% [20]. Despite these advances, progressive renal dysfunction, fibrosis and scarring remain the major hurdles to long-term allograft survival. This clinical–pathologic scenario is the cumulative consequence of any and all immunologic and non-immunologic injuries to the renal allograft [6, 14, 21]. Importantly, pre-existing conditions in the donor organ also affects the outcome of the graft. Approximately, 30–40% of donor grafts at the time of transplantation show a pattern of mild histologic change, as seen in so-called CAN or IF/TA [22, 23].

Recurrent and late clinical rejections remain a major risk factor for development of this destructive process. Steroid withdrawal may be associated with an increased risk of acute rejection or accelerated graft scarring in the absence of overt rejection [24]. Steroid-free immunosuppression with CNI, mycophenolate or sirolimus has resulted in good graft survival with little or no increase in the rate of acute rejection [25–33]. A newer approach using Alemtuzumab induction followed by CNI and mycophenolate maintenance therapy either without steroids [34–36] or with early steroid withdrawal [37, 38] has also shown good allograft survival without increasing the incidence of acute clinical rejection. However, mild rejection and early allograft injury could have gone undetected since periodic renal biopsies were not done.

Glucocorticoids exert their action via the glucocorticoid receptor, which has been described to have pleiotropic effects on multiple signaling pathways that mediate the anti-inflammatory and immunosuppressant effect of these compounds [39]. Interference with fibroblast proliferation by induction of a cyclin kinase inhibitor is one of the identified anti-fibrotic actions of glucocorticoids [40–42]. Would steroid-free maintenance increase the incidence and progression of graft fibrosis and consequent functional impairment? Our data does not support this notion. Alemtuzumab induction, low-dose CNI and mycophenolate without maintenance corticosteroids >2 years, was associated with little evidence of progressive graft injury by the CADI-scored protocol biopsies and eGFR in the group who experienced no or only subclinical (borderline) rejection.

Nematalla et al. [43] reported no difference in the incidence of acute rejection and 1-year graft survival in patients induced with basiliximab (Simulect; Novartis) and treated with only tacrolimus, mycophenolate mofetil compared to the group maintained on tacrolimus, mycophenolate mofetil and corticosteroids. Hypertension, diabetes mellitus and weight gain, all of which can result from the actions of glucocorticoids [39], occurred more frequently in the patients receiving steroids. The CADI score of biopsy specimens at 1-year follow-up was comparable in both groups. In another study, steroid

**Table 4. eGFRs at different time points**

<table>
<thead>
<tr>
<th></th>
<th>3 Months</th>
<th>6 Months</th>
<th>9 Months</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with no acute rejection</td>
<td>54.76 ± 2.31</td>
<td>54.54 ± 2.49</td>
<td>53.85 ± 2.63</td>
<td>54.38 ± 2.63</td>
<td>54.29 ± 2.83</td>
</tr>
<tr>
<td>With 24 months biopsy</td>
<td>52.22 ± 2.37</td>
<td>52.90 ± 2.65</td>
<td>52.95 ± 3.14</td>
<td>53.54 ± 2.7</td>
<td>53.66 ± 2.76</td>
</tr>
<tr>
<td>Without 24 months biopsy</td>
<td>50.52 ± 3.68</td>
<td>49.57 ± 4.01</td>
<td>48.31 ± 3.74</td>
<td>49.35 ± 3.64</td>
<td>49.13 ± 3.48</td>
</tr>
<tr>
<td>Patients with borderline rejection</td>
<td>49.18 ± 4.18</td>
<td>53.40 ± 4.67</td>
<td>50.90 ± 4.29</td>
<td>52.18 ± 4.12</td>
<td>52.45 ± 4.71</td>
</tr>
<tr>
<td>Patients with acute rejection</td>
<td>47.18 ± 5.78</td>
<td>52 ± 4.30</td>
<td>49.40 ± 4.79</td>
<td>51.20 ± 5.75</td>
<td>48.20 ± 5.83</td>
</tr>
</tbody>
</table>

*a Data expressed as mean eGFR (Modification of Diet in Renal Disease) ± SEM.*
withdrawal in African-American recipients with multiple high-risk factors was associated with excellent 1-year graft survival outcomes and minimal progression of graft scarring measured by Banff grading of surveillance biopsies [44]. Finally, Woodle et al. [45] conducted a double-blind placebo, but not surveillance biopsy controlled, multicenter study and showed that steroid withdrawal was associated with an increased rate of usually reversible acute rejection but had no substantial effect on graft function and survival ≥5 years.

CNI can cause microvascular and glomerular damage, arteriolar hyaline deposition and interstitial fibrosis [46]. Nephrotoxicity in the first year post-transplant correlates with the 60% rate of such pathology in CNI-treated recipients [47]. We targeted relatively low tacrolimus trough levels of 5–8 ng/mL in the immediate post-transplant period and yet found evidence suggesting calcineurin toxicity in 5 of 56 (9%) patients at 3 months. The dose of tacrolimus was decreased to the lower limit of the target range and no evidence of toxicity was noted in the subsequent biopsies.

The composite CADI score was employed to assess the progression of chronic graft histologic injury. Evaluation of the six CADI score components is routine for biopsy assessment. The application of established specific quantitative criteria for each histological component allows for reproducible numerical comparisons of chronic changes in serial biopsies [3, 14, 16]. One year CADI score can predict graft survival even when the graft function is still normal. Elevated 2-year CADI score forecasted subsequent failure of clinically healthy grafts 6–8 years post-transplant [47].

CADI scoring is a useful surrogate endpoint in prevention trials, helps to identify patients at risk for intervention and to predict long-term graft survival and function [16, 48]. CADI scoring, however, cannot differentiate between immunological and non-immunological causes of the same pathological findings. Histological changes can be focal, allowing sampling errors. The score may rise and fall as acute rejection is treated. Patients with acute rejection may be viewed separately since their CADI scores may be influenced by the potentially reversible inflammatory component of the rejection reaction and not have the same prognostic implications. Few studies have employed IF/TA as a predictor of graft survival. Seron used the IF/TA grading system [49] where cyclosporine was discontinued and reported less severe chronic lesions in protocol biopsies at 3 years and improved graft survival at 4 years. The value of IF/TA as a surrogate for graft survival shows promise [50]; however, data from larger trials are required. The ideal scoring system to assess graft prognosis may yet to be devised [51].

Our patient group was at above average risk to develop acute rejection. Thirty percent of patients were African-American and/or Hispanics, 18.7% had PRA >10, ~60% of patients with four or more human leukocyte antigen mismatches, 14.3% had DGF and 10% who had prior transplants, yet only 16.3% experienced acute rejection [1, 2, 14, 20, 52]. Alemtuzumab induction has been shown to reduce the rate of acute rejection only in low-risk and not in high-risk patients [53]. Following treatment for acute rejection which included corticosteroids, >60% of the patients fared well as evidenced by GFR and histology but this group experienced the highest graft loss rate. Half of the graft losses occurred in patients who experienced antibody-mediated rejection. Woodle et al. [45] found a similar rate of acute rejection, death and graft loss at 2 years in patients in the corticosteroid withdrawal arm of a study designed to compare steroid cessation to continued low-dose corticosteroids in subjects at somewhat lower risk to develop acute rejection.

Surveillance biopsies in 34 of our patients with no rejection 2 years after transplant showed no change from the 1-year biopsy results. In the subgroup of 19 remaining patients (3 died) not biopsied, serum creatinines were available for most subjects. The mean eGFR in this subgroup was not different from the biopsied group, suggesting that selection bias did not occur.

Subclinical rejection episodes may lead to persistent chronic inflammation and have been associated with poor graft survival [54, 55]. Surveillance biopsies in the patients reported herein demonstrated lack of progressive graft injury and frequently guided care. For instance, the borderline histological changes identified in 18.6% of all biopsied patients were treated only by adjusting the tacrolimus and/or mycophenolate with no supplemental glucocorticoids. Employing this approach, we found that none of the 16 patients with borderline or less evidence of rejection by Banff criteria progressed from low score to a higher CADI score group by 1 year, but 1 of the 8 patients in this group showed progression from a low to a higher CADI score from the 1- to the 2-year biopsy. The eGFRs of these patients remained stable.

Our report has two major limitations. Firstly, a control group treated with a steroid-based higher trough CNI targeted immunosuppressive maintenance was not employed. Secondly, only 61% of the 72 patients with no clinical rejection underwent a 2-year protocol biopsy. The remainder who refused biopsy or transferred care at the 24-month interval, however, had eGFR no different from the biopsied majority.

In summary, renal transplant recipients who did not experience clinical rejection induced with Alemtuzumab and maintained on a steroid-free low-dose tacrolimus and mycophenolate protocol for 2 years showed little or no evidence of progressive graft damage as assessed by CADI-scored surveillance biopsies and serial eGFRs. Whereas all patients who experienced acute rejection and some with borderline changes appeared to be at risk of continuing graft injury. Biopsies proved useful not only to assess graft inflammation and scarring but sometimes affected care and may have abrogated graft injury. Graft protection afforded by maintenance corticosteroids, however, is still felt by many to outweigh the potential side effects of these agents [56]. Extended controlled studies employing periodic biopsies may be required to define the risk/benefit ratio of maintenance corticosteroid low-dose calcineurin therapy in various risk categories of renal transplant recipients.

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Conflict of interest statement. None declared.
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