Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Comparison of efficacy of induction therapy in low immunologic risk African-American kidney transplant recipients

James N. Fleming,[1,4] David J. Taber,[1] Nicole A. Weimert,[1] and Acknowledgement as participating investigators and scientific advisors: Maria F. Egidi,[2] John McGillicuddy,[3] Charles F. Bratton,[3] Angello Lin,[3] Kenneth D. Chavin[3] and Prabhakar K. Baliga[3]

1 Department of Pharmacy Services, Medical University of South Carolina, Charleston, SC, USA
2 Department of Medicine, Division of Nephrology, Medical University of South Carolina, Charleston, SC, USA
3 Department of Surgery, Division of Transplant, Medical University of South Carolina, Charleston, SC, USA
4 Department of Pharmacy Services, Henry Ford Hospital, Detroit, MI, USA

Keywords
African-American, ethnicity, graft survival, induction, kidney, transplant.

Correspondence
David Taber PharmD, BCPS, Department of Pharmacy Services, Medical University of South Carolina, 150 Ashley Avenue, PO Box 250584, Charleston, SC 29425, USA. Tel.: (843) 792-8532; fax: (843) 792-0566; e-mail: taberd@musc.edu

Received: 30 June 2009
Revision requested: 30 July 2009
Accepted: 19 October 2009
Published online: 20 November 2009

doi:10.1111/j.1432-2277.2009.01004.x

Summary

African-Americans (AA) have higher acute rejection rates and poorer long-term graft survival rates when compared with non-AA. It is yet to be demonstrated that the type of induction therapy modifies outcomes in this 'high-risk' population. This retrospective analysis compares the efficacy of induction therapy [antilymphocyte antibodies (ALA) versus interleukin-2 receptor antagonists (IL-2RA)] in the AA population. Some 189 AAs were included. There was no difference in acute rejection at one year between the groups (ALA (12%) or IL-2RA (12%), $P = 0.89$). Type of induction therapy had no significant effect on death-censored ($P = 0.61$) or uncensored graft survival ($P = 0.32$). There was no difference between CMV or BK virus infections between the groups ($P = 0.14$ and 0.94 respectively). Type of induction therapy does not appear to affect acute rejection rates or long-term graft survival in low-risk AA kidney transplant recipients.

Introduction

African-American (AA) kidney transplant recipients have historically been shown to have higher rates of biopsy-proven acute cellular rejection (BPAR) and lower graft survival when compared with non African-Americans (non-AAs). In one of the most current reviews of the United Network for Organ Sharing (UNOS) database for the period 1997–2006, standard criteria deceased (SCD) donor kidney adjusted graft survival at 5 years was 62% for AA compared to 72%, 74%, and 78% for Caucasian, Hispanic, and Asian recipients [1]. Many theories for this discordance have been suggested. Non-immunologic explanations, such as the 'center effect', poorly controlled hypertension, higher incidence of diabetes mellitus, longer wait times on dialysis, socioeconomic factors including noncompliance, educational background, less access to care, and delayed or decreased referral for transplant have been scrutinized, but many of these lack strong causative relationships [2–5].

Several immunologic mechanisms have also been implicated, including immune hyperresponsiveness, racial mismatching of minor-blood-group (Duffy) antigens, greater variation in human leukocyte antigen (HLA) polymorphisms, differences in immunosuppressive requirements, and variability in pharmacokinetics of immunosuppressive medications [6–10]. Because induction therapy has been shown to lead to less acute rejection, an independent risk factor for long-term graft survival, the use of induction therapy in AA kidney transplant recipients may help mitigate some of these immunologic risk factors [11,12]. In fact, many centers consider all AA 'high

immunologic risk' and give all of their AA kidney recipients T-cell depletive induction therapy and more aggressive maintenance immunosuppression when compared with their non-AA counterparts [4,8,9]. Despite this common practice, there is a paucity of evidence that antilymphocyte antibody (ALA) induction improves graft survival outcomes in the AA population when compared with interleukin-2 receptor antagonists (IL-2RAs).

The more recently developed IL-2RAs (basiliximab and daclizumab) have been studied to a greater degree in randomized trials than ALA and have demonstrated fewer BPAR when compared with no induction (NI). However, similar to ALA, they have not demonstrated any effect on long-term graft survival [11–13]. IL-2RAs have not been observed to have any short- or long-term adverse effects in regards to incidence of CMV infection or malignancy. This makes them an attractive option for induction use in low-risk kidney transplant recipients. However, in one recent prospective, randomized study, Thymoglobulin®, an ALA, was shown to be more effective at reducing the incidence of BPAR when compared with basiliximab in patients at high risk for delayed graft function (DGF) or rejection, including AAs [14].

Although it has not been proven to this point, there is speculation that AA ethnicity may no longer be a risk factor for higher incidence of acute rejection. This is possibly attributable to more potent immunosuppressive regimens and significant effort in ensuring coverage for transplant immunosuppressants [4,5]. Our institution has made a decision based on our experience not to consider AA ethnicity alone 'high immunologic risk' and has achieved similar short-term outcomes to our non-AA population in our most recent era of immunosuppression [15].

The study presented hereunder analysed 189 AA kidney transplant recipients that were immunologically low-risk and compared graft outcomes in terms of induction agent.

Materials and methods

Study design

This single-center evaluation was an analysis of all low-risk AA kidney transplant recipients that received induction therapy transplanted between August 1996 and June 2007 at our institution designed to investigate graft outcomes comparing induction therapy (ALA versus IL-2RA). This analysis was approved by the MUSC Institutional Review Board (IRB).

Immunosuppressant regimens

All patients initially received triple immunosuppressant regimens consisting of calcineurin inhibition, mycophenolate mofetil, and corticosteroids. Prior to 2004, most patients received cyclosporine-based regimens. After 2004, most patients were initiated on tacrolimus-based regimens unless adverse effects necessitated change to cyclosporine- or sirolimus-based regimens. Mycophenolate mofetil was dosed to target 1 gm twice daily in all patients receiving tacrolimus, while AA patients receiving cyclosporine received 1.5 gm twice daily; reduction was effected if necessitated because of adverse effects. All patients were started on a standard corticosteroid taper post-transplant, with a goal of 10 mg of oral prednisone daily by 3 months post-transplant. Induction therapy was based on protocol guidelines and transplant risk factors. Patients included in this analysis met our institution's guidelines for 'low immunologic risk' and would receive induction therapy with an IL-2RA. However, the ultimate decision on induction therapy was at the discretion of the attending surgeon performing the operation. Therefore, some patients received ALA based on surgeon's discretion, allowing for this comparison study. Patients that received ALA induction received Thymoglobulin® intravenously (IV) 1.5 mg/kg daily for 5 to 9 doses. Patients who received IL-2RA induction received either basiliximab 20 mg IV for two doses on days 0 and 4 (as practiced prior to January 2005) or daclizumab 1 mg/kg IV daily for two doses on days 0 and 7 (as practiced after January 2005). Immunosuppressive regimens were based on protocols that were in place before and during this entire analysis. Target 12-h whole blood trough concentrations for cyclosporine were as follows: weeks 1–6, 200–275 ng/ml, weeks 7–12, 175–225 ng/ml, months 3–12, 125–175 ng/ml, after 1 year, >70 ng/ml or as clinically indicated. Target 12-h whole blood trough concentrations for tacrolimus were as follows: weeks 1–6, 10–15 ng/ml, weeks 7–12, 8–12 ng/ml, months 3–12, 6–10 ng/ml, after 1 year, >5 ng/ml or as clinically indicated.

Patients

All eligible patients, transplanted between August 1996 and June 2007, were included in this study. Patients were included if they were of African-American race, received a kidney transplant at the MUSC Transplant Center, and were at least 18 years of age at the time of transplant. Patients were excluded if they were multiorgan transplant recipients, received investigational drug-based maintenance regimens, or were high immunologic risk patients (panel reactive antibody greater than 20% (PRA >20%), retransplants, B-cell positive cross-matches, and those that developed or were at high risk to develop delayed graft function (DGF) based on cold-ischemic time). No patients were excluded from this analysis because of being lost to follow-up.

Definitions

Acute rejection was defined as biopsy-proven acute rejection based on Banff 1997 criteria. Borderline rejections were included in this analysis if they had clinical signs and symptoms of rejection and were treated as an acute rejection episode with pulse-dose corticosteroids. Patients were considered to have DGF if they required dialysis within the first week post-transplant. Graft failure was defined as return to chronic dialysis. CMV syndrome was defined as CMV DNAemia with a fever ≥100.5°F on two occasions >24 h apart but within 7 days and at least one of the following: new or increased malaise, white blood cell count <3500/mm^3 or platelet count <100 000/mm^3. CMV disease was defined as signs or symptoms of organ dysfunction and evidence of a localized CMV infection in a biopsy. Patients were considered to have BK virus nephropathy if they had BK DNAemia with a biopsy consistent with BK nephropathy.

Outcomes

The primary outcomes of the analysis were acute rejection (ACR) at 1 year post-transplant and both death-censored and uncensored graft survival post-transplant. Secondary outcomes included incidence of CMV, BK virus infection, and SrCr at 1 year.

Statistical analysis

For univariate analysis, baseline demographics and outcomes were compared between the groups using the Student's *t*-test and one-way ANOVA for continuous data and chi-squared test for nominal data. Kaplan–Meier analysis was conducted for both death-censored and uncensored graft survival. Multivariate analysis was performed using Cox Proportional Hazards Survival Regression Analysis for graft survival rates to determine which covariates could independently influence these outcomes. This analysis was performed in the backward elimination fashion. Covariates included in the original model include primary maintenance agent (tacrolimus versus other), pre-emptive transplant versus dialysis-dependent, type of adjunctive agent (mycophenolate versus other), and1-year ACR. Statistical analysis was conducted using SPSS version 13.0 (SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered statistically significant.

Results

One hundred and eighty-nine patients met the inclusion criteria and were included in this study. Of these, 43 received ALA induction and 146 patients received IL-2RA. Baseline characteristics of the two groups are summarized in Table 1. Groups were well-matched and demographics and transplant characteristics were similar across induction regimens with the exception that significantly more patients in the IL-2RA group received cyclosporine as their primary maintenance agent (Tables 1 and 2).

As seen in the Kaplan–Meier analyses (Figs 1 and 2), there were no significant differences in either the death-censored or uncensored graft survival between the induction groups. Patient outcomes are reviewed in Table 3. There was no significant difference in the primary outcome of acute rejection at 1 year between the ALA (12%) and the IL-2RA (12%) groups. SrCr at 1 year was similar between the groups as well. There were also no significant differences in the length of follow-up or incidence of CMV or BK virus infections between the groups.

Table 1. Baseline demographics.

Baseline demographic	Anti-lymphocyte antibody AA (*N* = 43)	IL-2 receptor antagonist AA (*N* = 146)	*P*-value
Age	47 ± 11	47 ± 13	1.00
Gender			
Male	53%	55%	0.89
Female	47%	45%	
Years on Dialysis	3.8 ± 2.9	3.7 ± 2.2	0.81
Living Donor	5%	11%	0.29
Donor Gender			
Male	50%	68%	0.07
Female	50%	32%	
Donor Race			
AA	43%	25%	0.06
Non-AA	57%	75%	
Donor Age	27 ± 18	32 ± 14	0.06

Table 2. Immunologic characteristics.

Immunologic characteristics	Anti-lymphocyte antibody AA (*N* = 43)	IL-2 receptor antagonist AA (*N* = 146)	*P*-value
Cold ischemic time	1016 ± 550	992 ± 538	0.79
Warm ischemic time (min)	36 ± 10	36 ± 9	1.00
HLA mismatch	5	5	1.00
Pre-emptive	0%	3%	0.59
Perfusion	21%	32%	0.22
Maintenance			
Cyclosporine	33%	66%	0.001
Tacrolimus	67%	32%	
mTOR	0%	2%	
Adjunctive agent			
MMF/MPA	98%	91%	0.26
Other	2%	9%	

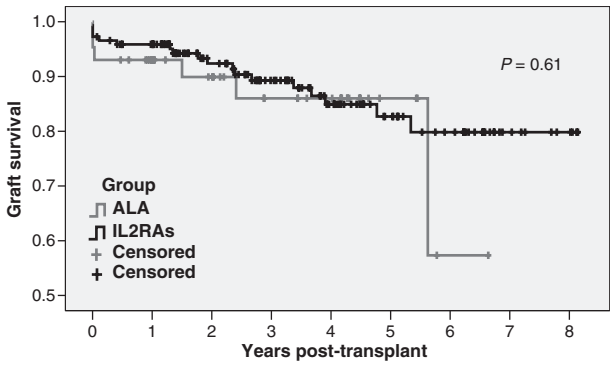

Figure 1 Kaplan–Meier death-censored graft survival curve.

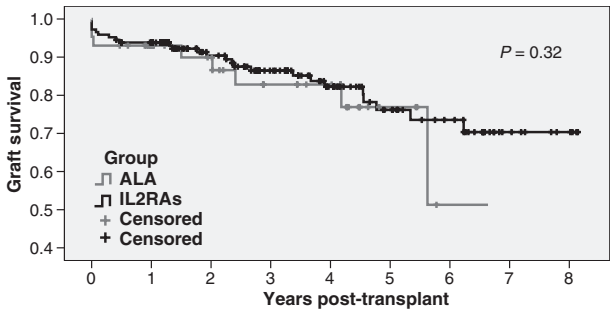

Figure 2 Kaplan–Meier uncensored graft survival curve.

In order to determine any effect baseline demographics and immunologic characteristics had on graft survival, multivariate analysis was conducted using a multivariate Cox Proportional Hazard Regression Analysis. These results are summarized in Table 4. Based on the results of the analysis, patients who developed ACR within 1 year were 2.87-fold more likely to have graft failure than those who did not develop ACR ($P = 0.03$). Although mycophenolate mofetil as an adjunctive agent trended towards being protective against graft failure, it did not meet statistical significance.

Discussion

The results of this single-center analysis suggest that despite AA patients having historically poorer long-term graft survival, induction therapy with potent cytolytic therapy does not improve outcomes in recipients considered at low immunologic risk. This is evident by the demonstration that there was no clinically or statistically significant difference between our induction groups in regards to acute rejection at 1 year or overall graft survival.

The data that we have presented is the largest analysis available in the literature to date with the longest follow-up on graft survival outcomes comparing induction agents in AA renal transplant recipients. In addition, no previous study has attempted to differentiate low-immunologic risk AA from otherwise high-immunologic risk populations.

Haririan *et al.* performed one of the previously largest comparisons of induction agents in AA renal transplant recipients. They retrospectively reviewed 88 AA recipients to analyse graft outcomes between patients who received Thymoglobulin® (36 pts) and basiliximab (52 pts) with an average follow-up of 19 months. It was found that there was no significant difference between the two groups in regards to patient survival (94% (ALA) vs. 88% (IL-2RA), $P = 0.8$), overall graft survival (86% vs. 81%, $P = 0.84$), death-censored graft survival (both 91%), or acute rejection (14% (ALA) vs. 29% (IL-2RA), $P = 0.1$) [16]. When compared with our study, the total number of patients in this study is much smaller and the follow-up period much shorter. In addition, Haririan, *et al.*

Table 3. Outcomes.

	Anti-lymphocyte antibody	IL-2 receptor antagonist	
Outcomes	AA (*N* = 43)	AA (*N* = 146)	*P*-value
1-year ACR	12%	12%	0.89
SrCr at 1 year	1.4 ± 0.4	1.5 ± 0.5	0.22
CMV infection	12%	4%	0.14
BK infection	2%	1%	0.94
Follow-up (days)	1043 ± 669	1230 ± 785	0.15

compare two groups with significant differences in baseline and immunologic characteristics. They are comparing high-risk AA recipients receiving ALA to low-risk AA receiving IL-2RA. Although an attempt was made to adjust for high-risk characteristics, a comparison cannot be made between Thymoglobulin® and basiliximab in similar risk groups among AAs.

In a prospective, randomized, international study using maintenance therapy of cyclosporine, mycophenolate mofetil and corticosteroids, Brennan, *et al.* compared 278 kidney transplant recipients to either Thymoglobulin® induction [141 pts (41 AAs)] or basiliximab [137 pts (39 AAs)] with a 12-month follow up. Patients who received Thymoglobulin® induction had significantly fewer episodes of acute rejection than those who received basiliximab (15.6% vs. 25.5%, $P = 0.02$). However, there were no significant differences between groups in regards to 1-year graft survival. Contrary to the analysis presented here, this study only included patients at 'high risk' for the development of DGF and acute rejection. Interestingly, although a subgroup analysis found a trend toward fewer incidences of acute rejection in the AA Thymoglobulin® group (20% vs. 33%), the difference did not meet statistical significance ($P = 0.14$) [14]. The study methodology in the Brennan article is more consistent with our analysis as compared with the Haririan study because it delineates high-risk versus low-risk recipients. However, their study only analyses high-risk recipients as compared with low-risk recipients in our analysis. Although this study had a large sample size, the number of AAs was still only 80. It was not specifically designed to analyse AA recipients or powered to detect a difference in AA recipient outcomes.

In a recent retrospective analysis, Hammond, *et al.* reviewed the efficacy of induction on acute rejection and graft outcomes in 175 kidney transplant recipients at a single-center. They found that there were significantly fewer acute rejection episodes at 1 year in patients who received either Thymoglobulin® or an IL-2RA compared to patients who received no induction (18% vs. 26% vs. 47%). The also found that patients who received IL-2RA had significantly better 3-year graft survival rates compared to patients who did not receive induction (85% vs. 68%). It is important to note that, while Hammond included a large number of AAs in the analysis, there was no differentiation between high- and low-immunologic risk recipients. There were a relatively large number of patients included who were retransplants, had PRA >20%, or developed DGF. This differs from our analysis significantly, as we only included low-immunologic risk recipients [19].

Table 4. Multivariate Cox regressions analysis.

Risk factor	Hazards ratio	95% confidence interval	*P*-value
Mycophenolate as adjunctive agent	0.39	0.15–1.06	0.07
Rejection at 1 year	2.87	1.13–7.32	0.03

The study presented here is a unique analysis of a large population of otherwise low-risk AA primary kidney transplant recipients. It is the largest analysis comparing induction regimens in this population with long-term follow-up. While it has been observed, as reported by Lebranchu among others, that low-risk *non-AA* kidney transplant recipients show no benefit in graft outcomes with Thymoglobulin® compared with IL-2RA, we report the first comparison of low-risk AA kidney transplant recipients [17,18].

The multivariate analysis in this study demonstrates that one of the most clinically significant independent risk factors for graft loss we found was acute rejection, which is similar to what Haririan, *et al.* found [16]. Haririan's group found DGF, number of HLA mismatches, and acute rejection to be independently associated with graft loss by multivariate Cox Regression Analysis. This is likely because of the high-risk population in their analysis.

Several limitations to this study must be addressed. First of all, this was a retrospective chart review and patients were not prospectively randomized to treatment groups. This led to an unavoidable uneven distribution in the number of patients in each group. Additionally, the majority of the patients should have been in the IL-2RA group by nature of our low-risk protocol, however,

donor- and intraoperative circumstances led the surgeons to use ALA for reasons that cannot be deciphered in this retrospective review. It is unclear what effects these circumstances could have on outcomes. However, we tried to account for this by including all relevant donor- and recipient characteristics that have been historically associated with graft outcomes.

The classification of AA as a 'high-immunologic risk factor' is based on historical data demonstrating higher acute rejection rates and lower long-term graft survival. This analysis demonstrates that the use of ALA induction therapy does not appear to reduce acute rejection rates at 1 year or improve long-term graft outcomes in an otherwise low-risk population. Our results confirm the current practice at some centers of not considering AA ethnicity alone as a high-risk characteristic for induction therapy and advocate the use of IL-2RA in AA kidney transplant recipients that have characteristics that would otherwise place them in a low-immunologic risk group. Further prospective studies addressing the choice of induction therapy (Thymoglobulin® or IL-2RA) in low-risk AA renal transplant recipients are warranted to confirm these findings.

Authorship

JF: collected data, analysed data, wrote paper. DT: designed study, collected data. NW: designed study, collected data.

References

1. US Department of Health and Human Services and the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recpients. *2007 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1997-2006*. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, 2007. Available at: http://www.ustransplant.org/annual_Reports/current/Preface_Contributors.htm#citation. Accessed 26 June 2008.
2. Gjertson DW. Center-dependent transplantation factors: an analysis of renal allografts reported to the United Network for Organ Sharing Registry. In: Terasaki PI, Cecka JM, eds. *Clinical Transplants. 1993*. Los Angeles: UCLA Tissue Typing Laboratory, 1994: 445–468.
3. Butkus DE, Dottes AL, Meydrech EF, Barber WH. Effect of poverty and other socioeconomic variables on renal allograft survival. *Transplantation* 2001; **72**: 261.
4. Young CJ, Gaston RS. Renal transplantation in black Americans. *NEJM* 2000; **343**: 1545.
5. Epstein AM, Ayanian JZ, Keogh JH, *et al.* Racial disparities in access to renal transplantation – appropriate or due to underuse or overuse? *NEJM* 2000; **343**: 1537.
6. Kerman RH, Kimball PM, Van Buren CT, *et al.* Influence of race on crossmatch outcome and recipient eligibility for transplantation. *Transplantation* 1992; **53**: 64.
7. Zachary AA, Steinberg AG, Bias WB, Leffel MS. The frequencies of HLA alleles and haplotypes and their distribution among donors and renal patients in the UNOS registry. *Transplantation* 1996; **62**: 272.
8. Neylan JF. Immunosuppressive therapy in high-risk transplant patients: dose-dependent efficacy of mycophenolate mofetil in African-American renal allograft recipients. *Transplantation* 1997; **64**: 1277.
9. Lindholm A, Welsh M, Alton C, Kahan BD. Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: racial differences in bioavailability. *Clin Pharmacol Ther* 1992; **52**: 358.
10. Alkalin E, Neylan JF. The influence of Duffy blood group on renal allograft outcome in African Americans. *Transplantation* 2003; **75**: 1496.
11. Mourad G, Garrigue V, Squifflet JP, *et al.* Induction versus noninduction in renal transplant recipients with tacrolimus-based immunosuppression. *Transplantation* 2001; **72**: 1050.
12. Vincenti F, Kirkman R, Light S, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. *NEJM* 1998; **338**: 161.
13. Bumgardner GL, Hardie I, Johnson R, *et al.* Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001; **72**: 839.
14. Brennan DC, Daller JA, Lake KD, *et al.* Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *NEJM* 2006; **355**: 1967.
15. Taber DJ, Weimert NA, Fleming JN, *et al.* Reducing the disparities between ethnicities for kidney transplant outcomes by optimizing immunosuppression. Poster presentation; ATC 2008.
16. Haririan A, Morawski K, Sillix DH, *et al.* Induction therapy with basiliximab versus thymoglobulin in African-American kidney transplant recipients. *Transplantation* 2005; **79**: 716.
17. Sollinger H, Kaplan B, Pescovitz MD, *et al.* Basiliximab versus antithymocyte induction for prevention of acute renal allograft rejection. *Transplantation* 2001; **72**: 1915.
18. Lebranchu Y, Bridoux F, Buchler M, *et al.* Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patient receiving MMF-containing triple therapy. *AJT* 2002; **2**: 48.
19. Hammond EB, Taber DJ, Weimert NA, *et al.* Efficacy of induction therapy on acute rejection and graft outcomes in African American kidney transplantation. *Clin Transplant* 2009; 1 [Epub ahead of print].

