GAVIN PUBLISHERS

Journal of Pharmacovigilance and Pharma cotherapeutics

Duhart B, et al. J Pharmacovigil Pharm Ther: JPPT-120.
DOI: 10.29011/JPPT-120. 100120

Research Article

Comparison 0f Standard and Reduced Dose Rabbit Antithymocyte Globulin Induction for Kidney Transplant Recipients with Delayed Graft Function

Benjamin Duhart[1*], Heather Snyder[1,2], Amy Krauss[2], Alison Apple[2], Julie Martin[2], Song Hee Hong[3]

[1]Department of Clinical Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA

[2]Department of Pharmacy, Methodist University Hospital, Memphis, TN, USA

[3]Department of Pharmacy, College of Pharmacy, Seoul National University, Korea

[*]**Corresponding author:** Benjamin Duhart, Department of Pharmacy, University of Tennessee College of Pharmacy, Memphis, TN381632198, USA. Tel: +19014484758; Email: btduhart@uthsc.edu

Citation: Duhart B, Snyder H, Krauss A, Apple A, Martin J, et al. (2017) Comparison 0f Standard and Reduced Dose Rabbit Antithymocyte Globulin Induction for Kidney Transplant Recipients with Delayed Graft Function. J Pharmacovigil Pharm Ther: JPPT-120. DOI: 10.29011/JPPT-120. 100120

Received Date: 28 August, 2017; **Accepted Date:** 8 September, 2017; **Published Date:** 13 September, 2017

Abstract

Background/Purpose: Delayed Graft Function (DGF), a post-transplant complication that requires dialysis within one week following kidney transplantation, is associated with inferior graft outcomes and superior incidence of acute rejection. Utilization of rabbit Antithymocyte Globulin (rATG) as induction therapy is known to preserve graft function and prevent acute rejection. However, the optimal cumulative dose of rATG required to achieve these goals has not been established. The purpose of this study is to compare 1, 3, 6, and 12-month outcomes of reduced versus standard rATG in deceased donor kidney transplant recipients with DGF.

Methodology: A retrospective chart review was conducted for adult deceased kidney recipients with DGF (defined as the kidney recipient requiring hemodialysis within the first 7 days post-transplant) transplanted from January 2005 to April 2011. Reduced dose rATG was defined as a cumulative dose of <7 mg/kg during the early postoperative course. Patients were excluded if they did not meet the DGF study criteria, experienced graft loss within the first week of transplant, received alternate induction therapy, had a simultaneous liver or pancreas transplant, or were lost to follow-up. Outcomes measures included Serum Creatinine (SCr), estimated Glomerular Filtration Rate (eGFR), patient/graft survival, Biopsy Proven Acute Rejection (BPAR), BK viremia, and CMV viremia.

Results: Results of the first 78 patients studied, 26 received reduced dose rATG with an average cumulative dose of 6.04 mg/kg, and 52 received high dose rATG with an average cumulative dose of 8.11 mg/kg ($p < 0.001$). There was no significant difference between the two groups in SCr or e GFR at 1, 3, 6, and 12 months post-transplant. Patient and graft survivals were also similar between the groups at all the time points. Neither significant was the difference in the incidence of BPAR, BK viremia, or CMV viremia.

Conclusions: The reduced dose rATG induction strategy consisting of a mean cumulative dose of 6 mg/kg may be a feasible option for deceased donor kidney transplant recipients with DGF.

Introduction

Rabbit Antithymocyte globulin (rATG) is a polyclonal antibody indicated for the treatment of acute rejection in renal transplant recipients [1]. Transplant centers across the nation are also utilizing this agent for induction therapy in kidney transplantation [2,3]. The approved FDA indication of 1.5 mg/kg/day for 4 to 7 days is supported by clinical trials that have shown rATG to be as effective as other induction agents in preventing acute rejection [4-7]. However, some studies report that the use of rATG is associated with several adverse effects, including an increased risk of infectious complications, a grave concern for kidney transplant recipients [4-6]. While the tradeoff between the benefit and the risk is yet to be established, evidence suggests that the immunosuppressive benefit of rATG may outweigh risks of infection when administered to patients with high immunologic risk, such as kidney transplant recipients with Delayed Graft Function (DGF) [8-11].

DGF is defined as a post-transplant complication that requires dialysis within one week following kidney transplantation. Its occurrence is associated with inferior graft outcomes and increased risk of graft rejection [9,12]. Immediate initiation of calcineurin inhibitors post-transplant may prolong renal transplant recovery from DGF because of its nephrotoxicity. Administration of rATG induction helps delay initiation of calcineurin inhibitors without increasing the risk of rejection post-transplant.

However, a study has suggested that doses of greater than 7 mg/kg of rATG for induction in the early postoperative period may be associated with an increased incidence of infectious episodes [13]. Therefore, there is a critical need to examine whether there exists an optimal cumulative dose of rATG induction that is effective for high risk renal transplant patients, as well as, minimizes infectious episodes without compromising allograft outcomes in renal transplant recipients with DGF. The purpose of this study is to compare outcomes of reduced dose versus standard dose rATG in deceased donor kidney transplant recipients with DGF.

Methods

Study Design and Patients

The study design was a retrospective chart review of adult deceased donor kidney recipients who developed DGF following transplantation at Methodist University Hospital from January 1, 2005 to April 30, 2011. Patients were included if they received dialysis for the treatment of DGF within the first week after renal transplantation, (2) received rATG induction therapy preoperatively, and (3) had a minimum of one-year follow-up. Patients were excluded if (1) they received multiple transplants, such as simultaneous liver-kidney or kidney-pancreas, (2) experienced graft loss within the first week post-transplant.

Treatment Assignment

Patients receiving a cumulative rATG dose of < 7 mg/kg were placed in the reduced dose group while those receiving a cumulative dose of ≥ 7 mg/kg were in the high dose group. Induction with rATG was initiated according to the institution's immuno suppression protocol. Based on the patient's actual body weight at the time of transplant, rATG was given intra operatively using an Intravenous (IV) dose of 1.5 mg/kg. Postoperatively, patients received 3 to 6 additional doses of 1.5 mg/kg daily.

For the first rATG dose, patients received methyl prednisolone 500 mg preoperatively followed by a steroid taper to a goal of prednisone 5 mg daily by 30 to 60 days post-transplant. Patients were also pre-medicated with acetaminophen 650 mg PO and diphenhydramine 25-50 mg PO/IV, 30 minutes prior to each infusion. After the first rATG dose, patients were premeditated with hydrocortisone 50-100 mg IV instead of methyl prednisolone. Mycophenolate mofetil was started at 500 mg twice a day on the day of transplant and titrated to a goal of 2000 mg daily in divided doses as tolerated. Tacrolimus was started per transplant nephrologist's preference. A trough level of 8-15 ng/mL was targeted for the first three months, 8 10 ng/mL for months 3 through 6, and 7-9 ng/mL for months 6-12. All patients received an antifungal, antiviral, and Pneumocystis jiroveci pneumonia prophylaxis following transplantation. Prophylactic medications were adjusted for renal function.

Measures of Study End Points

The primary endpoint consisted of renal outcomes measured by Serum Creatinine (SCr) and calculated estimated Glomerular Filtration Rate (eGFR) at 1, 3, 6, and 12 months. Estimated GFR (eGFR) was calculated using the abbreviated MDRD (Modification of Diet in Renal Disease) equation [14] Secondary endpoints included patient and graft survival at each time point, episodes of Biopsy-Proven Acute Rejection (BPAR), and infectious episodes of BK virus (BKV) and/or Cytomegalovirus (CMV) within the first-year post-transplant. Episodes of BPAR were further classified into T-cell vs. antibody mediated ones. Infectious episodes of BKV and/or CMV were determined by a positive Polymerase Chain Reaction (PCR).

Statistical Analysis

Endpoints were compared between treatment groups using the chi-square analysis for categorical data and the t-test for continuous data. The Grubbs tests were used to detect any significant outliers. Statistical significance was defined as a P value less than 0.05. SAS 9.4 (Cary, North Carolina) was used to perform the statistical test.

Results

Description of Study Subjects

Of the 131 patients previously categorized as DGF, 41 were excluded because they did not receive dialysis for the treatment of DGF within the first week of transplant (Figure 1).

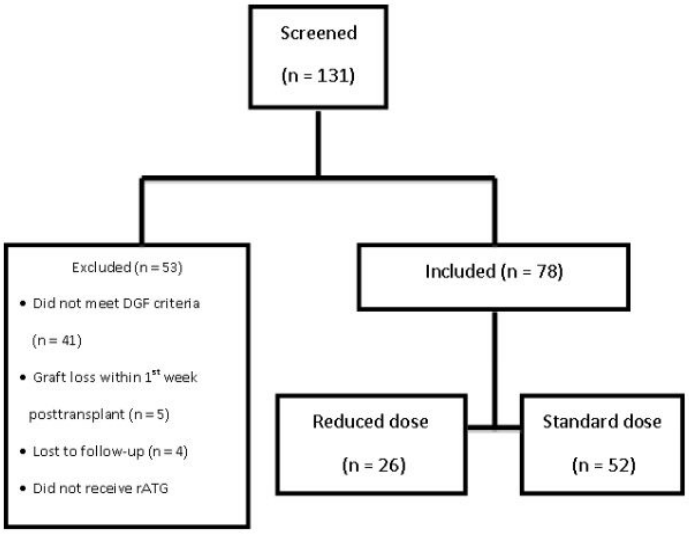

Figure 1: Study Enrollment.

Five were excluded for graft loss within the first week post-transplant, 4 were lost to follow-up, and 3 did not receive rATG intra operatively. Of the 78 patients who met inclusion/exclusion criteria, 26 were in the reduced dose rATG group and 52 were in the standard dose rATG group. Baseline recipient characteristics were similar between groups (Table 1)

Baseline Characteristic	Reduced Dose (n = 26)	Standard Dose (n = 52)	P values
Age at transplant (years)	51.9 ± 12.1	48.2 ± 11.6	0.1869
Male (no. patients)	15 (57.7%)	36 (69.2%)	0.3126
African American (no. patients)	22 (84.6%)	43 (82.7%)	0.7759
BMI (kg/m^2)	29.1 ± 6.0	28.7 ± 5.6	0.7609
Dialysis duration (years)	4.5 ± 3.0	4.2 ± 2.9	0.6533
Cause of renal failure (no. patients)			
Hypertension	22 (84.6%)	36 (69.2%)	0.1424
Diabetes	8 (30.8%)	10 (19.2%)	0.2542
Glomerulonephrosis	0 (00.0%)	3 (5.8%)	0.2217
Graft failure history	2 (7.7%)	9 (17.3%)	0.2501
Other/unknown	2 (7.7%)	5 (9.6%)	0.7794
Notes: ± indicates Mean ± SD (standard deviation).			

Table 1: Comparison of Baseline Patient Characteristics between Two Different Dosing rATG Induction Groups.

The population was predominantly male (65.4%) and African American (83.3%). The leading causes of renal failure were hypertension and diabetes (74.4% and 23.1%, respectively), and 14% of patients had received a previous kidney transplant. Donor and transplant characteristics were also similar between groups (Table 2), except the standard dose rATG group received significantly more standard criteria donor organs compared to the reduced dose rATG group (P = 0.043). The mean cumulative rATG dose (±SD) in the reduced dose group was 6.0 ± 0.9 mg/kg compared to 8.1 ± 0.9 mg/kg in the standard dose group. Maintenance immuno suppression upon discharge was also similar between groups.

Characteristic	Reduced dose (n = 26)	Standard dose (n = 52)	P values
Cold ischemic time (hours)	17.9 ± 6.7	18.9 ± 6.3	0.5177
Donor source (no. patients)			0.0319
Standard criteria donor	14 (53.9%)	41 (78.9%)	
Expanded criteria donor	5 (19.2%)	2 (3.8%)	
Donation after cardiac death	7 (26.9%)	9 (17.3%)	
Cumulative rATG dose (mg/kg)	6.0 ± 0.9	8.1 ± 0.9	<.0001
Dialysis after discharge (no. patients)	9 (34.6%)	24 (46.2%)	0.3309

Table 2: Donor and Transplant Characteristics between Two Different Dosing rATG Groups.

Primary Outcomes

Renal outcomes were similar between groups at all the time points. Mean serum creatinine was similar between the reduced dose group and the standard dose rATG group upon discharge (8.68 vs. 9.06 mg/dL), at 1-month post-transplant (2.37 vs. 2.44 mg/dL), at 3 months post-transplant (1.86 vs. 1.9 mg/dL), at 6 months post-transplant (1.9 vs. 1.7 mg/dL), and at 12 months post-transplant (1.62 vs. 1.7 mg/dL), respectively (Figure 2). Calculated e GFR was also similar between the reduced dose group and the standard dose group upon discharge (8 vs. 8.61 mL/min/1.73 m2), at 1-month post-transplant (37.77 vs. 43.4 mL/min/1.73 m2), at

3 months post-transplant (50.96 vs. 51.42 mL/min/1.73 m2), at 6 months post-transplant (49.48 vs. 56.04 mL/min/1.73 m2), and at 12 months post-transplant (55.88 vs. 56.28 mL/min/1.73 m2), respectively (Figure 3).

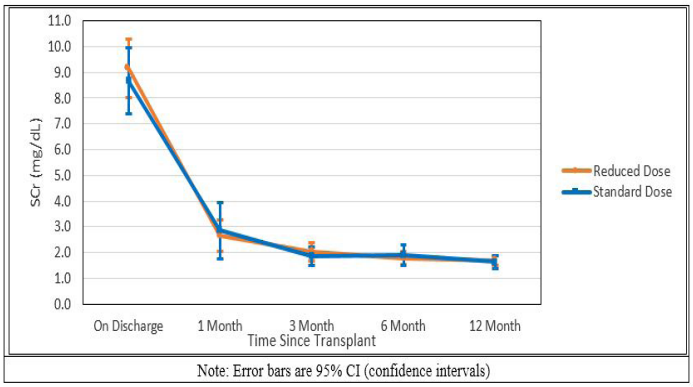

Figure 2: Comparison of Serum Creatinine Values between Reduced Dose rATG (N=26) and Standard Dose rATG (N=52) Induction Groups.

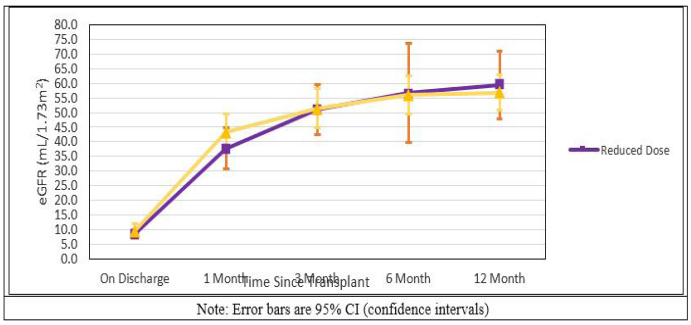

Figure 3: Comparison of e GFR Values between Reduced Dose rATG (N=26) and Standard Dose rATG (N=52) Induction Groups.

Secondary Outcomes

Patient and graft survival were not significantly different between groups at all the time points (Table 3).

Variable	Reduced Dose (n = 26)	Standard Dose (n = 52)	P Value
Patient Survival, n (%)			
at Discharge	26 (100)	52 (100)	1
at 1 month	26 (100)	52 (100)	1
at 3 months	26 (100)	51 (98.1)	1
at 6 months	26 (100)	50 (96.1)	0.55
at 12 months	26 (100)	50 (96.1)	0.55
Graft Survival, n (%)			
at Discharge	26 (100)	52 (100)	1
at 1 month	26 (100)	52 (100)	1
at 3 months	26 (100)	48 (92.3)	0.3
at 6 months	26 (100)	46 (88.5)	0.17
at 12 months	25 (96.2)	46 (88.5)	0.17

Table 3: Comparison of Patient and Graft Survivals between Two Dosing Induction Groups.

Although not significantly different, patient survival was lower in the standard dose group (96.1%) than it was in the reduced dose group (100%) at 12-months post-transplant. Further patients in the standard dose group, although not significantly different from those in the reduced dose group, began to experience graft loss at approximately 3 to 6 months post-transplant. Episodes of BPAR, both T-cell mediated and antibody mediated, did not differ significantly between both groups (Figure 4). Comparison of infections with BKV and CMV were also similar between the reduced and standard dose groups (Figure 5).

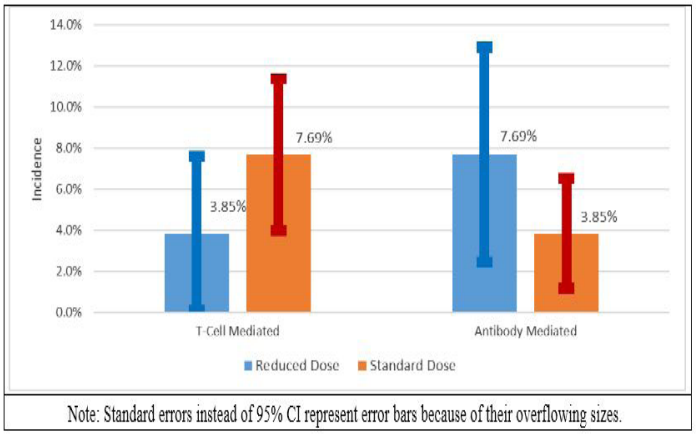

Figure 4: Comparison of Episodes of T-Cell and Antibody Mediated Acute Rejection between Reduced Dose rATG (N=26) And Standard Dose rATG (N=52) Induction Groups.

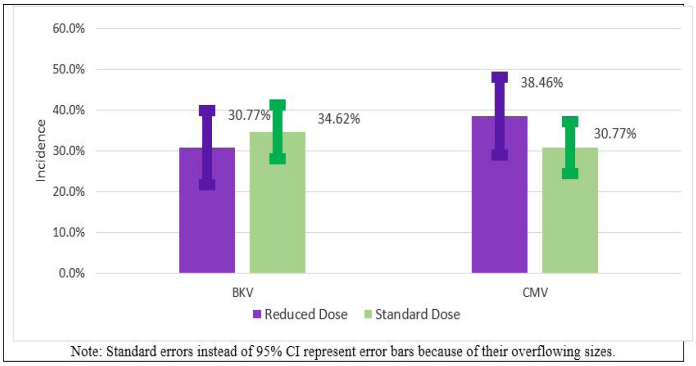

Figure 5: Comparison of Episodes of BK Virus and Cytomegalovirus Infections between Reduced Dose rATG (n=26) and Standard Dose rATG (n=52) Induction Groups.

Discussion

The primary goal of rATG induction is to prevent acute rejection and preserve graft function by delaying the use of calcineurin inhibitors. However, rATG exposure should be minimized to prevent infectious complications related to BKV and CMV [13]. Our study found no significant difference in primary renal outcome measures such as SCr and eGFR as well as in secondary outcome measures such as patient/graft survival, episodes of BPAR, and infections with BKV and CMV between the reduced dose group and the standard dose group. In other words, a cumulative rATG dose of < 7mg/kg was found to be as effective as that of ≥ 7 mg/kg based on 1-year allograft outcomes.

It is worthwhile to note that the risk of infection related to BKV or CMV was not significantly different between the two groups. This non-significant finding was rather unexpected because previous studies reported that higher doses (cumulative dose >7 mg/kg) of rATG induction increased the risk of post-transplant infections [4,6,7,13,15]. Unlike the previous studies, our population predominantly consisted of African-American patients (~83% of the study population). African-American ethnicity, considered a risk factor for acute rejection possibly due to hyper immune responsiveness [16]. Could have contributed to the similar incidence of infection that was identified between groups in this study

It is also worthwhile to note that baseline characteristics were similar between the two different dose groups except for donor criteria. The transplant center from which the study subjects were recruited expanded the criteria for acceptance of donor kidneys in order to increase its donor pool for kidney transplantation. A study reports that kidney transplant patients who have received the expanded-criteria donors display inferior graft outcomes when compared to those who have received standard-criteria donors [17] our study found similar graft outcomes despite the increased incidence of expanded-criteria donors in the reduced dose rATG group. Had the two dosing groups received the same criteria donor, the reduced dose group could have produced more favorable outcomes than the standard dose group. Future studies need to compare cost-effectiveness between low vs. high dose rATG inductions. Our study found no significant differences in primary as well as in secondary outcome measures between two different dosing strategies.

This finding suggests that the reduced dosing strategy would be more cost-effective than the standard dosing one considering the current cost of rATG at $797.35 per 25mg vial [18]. The exact cost-effectiveness of the reduced dosing strategy should factor in all costs related to drug preparation, hospital length of stay, and readmissions for post-transplant complications. A well-designed cost effectiveness study will inform transplant centers of efficient resource allocations between different dosing strategies of rATG induction for kidney transplant patients with DGF. This study had two limitations related to study sample. First, the sample size was small (n= 78), and thus may not be enough patients included in the study to detect a significant difference between two different dosing strategies. However, significant differences were identified with the donor source and cumulative rATG dose between groups. Secondly, prescribers could have assigned more high-risk patients to the standard dosing strategy than to the reduced dose one. However, it is important to note that baseline characteristics were not significantly different between two different dosing strategies except for donor source.

Conclusions

The reduced dosing strategy of rATG induction which consisted of a mean cumulative dose of 6 mg/kg was as effective as the standard dosing strategy which consisted of a mean cumulative dose of 8 mg/kg based on 1- year outcomes for adult deceased donor kidney transplant recipients with DGF. The results of this study suggest that 6 mg/kg of rATG induction may be a feasible option for adult kidney transplant recipients with DGF.

References

1. Deeks ED, Keating GM (2009) Rabbit Antithymocyte globulin (thymoglobulin): a review of its use in the prevention and treatment of acute renal allograft rejection. Drugs 69: 1483-1512.

2. Gaber AO, Knight RJ, Patel S, Gaber LW (2010) A review of the evidence for use of thymoglobulin induction in renal transplantation. Transplant Proc 42: 1395-1400.

3. US Renal Data System. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Rockville, Md 2010.

4. Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D (2006) Rabbit Antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med 355: 1967-1977.

5. Gabardi S, Martin ST, Roberts KL, Grafals M (2011) Induction immunosuppressive therapies in renal transplantation. Am J Health Syst Pharm 68: 211-218.

6. Hardinger KL, Rhee S, Buchanan P, Koch M, Miller B, et al. (2008) A prospective, randomized, double-blinded comparison of thymoglobulin versus Atgam for induction immunosuppressive therapy: 10-year results. Transplantation 86: 947-952.

7. Willoughby LM, Schnitzler MA, Brennan DC, Pinsky BW, Dzebisashvili N, et al. (2009) Early outcomes of thymoglobulin and basiliximab induction in kidney transplantation: application of statistical approaches to reduce bias in observational comparisons. Transplantation 87: 1520-1529.

8. Gurk-Turner C, Airee R, Philosophe B, Kukuruga D, Drachenberg C, et al. (2008) Thymoglobulin dose optimization for induction therapy in high risk kidney transplant recipients. Transplantation 85: 1425-1430.

9. Patel SJ, Knight RJ, Suki WN, Abdellatif A, Duhart BT Jr, et al. (2011) Rabbit Antithymocyte induction and dosing in deceased donor renal transplant recipients over 60 yr of age. Clin Transplant 25: E250-256.

10. Klem P, Cooper JE, Weiss AS, Gralla J, Owen P, et al. (2009) Reduced dose rabbit anti-thymocyte globulin induction for prevention of acute rejection in high-risk kidney transplant recipients. Transplantation 88:891-896.

11. Kasiske BL, Zeier MG, Craig JC, Ekberg H, Garvey CA, et al. (2009) KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 9 Suppl 3: S1-155.

12. US Department of Health & Human Services. Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. Rockville, Md 2009.

13. Clesca P, Dirlando M, Park S-I, García R, Ferraz E, et al. (2007) Thymoglobulin and rate of infectious complications after transplantation. Transplant Proc 39: 463-464.

14. Evans M, van Stralen KJ, Schön S, Prütz KG, Stendahl M, et al. (2013) Glomerular filtration rate-estimating equations for patients with advanced chronic kidney disease. Nephrol Dial Transplant 28: 2518-2526.

15. Patel SJ, Duhart BT Jr, Krauss AG, Moore LW, Egidi MF, et al. (2008) Risk factors and consequences of delayed graft function in deceased donor renal transplant patients receiving Antithymocyte globulin induction. Transplantation 86: 313-320.

16. Young CJ, Kew C (2005) Health disparities in transplantation: focus on the complexity and challenge of renal transplantation in African Americans. Med Clin North Am 89: 1003-1031.

17. Ramalho ALAS, Custodio FB, Tokuda BM, Caldas HC, Fernandes IM, et al. (2013) Clinical and histopathologic comparative analysis between kidney transplant recipients from expanded-criteria donors and standard-criteria donors. Transplant Proc 45: 3234-3238.

18. James A, Mannon RB (2015) The cost of transplant immunosuppressant therapy: is this sustainable? Current Transplant Rep 2: 113-121.