REVIEW ARTICLE

Drugs 2009; 69 (15): 2045-2062
0012-6667/09/0015-2045/$55.55/0

African American Kidney Transplantation Survival

The Ability of Immunosuppression to Balance the Inherent Pre- and Post-Transplant Risk Factors

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Abstract

Among organ transplant recipients, the African American population historically has received special attention. This is because secondary to their disposition to certain disease states, for example hypertension, an African American patient has a propensity to reach end-stage renal disease and require renal replacement earlier than a Caucasian patient. Regardless of the initiative to replace dialysis therapy with organ transplantation, the African American patient has many barriers to kidney transplantation, thus extending their time on dialysis and waiting time on the organ transplant list. These factors are among the many negative causes of decreased kidney graft survival, realized before kidney transplantation.

Unfortunately, once the African American recipient receives a kidney graft, the literature documents that many post-transplant barriers exist which limit successful outcomes. The primary post-transplant barrier relates to designing proper immunosuppression protocols. The difficulty in designing protocols revolves around (i) altered genetic metabolism/lower absorption, (ii) increased immuno-active cytokines and (iii) detrimental effects of noncompliance. Based on the literature, dosing of immunosuppression must be aggressive and requires a diligent practitioner. Research has indicated that, despite some success with proven levels of immunosuppression, the African American recipient usually requires a higher 'dose per weight' regimen. However, even with aggressive immunosuppressant dosing, African Americans still have worse outcomes than Caucasian recipients. Additionally, many of the targeted sites of action that immunosuppression exerts its effects on have been found to be amplified in the African American population. Finally, noncompliance is the most discouraging inhibitor of long-term success in organ transplantation. The consequences of noncompliance are biased by ethnicity and affect the African American population more severely.

All of these factors are discussed further in this review in the hope of identifying an ideal healthcare model for caring for the African American transplant recipient, from diagnosing chronic kidney disease through to successful kidney graft outcomes. An indepth review of the literature is described and organized in a fashion that highlights all of the issues affecting success in African Americans. The compilation of the literature in this review will enable the reader to get closer to understanding the caveats of kidney transplantation in the African American patient, but falls short of delivering an actual 'equation' for post-transplant care in an African American kidney recipient.

According to the Interagency Committee for the Review of the Racial and Ethnic Standards, falling under the Office of Management and Budget of the US Government, the term 'Black or African American' refers to people ''having origins in any of the Black racial groups of Africa''.[1] African Americans are susceptible to an increased incidence of diabetes mellitus, hypertension, chronic kidney diseases (CKDs) and end-stage renal disease (ESRD).[2,3] Additionally, outcomes of renal transplantation in African American patients are reported to be inferior compared with other racial ethnicities in the US.[4-6] Despite the introduction of potent and targeted immunosuppressive therapy, acute rejections remain higher and graft survival remains lower in African American renal transplant recipients than in non-African American recipients. As a result of these outcome differences, African American renal transplant recipients are considered as one of the 'immunologically high risk kidney transplant recipients'. Nevertheless, two separate editorial comments in the *New England Journal of Medicine* challenge the medical community to go beyond 'racial profiling' and encourage healthcare professionals not to be satisfied in a conclusion that the 'genes that determine different responses, or the lack thereof, are somehow determined by the genes that determine race'.[7,8] This review attempts to argue a similar point that solid organ transplant outcomes should not be predicted by the genes that determine the colour of the skin.

Currently the Scientific Registry for Transplant Recipients (SRTR) adjusts patient and graft survival for a number of factors, including: panel reactive

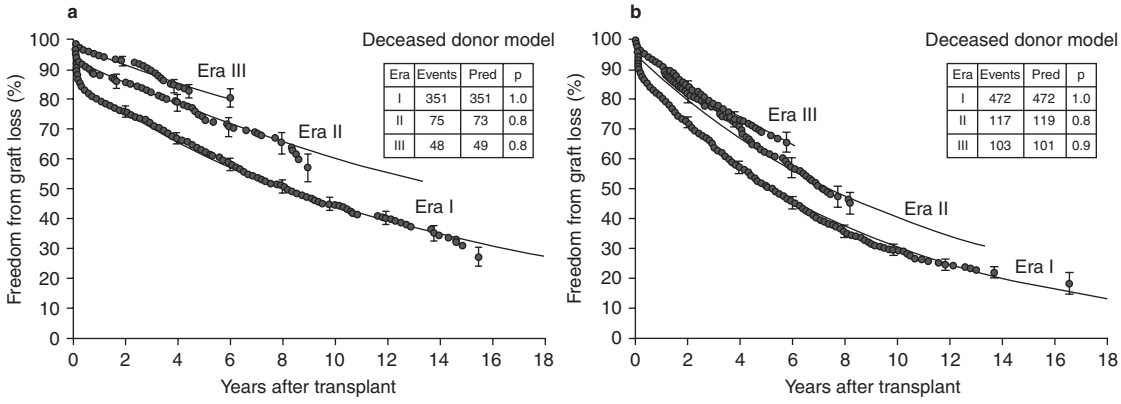

Fig. 1. Adult primary kidney graft survival is shown as a percentage vs time and era. (**a**) Non-African American graft survival and (**b**) African American graft survival. The solid lines are what our model predicts (Pred) vs the plotted actuarial results. Deceased donors, University of Alabama at Birmingham, Birmingham, AL, May 1987 to December 2004 (n = 2453) [reprinted from Eckhoff et al.,[9] copyright 2007, with permission from Elsevier]. **p** = p-value.

antibody level, cold ischaemia time, expanded criteria donor, deceased donor, cross-match and recipients of African American descent. Most of these factors are dependent on variables that develop during the recipient's waiting time or are based on a chosen donor. Unfortunately, ethnicity is predetermined for the recipient even before renal dysfunction has been diagnosed. The risk for graft loss after kidney transplantation is delineated in two phases: the early phase including day 0 to 3 months, and the constant phase for everything after 3 months (see figure 1).[9] While adjusting risk for certain variables, the African American population has benefited less from modern targeted immunosuppression with regards to long-term graft survival.

This review describes the evolution of patient and graft outcomes in African American kidney transplantation. We attempt to answer the question as to why outcomes in African American kidney transplantation are reported to be inferior to other groups, and simply not blame it on the colour of their skin. Some of the post-transplant outcomes are influenced by the pre-transplant factors, such as hypertension, diabetes, length of wait time and length of pre-transplant dialysis. This review discusses some of these pre-transplant factors, as well as post-transplant influences, to explain the outcomes of kidney transplantation in African American recipients.

1. Methods of Literature Review

A qualitative non-systematic literature review was performed to explain the high-risk nature of kidney transplantation in the African American population. Article topics were reviewed for attributes specific to African Americans pertinent to the following subjects: pre-transplant (e.g. increased likelihood of ESRD), listing for transplant (e.g. lack of well matched donors and referrals) and post-transplant (e.g. immunosuppression protocols and genetic polymorphisms).

2. End-Stage Renal Disease in the African American Population

There are many studies that show the incidence and prevalence of ESRD is significantly higher in the African American population. It has been estimated that during 1993–5, 2% of White men, 1.7% of White women, 5.5% of Black men and 6.3% of Black women developed ESRD during their lifetime.[10] Progressive loss of renal function causes CKD and ends in ESRD. The number of patients with CKD or ESRD treated with dialysis or transplantation in the US is projected to increase from 340 000 in 1999 to 651 000 in 2010.[11]

According to the United States Renal Data System (USRDS), the adjusted incidence of

ESRD is about 3- to 4-fold higher in the African American and American Indian populations compared with the White population.[12-14] Racial disparity was noted in the frequency of positive family history of ESRD with 14.1% in White men, 14.6% in White women, 22.9% in African American men and 23.9% in African American women.[15] More African American ESRD patients are reported to have a significant family history of ESRD compared with other groups.[16]

The NHANES (National Health and Nutrition Examination Survey) III study showed that the relative risk of ESRD was 5-fold higher among the African American cohort than in Caucasians.[17] Despite adjustment for age, sex and diabetes, the African American race continued to be associated with higher blood pressures and albuminuria.[17]

Additionally, socioeconomic analyses has shown that poverty, level of education, household income and access to healthcare were also independently associated with higher ESRD risk.[18-22]

Five factors have been traditionally considered in the development of progressive kidney disease: hypertension, glucose intolerance, insulin resistance, salt sensitivity and hyperlipidaemia.[23] These listed risks in concert may affect renal outcomes in African American and American Indian populations.[23]

The African American race represent about 12% of the US population but account for 32% of those with chronic kidney failure and are four times more likely than Caucasians to develop ESRD requiring dialysis or a kidney transplant.[24]

HIV has emerged as an important cause of CKD and ESRD in African American patients since the 1990s. Clustering of ESRD cases associated with HIV and AIDS was noted in young African American men in the 25- to 44-year-old age group.[25] Cumulative statistics from the USRDS database showed that between 1992 and 1997, 0.97% of ESRD patients had HIV infection or AIDS, and 87.8% of those patients were African American.[26] The risk of developing ESRD is estimated to be 50 times higher for HIV-infected African Americans than in HIV-infected Caucasians.[27] HIV-associated nephropathy was found exclusively in African Americans. African Americans constituted just 16% of a national cohort of US veterans, but accounted for 53.6% of HIV-infected patients.[28] To that endpoint, HIV was found to be a strong risk factor for progressing to ESRD in the African American population (hazard ratio = 4.56).

3. Transplant Evaluation Barriers

Data over the 12 years beginning in 1991, has repeatedly shown that an African American with ESRD is less likely to be referred for a transplant evaluation than a Caucasian patient.[3] For example, one study showed that an African American was less likely than a Caucasian to be referred for transplant (9% vs 20.0%) and less likely to complete their evaluation for transplant (38.8% vs 46.5%). When reviewed for appropriateness for transplant, African Americans were deemed less appropriate than Caucasians for transplant (9.8% vs 21.4%), with the most common reason given being a body mass index (BMI) of >35. Compared with long-term dialysis, cadaveric renal transplantation generally offers a longer lifespan, a better quality of life and lower healthcare costs.[29] However, another study showed that nephrologists believed that African Americans did not have a better survival after transplantation due to lack of resource for living donors and high prevalence of co-morbid conditions.[30]

Since making advances in immunosuppression therapy as a result of greater understanding of the immune system, human leukocyte antigen (HLA) matching has become less important. Transplantation of HLA-mismatched organs is a common practice among transplant centres in the US. The deceased donor population that is deemed suitable for donation tends to be predominately Caucasians, making a 6-antigen match kidney for an African American more difficult.[31] African Americans have been shown to exhibit presensitization to major histocompatibility complex antigens that lead to a heightened immune response following transplantation. This has been shown to increase the wait time for transplantation and result in poorer post-transplant outcomes. Research has shown that an African

American has an inferior 5-year graft survival compared with other populations.[5,6] Another explanation for accelerated graft loss in African Americans is the possibility that they have a clinically undetectable high degree of HLA mismatching only measurable using high-resolution DNA-based typing.[31]

4. Post-Transplant Outcomes

With much credit going to some large urban transplant centres and increased awareness among the community, the frequency of kidney transplantation among African American patients has increased by 18% in the last 20 years.[4] Despite these efforts, long-term graft survival still lags behind Caucasians by 4–8% for living donor transplantation and by 7–10% for deceased donor transplantation.[5,6] Long-term outcomes indicate that African Americans are not able to sustain graft and patient survival secondary to an increased incidence of acute and chronic rejection rates compared with Caucasians.[32,33]

Areas that have been proposed to improve survival, and have thus been researched, include standardizing immunosuppression for African Americans (tables I and II), identifying immunological polymorphisms and improving compliance. This section focuses on each of these areas.

4.1 Standardizing Immunosuppression

4.1.1 Induction Therapy

Induction therapy potentiates prophylactic immunosuppression in the early post-transplant period when acute rejections are more common and severe. Over the last two decades, four groups of induction agents have been investigated to improve outcomes peri-operatively, in the hope of translating early successes to late outcomes.

In the late 1980s, muromonab CD3 (OKT3), a monoclonal antibody to CD3, was introduced as a strong induction agent. Outcomes of African American and Caucasian deceased donor recipients receiving ciclosporin, azathioprine and maintenance corticosteroid therapy with or without OKT3 were reviewed.[34] Adding OKT3 was successful for the African American recipients as it increased survival and delayed the first rejection. Unfortunately, as seen in other literature, the Caucasian group still had better survival rates.

In the 1990s, protocols using the interleukin (IL)-2 receptor antagonists (blockers) [IL2RBs], namely daclizumab and basiliximab, were initiated. Daclizumab was added to ciclosporin, mycophenolate mofetil (MMF) and corticosteroid maintenance in a high-risk ethnic group, including Hispanics and African Americans, and was compared with no induction.[35] The group that received daclizumab versus no induction again had a delayed first rejection and improved rejection-free survival. Basiliximab was compared with OKT3 along with calcineurin inhibitors (CNIs), MMF and corticosteroid maintenance.[36] The historical OKT3 African American group had more rejections and increased graft loss at 2 years than the African American group receiving basiliximab induction.

With the introduction of rabbit anti-thymocyte globulin (Thymoglobulin®; rATG), clinicians felt that rATG could impose stronger induction than the IL2RBs as a result of its polyclonal affinities. After 1.5-year follow-up, African American recipients receiving triple maintenance therapy in conjunction with either rATG or basiliximab were found to have comparable survivals and rejection rates.[37] The results were satisfactory for the African American group, but the authors noted that the rATG group had higher risk factors pre-transplant.

More recently, alemtuzumab has been suggested as an induction agent not only to bring the transplant community closer to tolerance, but also to equalize outcomes across high-risk groups, including African Americans. In a three-arm study, groups were randomized to alemtuzumab versus rATG versus daclizumab over 2 years.[38] The study included varying numbers of African Americans, ranging from 23% (rATG) to 40% (daclizumab). All patients were to be treated with tacrolimus (varying level goals), MMF (dose adjusted based on haematological adverse effects) and corticosteroid maintenance. Alemtuzumab use resulted in comparable rates of acute rejection and a worse incidence of chronic allograft nephropathy (CAN) at the end of the study. The

Table I. Immunosuppression comparisons in studies enrolling African American transplant reciepients

Study	Immunosuppression	Control arm(s)	Rejection rates [p-value]	Rejection rates time period	Patient/graft survival [p-value]	Survival time period
Induction						
Reinitz et al.[34]	CSA, AZA, cSTD	OKT3, CSA, AZA, cSTD	65% (–OKT3) 61% (+OKT3) [p < 0.05]	Prior to 30 d post-transplant	76%/61% (–OKT3) 91%/78% (+OKT3) [p < 0.05]	2 y
Meier-Kriesche et al.[35]	CNI, MMF, cSTD (54% AA)	DAC, CNI, MMF, cSTD (59% AA)	37.5% (–DAC) 24.5% (+DAC)	12 mo		
Kumar et al.[36]	OKT3, CNI, MMF, cSTD	BAS, CNI, MMF, cSTD	16% (BAS) 30% (OKT3) [p < 0.05]		Graft survival 87% (BAS) 76% (OKT3) [p < 0.05]	2 y (actuarial)
Haririan et al.[37]	BAS, MMF, cSTD, TAC vs SRL	rATG, MMF, cSTD, TAC vs SRL	14% (rATG) 29% (BAS) [p = ns]		94%/86% (rATG) 88%/81% (BAS) [p = ns]	
Ciancio et al.[38]	Alem, TAC, MMF, SW	rATG or DAC, TAC, MMF, cSTD	17 ± 7% (rATG) 24 ± 8% (Alem) 25 ± 8% (DAC)	36 mo (actuarial)	85%/81% (rATG) 88%/74% (Alem) 85%/82% (DAC)	Actuarial
Calcineurin inhibitors						
Cibrik et al.[39]	High-risk group: BAS, MPS, cSTD, CSA (C_2 levels) [subgroup analysis]	High and low C_2 levels	24.2% (high C_2) 14.7% (low C_2) 20.2% (high risk)	12 mo	99.4%/95.7% (high + low C_2) 100%/93.9% (high risk)	12 mo
Jarzembowski et al.[40]	OKT3, cSTD, CSA	OKT3, cSTD, TAC	21% (TAC) 48% (CSA)	12 mo	86%/86% (TAC) 95%/95% (CSA)	12 mo
					78.6%/78.6% (TAC) 95.2%/95.2% (CSA)	3 and 5 y
Antiproliferatives						
Mital et al.[41]	rATG, SW, SRL, TAC (26% AA and H)	Short-term MMF/ delayed TAC/SRL (23% AA and H)	10.8% (each group)	12 mo	100% (each group)	12 mo
Lo et al.[42]	rATG, STD, std TAC, low SRL (75% AA)	rATG, STD, low TAC, std SRL (83% AA)	6% (std TAC/low SRL) 5% (low TAC/std SRL)	6 mo	94%/94% (std TAC/low SRL) 100%/83% (low TAC/std SRL)	6 mo
Ferreira et al.[43]	CSA, cSTD, std SRL	CSA, cSTD, high-level SRL	18% (std) vs 8% (high)	12 mo	100%/97% (std) vs 100%/94% (high)	12 mo
Corticosteroids						
Kumar et al.[44]	BAS, CSA, MMF, cSTD (62% AA)	BAS, CSA, MMF, SW (62% AA)	CAR 16% (SW) 13% (cSTD) [p = ns]	12 mo	100%/95% (SW) 100%/98% (cSTD) [p = ns]	12 mo

Continued next page

Table I. Contd

Study	Immunosuppression	Control arm(s)	Rejection rates [p-value]	Rejection rates time period	Patient/graft survival [p-value]	Survival time period
			SCAR 21% (SW) 30% (cSTD) [p = ns]			
Hricik et al.[45]	SRL, TAC, cSTD	SRL, TAC, SW	AA (cSTD + SW) 16%	Mean 20.9 mo	AA (cSTD + SW) 100%/90%	Mean 20.9 mo
Hricik et al.[46]	SRL, TAC, cSTD	SRL, TAC, SW	41% (SW) 33% (cSTD)	Mean 48.5 mo	94%/75% (SW) 87%/67% (cSTD) [p = ns]	Mean 48.5 mo
Zeng et al.[47]	rATG, MMF, TAC or SRL, SW		18%	Mean 23 mo	98%/96%	12 mo
Haririan et al.[48]	rATG, MMF, TAC or SRL, cSTD	rATG, MMF, TAC or SRL, SW	13% (SW) 24% (cSTD) [p = ns]		98%/98% (SW) 94%/85% (cSTD) [p = ns]	16 mo

AA = African Americans; **Alem** = alemtuzumab; **AZA** = azathioprine; **BAS** = basiliximab; **C_2** = 2-hour post-dose level; **CAR** = rejections based on clinically indicated biopsies; **CNI** = calcineurin inhibitors; **CSA** = ciclosporin; **cSTD** = maintenance corticosteroids; **DAC** = daclizumab; **H** = Hispanics; **MMF** = mycophenolate mofetil; **MPS** = mycophenolate sodium (Myfortic®); **ns** = not statistically significant; **OKT3** = muromonab; **rATG** = rabbit anti-thymocyte globulin; **SCAR** = subclinical acute rejection rate; **SRL** = sirolimus; **std** = standard; **SW** = corticosteroid withdrawal; **TAC** = tacrolimus; + indicates with; – indicates without.

authors summarized the CAN results stratified according to ethnicity. The resultant chart indicated that, although the CAN outcomes were higher in the alemtuzumab group, the percentages were similar across ethnicities, i.e. 50% CAN in Caucasians versus 45% in African American, when both received alemtuzumab.

4.1.2 Maintenance Immunosuppression

Calcineurin Inhibitors

Much of our success in organ transplantation stems from the introduction of ciclosporin in the early 1980s. It was a drug ultimately found to inhibit an essential step in the mounting of an immunological response. Since the inception of ciclosporin, research has sought to identify the proper dosing and therapeutic levels to improve African American outcomes. Much of this research has led to innovative ways of dosing ciclosporin in African Americans, namely the area under the concentration-time curve (AUC) and monitoring 2-hour post-dose levels (C_2). One group cited improved rejection rates in the critical early period (<6 months) were a result of intense asymmetrical AUC monitoring in conjunction with trough levels.[56] By selectively choosing to measure both an AUC following the morning and evening dose, more focused care was provided to the 'high risk' African American group, resulting in lower early rejection rates. Unfortunately, the authors hinted that some racial differences became more apparent after 1 year.

C_2 monitoring has recently been suggested as a way to improve African American outcomes following kidney transplantation. In the multicentre, US-based, CONCERTO (Correlation Of Neoral® C_2 Exposure and Renal Transplant Outcome) study, C_2 monitoring was studied in all *de novo* patients.[50] The authors conducted a subgroup analysis of the African American versus Caucasian recipients. Although the authors documented success in the rates of early rejection, this trend did not continue across the African American participants, despite having similar C_2 levels to Caucasians. It is possible that this outcome might have been avoided if perhaps more of

Table II. Ethnicity comparisons in renal transplant studies

Study	AA immunosuppression	Comparator group	Rejection rates [p-value]	Rejection rates time period	Patient/graft survival [p-value]	Survival time period
Ciancio et al.[49]	DAC, TAC, MMF, cSTD	H, non-H/non-AA	8.1% (AA) 4.7% (H) 4.5% (non-H/non-AA) [p = ns]	12 mo	97%/95% (AA) 98%/98% (H) 96%/95% (non-H/non-AA) [p = ns]	12 mo
Vincenti et al.[50]	BAS, MMF, cSTD, CSA (with C_2 levels)	CAU (subgroup analysis)	18.4% (AA) 2.8% (CAU) [p < 0.05]	6 mo		
Weber et al.[51]	TAC vs CSA, MMF vs AZA, cSTD	CAU	AZA/CSA: 55.1% (CAU) 61.8% (AA) MMF/CSA: 20% (CAU) 61.8% (AA) [p < 0.05] MMF/TAC: 16.6% (AA)			
Neylan[52]	OKT3/eATG, AZA, cSTD, TAC vs CSA	CAU	23.2% (AA/TAC) 47.9% (AA/CSA) [p < 0.05] 29.8% (CAU/TAC) 46.3% (CAU/CSA) [p < 0.05]	12 mo	94.6%/91.1% (AA/TAC) 94.7%/90.4% (CAU/TAC) 97.9%/91.7% (AA/CSA) 95.9%/84.6% (CAU/CSA) [p = ns]	12 mo
Meier-Kriesche et al.[32]	US Scientific Renal Transplant Registry: MMF vs AZA	CAU	AA: 20.5% (MMF) 32.8% (AZA) [p < 0.001]	6 mo	96.3%/85.8% (MMF) 93.2%/75.1% (AZA) [p < 0.001] MMF and death with functioning graft: CAU vs AA [p = ns] MMF and death-censored graft loss: CAU vs AA [p < 0.05, RR = 1.3]	3 y
Podder et al.[53]	CSA, cSTD ± SRL	CAU: (+) SRL	43.3% (–SRL) 19.2% (+SRL) [p < 0.05] 19.2% (+SRL) vs 20.8% (CAU) [p = ns]	2 y	97.8%/85.6% (–SRL) vs 95.7%/97.9% (+SRL) [p < 0.05, graft survival] 95.7%/97.9% (+SRL) vs 96.7%/91.7% (CAU) [p = ns]	2 y
Kumar et al.[54]	BAS, SW, CNI, MMF or SRL	Non-AA	CAR: 16% (AA) 13% (non-AA) [p = ns] SCAR: p < 0.05 at 1 mo p = ns at 6 and 12 mo	12 mo	96%/88% (AA) 97%/89% (non-AA) [p = ns]	12 mo
Kumar et al.[33]	BAS, SW, CNI, MMF or SRL	Non-AA	SCAR: significantly higher in AA at 1 mo, 2, 3, 4 and 5 y	5 y	88%/81% (AA) 90%/82% (non-AA) [p = ns]	5 y
Boardman et al.[55]	CNI, MMF, SA or SW ± rATG ± SRL	Non-AA	23% (AA) 18% (non-AA) [p = ns]	12 mo	96%/95% (AA) 96%/93% (non-AA) [p = ns]	12 mo

AA = African Americans; **AZA** = azathioprine; **BAS** = basiliximab; **C_2** = 2-hour post-dose level; **CAR** = rejections based on clinically indicated biopsies; **CAU** = Caucasians; **CNI** = calcineurin inhibitors; **CSA** = ciclosporin; **cSTD** = maintenance corticosteroids; **DAC** = daclizumab; **H** = Hispanics; **eATG** = equine anti-thymocyte globulin (ATGAM®); **MMF** = mycophenolate mofetil; **ns** = not statistically significant; **OKT3** = muromonab; **rATG** = rabbit anti-thymocyte globulin; **RR** = relative risk; **SA** = steroid avoidance; **SCAR** = subclinical acute rejection rate; **SRL** = sirolimus; **SW** = corticosteroid withdrawal; **TAC** = tacrolimus; + indicates with; – indicates without.

the group, including African Americans, met the C_2 goals prescribed during the study design.

Degrees of C_2 monitoring have been studied using a parallel designed format with long-term follow-up (up to 2 years) using high and low C_2 levels.[39] The population included 26% African Americans among the total population. *Post hoc* analysis of the 'high risk subpopulation' included greater HLA mismatches, African American, re-transplants and panel reactive antibody (PRA) >35%, listed in descending order of the number of patients in each group. The authors noted that, in total, there were seven graft losses during the study, six of which occurred in the high-risk subpopulation. Additionally, numerically, the calculated renal function was diminished in this group compared with the whole group.

Many studies have attempted to improve outcomes in African Americans by selecting tacrolimus instead of ciclosporin. One such study lowered rejection rates significantly by using tacrolimus over ciclosporin in conjunction with MMF and corticosteroid maintenance.[51] Jarzembowski et al.[40] prospectively randomized a group of African Americans to either tacrolimus or ciclosporin; the total group included 35 patients, and showed no difference in patient and graft survival, acute and chronic rejection rates, or post-transplant diabetes (PTDM). At 1 year, the tacrolimus group had a lower serum creatinine and cholesterol; however, this difference did not continue long term.

Neylan[52] examined CNI choice between African American and Caucasian recipients, and the data showed that African Americans required higher doses of both tacrolimus and ciclosporin to obtain similar trough levels to Caucasians. Furthermore, it was reported that renal function and survival rates were comparable between Caucasian and African American kidney recipients treated with either tacrolimus or ciclosporin. Additionally, rejection rates were lower among the tacrolimus treated groups, regardless of ethnicity, compared to the ciclosporin groups. Also, medications to treat post-transplant complications, namely diabetes and hypertension, were more commonly used in the African American group.

Another study employed a tacrolimus-based immunosuppression protocol to eliminate racial differences.[49] At the end of the study, there was equal survival, relative risk of rejection and calculated renal function. However, with that in mind, although tacrolimus levels were comparable at the end of 1 year, throughout the study African American required statistically more tacrolimus (mg/kg) than the Hispanic and non-African American/non-Hispanic groups.

Many immunosuppressive medications, especially the CNIs, have a narrow therapeutic index, so that too much will induce toxicity and not enough will ineffectively prevent rejection. The mediators of this 'index' are metabolic enzymes that determine the disposition of each of these drugs and, thus, their effect. Studies have been conducted to identify if there are genetic differences in the concentration of such enzymes that would explain why higher doses are required in African Americans to achieve similar pharmacokinetics to Caucasians. Specifically, these enzymes are referred to as P-glycoprotein and the cytochrome P450 (CYP) group. Statistically, the African American group attained lower levels with standardized doses versus the other ethnicities in a study that prospectively monitored tacrolimus levels and attempted to correlate these with CYP3A levels.[57] As the genotypes were delineated for each group, more Caucasians were likely to have homozygous CYP3AP1 and multi-drug resistance-1 genotypes, which is theorized to result in the highest bioavailability and lowest enzyme activity. This was compared with the African Americans, who possessed numerically more genotypes (either hetero- or homozygous alleles) that resulted in lower tacrolimus levels. In another study,[58] African American, Latin American and Caucasian recipients received tacrolimus by intravenous and oral administration. A review of the pharmacokinetics of tacrolimus in African Americans versus other ethnicities showed that there were clear differences between various ethnicities after oral administration. The authors noted that the African Americans had numerically lower exposure to tacrolimus, and a statistically lower bioavailability and maximum concentration than the

other groups. Since there was no difference in the pharmacokinetic parameters associated with the measured metabolites, the authors concluded that the higher requirements of tacrolimus needed in African Americans is as a result of an increased expression of P-glycoprotein in the gut, leading to more efflux of drug post-ingestion.

Antiproliferatives

Most transplant centres feel that a CNI-based immunosuppression is vital to early survival success; nevertheless, there remains debate as to which antiproliferative is better across all ethnicities. Mycophenolic acid products have been touted as improving outcomes following renal transplantation, and have mostly eliminated azathioprine as the antiproliferative of choice. In an examination of the SRTR, Meier-Kriesche et al.[32] found that MMF could not erase the African American versus Caucasian difference with regards to graft loss and chronic allograft failure. Again, pharmacokinetics were relied upon to explain the ethnicity difference; but no such explanation could be elucidated to describe the discrepancies.[59] Patients enrolled in the study were an average of 2–3 years post-transplant, and receiving ciclosporin and corticosteroid maintenance.

Sirolimus was released onto the market after MMF, but has been similarly reviewed for its potential in the African American recipient. A 2-year survival follow-up compared African Americans receiving ciclosporin and corticosteroid maintenance with or without sirolimus and Caucasians receiving ciclosporin, corticosteroid maintenance plus sirolimus.[53] This study was able to show similar rejection and survival rates in African Americans to those in Caucasians. Additionally, the African Americans receiving sirolimus faired statistically better than the African Americans not receiving sirolimus with regards to rejection rates and graft survival at 2 years.

In an attempt to minimize the occurrence of delayed graft function, a sirolimus-based regimen that relied on rATG induction and exchanged MMF for tacrolimus until renal function improved post-transplant, while maintaining corticosteroid withdrawal was studied.[41] Survival was 100% up to 1 year and rejection rates were reasonable at 10.8%. The patient population was 57% African American and Hispanic.

A high-risk deceased donor transplant group, consisting of >75% African Americans, received rATG and corticosteroid maintenance, and varying goals for sirolimus and tacrolimus levels.[42] The authors succeeded in achieving great patient survival and rejection rates at 6 months; however, more of the standard sirolimus group reached the composite endpoint, albeit not a statistically significant proportion, secondary to the overall lower graft survival. On the other hand, the standard tacrolimus group had more biopsied CNI nephrotoxicity within 6 months. Therefore, the authors concluded that care should be taken when initiating this protocol to balance graft failure caused by nephrotoxicity and early complications of normal to high sirolimus levels.

In another study of sirolimus-based immunosuppression, a population of 100% African Americans was randomized to one of two different trough level goals of sirolimus (8–12 ng/mL or 15–20 ng/mL).[43] All patients received ciclosporin, sirolimus and corticosteroid maintenance, with one group reaching normal to high sirolimus levels, and the comparison group reaching very high sirolimus levels. Antibody use for induction was excluded from the study. Both groups had comparable composite endpoints, with a trend toward lower rejection rates in the very high sirolimus level group. However, statistically more patients discontinued the very high sirolimus level protocol, mostly due to adverse events from either sirolimus or ciclosporin. Additionally, most of this group had lower haemoglobin at 6 months, and lower renal function at both 6 and 12 months.

While each immunosuppressant agent, as part of an immunosuppression protocol, has shown a benefit in African American outcomes, a prospective study randomized recipients to four different immunosuppression protocols.[60] In this study, the authors compared each combination of either tacrolimus or ciclosporin plus either MMF or sirolimus; a total of four groups. Pertinent to this review, each group enrolled >50% African

Americans. The authors noted in a subgroup analysis of African Americans versus non-African Americans that outcomes and clinically indicated biopsy-diagnosed rejections were comparable. Unfortunately, subclinical acute rejection rates as well as rates of chronic allograft injury secondary to hypertension and interstitial fibrosis/tubular atrophy were significantly worse in African Americans at 5 years.

Corticosteroids

When ciclosporin was introduced, it seemed that corticosteroid elimination was on the top of most transplant centre's agendas. While this has been achieved in most groups with varying degrees of success, the high-risk groups, including African Americans, have always been more resistant to good outcomes. Prasad et al.[61] utilized a questionnaire in the hope of eliciting honest responses among transplant recipients regarding their immunosuppression regimens in the outpatient setting. Overwhelmingly, corticosteroids were the one medication that recipients wanted removed from their management. And although African Americans only represented 7% of the demographic, compared with non-African Americans, they were significantly more likely to report that corticosteroids were the aetiology of some serious adverse events, for example diabetes.

Corticosteroid use is entrenched in every facet of immunosuppression management, specifically induction, rejection and maintenance therapy. Currently, induction therapy with corticosteroids seems to be a requirement for transplant protocols across all types of recipients, either alone or as a premedication. Corticosteroids are the first line for rejection therapy, primarily to avoid unnecessary over-immunosuppression. However, Vasquez et al.[62] indicated that African Americans respond less effectively to corticosteroid boluses than non-African Americans, thus requiring more intense and potent immunotherapy, such as OKT3, equine ATG (ATGAM®; eATG) or Minnesota anti-lymphocyte globulin.

Clearly, corticosteroid maintenance therapy seems to lend itself most to manipulation in the African American population, as well as in other populations. Many articles have described success in African Americans in early, intermediate and long-term outcomes. In a randomized, prospective, steroid-withdrawal trial that included 30% African Americans, there was no significant difference in rejection rates between groups; however, all of the rejections that occurred in the steroid-withdrawal group were among African Americans patients.[63]

One particular study prospectively followed African American transplant recipients to assess the benefits of early corticosteroid withdrawal.[55] It documented outcomes not only including renal function, rejection rates and survival, but also cardiovascular risk factors. All but one protocol included <7 days of corticosteroids, and the other one required no corticosteroids. Although African Americans had a higher PRA and more deceased donors, rejection rates were comparable, with the exception of those who experienced delayed graft function. Delayed graft function resulted in a higher serum creatinine at last follow up, and a trend toward more rejections among African Americans versus non-African Americans. Survival rates and the incidence and level of cardiovascular risk factors were comparable, namely (i) measured blood pressure, (ii) cholesterol panels, (iii) incidence of diabetes post-transplant and (iv) weight gain. The African American group required more antihypertensives to maintain similar blood pressure readings to non-African Americans.

Recently, three groups have described short- and long-term data on corticosteroid withdrawal in African Americans through multiple publications.[33,44,45-48,54] One such study enrolled 44 African American patients 3–5 months post-transplant in whom oral corticosteroids were discontinued.[45,46] No induction therapy was used in any patient, and maintenance therapy consisted of tacrolimus and sirolimus. At the time of the reported 1-year follow-up, patient survival was 100%, graft survival was 90% and the rejection rate was 16% (mean follow-up 20.9 months).[45] Additionally, 90% of the 30 enrolled patients were still corticosteroid free at last follow up. The authors noted improved blood pressure and cholesterol panels, but a trend toward an increasing serum creatinine level, excluding failed grafts, did occur. With a mean follow-up of 48.5 months,

outcomes were again compared among African Americans who were eligible for corticosteroid withdrawal and those who, because of exclusion criteria, were not eligible.[46] During this time period, in the steroid-withdrawal group there was 34% noncompliance, a 41% rejection rate and only 41% remained corticosteroid free. It was the noncompliance and rejection occurrences that proved to be a significant variable in a regression analysis of serum creatinine. At the end of the study, there was no difference in survival rates between the two groups. Nevertheless, in the per protocol analysis, there was significant difference in serum creatinine levels at last follow up. Noncompliance and the increased rejection rate were attributed for worsening renal function after corticosteroid withdrawal.

Two studies were published from a single transplant group, which described experiences of African Americans transplanted from June 2003 to June 2005[47] and July 2001 to November 2004.[48] Both had similar immunosuppression protocols, using rATG, 4 days of corticosteroids, MMF, and either tacrolimus or sirolimus. The first study reported on 57 African American patients, all enrolled in the steroid-withdrawal protocol with a mean follow-up of just under 2 years. One-year results reported good patient and graft survival, and improved renal function. The rejection rate was 18% at 1 year, with the majority occurring within the first year. The only significant feature of those experiencing rejection related to more patients being initiated on sirolimus than tacrolimus. At the end of the study, 81% remained corticosteroid free. Interestingly, the rate of PTDM (defined as two separate readings of fasting blood glucose levels >125 over a 1-month period) at the end of follow-up was 16%, all while being corticosteroid free. Haririan et al.[48] compared African Americans receiving a steroid-withdrawal protocol with a cohort of African Americans transplanted prior to June 2003 on maintenance corticosteroids. Immunosuppression protocols were similar to those listed previously. Significant differences between the two groups were seen in PRA, with an increased peak and current PRA in the corticosteroid maintenance group. Both patient and graft survival were comparable at the end of the study; there were no statistically significant differences in rejection rates between the two groups, but they were numerically lower among the steroid-withdrawal group. Unadjusted renal function, weight gain and PTDM data revealed no significant difference between the groups. Finally, the authors documented that corticosteroid maintenance, or the dose of corticosteroids used, had an independent association with renal function, weight gain, total cholesterol and PTDM at different timepoints.

Additionally, another single centre has published three articles citing their experience with corticosteroid withdrawal in all patients, as well as in a cohort of African Americans.[33,44,54] In their first report of a prospectively randomized study of corticosteroid maintenance versus withdrawal, 62% of the 77 recipients enrolled were African Americans.[44] In the few endpoints in which they were able to stratify across ethnicity, similar survival and rejection rates were noted; however, there was a trend towards increased subclinical rejections at 1 and 12 months in African Americans. The next reported study compared corticosteroid withdrawal between African Americans and non-African Americans.[54] The immunosuppression protocol included basiliximab, 2 days of intravenous corticosteroids and a CNI-based regimen. Additionally, the authors separated rejection rates into those biopsies performed for clinical and protocol indications. Examining biopsies performed for clinical indications revealed that rejection rates and severity were similar between the two groups. However, there was a slight trend toward rejection being associated with delayed graft function in the African American group. When reviewing rejection diagnoses following protocol indicated biopsies, there was a statistical difference between the two groups in subclinical acute rejection rates. Renal function and survival rates were comparable at the end of 1 year. The African American group required numerically higher ciclosporin, tacrolimus, sirolimus and MMF doses. Comparable values were obtained for both groups with regards to blood pressure, weight gain and cholesterol panel. These authors have also published the results of a 5-year follow-up study (see figure 2).[33] Thoughout the 5-year

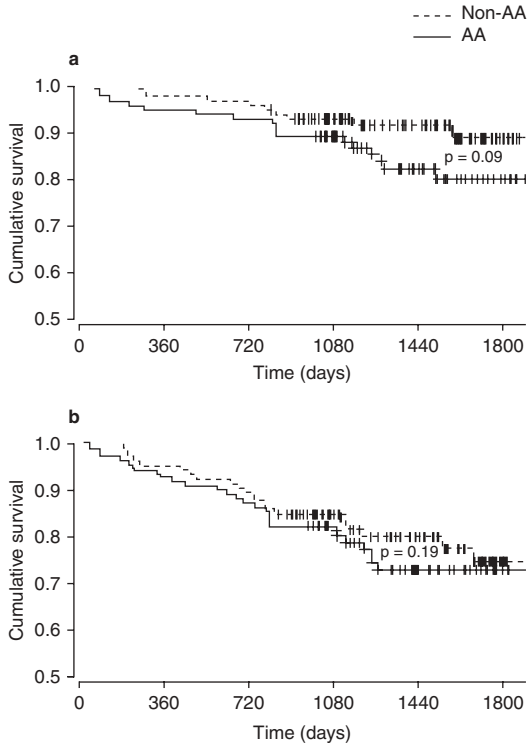

Fig. 2. Five-year (**a**) patient and (**b**) graft survival in African American (AA) and non-African American kidney recipients with early corticosteroid withdrawal. **p** = p-value.

follow-up, the African American group was noted to have more treated rejections after the 1-year timepoint, with biopsies performed for both clinical and protocol indications. With regards to chronic allograft injury, African Americans had more interstitial fibrosis/tubular atrophy- or hypertension-associated changes. Actuarial survivals were similar at the end of the 5-year follow-up. Finally, renal function was worse in the African American group at the end of the study.

4.2 Pre-Transplant Risk Factors

Many factors have been identified as being associated with negative outcomes after kidney transplantation. Unfortunately, many of these factors are attributes possessed by African Americans. A multivariate analysis indicated that being African American is a statistical risk factor for being hepatitis C virus-positive at the time of transplantation, and this has been shown to influence patient survival.[64] Diabetes is a known risk factor for many cardiovascular complications in all patients, including renal transplant recipients. Additionally, it has been shown that African American ethnicity is a risk factor versus Caucasian ethnicity for future development of PTDM.[65] As discussed in section 3, many barriers prevent the timely listing of African American ESRD patients for transplant; therefore, further concern is focused on the time spent by African Americans on haemodialysis prior to transplant. Waiting time on dialysis was isolated as an independent risk factor for death-censored graft loss and patient loss in a retrospective review.[66]

As stated earlier (section 2), the risk of developing ESRD is greater for HIV-positive African Americans compared with HIV-positive Caucasians.[27] The success of transplanting kidney grafts in HIV-positive recipients was characterized in a study in which 39 of 40 recipients were African American.[67] Outcomes were lower than currently expected rates,[6] namely patient and graft survival of 85% and 75% (1 year) and 82% and 71% (2 year), respectively. Rejection rates during the study were 22% for the HIV-positive group.

Much attention has been focused on genetic testing as a way of explaining the ethnicity differential. One group surveyed 77 African Americans for genetic polymorphisms and transplant outcomes and found that those identified as having rejection episodes were likely to be heterozygous for IL-2, a high producer genotype for transforming growth factor B1, a low producer genotype for IL-10 and an intermediate producer for interferon (IFN)-γ.[68] Additionally, using enzyme-linked immunosorbent spot (ELISPOT) assay to identify high producers of IFNγ in African Americans predicted lower renal function and increased rejections post-transplant.[69] One multicentre prospective study failed to link the expression of Duffy antigen receptor complex polymorphisms with African Americans as an explanation of rejections and delayed graft function.[70] Recently, attention has been devoted to new medications directed towards the second step in activating

T helper-2 cells, specifically the co-stimulatory receptors. Belatacept is undergoing investigation as a mainstay of immunosuppression protocols because it binds with high affinity to the B7 co-stimulatory molecules on antigen-presenting cells. It is believed that the interaction of CD28 and B7 is essential for proper immune response. By studying both healthy volunteers and paediatric transplant recipients, it has been shown that African Americans possess a higher density of B7 co-stimulatory molecules on antigen-presenting cells than Caucasians.[71,72]

4.3 Post-Transplant Compliance

Many centres have identified and approached the discrepancies affecting African Americans from a socioeconomic point-of-view. In a large, single-centre, retrospective review, one group re-examined grafts documented as lost to chronic rejection 6 months after transplantation.[73] Using predefined criteria to review the records, the authors concluded that 48 of the 81 patients for whom chronic rejection was listed as the cause of graft failure actually had some documentation suggesting noncompliance. Statistically, noncompliance occurred more often in the African American population.

4.3.1 Effects of Compliance on Survival

Other reports have attempted to define the role of compliance on graft survival, as well as whether ethnicity plays a role in compliance. A living-related donor transplant review compared outcomes associated with compliance.[74] First and foremost, being African American conferred a 1.8 hazard risk on loss of graft at 8 years. Statistically significantly more African American graft loss was due to chronic rejection than Caucasians and numerically, but not significantly, there was more noncompliance listed. Another group reviewed 5-year outcomes among ethnicities and noted similar survival between Caucasians and African Americans.[75] However, of the late graft losses, seven were noted to be secondary to noncompliance; five of these were African Americans. The authors concluded that noncompliance was the explanation for the late acute rejections.

4.3.2 Causes of Noncompliance

Studies have indicated that, although African American graft outcomes are adversely affected by noncompliance more than in Caucasians, noncompliance is not completely explained by socioeconomic means.[76-78] Additionally, just as compliance weighs heavily on graft outcome, some literature has suggested that ethnicity, in turn, affects compliance.[79]

Pursuing a more detailed explanation of how graft survival is affected by African American-related noncompliance, Butkus et al.[77] conducted a multifactorial, socioeconomic analysis of outcomes. The authors included many socioeconomic factors (e.g. income, insurance provider and literacy) among African Americans and Caucasians, then analysed these for effect. Significant pre-transplant socioeconomic differences between the two ethnicities indicated that African Americans had lower income, fewer years of education and more reliance on Medicaid. No differences were noted in survivals, but the group did conclude the causes of graft loss were very different. With that being said, recipients with immunological graft loss versus either non-immunological graft loss or continued graft function were more likely to have the following demographics: African American, younger age, lower income and greater HLA mismatch. The authors noted that noncompliance played a large role in the cause of immunological graft loss in African Americans, irrespective of their ability to pay for medications. Additionally, having an income below the poverty level had more of a negative effect on death-censored graft survival for African Americans than Caucasians.

4.3.3 Approaches to Improve Noncompliance

An alternate examination on compliance differences between African Americans and non-African Americans utilized the Veteran Affairs (VA) department records, thus eliminating financial barriers.[78] Among VA and non-VA users, African Americans had worse graft survival, both for adjusted and non-adjusted survival. The

authors concluded that universal access to care (e.g. the VA system) could not eliminate the racial differences.

Compliance in both African American and non-African American patients may be improved by avoiding medications widely known to have a myriad of adverse effects. Chronic corticosteroid therapy has many adverse effects that include increases in BMI, central lipodystrophy, hirsutism, and other metabolic complications such as diabetes, hypertension, cardiovascular diseases and osteoporosis. Eliminating corticosteroids from maintenance therapy has been shown to avoid these adverse effects.[33,47,48,55,60,63] Additionally, many investigators and patient advocates question the choice to exchange dialysis for diabetes and other long-term corticosteroid-related adverse effects. Studies have shown that PTDM has similar mortality and morbidity to existing pre-transplant diabetes.[65,80] Avoidance of long-term corticosteroid therapy significantly reduces both PTDM and cardiovascular morbidities.[44,47,48,55,63] It is possible to avoid long-term corticosteroid therapy in African American kidney recipients and reduce the adverse effects without compromising the patient and graft survival rates.[33,44,47,48,55,60]

5. Conclusion

African American ethnicity has historically been viewed as an obstacle to consistent transplant success. Although we strive to break the 'racial profiling' associated with the use of medicine and research, ethnicity continues to permit some predictions about outcomes, both good and bad.[5,6]

In this review, the African American transplant population was dissected from multiple angles in an attempt to identify what the key barriers are to successful kidney transplantation. Specifically, we focused on the predisposition to eventual need for renal replacement, inconsistent evaluations for kidney transplantation and enhancement of post-kidney transplant care. The medical community must continue to view the African American patient as vulnerable and must not shy away from using proactive approaches to initiating kidney transplant evaluations. The African American patient will have a higher risk for nephrotoxic disease states, for example hypertension and diabetes, and, therefore, needs to be identified quickly. Once identified, the patient should be supported by their medical team, including the referring nephrologists, dialysis centre and social worker. The patient needs to have the attention of the listing transplant centre, so that all avenues, such as live donations, are examined.

Once transplanted, the post-transplant care of the African American recipient will require careful consideration, more so than that for most other recipients. As Eckhoff et al.[9] discovered, the African American population is inherently sensitive to early success, and therefore much forethought must be used to protect them from rejection. This includes aggressive dosing to overcome genetically low absorption/high metabolism, and aggressive immunosuppression management. Much success has been found with antibody induction, although a specific agent has yet to be determined.

The combination of a CNI and an antiproliferative agent is mandatory, and essential to much of the documented success in African American kidney transplantation. As the understanding of using these two types of agent has evolved, we have come closer to achieving good results without corticosteroids. Literature supports that corticosteroid withdrawal is a possibility, even with the long-term results described.[33,47,48,54] Additionally, by strengthening the maintenance immunosuppression to remove corticosteroids, we have to examine other options such as surveillance biopsies. Kumar et al.[33,60] documented good success in African Americans, but alluded to the need for diligent follow-up, as subclinical rejections can lead to damaging chronic injury.

Replacement of one of the two maintenance immunosuppressants is becoming a valid consideration with some of the new immunosuppressive medications in the pipeline, such as belatacept. Hutchings et al.[71,72] provided information that would form a foundation for the use of this agent as an exciting approach to limiting toxicities and maintaining adequate immunosuppression in the African American recipient.

Finally, we know that compliance to medication schedules is just as important, if not more so, than the actual medications themselves. Unfortunately, the African American population is more sensitive to the detrimental consequences of noncompliance than most other groups.[75,76,79] With that in mind, the post-transplant care must include continued support from the transplant staff, as well as primary physicians and nephrologists.

In conclusion, we fell short of identifying the exact genetic reason why the African American population has worse outcomes with regards to organ transplant survival than other ethnicities. We continue to 'profile' this population, enabling the community to predict survival rates and rejection frequency. Nevertheless, with the literature available to us, we have new hope regarding the treatment of the African American recipient. We know with diligent care from the point of identifying ESRD to post-transplantation, we can achieve good outcomes.

Acknowledgements

The data and analyses reported in the 2007 Annual Report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients have been supplied by UNOS and Arbor Research under contract with HHS contract 231-00-0115. The authors alone are responsible for reporting and interpreting these data; the views expressed herein are those of the authors and not necessarily those of the US Government. No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review. The authors would like to express their appreciation to Danielle Marie, NP, for assisting with providing comments during the original reviewing and editing of the article.

References

1. U.S. Census Bureau. Recommendations from the Interagency Committee for the Recommendations from the Interagency Committee for the Review of the Racial and Ethnic Standards to the Office of Management and Budget concerning changes to the standards for the classification of Federal data on race and ethnicity [online]. Available from URL: http://www.census.gov/population/www/socdemo/race/Directive_15.html [Accessed 2009 Apr 10]
2. Young CJ, Kew C. Health disparities in transplantation: focus on the complexity and challenge of renal transplantation in African Americans. Med Clin North Am 2005 Sep; 89 (5): 1003-31
3. Wolfe WA. Achieving equity in referrals for renal transplant evaluations with African-American patients': the role of nephrology social workers. Soc Work Health Care 2003; 37 (3): 75-87
4. U.S. Department of Health & Human Services, Organ Procurement and Transplantation Network. Transplants in the US recipient ethnicity 1/1/88 – 12/31/08 [online]. Available from URL: http://optn.transplant.hrsa.gov/latestData/rptData.asp [Accessed 2009 Aug 21]
5. U.S. Department of Health & Human Services. Adjusted graft survival, living donor kidney transplants. Survival at 3 months, 1 year, 3 years, and 5 years [online]. Available from URL: http://www.ustransplant.org/annual_reports/current/508c_can-race_ki.htm [Accessed 2009 Mar 24]
6. U.S. Department of Health & Human Services. Adjusted graft survival, deceased donor non-ECD kidney transplants. Survival at 3 months, 1 year, 3 years, and 5 years [online]. Available from URL: http://www.ustransplant.org/annual_reports/current/508a_can-race_ki.htm [Accessed 2009 Mar 24]
7. Schwartz RS. Racial profiling in medical research. N Engl J Med 2001 May; 344 (18): 1392-3
8. Cooper RS, Kaufman JS, Ward R. Race and genomics. N Engl J Med 2003 Mar; 348 (12): 1166-70
9. Eckhoff DE, Young CJ, Gaston RS, et al. Racial disparities in renal allograft survival: a public health issue? J Am Coll Surg 2007; 204: 894-903
10. Merrill RM, Kessler LG, Udler JM, et al. Comparison of risk estimates for selected diseases and causes of death. Prev Med 1999; 28: 179-93
11. Excerpts from the United States Renal Data System's 2000 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis 2000; 36 (6 Suppl. 2): S1-279
12. US Renal Data System, USRDS 1993 annual data report: atlas of end-stage renal disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1993
13. US Renal Data System. USRDS 1994 annual data report: atlas of end-stage renal disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1994
14. US Renal Data System. USRDS 1995 annual data report: atlas of end-stage renal disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995
15. Freedman BI, Soucie JM, McClellan WM. Family history of end-stage renal disease among incident dialysis patients. J Am Soc Nephrol 1997; 8: 1942-5
16. Freedman BI, Tuttle AB, Spray BJ. Familial predisposition to nephropathy in African-Americans with non-insulin-dependent diabetes mellitus. Am J Kidney Dis 1995; 25: 710-3
17. Hsu CY, Lin F, Vittinghoff E, et al. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. J Am Soc Nephrol 2003; 14: 2902-7
18. Rostand SG, Brown G, Kirk KA, et al. Renal insufficiency in treated essential hypertension. N Engl J Med 1989; 320: 684-8
19. Whittle JC, Whelton PK, Seidler AJ, et al. Does racial variation in risk factors explain black-white differences in the incidence of hypertensive end-stage renal disease? Arch Intern Med 1991; 151: 1359-64

20. Brancati FL, Whittle JC, Whelton PK, et al. The excess incidence of diabetic end-stage renal disease among blacks: a population-based study of potential explanatory factors. JAMA 1992; 268: 3079-84
21. Perneger TV, Whelton PK, Klag MJ. Race and end-stage renal disease: socioeconomic status and access to health care as mediating factors. Arch Intern Med 1995; 155: 1201-8
22. Brancati FL, Whelton PK, Randall BL, et al. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. JAMA 1997; 278: 2069-74
23. Powers DR, Wallin JD. End-stage renal disease in specific ethnic and racial groups: risk factors and benefits of antihypertensive therapy. Arch Intern Med 1998 Apr; 158: 793-800
24. US Renal Data System. USRDS 2005 annual data report: atlas of end-stage renal disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005
25. Winston JA, Klotman PE. Are we missing an epidemic of HIV-associated nephropathy? J Am Soc Nephrol 1996; 7: 1-7
26. Abbott KC, Hypolite I, Welch PG, et al. Human immunodeficiency virus/acquired immunodeficiency syndrome-associated nephropathy at end-stage renal disease in the United States: patient characteristics and survival in the pre–highly active antiretroviral therapy era. J Nephrol 2001; 14: 377-83
27. Eggers PW, Kimmel PL. Is there an epidemic of HIV Infection in the US ESRD Program? J Am Soc Nephrol 2004; 15: 2477-85
28. Choi AI, Rodriguez RA, Bacchetti P, et al. Racial differences in end-stage renal disease rates in HIV infection versus diabetes. J Am Soc Nephrol 2007; 18: 2968-74
29. Alexander GC, Sehgal AR. Barriers to cadaveric renal transplantation among Blacks, women and the poor. JAMA 1998; 280: 1148-52
30. Navaneethan SD, Singh S. A systemic review of barriers in access to renal transplantation among African Americans in the United States. Clin Transplant 2006; 20: 769-75
31. Karmoun AK, Israni MM, Joffe MM, et al. Assessment of differences in HLA-A, -B, and -DRB1 allele mismatches among African-American and non-African-American recipients of deceased kidney transplants. Transplant Proc 2007; 39: 55-63
32. Meier-Kriesche HU, Ojo AO, Leichtman AB, et al. Effect of mycophenolate mofetil on long-term outcomes in African American renal transplant recipients. J Am Soc Nephrol 2000; 11: 2366-70
33. Kumar MSA, Khan S, Ranganna K, et al. Long-term outcome of early corticosteroid withdrawal after kidney transplantation in African American recipients monitored by surveillance biopsy. Am J Transplant 2008; 8: 574-85
34. Reinitz ER, Kaplan MP, Sillix DH, et al. OKT3 induction therapy and cadaveric renal transplantation in black patients. Transplant Proc 1997; 29: 3703-5
35. Meier-Kriesche HU, Kaza H, Palekar SS, et al. The effect of daclizumab in a high-risk renal transplant population. Clin Transplant 2000; 14: 509-13
36. Kumar AMS, Fa K, Vankawala R, et al. Simulect, calcineurin inhibitor, mycophenolate mofetil, and prednisone is more effective than OKT3, calcineurin inhibitor, mycophenolate mofetil, and prednisone in African American kidney recipients in reducing acute rejections and prolonging graft survival. Transplant Proc 2001; 33: 3195-6
37. Haririan A, Morawski K, Sillix DH, et al. Induction therapy with basiliximab versus thymoglobulin in African-American kidney transplant recipients. Transplantation 2005 Mar; 79 (6): 716-21
38. Ciancio G, Burke GW, Gaynor JJ, et al. A randomized trial of thymoglobulin vs. alemtuzumab (with lower dose maintenance immunosuppression) vs. daclizumab in renal transplantation at 24 months of follow-up. Clin Transplant 2008; 22: 200-10
39. Cibrik D, Meier-Kriesche H-U, Bresnahan B, et al. Renal function with cyclosporine C_2 monitoring, enteric-coated mycophenolate sodium and basiliximab: a 12-month randomized trial in renal transplant recipients. Clin Transplant 2007; 21: 192-201
40. Jarzembowski T, Panaro F, Raofi V, et al. Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African-American recipients of primary cadaver renal transplant. Transpl Int 2005; 18: 419-22
41. Mital D, Podlasek W, Jensik SC. Sirolimus-based steroid-free maintenance immunosuppression. Transplant Proc 2002; 34: 1709-10
42. Lo A, Egidi MF, Gaber LW, et al. Observations regarding the use of sirolimus and tacrolimus in high-risk cadaveric renal transplantation. Clin Transplant 2004; 18: 53-61
43. Ferreira AN, Machado PG, Felipe CR, et al. Concentration-controlled use of sirolimus associated with reduced exposure of cyclosporine in black recipients of primarily living renal allograft donors: 12-month results. Clin Transplant 2005; 19: 607-15
44. Kumar AMS, Xian S-G, Fyfe B, et al. Steroid avoidance in renal transplantation using basiliximab induction, cyclosporine-based immunosuppression and protocol biopsies. Clin Transplant 2005; 19: 61-9
45. Hricik DE, Knauss TC, Bodziak KA, et al. Withdrawal of steroid therapy in African American kidney transplant recipients receiving sirolimus and tacrolimus. Transplantation 2003 Sep; 76 (6): 938-42
46. Hricik DE, Augustine JJ, Knauss TC, et al. Long-term graft outcomes after steroid withdrawal in African American kidney transplant recipients receiving sirolimus and tacrolimus. Transplantation 2007 Feb; 83 (3): 277-81
47. Zeng X, El-Amm JM, Doshi MD, et al. Intermediate-term outcomes with early steroid withdrawal in African-American renal transplant recipients undergoing surveillance biopsy. Surgery 2007; 142: 538-45
48. Haririan A, Sillix DH, Morawski K, et al. Short-term experience with early steroid withdrawal in African-American renal transplant recipients. Am J Transplant 2006; 6: 2396-402
49. Ciancio G, Burke GW, Suzart K, et al. The use of daclizumab, tacrolimus and mycophenolate mofetil in African-American and Hispanic first renal transplant recipients. Am J Transplant 2003 Apr; 3: 1010-6
50. Vincenti F, Mendez R, Curtis J, et al. A multicenter, prospective study of C2-monitored cyclosporine microemulsion in a U.S. population of de novo renal transplant recipients. Transplantation 2005 Oct; 80 (7): 910-6
51. Weber M, Deng S, Arena J, et al. Decreased rejection episodes in African-American renal transplant recipients

receiving mycophenolate mofetil/tacrolimus therapy. Transplant Proc 1997; 29: 3669-70

52. Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. Transplantation 1998 Feb; 65 (4): 515-23
53. Podder H, Podbielski J, Hussein I, et al. Sirolimus improves the two-year outcome of renal allografts in African-American patients. Transpl Int 2001; 14: 135-42
54. Kumar MSA, Moritz MJ, Saaed MI, et al. Avoidance of chronic steroid therapy in African American kidney transplant recipients monitored by surveillance biopsy: 1-year results. Am J Transplant 2005; 5: 1-10
55. Boardman RE, Alloway RR, Alexander JW, et al. African-American renal transplant recipients benefit from early corticosteroid withdrawal under modern immunosuppression. Am J Transplant 2005; 5: 356-65
56. Emovon OE, King JAC, Holt CO, et al. Effect of cyclosporine pharmacokinetics on renal allograft outcome in African-Americans. Clin Transplant 2003; 17: 206-11
57. Macphee IAM, Fredericks S, Tai T, et al. Tacrolimus pharmacogenetics: polymorphisms associated with expression of cytochrome p4503A5 and p-glycoprotein correlate with dose requirement. Transplantation 2002 Dec; 74 (11): 1486-9
58. Mancinelli LM, Frassetto L, Floren LC, et al. The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. Clin Pharmacol Ther 2001; 69 (1): 24-31
59. Pecovitz MD, Guasch A, Gaston R, et al. Equivalent pharmacokinetics of mycophenolate mofetil in African-American and Caucasian male and female stable renal allograft recipients. Am J Transplant 2003; 3: 1581-6
60. Kumar MSA, Saeed MI, Ranganna K, et al. Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: five-year outcomes. Transpl Immunol 2008; 20: 32-42
61. Prasad GVR, Nash MM, McFarlane PA, et al. Renal transplant recipient attitudes toward steroid use and steroid withdrawal. Clin Transplant 2003; 17: 135-9
62. Vasquez EM, Benedetti E, Pollack R. Ethnic differences in clinical response to corticosteroid treatment of acute renal allograft rejection. Transplantation 2001 Jan; 71 (2): 229-33
63. Laftavi MR, Stephan R, Stefanick B, et al. Randomized prospective trial of early steroid withdrawal compared with low-dose steroids in renal transplant recipients using serial protocol biopsies to assess efficacy and safety. Surgery 2005; 137: 364-71
64. Batty DS, Swanson SJ, Kirk AD, et al. Hepatitis C virus seropositivity at the time of renal transplantation in the United States: associated factors and patient survival. Am J Transplant 2001; 1: 179-84
65. Kasiske BL, Snyder JJ, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003; 3: 178-85
66. Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. Kidney Int 2000; 58: 1311-7
67. Kumar MSA, Sierka DR, Damask AM, et al. Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. Kidney Int 2005; 67: 1622-9
68. McDaniel DO, Barber WH, Nguyan C, et al. Combined analysis of cytokine genotype polymorphism and the level of expression with allograft function in African-American renal transplant patients. Transpl Immunol 2003; 11: 107-19
69. Augustine JJ, Siu DS, Clemente MJ, et al. Pre-transplant IFN-γ ELISPOTs are associated with post-transplant renal function in African-American renal transplant recipients. Am J Transplant 2005; 5: 1971-5
70. Mange KC, Prak EL, Kamoun M, et al. Duffy antigen receptor and genetic susceptibility of African Americans to acute rejection and delayed function. Kidney Int 2004; 66: 1187-92
71. Hutchings A, Purcell WM, Benfield MR. Peripheral blood antigen-presenting cells from African-Americans exhibit increased CD80 and CD86 expression. Clin Exp Immunol 1999; 118: 247-52
72. Hutchings A, Purcell W, Benfield MR. Increased costimulatory responses in African-American kidney allograft recipients. Transplantation 2001 Mar; 71 (5): 692-5
73. Gaston RS, Hudson SL, Ward M, et al. Late renal allograft loss: noncompliance masquerading as chronic rejection. Transplant Proc 1999; 31 (4A Suppl.): 21S-3S
74. Isaacs RB, Conners Jr A, Nock S, et al. Noncompliance in living-related donor renal transplantation: the United Network of Organ Sharing experience. Transplant Proc 1999; 31 (4A Suppl.): 19S-20S
75. Jarzembowski T, John E, Panaro F, et al. Impact of noncompliance on outcome after pediatric kidney transplantation: an analysis in racial subgroups. Pediatr Transplantation 2004; 8: 367-71
76. Chisholm MA, Vollenweider LJ, Mulloy LL, et al. Renal transplant patient compliance with free immunosuppressive medications. Transplantation 2000 Oct; 70 (8): 1240-4
77. Butkus DE, Dottes AL, Meydrech EF, et al. Effect of poverty and other socioeconomic variables on renal allograft survival. Transplantation 2001 Jul; 72 (2): 261-6
78. Chakkera HA, O'Hare AM, Johansen KL, et al. Influence of race on kidney transplant outcomes within and outside the Department of Veteran Affairs. J Am Soc Nephrol 2005; 16: 269-77
79. Weng FL, Israni AK, Joffe MM, et al. Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. J Am Soc Nephrol 2005 Jun; 16 (6): 1839-48
80. Cosio FG, Hickson LJ, Griffin MD, et al. Patient survival and cardiovascular risk after kidney transplantation: the challenges of diabetes. Am J Transplant 2008; 8: 593-9

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