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Outcomes in Ethnic Minority Renal Transplant Recipients Receiving Everolimus versus Mycophenolate: Comparative Risk Assessment Results From a Pooled Analysis

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Background. Everolimus (EVR) has demonstrated good efficacy after renal transplantation. Racial disparities in clinical outcomes after de novo renal transplantation are well documented; whether the efficacy of EVR varies based on recipient ethnicity is unknown. We conducted a comparative risk assessment of EVR by ethnicity.

Methods. Data on 2004 renal transplant recipients from three EVR studies were pooled to identify the impact of ethnicity on efficacy outcomes across EVR dosing groups and control groups. Ethnic groups compared were African Americans, non-U.S. blacks, Asians, Hispanics, and Caucasians. EVR groups received either 1.5 or 3 mg per day, with either standard-dose cyclosporine or reduced-dose cyclosporine. Control groups received mycophenolic acid (MPA) with standard-dose cyclosporine. Composite efficacy failure endpoint was graft loss, death, biopsy-proven acute rejection, or lost to follow-up. Adjusted odds ratios were calculated using a logistic regression model.

Results. The proportion of renal transplant recipients who met the composite endpoint was African Americans (46%), non-U.S. black (35%), Caucasian (31%), Hispanic (28%), and Asian (25%). The odds of meeting the composite endpoint were significantly (P=0.0001) greater for African Americans versus Caucasians but did not differ among the other ethnic groups (ethnic groups were only compared with Caucasians). EVR and MPA were associated with similar efficacy among each of the ethnic groups.

Conclusion. In this pooled data analysis in more than 2000 renal transplant recipients, EVR versus MPA resulted in similar composite endpoint incidence events across ethnicities. Consistent with previously published data, African Americans had poorer clinical outcomes. EVR is efficacious regardless of ethnicity.

Keywords: Everolimus, Mycophenolate, African American, Renal transplantation.

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Racial disparities in clinical outcomes after renal transplantation have been well documented. African Americans experience poorer graft function and survival and increased rejection rates compared with non–African Americans (*1–6*). There are less published data available on clinical outcomes of black kidney transplant recipients outside of the United States. Reported results suggest similar outcomes between blacks and whites in Canada (*7*) and France (*8*) and poorer survival among blacks versus whites and Asians in the United Kingdom (*9*). Data from the United States demonstrate that

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Asian and Hispanic renal transplant recipients have higher graft and patient survival rates compared with whites (*10*).

Everolimus (EVR) is associated with similar efficacy compared with mycophenolic acid (MPA) after renal transplantation (*11–15*). In addition, EVR allows for a lower exposure to calcineurin inhibitors (CNI) than does MPA while maintaining efficacy (*11, 16, 17*). Whether EVR and MPA are associated with similar efficacy among specific ethnic groups has not been previously reported.

Using data from several large clinical trials (B201, B251, and A2309), an analysis of pooled data was conducted to examine the association between EVR and clinical outcomes in African-American renal transplant recipients, black renal transplant recipients outside of the United States, and Asian, Hispanic, and white renal transplant recipients compared with MPA.

RESULTS

Patient Characteristics by Drug Group

Data from 2004 de novo renal transplant recipients were included in the analysis (EVR 1.5 mg [n=664], EVR 3.0 mg [n=671], and MPA [n=669]). Recipients in the three groups were similar in age, race, cause of end-stage disease, human leukocyte antigen (HLA) mismatches, delayed graft function (DGF), and donor age and type (Table 1). There was a gender difference. Mean follow-up time was 1031 days in the 3.0 mg EVR group, 1055 days in the EVR 1.5 mg group, and 1089 days in the MPA group (overall comparison among the three groups: P=0.04). The proportion of patients who dropped out of the studies before study completion was 19.1% (EVR 1.5 mg), 19.7% (EVR 3.0 mg), and 16.6% (MPA).

Patient Characteristics by Ethnicity

Overall, 7% (133 of 2004) of patients were Hispanic, 7% (132 of 2004) were Asian, 9% (179 of 2004) were African American, 3% (57 of 2004) were non-U.S. black, 71% (1425 of 2004) were Caucasian, and 4% (78 of 2004) were other ethnicities. Non-U.S. black recipients were from the following countries: Germany, Italy, Great Britain, South Africa, Brazil, France, and The Netherlands. Approximately half of the African Americans (n=83) were from study A2309. Table 2 displays the patient characteristics by ethnicity. Donor source varied across ethnic groups; the proportion recipients who received kidneys from living donors was similar between African American (35%) and Caucasian recipients (36%). The proportion of recipients who received kidneys from a living donor by drug treatment (EVR 1.5 mg, EVR 3.0 mg, and MPA, respectively) and ethnicity was 30%, 28%, and 45% (African American); 47%, 52%, and 43% (non-U.S. black); 67%, 55%, and 57% (Asian); 52%, 71%, and 52% (Hispanic); and 36%, 35%, and 37% (Caucasian); $P \leq 0.001$. The proportion of recipients who received kidneys from a deceased non-heart-beating donor by drug treatment (EVR 1.5 mg, EVR 3.0 mg, and MPA, respectively) and ethnicity was 2%, 3%, and 5% (African American); 0%, 0%, and 5% (non-U.S. black); 0%, 2%, and 2% (Asian); 0%, 0%, and 0% (Hispanic); and 4%, 4%, and 5% (Caucasian); P=0.067.

Mean follow-up time was similar among the drug groups for African-American recipients (930 days [EVR 1.5 mg],

TABLE 1. Demographic and baseline characteristics of the recipients and donors, pooled studies B201, B251, and A2309

	EVR 1.5 mg (n=664)	EVR 3.0 mg (n=671)	MPA (n=669)	*P*
Recipient age in years, mean±SD	44.9±12.28	44.5±12.58	45.8±12.52	0.139
Male, n (%)	401 (60.4)	441 (65.7)	460 (68.8)	0.005
Race				0.634
African American, n (%)	53 (7.9)	64 (9.5)	62 (9.3)	
Asian, n (%)	39 (5.9)	49 (7.3)	44 (6.6)	
Non-U.S. black, n (%)	15 (2.3)	21 (3.1)	21 (3.1)	
Caucasian, n (%)	491 (73.9)	464 (69.2)	470 (70.3)	
Hispanic, n (%)	42 (6.3)	41 (6.1)	50 (7.5)	
Delayed graft function, n (%)	87 (13.1)	91 (13.6)	76 (11.4)	0.439
End-stage disease leading to transplantation, n (%)				0.129
Glomerulonephritis/glomerular disease	166 (25.0)	170 (25.3)	162 (24.2)	
Pyelonephritis/interstitial nephritis	36 (5.4)	38 (5.7)	30 (4.5)	
Polycystic disease	104 (15.7)	73 (10.9)	97 (14.5)	
Hypertension/nephrosclerosis	96 (14.5)	120 (17.9)	104 (15.5)	
Diabetes mellitus	73 (11.0)	77 (11.5)	94 (14.1)	
Other/missing/unknown	189 (28.5)	193 (28.8)	182 (27.2)	
≥3 HLA mismatches, n (%)	487 (73)	471 (70)	477 (71)	0.434
Donor age in years, mean±SD	39.8±14.16	40.2±13.52	40.5±14.36	0.655
Donor type, n (%)				0.482
Deceased heart-beating	384 (58)	388 (58)	367 (55)	
Deceased non-heart-beating	20 (3)	22 (3)	29 (4)	
Living-related	170 (26)	187 (28)	193 (29)	
Living-unrelated	89 (13)	74 (11)	79 (12)	

EVR, everolimus; HLA, human leukocyte antigen; MPA, Mycophenolic acid.

TABLE 2. Demographic and baseline characteristics by ethnicity, pooled studies B201, B251, and A2309

	African Americans (n=179)	Non-U.S. black (n=57)	Asian (n=132)	Hispanic (n=133)	Caucasian (n=1425)
Recipient age in years, mean±SD	44.6±12.76	40.0±10.67	44.3±11.48	40.6±12.86	46.1±12.38
Male, n (%)	105 (58.7)	39 (68.4)	77 (58.3)	83 (62.4)	948 (66.5)
Delayed graft function, n (%)	26 (14.5)	8 (14.0)	14 (10.6)	15 (11.3)	182 (12.8)
Most recent panel-reactive antibody, mean±SD	3.7±13.0	1.5±5.5	1.9±6.0	2.4±10.0	2.4±8.3
End-stage disease leading to transplantation, n (%)					
Glomerulonephritis/glomerular disease	19 (10.6)	14 (24.6)	29 (22.0)	23 (17.2)	391 (27.4)
Pyelonephritis/interstitial nephritis	1 (0.6)	0 (0)	5 (3.8)	2 (1.5)	95 (6.7)
Polycystic disease	5 (2.8)	2 (3.5)	3 (2.3)	6 (4.5)	254 (17.8)
Hypertension/nephrosclerosis	91 (50.8)	18 (31.6)	30 (22.7)	32 (24.1)	135 (9.5)
Diabetes mellitus	36 (20.1)	2 (3.5)	15 (11.4)	28 (21.1)	153 (10.7)
Other/missing/unknown	27 (15.1)	21 (36.8)	50 (37.9)	42 (31.6)	397 (27.8)
≥3 HLA mismatch, n (%)	132 (73.7)	50 (87.7)	93 (70.5)	88 (66.2)	1007 (70.7)
Donor age in years, mean±SD	33.8±12.90	37.8 (12.7)	40.6±13.40	36.0±13.30	41.7±13.94
Donor type, n (%)					
Deceased heart-beating	110 (61.5)	29 (50.9)	52 (39.4)	56 (42.18)	851 (59.7)
Deceased non-heart-beating	6 (3.4)	1 (1.8)	2 (1.5)	0 (0)	60 (4.2)
Living-related	48 (26.8)	17 (29.8)	61 (46.2)	64 (48.1)	335 (23.5)
Living-unrelated	14 (7.8)	10 (17.5)	17 (12.9)	13 (9.8)	178 (12.5)
Missing	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (0.1)
Cold ischemia time (hr), mean±SD	12.6±10.0	9.4±9.7	7.1±8.9	9.2±11.0	12.1±9.7

HLA, human leukocyte antigen.

944 days [EVR 3.0 mg], and 878 days [MPA]; *P*=0.6380), non-U.S. black recipients (1091 days [EVR 1.5 mg], 949 days [EVR 3.0 mg], and 1029 days [MPA]; *P*=0.6742), Asian recipients (752 days [EVR 1.5 mg], 832 days [EVR 3.0 mg], and 825 days [MPA]; *P*=0.3724), and Hispanic recipients (995 days [EVR 1.5 mg], 916 days [EVR 3.0 mg], and 1000 days [MPA]; *P*=0.9743). Among Caucasian recipients, mean follow-up time was significantly (*P*=0.0156) different (1099 days [EVR 1.5 mg], 1079 days [EVR 3.0 mg], and 1153 days [MPA]).

The study drug discontinuation rates over the length of all three studies were 53.2% (353 of 664) for EVR 1.5 mg, 58.6% (393 of 671) for EVR 3 mg, and 42.5% (284 of 669) for MPA. Due to differences in discontinuation rates, there were differences in drug exposure. A significant difference (*P*=0.0002) in mean days of drug exposure (treatment time) was found among Caucasian recipients (829 days [EVR 1.5 mg], 763 days [EVR 3.0 mg], and 937 days [MPA]). Mean days of drug exposure among the other ethnic groups followed the same trend as that of the Caucasians; however, no significant differences were found likely due to smaller sample sizes. Mean treatment times were 702 days (EVR 1.5 mg), 561 days (EVR 3.0 mg), and 684 days (MPA; *P*=0.2975) for African-American recipients; 946 days (EVR 1.5 mg), 650 days (EVR 3.0 mg), and 848 days (MPA; *P*=0.4666) for non-U.S. black recipients; 644 days (EVR 1.5 mg), 601 days (EVR 3.0 mg), and 708 days (MPA; *P*=0.3237) for Asian recipients; and 832 days (EVR 1.5 mg), 597 days (EVR 3.0 mg), and 773 days (MPA; *P*=0.2974) for Hispanic recipients.

Immunosuppression

Mean EVR trough levels ranged from 2.2 to 5.9 ng/mL for the EVR1.5 mg group and 4.5 to 8.5 ng/mL for the EVR 3 mg group. MPA doses were similar across the studies. Mean cyclosporine A (CsA) trough levels were consistently higher for the MPA group compared with the EVR groups (Table 3). Mean CsA dose (mg/kg) was numerically higher for the MPA group (with the exception of the non-U.S. black group at month 1 [MPA 5.26±1.73 and EVR 1.5 mg 5.42±2.11] and month 3 [MPA 3.64±0.97 and EVR 1.5 mg 3.66±1.18]) than the EVR 1.5 mg and 3.0 groups over the study period. CsA doses decreased over the study period for all drug groups and ethnicities. African-American recipients

TABLE 3. Mean CsA trough levels (ng/mL) by treatment, visit, and ethnicity

Visit	EVR 1.5 mg	EVR 3.0 mg	MPA
Day 3	203	207	238
Week 1	219	233	241
Week 2	242	236	283
Month 1	233	227	245
Month 2	190	193	215
Month 3	165	172	189
Month 4	113	109	166
Month 6	132	129	169
Month 7	78	78	158
Month 9	105	98	156
1 year	101	95	148
Month 18	89	80	141
2 years	88	84	145

CsA, cyclosporine; EVR, everolimus; MPA, mycophenolic acid.

tended to have the highest CsA dose (mg/kg) over the study period. The only exceptions were month 1 in the EVR 1.5 mg group where non-U.S. blacks had a higher mean dose (5.42±2.11) compared with African Americans (5.20±2.05) and month 6 in the MPA group where Hispanics had a numerically higher mean dose (4.11±1.95) compared with African Americans (3.86±1.50). Use of antithymocyte globulin (rabbit) as an induction agent was infrequent (used in 15% of patients). In study A2309, basiliximab use by ethnicity was 36% basiliximab and 64% no basiliximab (Caucasians), 54% basiliximab and 46% no basiliximab (non-U.S. blacks), 46% basiliximab and 54% no basiliximab (African Americans), 80% basiliximab and 20% no basiliximab (Asians), and 57% basiliximab and 43% no basiliximab (Hispanics).

Incidence of Composite Endpoint by Ethnicity and Treatment Group

Across the three treatment groups, there was no significant difference (P=0.9969) in the percentage of patients meeting the composite endpoint (32% in each group). Nor were there any significant differences among the treatment groups in the percentage of patients meeting the composite endpoint when examined specifically within the ethnic groups (African Americans: MPA 48%, EVR 1.5 mg 47%, and EVR 3.0 mg 42% [P=0.7623]; non-U.S. blacks: MPA and EVR 1.5 mg 33% and EVR 3.0 mg 38% [P=0.9362]; Asians: MPA 27%, EVR 1.5 mg 23%, and EVR 3.0 mg 24% [P=0.9027]; Hispanics: MPA 34%, EVR 1.5 mg 21%, and EVR 3.0 mg 27% [P=0.4059]; and Caucasians: MPA 30% and EVR 1.5 and 3.0 mg 32% [P=0.7174]). When examined across ethnicities, irrespective of treatment, the proportion of patients meeting the composite endpoint was lowest among Asians (25%) followed by Hispanics (28%), Caucasians (31%), non-U.S. blacks (35%), and African Americans (46%) (Fig. 1).

In terms of the individual efficacy components, there was no significant difference among the treatment groups in the incidence of biopsy-proven acute rejection (BPAR; MPA 23%, EVR 1.5 mg 21%, and EVR 3.0 mg 20%; P=0.2449), graft loss (MPA 7%, EVR 1.5 mg 11%, and EVR 3.0 mg 10%; P=0.1539), death (MPA 5%, EVR 1.5 mg 5%, and EVR 3.0 mg 8%; P=0.8191), or lost-to-follow-up (MPA 2.2%, EVR 1.5 mg 3.6%, and EVR 3.0 mg 2.7%; P=0.2821). By ethnicity, regardless of treatment, there was a significant difference in BPAR (African Americans [32%], non-U.S. blacks [26%], Caucasians [21%], Hispanics [19%], and Asians [17%]; P=0.0032); post-hoc analysis showed a significantly greater frequency of BPAR for African Americans compared with Caucasians, Asians, and Hispanics. There were no significant differences among ethnic groups in the proportion of patients with graft loss (African Americans [13%], non-U.S. blacks [7%], Caucasians [9%], Hispanics [5%], and Asians [6%]; P=0.0636), death (African Americans [6%], non-U.S. blacks [7%], Caucasians [6%], Hispanics [6%], and Asians [2%]; P=0.5667), or lost-to-follow-up (African Americans [5%], non-U.S. blacks [0%], Caucasians [3%], Hispanics [2%], and Asians [4%]; P=0.4064).

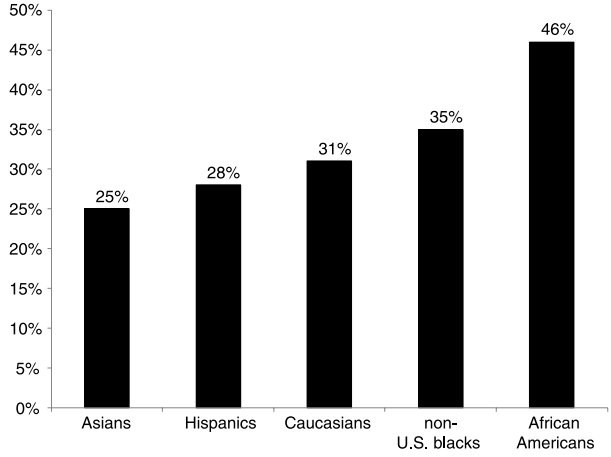

FIGURE 1. Proportion of renal transplant recipients meeting composite efficacy endpoint by ethnicity.

Adjusted Odds of Composite Endpoint by Ethnicity

African-American renal transplant recipients had a significantly (P=0.0001) increased adjusted odds ratio (OR) of 0.54 (95% confidence interval [CI], 0.39–0.74, for Caucasian vs. African American) of meeting the composite efficacy endpoint compared with Caucasian recipients. In terms of the individual efficacy components, African-American renal transplant recipients had a significantly increased adjusted odds of having BPAR (OR, 0.54; 95% CI, 0.38–0.75, P=0.0003, for Caucasian vs. African American) and graft loss (OR, 0.63; 95% CI, 0.39–0.998, P=0.0493, for Caucasian vs. African American); no significant difference was observed between African-American and Caucasian renal transplant recipients in the odds of death. No significant differences were found among the Hispanic, Asian, or non-U.S. black recipients and Caucasian recipients in the odds of meeting the composite efficacy endpoint or in the odds of meeting any of the individual efficacy components.

Creatinine Clearance

Table 4 displays mean creatinine clearances among the three drug groups, overall and by ethnicity, as assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Overall, significantly (P<0.05) higher creatinine clearances were found for the MPA group compared with the EVR 3.0 mg and EVR 1.5 mg groups at 1 and 2 years after transplantation, and at end of study. Creatinine clearance in the EVR 1.5 mg group was significantly higher than in the EVR 3.0 mg group at 1 year posttransplantation and at end of study. By ethnicity, creatinine clearances were significantly (P<0.05) higher those results were consistent among Caucasian recipients with significantly (P<0.05) higher creatinine clearances for the MPA group compared with the EVR 3.0 mg and EVR 1.5 mg groups among Caucasians at each time point and significantly higher for the EVR 1.5 mg versus the EVR 3.0 mg group at 1 year post-transplantation. There were no significant differences in creatinine clearance among the drug groups within the other ethnic cohorts, although small sample sizes may have prevented detecting statistical significance.

TABLE 4. Mean±SD creatinine clearance (CKD-EPI) (mL/min/1.73 m^2) at 1 and 2 years after transplantation and at the end of study, by ethnicity and treatment group, pooled studies B201, B251, and A2309

1 year after transplantation

	EVR 1.5 mg (n=567)	EVR 3.0 mg (n=561)	MPA (n=571)	*P* EVR 3.0 vs. 1.5 mg	*P* EVR 3.0 mg vs. MPA	*P* EVR 1.5 mg vs. MPA
All ethnic groups combined	48.60±19.31	46.26±18.98	50.99±17.39	**0.0303**	**<0.0001**	**0.0229**
	n=43	n=56	n=46			
Black	49.27±18.64	48.32±19.19	52.81±18.40	0.8673	0.2424	0.3483
	n=15	n=18	n=19			
Non-U.S. black	58.75±18.64	52.58±14.86	57.84±16.93	0.1831	0.2830	0.7127
	n=34	n=44	n=38			
Asian	56.43±25.61	53.40±26.56	54.36±22.50	0.6013	0.8793	0.7162
	n=38	n=36	n=42			
Hispanic	52.54±21.78	57.93±18.11	53.20±19.38	0.3138	0.3465	0.9192
	n=419	n=381	n=407			
Caucasian	46.71±18.34	43.59±17.48	49.53±16.34	**0.0137**	**<0.0001**	**0.0154**

2 years after transplantation

	EVR 1.5 mg (n=475)	EVR 3.0 mg (n=446)	MPA (n=494)	*P* EVR 3.0 vs. 1.5 mg	*P* EVR 3.0 mg vs. MPA	*P* EVR 1.5 mg vs. MPA
All ethnic groups combined	49.27±20.60	47.17±19.53	52.07±20.75	0.0764	**0.0001**	**0.0363**
	n=31	n=38	n=35			
Black	56.00±18.78	49.05±16.19	54.08±24.84	0.1662	0.3071	0.6957
	n=13	n=17	n=17			
Non-U.S. black	55.29±22.06	55.11±18.77	65.60±23.17	0.5631	0.1166	0.4063
	n=33	n=38	n=37			
Asian	51.61±30.69	55.75±30.88	53.37±25.36	0.6121	0.7656	0.8281
	n=31	n=23	n=32			
Hispanic	54.69±16.91	49.67±19.23	57.64±22.63	0.2908	0.1177	0.5777
	n=348	n=312	n=355			
Caucasian	47.18±19.57	45.31±17.60	50.55±19.20	0.1772	**0.0003**	**0.0213**

End of study

	EVR 1.5 mg (n=661)	EVR 3.0 mg (n=670)	MPA (n=665)	*P* EVR 3.0 vs. 1.5 mg	*P* EVR 3.0 mg vs. MPA	*P* EVR 1.5 mg vs. MPA
All ethnic groups combined	45.52±22.60	43.03±21.68	47.87±22.10	**0.0365**	**<0.0001**	**0.0458**
	n=50	n=64	n=60			
Black	48.66±24.97	42.62±21.05	43.16±26.53	0.1922	0.9060	0.2397
	n=15	n=21	n=21			
Non-U.S. black	58.57±23.57	54.60±22.21	63.89±23.26	0.3960	0.1449	0.6667
	n=39	n=48	n=44			
Asian	51.05±30.52	51.21±30.49	50.70±24.56	0.8183	0.7068	0.8936
	n=42	n=41	n=49			
Hispanic	52.00±19.61	51.22±20.77	47.69±24.32	0.7701	0.5280	0.3448
	n=491	n=464	n=469			
Caucasian	43.55±21.48	41.33±20.09	47.90±20.35	0.1020	**<0.0001**	**0.0009**

EVR, everolimus; MPA, mycophenolic acid.

Adverse Events

Adverse events (AE) and serious AEs are displayed in Table 5.

DISCUSSION

Previously reported data have shown that EVR is associated with similar efficacy as MPA and that EVR offers

TABLE 5. AEs and serious AEs by treatment group and ethnicity, pooled studies B201, B251, and A2309, n (%)

	EVR 1.5 mg					
AE	All subjects (n=664)	Caucasian (n=491)	African American (n=53)	Non-U.S. black (n=15)	Asian (n=39)	Hispanic (n=42)
Peripheral edema	273 (41)	207 (42)	23 (43)	6 (40)	8 (21)	20 (48)
Constipation	244 (37)	176 (36)	22 (42)	3 (20)	14 (36)	21 (50)
Hypertension	211 (32)	169 (34)	15 (28)	5 (33)	7 (18)	9 (21)
Anemia	188 (28)	131 (27)	22 (42)	4 (27)	6 (15)	16 (38)
Nausea	188 (28)	139 (28)	17 (32)	4 (27)	7 (18)	14 (33)
Hypercholesterolemia	165 (25)	110 (22)	11 (21)	8 (53)	17 (44)	12 (29)
Hyperlipidemia	164 (25)	128 (26)	9 (17)	1 (7)	9 (23)	12 (29)
Diarrhea	162 (24)	124 (25)	11 (21)	3 (20)	8 (21)	7 (17)
UTI	159 (24)	119 (24)	11 (21)	5 (33)	8 (21)	10 (24)
Blood creatinine increase	140 (21)	108 (22)	18 (34)	2 (13)	2 (5)	5 (12)
Pyrexia	140 (21)	99 (20)	14 (26)	3 (20)	2 (5)	13 (31)
Insomnia	132 (20)	93 (19)	5 (9)	4 (27)	12 (31)	13 (31)
Serious AE						
Dyspnea	5 (0.8)	4 (0.8)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increase	41 (6.2)	31 (6.3)	7 (13.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocele	39 (5.9)	27 (5.5)	2 (3.8)	0 (0.0)	1 (2.6)	4 (9.5)
Pyrexia	33 (5.0)	18 (3.7)	3 (5.7)	1 (6.7)	1 (2.6)	9 (21.4)
Complications of Tx kidney	15 (2.3)	8 (1.6)	3 (5.7)	0 (0.0)	0 (0.0)	3 (7.1)
	EVR 3 mg					
	All subjects (n=671)	**Caucasian (n=464)**	**African American (n=64)**	**Non-U.S. black (n=21)**	**Asian (n=49)**	**Hispanic (n=41)**
Peripheral edema	259 (39)	182 (39)	31 (48)	8 (38)	10 (20)	14 (34)
Constipation	265 (39)	174 (38)	29 (45)	11 (52)	19 (39)	23 (56)
Hypertension	204 (30)	149 (32)	17 (27)	5 (24)	10 (20)	16 (39)
Anemia	243 (36)	172 (37)	27 (42)	2 (10)	13 (27)	18 (44)
Nausea	193 (29)	127 (27)	27 (42)	2 (10)	12 (24)	16 (39)
Hypercholesterolemia	167 (25)	111 (24)	10 (16)	6 (29)	20 (41)	11 (27)
Hyperlipidemia	170 (25)	128 (28)	15 (23)	2 (10)	7 (14)	8 (20)
Diarrhea	166 (25)	120 (26)	16 (25)	4 (19)	11 (22)	5 (12)
UTI	143 (21)	100 (22)	16 (25)	4 (19)	6 (12)	7 (17)
Blood creatinine increase	160 (24)	116 (25)	17 (27)	2 (10)	8 (16)	10 (24)
Pyrexia	146 (22)	103 (22)	14 (22)	0 (0)	10 (20)	11 (27)
Insomnia	141 (21)	100 (22)	12 (19)	3 (14)	13 (27)	8 (20)
Serious AE						
Dyspnea	17 (2.5)	12 (2.6)	3 (4.7)	0 (0.0)	0 (0.0)	2 (4.9)
Blood creatinine increase	50 (7.5)	38 (8.2)	4 (6.3)	1 (4.8)	2 (4.1)	3 (7.3)
Lymphocele	56 (8.3)	43 (9.3)	5 (7.8)	0 (0.0)	3 (6.1)	3 (7.3)
Pyrexia	27 (4.0)	18 (3.9)	2 (3.1)	0 (0.0)	2 (4.1)	4 (9.8)
Complications of Tx kidney	15 (2.2)	11 (2.4)	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

Continued on next page

TABLE 5. *(Continued)*

	MPA					
	All subjects (n=669)	**Caucasian (n=470)**	**African American (n=62)**	**Non-U.S. black (n=21)**	**Asian (n=44)**	**Hispanic (n=50)**
Peripheral edema	225 (34)	160 (34)	22 (35)	3 (14)	12 (27)	19 (38)
Constipation	264 (39)	185 (39)	29 (47)	6 (29)	17 (39)	21 (42)
Hypertension	210 (31)	167 (36)	12 (19)	5 (24)	6 (14)	13 (26)
Anemia	175 (26)	122 (26)	21 (34)	5 (24)	8 (18)	12 (24)
Nausea	187 (28)	132 (28)	22 (35)	4 (19)	8 (18)	14 (28)
Hypercholesterolemia	122 (18)	80 (17)	7 (11)	6 (29)	15 (34)	11 (22)
Hyperlipidemia	117 (17)	81 (17)	18 (29)	2 (10)	4 (9)	10 (20)
Diarrhea	148 (22)	112 (24)	12 (19)	3 (14)	8 (18)	7 (14)
UTI	155 (23)	108 (23)	19 (31)	7 (33)	8 (18)	8 (16)
Blood creatinine increase	129 (19)	85 (18)	17 (27)	5 (24)	13 (30)	6 (12)
Pyrexia	107 (16)	63 (13)	14 (23)	6 (29)	5 (11)	11 (22)
Insomnia	132 (20)	101 (21)	12 (19)	2 (10)	7 (16)	7 (14)
Serious AE						
Dyspnea	3 (0.4)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increase	35 (5.2)	23 (4.9)	5 (8.1)	3 (14.3)	2 (4.5)	2 (4.0)
Lymphocele	20 (3.0)	15 (3.2)	3 (4.8)	1 (4.8)	1 (2.3)	0 (0.0)
Pyrexia	24 (3.6)	15 (3.2)	1 (1.6)	2 (9.5)	1 (2.3)	3 (6.0)
Complications of Tx kidney	7 (1.0)	3 (0.6)	2 (3.2)	0 (0.0)	1 (2.3)	1 (2.0)

AE, adverse event; EVR, everolimus; MPA, mycophenolic acid; UTI, urinary tract infection

the benefit of reduced exposure to CNIs compared with MPA while maintaining efficacy. This pooled data analysis, including more than 2000 renal transplant recipients administered EVR or MPA, demonstrated that EVR is associated with similar efficacy as MPA regardless of recipient ethnicity. Of note, EVR and MPA did not significantly differ in efficacy specifically in African Americans, a renal transplant population at increased risk for poorer clinical outcomes. These results also suggest that non-U.S. black renal transplant recipients have similar clinical outcomes as Caucasian recipients, whereas Asian and Hispanic recipients have improved clinical outcomes.

Consistent with these results, United Network for Organ Sharing (UNOS) data show that Asian and Hispanic kidney transplant recipients have the highest short-term and long-term graft and patient survival rates (*10*). UNOS data also demonstrate that African-American transplant recipients of deceased donors had lower rates of graft survival compared with other races and ethnicities at 1, 5, and 10 years after transplantation, whereas African Americans of living donor recipients had lower rates of long-term graft survival (i.e., 5 and 10 years after transplantation) compared with other races and ethnicities (*10*). In this study, the overall odds for experiencing a composite endpoint was significantly increased for African-American renal transplant recipients compared with Caucasians, corroborating previous reports that African Americans have an increased risk for poorer clinical outcomes, irrespective of treatment. Although this analysis did not explore the relationship of EVR and long-term outcomes in African Americans, results from a recently published analysis suggested that EVR may be associated with improved kidney graft survival particularly in patients of deceased donor transplants, despite a numerically greater number of rejection episodes (*18*).

We found that renal transplant recipients outside of the United States who self-identified themselves as black had similar outcomes as Caucasian recipients. The analysis of non-U.S. blacks was limited due to a small sample size. However, the results were consistent with those from a study from Canada of black Canadians (*7*) and from a study from France of black Europeans (*8*). Both the Canadian and French studies found similar clinical outcomes between the blacks and whites in the respective studies. In the present study, the non-U.S. black recipients had a mixture of high-risk and low-risk characteristics. Non-U.S. black recipients had an incidence of DGF that was similar to African Americans; they also had the highest proportion of recipients with three or more HLA mismatches. Conversely, the non-U.S. black group had a greater proportion of living donors. Interestingly, the CsA dosing of non-U.S. black recipients appeared to be more similar to the dosing employed in non-black recipients than African-American recipients. There are likely a myriad of factors that contribute to the discrepancy in outcomes between African Americans and other ethnic groups (e.g., access to care, biological differences, and comorbidities). The underlying reasons for differences in clinical outcomes are beyond the scope of this study.

The MPA group was found to have significantly higher mean creatinine clearance compared with the EVR groups. Those results are confounded by the fact that of the three trials included in the pooled analysis, only one (study 2309) used the current approved immunosuppression regimen of

low-dose CsA throughout the duration of the study with therapeutic dose monitoring of EVR. Analysis of creatinine clearance (CKD-EPI; mL/min/1.73 m^2) among African Americans in the 2309 study showed no significant differences between the MPA (52.3), EVR 1.5 mg (51.8), and EVR 3.0 mg (55.6) groups (*data on file*). Overall, the glomerular filtration rate (GFR) results in the EVR group suggest that if African-American renal transplant recipients have comparable renal function at 1 year after transplantation, they may continue to have good renal function longer-term after transplantation.

Clinical outcomes after kidney transplantation are currently characterized by low acute rejection rates and high 1-year graft and patient survival (*10*); however, long-term graft and patient survival is not optimal (*19–22*). Identifying immunosuppression drug regimens that are associated with decreasing the leading causes of long-term graft failure and patient death is a key focus of current transplant research efforts. In addition, employing immunosuppressants that are associated with efficacy particularly in populations at increased risk for poorer clinical outcomes may help to improve overall graft and patient survival rates. These data demonstrate good efficacy in a high-risk group of recipients. Previously reported data show that EVR has particular promise as an immunosuppressive drug that may attenuate causes of long-term graft loss and death (based on its efficacy in the face of low-dose CNIs as well as on its demonstrated cardioprotective and antitumor effects) (*23, 24*). The results from the present analysis add to the growing body of literature affirming the role of EVR as an important immunosuppressive in the cache of drugs available for immunosuppression therapy after kidney transplantation.

The proportion of African Americans in this study was lower than that of the general U.S. kidney transplant population. From the most recently available UNOS data, 31% of renal transplant recipients of deceased donors and 13% of renal transplant recipients of living donors transplanted in 2008 were African Americans (*10*). Based on the proportion of deceased versus living donors in the current study, 24% of the overall sample would be expected to be African American to mirror the ethnic breakdown of the U.S. transplantation trends; in this study, approximately 9% were African American. Due to the relatively small numbers of African Americans, we may have been underpowered to detect some important differences.

Basiliximab was permitted in one of the three trials (A2309) pooled in this analysis; there is the potential that differences in basiliximab use by ethnicity may have impacted the efficacy results. The small number of patients after stratification by basiliximab use and ethnicity, and the use of basiliximab in only one of the three included trials precluded a meaningful analysis to examine this potential confounder.

Generalizing the results from this analysis to the general U.S. population of kidney transplant recipients may be limited by the fact that participants in clinical trials may differ from nonparticipants and that the clinician's treating behavior may also differ from that of a nontrial setting. Overall, these results showed that EVR was associated with similar efficacy as MPA in the African-American population. Further study is warranted to determine if EVR is associated with similar or improved, or inferior, long-term outcomes compared with MPA across ethnic groups.

MATERIALS AND METHODS

Data Sources and Endpoints

Data from three randomized clinical trials were pooled for the present analysis (Fig. 2). Incidence of and the adjusted odds of meeting a composite endpoint defined as graft loss, death, treated BPAR, or lost to follow-up

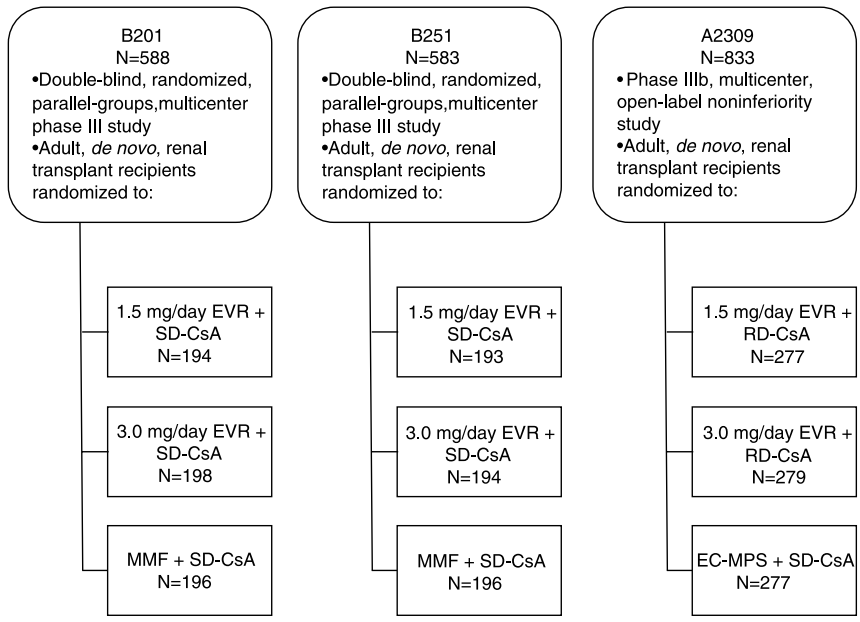

FIGURE 2. Description of the study designs of the three trials from which data were pooled for the present analysis. EC-MPS, enteric-coated mycophenolate sodium; EVR, everolimus; MMF, mycophenolate mofetil; RD-CsA: reduced dose cyclosporine; SD-CsA, standard dose cyclosporine.

after renal transplantation were compared between renal transplant recipients who received 1.5 mg per day EVR, 3.0 mg per day EVR, and MPA, separately for African-American recipients, non-U.S. black recipients, Asians, Hispanics, and Caucasians. All patient follow-up data were included; thus, outcomes were assessed for up to 5 years follow-up. Creatinine clearance at 1 and 2 years after transplantation and at end of study was also compared between the EVR and MPA groups among the ethnic groups. Creatinine was measure centrally (Jaffe method). The CKD-EPI equation (*25*) was used to estimated GFR. The CKD-EPI formulation has been shown to be a more accurate estimation of GFR than the Modification of Diet in Renal Disease formulation (*25, 26*).

Patient Population and Treatment

Patient selection (adult, de novo renal transplant recipients) and treatment have been described previously (*11, 14, 15*). In brief, studies B201 (n=588) and B251 (n=583) were both 12-month, multicenter, randomized, double-blind, parallel-group equivalence trials of two oral fixed doses of EVR (1.5 mg/day, B201 [n=194] and B251 [n=193] or 3 mg/day, B201 [n=198] and B251 [n=194]) versus mycophenolate mofetil (B201 [n=196] and B251 [n=196]); all three groups also received standard dosing of CsA microemulsion (Neoral) and corticosteroids. The original protocols for both studies were finalized in April 1998; in January 2001, both protocols were amended to reduced-dose CsA. EVR blood levels were recorded prospectively within these studies. Study A2309 (n=833) was a 24-month, multicenter, randomized, open-label, parallel-group noninferiority trial of two oral concentration-controlled doses of EVR (1.5 mg/day, targeted to trough levels of 3–8 ng/mL [n=277] and 3.0 mg/day, targeted to 6–12 ng/mL [n=279]) versus enteric-coated mycophenolate sodium (n=277). EVR was administered with reduced-dose CsA, whereas enteric-coated mycophenolate sodium was with standard-dose CsA. All three groups received basiliximab induction, and steroids were used according to local center practice.

Key exclusion criteria for all three studies included kidneys donated after cardiac death or with a cold ischemia time more than 40 hr; donor age more than 65 years; or recipients of multiorgan, ABO-incompatible, positive T-cell crossmatch, or HLA-identical living-related donor transplants. In A2309, an additional exclusion criteria was most recent anti-HLA class I panel-reactive antibodies more than 20% by a complement-dependent cytotoxicity (CDC)–based assay or more than 50% by flow cytometry or enzyme-linked immunosorbent assay. In addition, in study A2309, patients were excluded if they did not have graft function within 24 hr after transplantation.

All studies were approved by the Ethics Committee at all participating institutions and conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients gave written informed consent to participate in the original studies.

Statistical Analysis

Cochran–Mantel–Haenszel generalized association test controlled for study was used to compare categorical data between groups; analysis of variance with treatment and study as factors was used to compare continuous data. Logistic regression was used to calculate adjusted ORs for experiencing the composite endpoint. Drug group and study were included in the models as well as ethnicity.

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