Renal risk and renoprotection among ethnic groups with type 2 diabetic nephropathy: A *post hoc* analysis of RENAAL

D de Zeeuw[1], D Ramjit[2], Z Zhang[2], AB Ribeiro[3], K Kurokawa[4], JP Lash[5], J Chan[6], G Remuzzi[7], BM Brenner[8] and S Shahinfar[2]

[1]*Department of Clinical Pharmacology, Groningen University Medical Center, Groningen, The Netherlands;* [2]*Merck Research Laboratories, Merck & Co. Inc., Whitehouse Station, New Jersey, USA;* [3]*Nephrology Division-UNIFESP – EPM, Hospital Do Rim E Hipertensão-Fundação Oswaldo Ramos, Sau Paulo, Brazil;* [4]*Dean's Office, Tokai University School of Medicine, Kanagawa, Japan;* [5]*Section of Nephrology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA;* [6]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Hong Kong, China;* [7]*Mario Negri Institute for Pharmacological Research, Bergamo, Italy and* [8]*Renal Division, Department of Medicine, Brigham and Women's Hospital and Harvard School of Medicine, Boston, Massachusetts, USA*

Type 2 diabetes is becoming the leading cause of end-stage renal disease (ESRD) worldwide. Prevalence of ESRD and the antihypertensive response to renin–angiotensin system intervention are suggested to vary among different ethnicities. The Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, which included different ethnic groups, demonstrated a renoprotective effect of losartan. A *post hoc* analysis from RENAAL was performed where we examined in each ethnic group the ESRD risk, identified independent predictors for ESRD, effect of degree of baseline albuminuria, effect of 6-month antiproteinuric response to therapy on ESRD, and renoprotective effect of losartan assessed by albuminuria reduction and ESRD. Baseline albuminuria was the strongest predictor for ESRD in every ethnic group. Albuminuria reduction was associated with reduced risk of ESRD while losartan reduced albuminuria in every ethnic group. When accounting for independent predictors of ESRD, losartan exhibited renoprotection in all ethnic groups. In this type 2 diabetic population with nephropathy, baseline albuminuria is the predominant risk parameter for ESRD; early antiproteinuric effect of losartan predicts long-term renoprotection; and losartan appears to be renoprotective in all ethnic groups. Since the RENAAL study was not powered to determine ethnic responses, these results underline the need for prospective trials where the aim is renal protection among different ethnic groups.

Kidney International (2006) **69,** 1675–1682. doi:10.1038/sj.ki.5000326; published online 29 March 2006

Correspondence: *D de Zeeuw, Department of Clinical Pharmacology, University Medical Center Groningen, Ant Deusinglaan 1, Groningen 9713 AV, The Netherlands. E-mail: d.de.zeeuw@med.umcg.nl*

Received 18 January 2005; revised 19 November 2005; accepted 14 December 2005; published online 29 March 2006

KEYWORDS: albuminuria; proteinuria; ethnicity; type 2 diabetes; losartan; ESRD

Worldwide, diabetes mellitus is one of the most common diseases[1] and has become a major cause of end-stage renal disease (ESRD).[2,3] Ethnic differences in ESRD have been widely reported. Earlier and more recent population-based studies consistently have shown that in diabetic and non-diabetic patients, Black, and in some reports, Asian patients, experience higher rates of ESRD, whereas White patients experience lower rates.[4–8] Higher incidences of ESRD have been reported in Hispanic patients with or without diabetes, relative to White patients.[2,7–9]

Given the fact that nephropathy occurs in approximately 10–40% of diabetic patients,[10] early identification of patients with type 2 diabetes who are at increased risk for renal disease and early initiation of treatment to slow progression to ESRD is of great importance for all ethnic groups. Proteinuria, azotemia, anemia, hyperglycemia, hypertension, and hyperlipidemia have been shown to be risk factors for renal and cardiovascular outcomes in type 2 diabetes.[11–15] However, whether these risk factors for outcome play the same predictive role among different ethnicities is not known. Proteinuria is one of the most widely recognized risk factors for renal disease progression.[16–18] Proteinuria has been studied in different ethnic groups; however, the findings have been variable with respect to the prevalence and severity of proteinuria among those groups.[19–25]

Several large clinical trials have shown that intervention using antihypertensives that block the renin—angiotensin system (RAS) are beneficial in reducing the incidence of cardiovascular and renal outcomes in diabetic patients.[26–29] Whether such a treatment strategy is equally beneficial to

diabetic patients across different ethnicities is not known. In fact, it has been suggested that the *antihypertensive response* to RAS blockade is less effective than other therapeutic classes in Black patients relative to non-black patients.[30,31] However, limited data are available on the effect of RAS blockade on cardiovascular and renal outcomes comparing different ethnic groups simultaneously and prospectively.

The Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study was the first to demonstrate that RAS blockade with losartan is effective in reducing the incidence and delaying the onset of ESRD in patients with type 2 diabetes and nephropathy.[29] Additionally, baseline proteinuria has been shown to be the leading risk predictor for renal outcomes including ESRD in this population.[12] Furthermore, angiotensin II antagonist (AIIA)-induced reduction in proteinuria appears to be a good predictor for long-term renal and cardiovascular protection.[11,12] The RENAAL study, to our knowledge, is the only study that has recruited type 2 diabetic patients with renal disease worldwide, including relatively large numbers of White, Black, Hispanic, and Asian patients. ESRD was observed in each ethnic group, which has allowed us to explore risk of renal outcomes and the renoprotective effect of losartan therapy across those groups. We also investigated if similar renal risk factors are present in each ethnic group. Moreover, in each ethnic group, we examined whether the reduction in albuminuria affords the same renal protection, and whether RAS intervention with losartan leads to the same risk reduction in ESRD. In the present report, we focus on the irreversible renal outcome of ESRD, as this outcome was ascertained in all patients randomized to the study, and represents the final stage of renal disease progression, and the ultimate therapeutic target for renal protection.

RESULTS

Baseline risk factors as predictors of ESRD by ethnic group

Table 1 summarizes baseline demographic parameters for the RENAAL population stratified by ethnic group. We observed expected differences in weight among the ethnic groups, with the Asian patients having the lowest weight (64 kg) and the Black and White patients having the highest weights (92 and 88 kg, respectively) in the study.

Hemoglobin was lowest in the Black patients and highest in White patients (12.0 and 12.8 mg/dl, respectively). Serum creatinine, systolic blood pressure (BP), and diastolic BP were comparable among all ethnic groups. Notable differences were observed among the groups in baseline albuminuria, which was considerably higher in Hispanic and Asian patients (2.40 and 2.01 g/g, respectively) and lowest in Black patients (1.22 g/g). Figure 1 clearly illustrates that the distribution of baseline albuminuria levels varied among ethnic groups.

The risk for ESRD among ethnic groups is depicted in Figure 2. The Hispanic and Asian populations show a somewhat higher risk for ESRD than the Black and White populations. A multivariate analysis was performed to determine the relative impact of selected baseline risk factors on ESRD in the different ethnic groups. Table 2 shows that of the selected baseline risk factors included in the multivariate model, baseline albuminuria was the strongest independent predictor of ESRD in all ethnic groups: Asian (hazard ratio (HR) = 1.33), Black (HR = 1.81), Hispanic (HR = 1.46), and White (HR = 1.62).

The distribution of baseline albuminuria was variable among ethnic groups. Despite these differences, we observed that a similar degree of albuminuria predicted a similar degree of risk for ESRD across ethnic groups. As shown in Figure 3, higher levels of baseline albuminuria were associated with progressively increased risk of ESRD (controlled for baseline risk factors) for all ethnic groups.

Six-month change in albuminuria as a predictor for ESRD by ethnic group

Data from the RENAAL study suggest that albuminuria reduction observed in the first 6 months of treatment is predictive of the efficacy of treatment on renal outcomes.[12] The relationship between different degrees of month-6 albuminuria reduction and the risk for ESRD is depicted in Figure 4 for each ethnic group. Similar to the overall population,[12] albuminuria reduction was associated with reduced risk of ESRD (controlled for baseline and changes in month-6 risk factors) in all ethnic groups.

Renoprotective effect of losartan by ethnic group

Losartan-reduced albuminuria in the overall population by 34%.[29] Figure 5 illustrates mean change in albuminuria during the course of the study in each ethnic group. Over time, mean reductions in albuminuria were observed in the placebo groups of each ethnic group, especially after the first 12 months of the study. The albuminuria reductions with placebo most likely were influenced by premature discontinuation of study drug, ESRD or death. Progressive reductions in albuminuria with losartan were observed as early as month-3 in all ethnic groups (Figure 5).

The renoprotective effect of losartan in the overall RENAAL population was characterized by a 28% risk reduction in ESRD when comparing losartan to placebo, with both treatment groups on a background of conventional antihypertensive treatment.[29] Figure 6 illustrates the losartan treatment effect for ESRD by ethnic group. The renoprotective effect of losartan based on the pre-specified analysis (Figure 6, solid lines), was most favorable in the White and Asian groups followed by the Black group; while a neutral treatment effect for ESRD was observed in the Hispanic ethnic group. However, given the importance of baseline albuminuria and other variables as independent predictors of risk, the treatment effects for ESRD for each ethnicity were controlled for their respective baseline risk predictors identified in the multivariate analysis (Table 2). The renoprotective response of losartan when accounting for these risk factors (Figure 6, dashed lines) was improved in all