Changes in the Incidence of Endstage Renal Disease Due to Lupus Nephritis in the United States, 1996–2004

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ABSTRACT. ***Objective.*** To determine if the incidence of endstage renal disease (ESRD) due to lupus nephritis has decreased from 1996 to 2004.

Methods. Patients age 15 years or older with incident ESRD due to lupus nephritis in 1996-2004 and living in one of the 50 United States or the District of Columbia were identified using the US Renal Data System, a national population-based registry of all patients receiving renal replacement therapy for ESRD. Incidence rates were computed for each calendar year, using population estimates of the US census as denominators.

Results. Over the 9-year study period, 9199 new cases of ESRD due to lupus nephritis were observed. Incidence rates, adjusted to the age, sex, and race composition of the US population in 2000, were 4.4 per million in 1996 and 4.9 per million in 2004. Compared to the pooled incidence rate in 1996-1998, the relative risk of ESRD due to lupus nephritis in 1999-2000 was 0.99 (95% CI 0.93–1.06), in 2001-2002 was 0.99 (95% CI 0.92–1.06), and in 2003-2004 was 0.96 (95% CI 0.89–1.02). Findings were similar in analyses stratified by sex, age group, race, and socioeconomic status.

Conclusion. There was no decrease in the incidence of ESRD due to lupus nephritis between 1996 and 2004. This may reflect the limits of effectiveness of current treatments, or limitations in access, use, or adherence to treatment. (First Release Nov 1 2008; J Rheumatol 2009;36:63–67; doi:10.3899/jrheum.080625)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS — LUPUS NEPHRITIS
ENDSTAGE RENAL DISEASE — INCIDENCE

The primary goal of treatment of lupus nephritis is to limit kidney damage and prevent endstage renal disease (ESRD) and its attendant morbidity and mortality. In individual patients, treatment effectiveness can be measured by stabilization or improvement in renal function. At the population level, the measure of effectiveness is the number of new cases of ESRD that develop over time. This rate represents the collective, cumulative, and ultimate result of treatment received by individual patients in the population. Because it includes patients with lupus nephritis who were not treated, or who received inadequate treatment, the incidence of ESRD is a useful indicator of how well available treatments are being used by all patients who could potentially benefit from them[1].

The incidence of ESRD due to lupus nephritis increased steadily from 1982 to 1995 in the United States, despite the introduction of efficacious treatments during this time[2]. Because renal failure may develop slowly and ESRD may occur years after the onset of lupus nephritis, changes in the incidence of ESRD may lag behind changes in treatment by many years. We examined if there was a decrease in the incidence of ESRD between 1995 and 2004.

MATERIALS AND METHODS

Data and patients. Information on patients with incident ESRD was obtained using the US Renal Data System (USRDS). The USRDS, operated by the National Institute of Diabetes and Digestive and Kidney Diseases and the Centers for Medicare and Medicaid Services, is a national population-based registry of all patients with ESRD[3]. Patients are enrolled in the USRDS after being certified as needing chronic renal replacement therapy (either dialysis or renal transplant) by their attending nephrologist. Patients receiving acute dialysis are not included. The USRDS includes information on patient demographic characteristics, the primary renal disease causing ESRD (by attribution of the attending nephrologist), type and sequence of renal replacement therapies, and outcomes.

Data were abstracted on all patients with incident ESRD due to lupus

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nephritis from January 1, 1996, to December 31, 2004 (the most recent year for which complete data were available), who resided in one of the 50 states or the District of Columbia. This information included patient age, sex, race (White, Black, Asian, or Pacific Islander, Native American, or other, as recorded by the attending nephrologist), Hispanic ethnicity, and ZIP code of residence at the time of initiation of ESRD treatment. Patient's socioeconomic status (SES) was assessed using a previously validated composite measure of economic indicators of their ZIP code of residence, based on US census data[4]. For the analysis, patients younger than 15 years of age were excluded, because ESRD due to lupus nephritis is rare in children, and

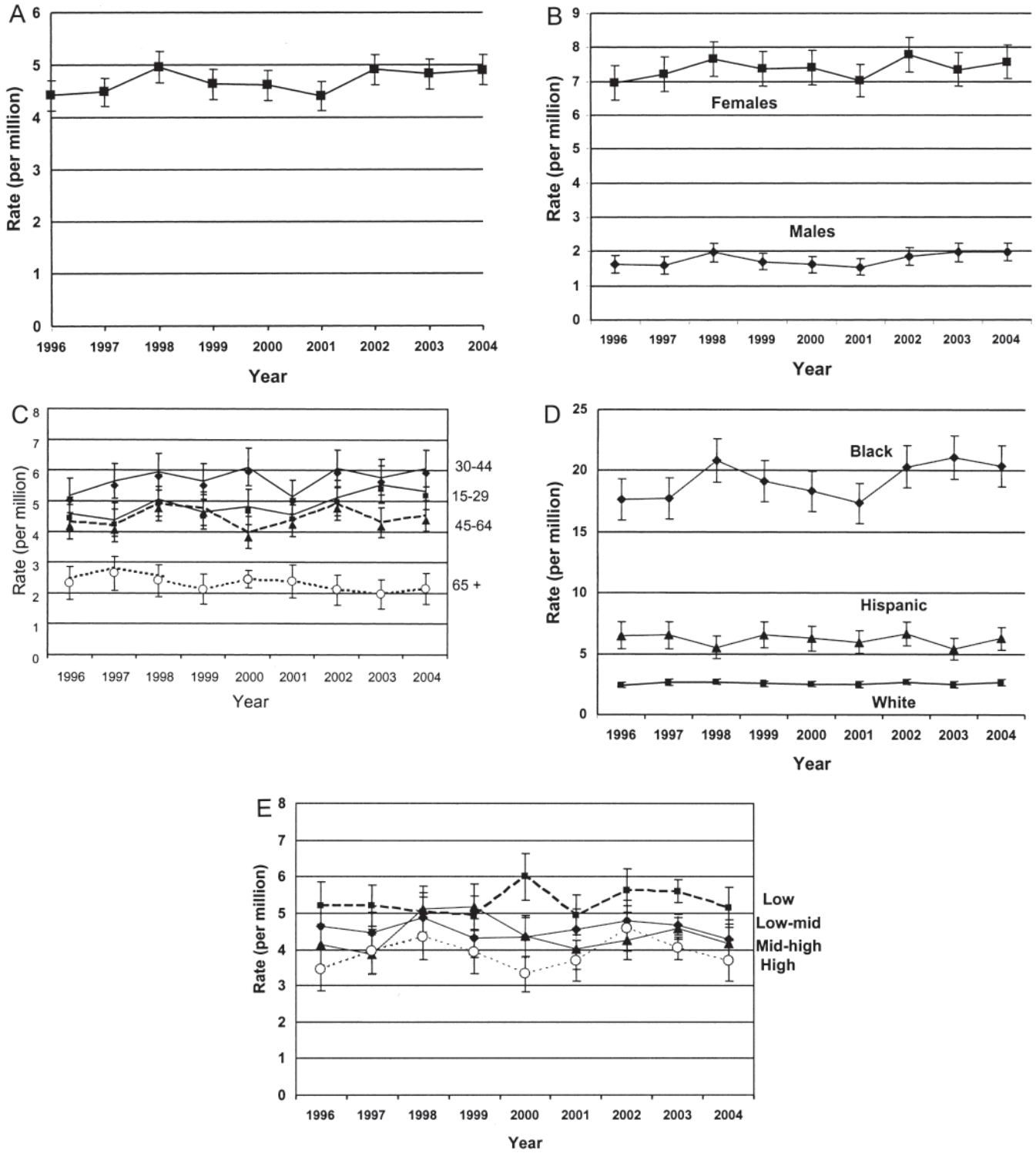

Figure 1. Incidence of endstage renal disease due to lupus nephritis (cases per million person-years) in 1996–2004, by calendar year, in all patients (A), by sex (B), by age group (C), by race/ethnicity (D), and by quartile of socioeconomic status score (E). Error bars represent 95% confidence intervals.

including this group with very low rates might have diluted changes in incidence over time.

The study protocol was reviewed by the National Institutes of Health Office of Human Subjects Research and exempted from human subjects review.

Statistical analysis. Incidence rates were computed using the number of new cases of ESRD due to lupus nephritis as the numerator, and population counts of the US census as the denominator, as recommended for these data[3]. Population counts for intercensal years were based on estimates and projections from the 2000 Census[5]. Incidence rates were age-, sex-, and race-adjusted to the 2000 Census by direct standardization, using 5-year age categories.

Data on ZIP code of residence were missing for 4.1% of patients. These patients were excluded from analyses of the association of SES with changes in incidence over time. Computation of incidence rates by SES required age-, sex-, and race-stratified data on population by ZIP code, which were available for the year 2000 but not for intercensal years. Estimates of population by ZIP code for the intercensal years were based on yearly changes in the population of the corresponding county[6].

We used Poisson regression models to calculate relative risks of ESRD over time, based on age-, sex-, and race-adjusted modeled incidence rates. To provide more stable estimates for these comparisons, rates were pooled over consecutive years, and risks in 1999-2000, 2001-2002, and 2003-2004 were compared to those in 1996-1998. Models were also tested for men and women, and for subgroups of age, race, Hispanic ethnicity, and quartile of the SES measure, to determine if these factors modified trends in incidence over time. SAS programs (SAS Institute, Cary, NC, USA) were used for all analyses. All hypothesis-testing was 2-tailed, and p values < 0.05 were considered statistically significant.

RESULTS

Over the 9-year study period, 9199 new cases of ESRD due to lupus nephritis occurred in patients age 15 years or older. The mean (± standard deviation) age of the patients was 40.9 ± 15.0 years. Eighty-two percent were women. The racial composition was 43.1% White, 48.0% Black, 4.6% Asian/Pacific Islander, 1.1% Native American, and 2.7% other race. Hispanic ethnicity was reported by 14.7%.

The incidence was stable over time, with an adjusted rate of 4.4 cases per million in 1996 and 4.9 cases per million in 2004 (Figure 1). Incidences were higher in women than men, as expected given the sex difference in the prevalence of SLE, but the female:male difference was smaller than that typically observed for prevalence. Rates were stable over time in both groups. Incidences were slightly higher among those age 30–44 than those age 15–29 or age 45–64, with average rates of 5.7 cases per million, 4.9 cases per million, and 4.8 cases per million, respectively, but in each age group there was no marked change in incidence over time. Rates were higher among Blacks than other racial groups, and higher among Asian/Pacific Islanders and Hispanics than Whites, but again, rates appeared stable over time.

Relative risks demonstrated no significant differences in rates in 1999-2000, 2001-2002, and 2003-2004 compared to those in 1996-1998 for all patients and for most patient subgroups (Table 1). However, the relative risk of incident ESRD was slightly lower in 2003-2004 than in 1996-1998 among Blacks and those 15–29 years old.

In the subset of 8817 patients who had information on SES, there was no association between calendar year and incidence of ESRD, adjusting for age, sex, race/ethnicity, and SES (Table 2). The incidence of ESRD was higher among patients with lower SES, but rates were stable over time in all SES subgroups (Figure 1). In addition, in models that adjusted for SES, the relative risks for incident ESRD in 2003-2004 were no longer statistically significant for Blacks (relative risk 0.96, 95% CI 0.88–1.04) or those age 15–29 years (relative risk 0.92, 95% CI 0.81–1.04). Adjusting for SES, the rate among Hispanics was marginally higher in 2003-2004 than in 1996-1998 (relative risk 1.15, 95% CI 0.99–1.35).

DISCUSSION

This study found no change in the incidence of ESRD due

Table 1. Relative risks of endstage renal disease due to lupus nephritis in 1999-2000, 2001–2002, and 2003–2004, compared to 1996–1998, adjusted for age, sex, and race. There were too few Native American and Other Race patients for meaningful stratified analyses.

Group	Relative Risk (95% CI)			
	1996–1998*	1999–2000	2001–2002	2003–2004
All patients	1.00	0.99 (0.93–1.06)	0.99 (0.92–1.06)	0.96 (0.89–1.02)
Women	1.00	0.98 (0.92–1.05)	0.98 (0.92–1.05)	0.98 (0.91–1.04)
Men	1.00	1.04 (0.90–1.21)	1.02 (0.88–1.18)	0.88 (0.76–1.01)
White	1.00	1.02 (0.92–1.14)	0.99 (0.90–1.10)	1.00 (0.91–1.12)
Black	1.00	1.00 (0.91–1.09)	0.99 (0.91–1.09)	0.90 (0.83–0.99)
Asian/Pacific Islander	1.00	0.85 (0.64–1.13)	0.94 (0.70–1.25)	1.00 (0.75–1.33)
Hispanic ethnicity, any race	1.00	0.96 (0.81–1.14)	0.95 (0.81–1.12)	1.06 (0.89–1.24)
Age				
15–29 yrs	1.00	0.99 (0.87–1.12)	0.97 (0.85–1.10)	0.86 (0.76–0.97)
30–44 yrs	1.00	0.95 (0.86–1.05)	1.00 (0.90–1.10)	0.95 (0.85–1.04)
45–64 yrs	1.00	1.04 (0.92–1.17)	0.97 (0.86–1.09)	1.01 (0.90–1.14)
65 or older	1.00	1.06 (0.89–1.28)	1.08 (0.90–1.30)	1.17 (0.97–1.41)

* Reference group.

Table 2. Relative risks of endstage renal disease due to lupus nephritis in 1999-2000, 2001–2002, and 2003–2004, compared to 1996–1998, adjusted for age, sex, and race, and socioeconomic status (SES).

Group	Relative Risk (95% CI)			
	1996–1998*	1999–2000	2001–2002	2003–2004
All patients	1.00	0.99 (0.93–1.05)	0.99 (0.93–1.05)	1.01 (0.95–1.07)
SES quartile				
1 (lowest)	1.00	1.01 (0.92–1.12)	1.00 (0.91–1.09)	0.99 (0.90–1.09)
2	1.00	1.08 (0.96–1.22)	0.97 (0.87–1.09)	1.04 (0.93–1.17)
3	1.00	0.89 (0.79–1.00)	1.04 (0.92–1.17)	0.99 (0.88–1.11)
4 (highest)	1.00	0.95 (0.84–1.08)	0.92 (0.81–1.03)	1.02 (0.90–1.16)

* Reference group.

to lupus nephritis in the United States from the mid-1990s to the mid-2000s. While stabilization of the incidence may be interpreted as a positive change after the steady increase in rates that occurred through the 1980s to the early 1990s[2], part of the increase in incidence during these years was likely due to improved diagnosis and reporting. Therefore, stabilization may not represent a true improvement in the community effectiveness of treatment. While it is certainly encouraging that the incidence is no longer increasing, the lack of a decrease in rates over 9 years indicates that as a nation, we have not made progress in preventing the development of ESRD in patients with lupus nephritis.

Several potential reasons could account for the absence of decrease in the incidence of ESRD due to lupus nephritis over recent years. Changes in the demographic composition of the general population might have led to an increase in groups at higher risk for lupus nephritis. Increases in new cases due to these groups might have obscured decreases in the incidence of ESRD among other segments of the population. This explanation is unlikely because the analyses were adjusted for demographic changes in the population, and similar results were present within demographic subgroups. The absence of a decrease in incidence may indicate that we have reached the limits of effectiveness of current treatments, and further decreases in rates will not occur until new, more effective treatments are developed and come into widespread use. Of note, the rates likely do not reflect the contributions of mycophenolate mofetil and rituximab, given that wider use of these medications to treat lupus nephritis postdated this study.

While more effective and better tolerated treatments would be welcomed, evidence from many other conditions suggests that gains could be achieved through improved use of existing treatments[7-10]. The difference in incidence of ESRD by SES supports this position. To the extent that the socioeconomic gradient in incidence represents limited access to effective treatment by patients of lower SES, further improvement in incidence should be possible with currently available treatments. Limited access to treatment is only one barrier to lowering incidences. Other potential barriers include misdiagnosis, delay in treatment, uncertainty about the best treatment, suboptimal dose or duration of treatment, and limited patient adherence[1,11-14].

The strengths of this study include the national population-based sample, the extended period of observation, and analyses stratified by demographic characteristics, including SES. The study used the US population as the group at risk, rather than patients with lupus nephritis, because national yearly population-based estimates of the prevalence of lupus nephritis are not available. The analysis is based on the assumption that changes in the number of patients with lupus nephritis over these years paralleled changes in the size of the general population. If the number of patients with lupus nephritis increased faster than the general population, this study could have missed a decrease in incidence over time. However, the number of patients with lupus nephritis would have had to increase 1.6 times faster than the general population to obscure a 25% decrease in incidence over the study period, and 2.7 times faster than the general population to obscure a 50% decrease in incidence. Such rapid recent increases have not been reported. The attribution of lupus nephritis as the cause of ESRD was based on clinical diagnosis rather than renal biopsies, possibly resulting in some misclassification of patients. Because data were not available on treatment prior to the onset of ESRD, the study is limited in not being able to identify the extent to which problems with access, appropriateness of treatment, or prompt initiation of treatment might have contributed to the results. Knowing the relative contributions of these factors would help identify interventions to improve the outcomes of patients with lupus nephritis.

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