The RENAAL Study Investigation

Reviewed by Meeta Sharma, MD

STUDY

Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving H-H, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001

SUMMARY

Design. An investigator-initiated, multicenter, double-blind, randomized, placebo-controlled study. Patients with type 2 diabetes and advanced renal disease were enrolled in a trial comparing losartan (Cozaar), 50–100 mg once daily, with placebo, both taken in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, α-blockers, β-blockers, and centrally acting agents), for a mean of 3.4 years.

Subjects. A total of 1,513 patients were enrolled from 250 centers in 28 countries in Asia, Europe, Central America, South America, and North America.

Primary hypothesis. Long-term treatment with losartan versus placebo (alone or in combination with conventional therapy not including angiotensin-converting enzyme [ACE] inhibition) in type 2 diabetic patients with nephropathy will increase the time to first event and decrease the incidence of doubling of serum creatinine, end-stage renal disease (ESRD), or death.

Secondary hypotheses. Losartan compared to placebo (alone or in combination with conventional non-ACE–inhibitor therapy) in patients with type 2 diabetes and nephropathy will increase the time to first event and decrease the incidence of cardiovascular morbidity and mortality, reduce proteinuria, and decrease the rate of progression of renal disease.

Results. Losartan treatment was associated with:

- 28% risk reduction of ESRD over a mean of 3.4 years ($P = 0.002$)
- 25% risk reduction of a doubling of the serum creatinine concentration ($P = 0.006$)
- 35% decrease in the level of proteinuria ($P < 0.001$)
- 32% risk reduction in the rate of first hospitalization for heart failure ($P < 0.005$)

The benefits exceeded those attributable to changes in blood pressure. Morbidity from cardiovascular causes was similar in the two groups, as was all-cause mortality.

Conclusion. Losartan conferred significant renal benefits in patients with type 2 diabetes and was generally well tolerated.

COMMENTARY

Although ESRD is one of the most devastating and expensive diabetes-related complications, there is little insight into its prevention, and co-therapies that have been touted to slow its progression are under-utilized.[1] Captopril (Capoten) is the only agent approved by the Food and Drug Administration as a treatment for slowing renal deterioration, but angiotensin-II-receptor blockers and ACE inhibitors are believed to be of benefit in treating renal complications and improving cardiovascular outcomes. In an alarming trend, ESRD has doubled in both prevalence and incidence in the past decade. In 2000, more than 90,000 patients were diagnosed with chronic renal failure in the United States. At present, ~300,000 patients receive dialysis, and 80,000 are living with transplanted kidneys.

Diabetes is the cause of the majority of this increase. Renal complications in diabetes occur at an estimated prevalence of 5.9% and 24% among patients with type 2 and type 1 diabetes, respectively.

If current trends continue and no change in medical practice ensues, it has been estimated that as many as 175,000 cases of uremia will be diagnosed annually by 2010. Medical care for ESRD consumes more than $18 billion annually in the United States and accounts for 6% of the Medicare budget.[2,3]

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study Investigation has demonstrated that losartan reduces the risk of renal progression in patients with type 2 diabetes by ~25%. The risk of ESRD was reduced by 28% with losartan during an average follow-up of 3.4 years.

This study included patients who had higher-grade proteinuria and established renal insufficiency. In patients whose disease was at this more advanced phase, the angiotensin-receptor blocker led to lower levels of proteinuria and lower rates of decline in glomerular filtration rate. On average, a reprieve from ESRD

of about 2 years seems to have been gained.

Simultaneous therapy with calcium channel antagonists did not detract from the beneficial effects of losartan despite the recent controversy regarding the role of calcium channel antagonists in the protection of the kidneys and heart.[4–6]

This study also showed that losartan therapy resulted in a significant reduction in hospitalizations for heart failure. This finding in patients without clinical heart failure at baseline mimics the findings from the Studies of Left Ventricular Dysfunction Prevention,[7] which did not include patients with impaired renal function. The Heart Outcomes Prevention Evaluation (HOPE)[8] study and its sub-study of patients with diabetes (MICRO-HOPE)[9] showed benefits of angiotensin-I-converting enzyme inhibition in terms of the signs and symptoms of heart failure, but failed to show significant differences in hospitalizations for heart failure.

In the RENAAL study, there was no significant difference between the losartan group and the placebo group in the composite secondary endpoint of morbidity and mortality from cardiovascular causes. This similarity of incidence may have resulted in part from the relatively small sample and the strict criteria for enrollment that excluded patients at high risk for cardiovascular events including heart failure.

Both the heart failure and renal benefits of losartan were largely independent of achieved blood pressure. Therefore, as compared with the other drugs, those that block the renin-angiotensin-aldosterone system probably lead to greater decreases in glomerular capillary pressure, greater reductions in fibroproliferative actions of aldosterone and angiotensin, or both.

Additionally, losartan's tolerability was similar to that of placebo. The addition of losartan to a conventional antihypertensive regimen did not increase the incidence of adverse effects.

Hispanic, Native-American, and African-American individuals carry risks of ESRD that are two to more than four times those of white people.[10] A recent report suggested that ACE inhibition relieved left ventricular dysfunction less effectively in African Americans than in whites.[11] Consequently, the racial representation in contemporary studies is of particular importance. The proportion of African Americans in the RENAAL study was less than the overall proportion of African-American patients among those with ESRD in the United States. Unfortunately, this study did not include a subset analysis of the treatment response according to race.

The public health implications of the RENAAL trial are myriad. Firstly, for diabetic patients at risk over a 3.5-year period, it is estimated that one case of ESRD can be prevented for every 16 treated. Losartan reduces days with ESRD by 32%. The reduction in days with ESRD saves $5,300 ($P = 0.0003$) per treated patient, and savings increase to $7,400 at 4 years. Extrapolating these results to the 595,000 type 2 diabetic patients with proteinuria in the United States, 37,500 ESRD cases could be avoided, with a reduction of $3.1 billion in the cost of ESRD care alone. Savings would increase to $4.4 billion at 4 years.

In conclusion, this study supports the proposition that drugs that inhibit the renin-angiotensin-aldosterone system slow the progression of kidney disease, albeit imperfectly. Clinicians and health care systems must be encouraged to use these treatments more effectively. It is clear, however, that further innovative approaches to the prevention of ESRD and novel treatments still need to be actively investigated.

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