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Effects of Losartan-Based Therapy on the Incidence of End-Stage Renal Disease and Associated Costs in Type 2 Diabetes Mellitus: A Retrospective Cost-Effectiveness Analysis in the United Kingdom

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ABSTRACT

Background: In the Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, the primary composite end point was the 2-fold increase in baseline serum creatinine concentration, the development of end-stage renal disease (ESRD), or death. The effects of losartan used for the prevention or delay of progression of diabetic nephropathy to ESRD were compared with those of conventional antihypertensive treatment (control) (calcium channel blockers, diuretics, α-blockers, β-blockers, and centrally acting agents), but not angiotensin-converting enzyme (ACE) inhibitors or angiotensin II antagonists (AIIAs), in 1513 adults with type 2 diabetes mellitus (DM-2) and nephropathy. Both treatment groups received conventional antihypertensive therapy (calcium channel blockers, diuretics, α-blockers, β-blockers, and/or centrally acting agents). ACE inhibitors and AIIAs were not allowed during the study period. The relative risk (RR) for composite outcome was 25% less, and the RR for ESRD was 28% less, in the losartan-treated group compared with the control group.

Objective: The aim of this retrospective cost-effectiveness analysis was to use data from the RENAAL study to determine the survival benefits and lifetime direct medical costs of a losartan-based regimen for the prevention of ESRD in patients with DM-2 and nephropathy in the setting of the UK National Health Service (NHS).

Methods: This analysis used life-years saved as the effectiveness measure. The effect of losartan-based treatment on ESRD risk was confined to the trial period (3.5 years). However, survival and the lifetime direct medical costs of managing ESRD were projected beyond the trial period to incorporate the full

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effects of ESRD on survival and resource use. The effect of altering key variables was examined using 1-way sensitivity analyses.

Results: ESRD-related costs were significantly lower in patients receiving losartan-based treatment compared with those in the control group (savings per patient, £7390 [95% CI, £11,366–£3414; $P < 0.001$] [£1 = US ~$1.75]). Incorporation of the cost of losartan into the assessment found reduced net costs (savings per patient, £6622 [95% CI, £10,591–£2653; $P = 0.001$]). The projected mean number of life years saved due to ESRD risk reduction with losartan was 0.44 years (95% CI, 0.16–0.71; $P = 0.002$). Losartan treatment was found to save costs in all cases, even if the cost of renal replacement therapy for patients with ESRD was reduced by 50%.

Conclusion: In this retrospective cost-effectiveness analysis using data from the RENAAL study, losartan-based treatment for the prevention or delay of progression of diabetic nephropathy to ESRD in patients with DM-2 and nephropathy was found to be potentially cost saving compared with conventional antihypertensive therapy from the perspective of the UK NHS. (*Curr Ther Res Clin Exp*. 2005;66:475–485) Copyright © 2005 Excerpta Medica, Inc.

Key words: losartan, economic analysis, diabetic nephropathy, end-stage renal disease, ESRD, cost.

INTRODUCTION

Type 2 diabetes mellitus (DM-2) affects ~3% to 6% of the UK adult population, and its prevalence is increasing due to the increasing age and rate of obesity in the population.[1] Approximately 37,500 patients in the United Kingdom receive renal replacement therapy (peritoneal dialysis, hemodialysis, or transplantation) each year,[1] and this number increases by ~7% annually.[1] Each year, diabetic nephropathy is associated with 18% of the new cases of patients requiring renal replacement therapy.[1] Length and quality of life are significantly reduced in patients whose condition progresses to end-stage renal disease (ESRD).[1]

In recent years, angiotensin II antagonists (AIIAs) have been studied for the control of blood pressure (BP) in patients with DM-2 and nephropathy. The Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study[2] was a randomized, double-blind trial comparing an antihypertensive regimen based on losartan (50–100 mg QD) with a regimen of conventional antihypertensive treatment (control) (calcium channel blockers, diuretics, α-blockers, β-blockers, and centrally acting agents), but not angiotensin-converting enzyme (ACE) inhibitors or AIIAs, in 1513 adults with DM-2 and nephropathy (losartan group, 751 patients; control group, 762 patients). The mean duration of follow-up was 3.4 years. The design and results of the study have been reported previously.[2,3] Briefly, the RENAAL study[2] found that adding losartan potassium to the conventional therapy regimen significantly reduced the relative risk (RR) for the primary composite end point (a 2-fold increase in serum creatinine concentration [SCr], development of ESRD [defined as the need for dialysis or transplantation], or death) by 25%

and reduced the RR for progression to ESRD by 28% compared with controls (P = 0.006 and 0.002, respectively). Moreover, the clinical benefits of losartan treatment exceeded those attributable to BP reduction alone.

In the Irbesartan Diabetic Nephropathy Trial[4] in 1715 patients with established neuropathy, irbesartan reduced the RR for the primary composite end point (2-fold increase in SCr, progression to ESRD, or death) by 20% compared with placebo and by 23% compared with amlodipine besylate (P = 0.02 and 0.006, respectively). The results from these 2 large studies suggest that AIIAs might have a major role in the management of DM-2 and renal disease.

We previously reported on a within-trial analysis of the economic implications of the results from the RENAAL study on the population of patients with DM-2 in the United Kingdom.[5] Over a prespecified time frame of 3.5 years, losartan use was associated with a reduction in the number of ESRD days (time from ESRD onset to death or end of study) by 33.6 days per patient at risk. As a result, losartan was associated with a net cost savings of £2515 per patient (£1 = US ~$1.75) over 3.5 years. These cost savings increased to £3721 over 4 years. Net savings were first realized at 2 years, the point at which ESRD-related cost savings (£543 per patient) more than offset losartan drug costs (£442 per patient). It was concluded that a losartan-based regimen might provide substantial cost savings compared with conventional treatment alone in the setting of the UK National Health Service (NHS).

The previous report based on the clinical findings of the RENAAL trial[2] was confined to the economic effects of the reduction of ESRD within the trial period.[5] No attempt was made to extrapolate the cost benefits beyond the trial period to the lifetime of the patient or to model the economic effects of an ongoing differential health benefit.

Thus, the present article reports an extension of the earlier cost-savings analysis. We examined the long-term costs (in terms of the lifetime direct medical costs of managing ESRD) and survival benefits of a losartan-based regimen for the prevention of ESRD in patients with DM-2 and nephropathy.

MATERIALS AND METHODS

This analysis of data from the RENAAL study[2] used life-years saved (LYSs) as the measure of cost-effectiveness. The assessment was conducted from the perspective of the UK NHS (direct medical costs).

End Points

The assessment combined aspects of a within-trial economic assessment and a lifetime projection of treatment benefit observed during the trial. The effects of losartan-based treatment on ESRD risk was confined to the trial period. No additional clinical benefit in ESRD risk was projected beyond the trial, and the costs of losartan medication were confined to the trial period or until a patient developed ESRD. However, survival and the lifetime direct medi-

cal costs of managing ESRD experienced during the trial were projected beyond the trial period to incorporate the full effects of ESRD on survival and resource use. This approach was similar to that used in the West of Scotland Coronary Prevention Study economic evaluation.[6]

It was conservatively assumed that there were no differences in the costs of nonstudy medications between the 2 treatment groups.[2] We assumed that patients who discontinued study medication incurred no additional costs. We did not include the costs associated with monitoring SCr and potassium concentration because this monitoring would be performed routinely in patients with DM-2 and renal disease. The costs of treating complications associated with dialysis were also excluded from the analysis.

Calculations

The cost of losartan treatment was estimated from the unit cost of losartan to the UK NHS multiplied by average number of days of treatment at different doses during the RENAAL study.[2]

The lifetime cost of ESRD (base-case analysis) was based on an annual average cost for hemodialysis and peritoneal dialysis[1] weighted according to the distribution of first renal replacement therapy, adjusted to 2004 prices, and the median survival time of patients undergoing diabetic renal replacement therapy age-matched to the RENAAL population.[7] The annual costs of hemodialysis and peritoneal dialysis were obtained from the UK Transplant Web site.[1] As a secondary analysis, the costs of hemodialysis and peritoneal dialysis from the UK 2-center European Dialysis and Cost-Effectiveness (EURODICE) study[8] were used.

The number of LYSs was estimated by multiplying the absolute risk reduction for ESRD in the losartan arm by the additional life-years expected by preventing ESRD during the trial period. Life-years gained by preventing/delaying ESRD was calculated as the difference in life expectancy between patients with and without ESRD. These life expectancies were estimated by means of Weibull models applied to the RENAAL data,[2] with baseline severity of proteinuria as a covariate. Assessments of uncertainty (95% CIs) were derived using a nonparametric "bootstrap" analysis.[9]

Costs were adjusted to 2004 prices, and costs and life-years were discounted at a rate of 3.5%. The following variables were used in 1-way sensitivity analyses: cost of daily renal replacement therapy using bottom-up and, alternatively, top-down costing from EURODICE; reducing the cost of daily renal replacement therapy by 50% (bottom-up costing); and increasing the life expectancy by 50% with losartan on dialysis.

RESULTS

The weighted annual average cost of dialysis as reported on the UK Transplant Web site[1] and used in the base-case analysis was £30,000. This cost represents £20,000 annually for peritoneal dialysis (30% of patients receiving dialysis) and

$34,500 annually for hemodialysis (70%). Data from the EURODICE study found a weighted average annual cost of $23,864 using top-down costing and $17,657 using bottom-up costing (**Table I**).[8]

Costs and cumulative incidence of ESRD and LYSs are presented in **Table II**. Losartan significantly reduced ESRD-related costs (savings per patient, $7390 [95% CI, $11,366–$3414; $P < 0.001$]), resulting in a significantly reduced net cost (savings per patient, $6622 [95% CI, $10,591–$2653; $P = 0.001$]). The estimate of a mean of 0.44 LYS (95% CI, 0.16–0.71; $P = 0.002$) with losartan therapy is in the context of a median survival time of 2.4 years after initiation of renal replacement therapy for diabetic patients age-adjusted to the RENAAL population.[7]

Results concerning costs and LYSs for the base-case and 4 sensitivity analyses found that losartan treatment was cost saving in all cases, even if the cost of renal replacement therapy was reduced by 50% (bottom-up costing) (**Table III**). The assumption of a 50% increase in life expectancy after dialysis in patients receiving losartan resulted in per-patient total cost savings ($101) that was statistically similar to that of conventional therapy, with an increase in overall life-years gained over the base-case analysis. A lifetime projection of ESRD, costs, and LYSs showed a reduction of 0.176, or 17%, in the cumulative incidence of ESRD, a reduction in total cost of $5483 per patient, and an increase of 0.67 LYS with losartan use.

DISCUSSION

The results of this analysis suggest that a losartan-based drug regimen in patients with DM-2 and nephropathy was projected to be cost saving from the perspective of the UK NHS because it reduced the incidence of ESRD compared

Table I. Costs of renal replacement therapy at 2 centers in the United Kingdom (2004 data).[8]*

Parameter	Top-Down, £	Bottom-Up, £	Difference, £
Peritoneal dialysis			
Center 1	17,408	16,677	731
Center 2	14,456	13,506	950
Mean	15,977	15,092	–
Hemodialysis			
Center 1	25,221	18,880	6341
Center 2	26,303	17,668	8635
Mean	25,672	18,274	–
Weighted			
Annual	23,864	17,657	6207
Daily	65.34	48.34	17

*£1 = US ~$1.75.

Table II. Costs, cumulative incidence of end-stage renal disease (ESRD), and life-years saved (LYSs).[8]*

Parameter	Losartan	Control	Difference	95% CI	*P*
Medication costs, £	768	0	768	707 to 820	<0.001
ESRD-related costs, £	14,009	21,399	–7390	–11,366 to –3414	<0.001
Net costs, £	14,777	21,399	–6622	–10,591 to –2653	0.001
ESRD†	0.193	0.296	–0.102	–0.157 to –0.047	<0.001
LYSs by delaying ESRD‡	–	–	4.3	3.0 to 5.6	
Life-years, mean	7.82	7.38	0.44	0.16 to 0.71	0.002

*£1 = US ~$1.75.
†Cumulative incidence at 4 years.
‡3.5% discounting.

Table III. Net cost savings and life-years saved (LYSs) by using losartan-based therapy versus conventional therapy alone in the base-case and sensitivity analyses.*

Parameter	Net Cost Savings, £	LYSs
Base case		
Value	6622	0.44
95% CI	2653 to 10,591	0.16 to 0.71
EURODICE bottom-up costing		
Value	3507	Same as base case
95% CI	1214 to 5800	–
EURODICE top-down costing		
Value	5010	Same as base case
95% CI	1907 to 8113	–
Reduce renal replacement therapy costs by 50%		
Value	2927	Same as base case
95% CI	985 to 4869	–
Increase life expectancy with losartan on dialysis by 50%		
Value	101	0.58
95% CI	–4695 to 4897	0.34 to 0.82
Continued benefits and costs beyond trial		
Value	5483	0.67
95% CI	–983 to 11,949	0.04 to 1.3

EURODICE = European Dialysis and Cost-Effectiveness study.[8]
*£1 = US ~$1.75.

with a non–ACE inhibitor/non-AIIA antihypertensive regimen. These findings are important for public health. ESRD is a source of substantial, long-term morbidity in an area of health care in which there is an unmet need in the United Kingdom.[10] Strategies to prevent or delay ESRD could reduce the lengths of transplantation waiting lists and demands on dialysis units.

The base-case analysis was based on a broad estimate of the costs of renal replacement therapy across the United Kingdom. However, the sensitivity analyses, based on data from 2 centers, supported the base-case analysis with the finding of net cost savings with losartan-based therapy across a wide range of conditions, including a conservative (bottom-up) estimate of renal replacement therapy costs.

A limitation of this analysis was that median life expectancy after initiation of dialysis was used to estimate lifetime renal replacement cost because mean data were unavailable. For this reason, and because mean survival would be expected to be higher than median survival, the results were considered conservative. Another limitation was the omission of costs related to complica-

tions of dialysis. Infectious complications in patients receiving long-term hemodialysis are common, particularly *Staphylococcus aureus* bacteremia.[11,12] Engemann et al[11] reported the mean cost of treating *S aureus* bacteremia in a tertiary care setting in the United States to be US $24,034 per episode. Due to the omission of these costs in our analysis, the actual costs of the non–losartan-based therapy might be significantly underestimated.

The results of the present analysis agree with those from previously published cost analyses with the use of losartan-based therapy. The first, a within-trial assessment based on the RENAAL trial, reported a significantly higher net cost savings of $3522 per patient over 3.5 years with the use of losartan-based treatment compared with conventional treatment (95% CI, $143–$6900; P = 0.041).[13] In Switzerland, a cost-effectiveness analysis of RENAAL data using a decision analytic model revealed a net cost savings of CHF 4084 ($2687) in patients with DM-2 and nephropathy who received losartan 50 to 100 mg of QD for 3.5 years compared with conventional therapy alone.[14]

In England and Wales, the National Institute for Clinical Excellence recommends routine use of ACE inhibitors in patients with DM-2 and nephropathy.[15] In the Micro-Heart Outcomes Prevention Evaluation substudy,[16] the largest trial (3577 patients) of an ACE inhibitor in patients with diabetes and renal disease to date, ramipril use was associated with decreased progression of microalbuminuria to overt nephropathy but not reduced prevalence of ESRD. A systematic review of 9 trials comparing the effects of ACE inhibitors with those of placebo found no statistically significant effect on the rate of progression to ESRD.[17]

International guidelines, such as those of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the National High Blood Pressure Education Program Coordinating Committee[18] and the American Diabetes Association,[19] recommend that hypertensive or normotensive patients with diabetic nephropathy receive an ACE inhibitor or AIIA as first-line treatment. Some evidence suggests that a combination of ACE inhibition with AII antagonism might effect clinical benefits. A meta-analysis of studies comparing combination treatment with an ACE inhibitor plus an AIIA with each component alone identified 8 studies in patients with varying degrees of proteinuria at baseline. An additional 30% reduction in proteinuria was noted over ACE inhibition alone and 39% over monotherapy with an AIIA.[20] However, these studies were not specifically focused on patients with diabetes. There is clearly a need for more data to guide treatment decisions.

At present, the relative cost-effectiveness of losartan versus ACE inhibitors in patients with DM-2 and nephropathy is unknown due to a lack of data concerning the extent to which ACE inhibitors delay the need for renal replacement therapy in this patient population. Similarly, the relative effects of ACE inhibitors and AIIAs on survival are unknown because of a lack of adequate trials directly comparing these 2 drug classes.[16] The cost-effectiveness of initiating treatment earlier in the course of the disease was assessed by Palmer et al.[21] In that analysis, early irbesartan treatment was projected to increase life ex-

pectancy and reduce costs in hypertensive patients with DM-2 and microalbuminuria. Life and cost savings were also projected in patients with overt nephropathy. Compared with conventional treatment, when irbesartan was initiated early and late, modelled savings ranged from $11.9 million to $3.3 million per 1000 patients, respectively.

The availability of effective medical treatment to reduce the risk for progression to ESRD has important implications for public health. ESRD is a common cause of morbidity and mortality; DM-2 is a common cause of ESRD. A treatment shown to reduce ESRD risk in patients with DM-2 could reduce the lengths of transplantation waiting lists and the demand for other types of renal replacement therapy, including the various types of dialysis.

CONCLUSION

In this retrospective cost-effectiveness analysis using data from the RENAAL study, losartan-based treatment for the prevention or delay of progression to ESRD in patients with DM-2 and nephropathy was found to be potentially cost saving compared with conventional antihypertensive therapy from the perspective of the UK NHS.

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