Kidney International, Vol. 66, Supplement 92 (2004), pp. S118–S120

Health economics studies assessing irbesartan use in patients with hypertension, type 2 diabetes, and microalbuminuria

ANDREW J. PALMER and ROGER A. RODBY

CORE–Center for Outcomes Research, Binningen/Basel, Switzerland; and Rush University Medical Center, Chicago, Illinois

Health economics studies assessing irbesartan use in patients with hypertension, type 2 diabetes, and microalbuminuria. Two studies comparing the cost-effectiveness of irbesartan to similar blood pressure control with standard antihypertensive medications (excluding angiotensin-converting enzyme inhibitors and other angiotensin receptor blockers) in treatment of patients with hypertension, type 2 diabetes, and microalbuminuria have been published to date; one in a United States setting, the other in a Spanish setting. Both studies were based on a Markov-based Monte Carlo simulation model, with the effects of irbesartan or standard blood pressure control taken from the Irbesartan Reduction of Microalbuminuria-2 (IRMA-2) and the Irbesartan in Diabetic Nephropathy Trial (IDNT) clinical trials. In both Spanish and U.S. settings, irbesartan was projected to delay the onset of end-stage renal disease (ESRD), reduce the cumulative incidence of ESRD, increase life expectancy, and reduce overall direct medical costs. Irbesartan treatment of patients with type 2 diabetes, hypertension, and microalbuminuria may lead to major improvements in long-term patient outcomes, with substantial cost savings as an added bonus to third party payers.

Diabetic nephropathy will develop in 30% to 40% of patients with type 2 diabetes. It is the most common cause of end-stage renal disease (ESRD) in Europe and the United States [1–3]. The incidence and prevalence of ESRD caused primarily by type 2 diabetes is increasing in the United States and Spain [4, 5], and will further rise with the increasing prevalence of diabetes [6]. Two clinical trials have recently investigated the blood pressure–independent renoprotective effects of the angiotensin II receptor antagonist irbesartan on the progression of renal disease in patients with hypertension and type 2 diabetes [7, 8]. In the Irbesartan Reduction of Microalbuminuria-2 (IRMA-2) study [7], the hazard ratio for progression from microalbuminuria to overt nephropathy for irbesartan 300 mg daily versus placebo control (standard hypertensive therapy with identical blood pressure targets) was 0.30 (95% CI 0.14–0.61) over a two-year follow-up period. In the Irbesartan in Diabetic Nephropathy Trial (IDNT) [8], treatment of hypertensive patients with type 2 diabetes and advanced overt nephropathy with irbesartan resulted in a reduction of 23% in the combined end point of death, ESRD, and doubling of serum creatinine (DSC) compared with amlodipine ($P = 0.006$), and a 20% reduction compared with the control group ($P = 0.02$) over a 2.6-year mean follow-up period.

The aim of this paper was to review the current published health economic evidence on irbesartan in the treatment of patients with microalbuminuria, hypertension, and type 2 diabetes. Studies specifically investigating health economic aspects of treatment of advanced overt nephropathy were not taken into consideration.

Two health economics studies have recently been published that investigated the cost-effectiveness of treating patients with type 2 diabetes, hypertension, and microalbuminuria with either irbesartan 300 mg daily or standard blood pressure control, which included standard antihypertensive medications as required to achieve a target blood pressure of <135/85 mm Hg [excluding angiotensin-converting enzyme (ACE) inhibitors, other angiotensin receptor antagonists, and dihydropyridine calcium channel blockers] [9, 10]. Both these studies were based on a computer simulation model that used clinical data from IRMA-2 and IDNT, as well as data drawn from other published sources to perform cost consequence analyses. The model used standard, well-accepted techniques (Markov-based Monte Carlo simulation) to describe the progression of patients with type 2 diabetes and hypertension through progressively worsening degrees of diabetic nephropathy—from microalbuminuria to early overt nephropathy, advanced overt nephropathy, DSC, ESRD treated with either dialysis or renal transplant, and death. Two treatment choices were simulated: (*1*) irbesartan—irbesartan 300 mg daily plus other adjunctive blood pressure medications (including diuretics, beta-blockers alpha/beta blockers, peripheral vasodilators, peripheral adrenergic blockers, and central adrenergic blockers, but excluded ACE inhibitors, other angiotensin receptor antagonists, and dihydropyridine calcium channel blockers) as required to achieve a

Key words: irbesartan, microalbuminuria, type 2 diabetes, hypertension, costs, modeling.

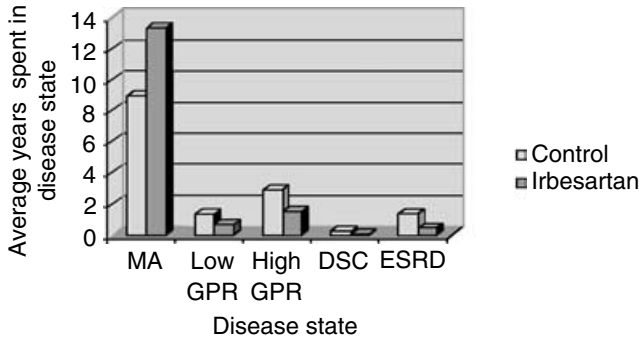

Fig. 1. Mean number of years per patient spent in each disease state with either standard blood pressure control or irbesartan treatment in the Spanish setting. MA, microalbuminuria; GPR, gross proteinuria; DSC, doubling of serum creatinine; ESRD, end-stage renal disease. Control, standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2-receptor antagonists, and dihydropyridine calcium channel blockers with equivalent blood pressure control. Irbesartan, standard antihypertensive medications plus 300 mg irbesartan daily, started when patients have microalbuminuria. Reproduced from [10].

target blood pressure of <135/85 mm Hg; and (*2*) placebo control (hereafter referred to as control)—standard antihypertensive medications as previously described as required to achieve the target blood pressure of <135/85 mm Hg.

RESULTS AND DISCUSSION

Compared with control, irbesartan reduced the cumulative incidence of ESRD, delayed the onset of ESRD, increased life expectancy, and led to overall direct medical cost savings in both the Spanish and United States settings. Irbesartan delayed the progression from microalbuminuria to more severe stages of diabetic renal disease. Patients spent more years in the state of microalbuminuria and fewer years in early and advanced proteinuria, DSC, or the ESRD states (where the annual risk of death was higher than that of patients who remained in the state of microalbuminuria) when treated with irbesartan (Fig. 1).

The cumulative incidence of ESRD in the Spanish setting was reduced from (mean ± standard deviation) 24% ± 1% to 9% ± 2% with irbesartan versus control, and from 20% ± 2% to 7% ± 1% in the United States setting. Irbesartan treatment led to 321 days of ESRD avoided in the Spanish setting, and 269 days in the United States setting versus control. Undiscounted life expectancy was improved from 14.78 ± 0.02 to 16.18 ± 0.26 years (an improvement of 1.40 ± 0.27 years with irbesartan) in the Spanish setting, and from 13.19 ± 0.03 to 14.75 ± 0.27 years (an improvement of 1.55 ± 0.27 years) in the United States setting. In the Spanish setting, costs were reduced from €25,119 ± 1,742 per patient with standard hypertension treatment to €14,038 ± 2,292 with irbesartan (cost savings after 25 years of €11,082 ± 2,996 per patient); and in the United States setting were reduced from $28,782 ± 2,045 to $16,859 ± 2,545 (cost savings after 25 years of $11,922 ± 3,250 per patient). Cost savings became evident after 8 to 10 years with irbesartan treatment versus control (Fig. 2). Sensitivity analysis revealed that conclusions were robust under a wide range of plausible assumptions. Differences in projected life expectancies between the two countries are due to differences in country-specific probabilities of age- and gender-specific annual mortality, and to differences in rates of kidney transplantation, dialysis transfer between the two modes of renal replacement therapy, and country-specific differences in survival rates for patients who develop ESRD. Differences in costs between the two settings were due to the differences in acquisition costs of medications, differences in the costs of treating ESRD, and different life expectancies projected in Spain and the United States.

The results of the two modeling studies published so far in the United States and Spanish setting are consistent—the use of irbesartan to treat patients with type 2 diabetes, hypertension, and microalbuminuria leads to substantial economic savings and major improvements in patient outcomes compared with treatment with standard blood pressure control alone (excluding ACE inhibitors), showing the importance of early treatment with irbesartan in these patients. Both studies considered only the direct medical costs of irbesartan and ESRD treatment. If a societal perspective had been taken, where indirect costs due to lost productivity secondary to absence from work and premature death were also considered, the costs savings expected with irbesartan would have been substantially higher.

Previous analyses based on the IDNT study demonstrated that irbesartan treatment started at a later stage of renal disease in patients with advanced overt nephropathy, hypertension, and type 2 diabetes also leads to delay in the onset of ESRD, improvements in life expectancy, and cost savings due to ESRD avoided compared with standard hypertension treatment or amlodipine in several European countries and in the United States [11–15]. Both early use of irbesartan (in patients with microalbuminuria) and late intervention (in patients with advanced overt nephropathy) were projected to lead to delay in the onset of ESRD, subsequent improvements in life expectancy, and substantial cost savings.

CONCLUSION

Studies published to date provide supportive evidence for the use of irbesartan in patients with type 2 diabetes, hypertension, and microalbuminuria in both Spanish and United States settings. Irbesartan initiated in the early stages of diabetic nephropathy was predicted to lead to

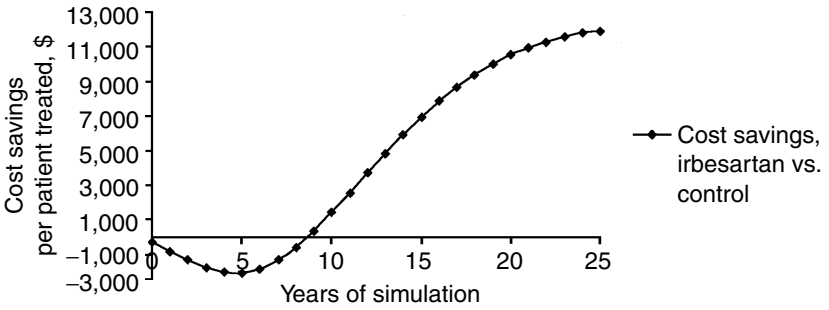

Fig. 2. Cost savings per treated patient, irbesartan versus control in the United States setting. Cost savings became evident after 9 to 10 years, and increased to a maximum of $11,922 per patient after 25 years. Modified from [9].

decreased incidence of ESRD, increased life expectancy, and cost savings.

Reprint requests to Dr. Andrew J. Palmer, MBBS, CORE—Center for Outcomes Research, Buendtenmattstrasse 40, 4102 Binningen/Basel, Switzerland.
E-mail: ap@thecenter.ch

REFERENCES

1. Lea JP, Nicholas SB: Diabetes mellitus and hypertension: Key risk factors for kidney disease. *J Natl Med Assoc* 94(8 Suppl):7S–15S, 2002
2. U.S. Renal Data System: *USRDS 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2001
3. Vora JP, Ibrahim HA, Bakris GL: Responding to the challenge of diabetic nephropathy: The historic evolution of detection, prevention and management. *J Hum Hypertens* 14:667–685, 2000
4. Muntner P, Coresh J, Powe NR, Klag MJ: The contribution of increased diabetes prevalence and improved myocardial infarction and stroke survival to the increase in treated end-stage renal disease. *J Am Soc Nephrol* 14:1568–1577, 2003
5. Lorenzo V, Martin UB: Epidemiologic analysis of the increase in terminal renal insufficiency associated with type 2 diabetes mellitus. *Nefrologia* 20(Suppl 5):77–81, 2000
6. Carretero-Dios D, Perez-Garcia R, Rodriguez-Benitez P, *et al*: Diabetes mellitus as cause of terminal renal failure. An epidemic of the 21st century? *Nefrologia* 21(Suppl 3):83–87, 2001
7. Parving HH, Lehnert H, Brochner-Mortensen J, *et al*: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345:910–912, 2001
8. Lewis EJ, Hunsicker LG, Clarke WR, *et al*: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
9. Palmer AJ, Annemans L, Roze S, *et al*: Cost-effectiveness of early irbesartan treatment versus control (standard antihypertensive medications excluding angiotensin converting enzyme inhibitors, other angiotensin-2-receptor antagonists and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease. *Diabetes Care* 27:1897–1903, 2004
10. Palmer AJ, Annemans L, Roze S, *et al*: Irbesartan is projected to be cost and life saving in a Spanish setting for treatment of patients with type 2 diabetes, hypertension, and microalbuminuria. *Kidney Int* 2004
11. Rodby RA, Chiou CF, Borenstein J, *et al*: The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. *Clin Ther* 25:2103–2119, 2003
12. Palmer AJ, Annemans L, Roze S, *et al*: An economic evaluation of irbesartan in the treatment of patients with type 2 diabetes, hypertension and nephropathy: Cost-effectiveness of Irbesartan in Diabetic Nephropathy Trial (IDNT) in the Belgian, and French settings. *Nephrol Dial Transplant* 18:2059–2066, 2003
13. Palmer AJ, Annemans L, Roze S, *et al*: An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. *J Hum Hypertens* 2004 (Epub ahead of print)
14. Palmer AJ, Annemans L, Roze S, *et al*: Gesundheitsökonomische Aspekte der Anwendung von Irbesartan in Deutschland. Health economic consequences of irbesartan treatment of type 2 diabetes patients with hypertension and nephropathy in Germany. *Dtsch Med Wochenschr* 129:13–18, 2004
15. Palmer AJ, Annemans L, Roze S, *et al*: Cost-effectiveness of Irbesartan in patients with type 2 diabetes, hypertension and nephropathy: A Spanish perspective. *Nefrologia* 24:231–238, 2004