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Effect of irbesartan on non-diabetic proteinuric renal diseases

M. C. de Gracia, M. Molina, M. J. Navarro and M. A. García Hernández
Nephrology Department. Santa María del Rosell Hospital. Cartegena. Spain.

SUMMARY

This randomized, prospective, two-arm clinical study evaluated the antiproteinuric and nephroprotective effects and the safety of treatment with an angiotensin II receptor antagonist (irbesartan) in patients with cronic glomerulonephritis (CGN) as compared to angiotensin-converting enzyme inhibitors (ACEIs). A total of 50 patients with CGN diagnosed by renal biopsy and protein levels in 24-hour urine higher than 1 g were enrolled. All patients received treatment for at least 24 months, 27 in group 1 (irbesartan) and 23 in group 2 (ACEs). A significant decrease in proteinuria ($p < 0.001$) was seen in both groups (49.2% in group, 1, and 44.8% in group 2) since the third month, and confirmed at 12 and 24 months of follow-up (58.1% and 62.7% in group 1, and 56.8% and 55.4% in group 2, respectively), with no significant differences being seen between the two groups. No differences were found in blood pressure control. No significant decrease was found in any of the groups in the glomerular filtration rate, but this showed higher values in the group treated with ACEIs (2.98 ± 7.77 vs *1.64 ± 6.84 ml/min/year), though the difference with irbersartan was not statistically significant. No side effects occurred among patients treated with irbesartan, whereas three patients initially treated with ACEIs showed intolerance (cough). In conclusion, irbesartan showed in our study an antiproteinuric and nephroprotective effect similar to ACEIs in patients with chronic glomerulonephritis, and its administration was also shown to be safe.*

Key words: ***Irbesartan. Proteinuria. Nephroprotection. Glomerulonephritis.***

EFECTO DEL IRBESARTÁN EN PATOLOGÍA RENAL PROTEINÚRICA NO DIABÉTICA

RESUMEN

Este estudio clínico aleatorizado, prospectivo, de dos brazos, evaluó el efecto antiproteinúrico y nefroprotector, así como la seguridad del tratamiento con un antagonista de los receptores de angiotensina II (irbesartán) en pacientes con glomerulonefritis crónica (GNC), comparándolo con inhibidores del enzima convertidor de angiotensina (IECA). Un total de 50 pacientes con GNC diagnosticada mediante

Correspondence: Dr. Manuel Molina Núñez
Servicio de Nefrología
Hospital Santa M.ª del Rosell
Paseo Alfonso XIII, 64
Cartagena. España
E-mail: manuel.molina4@carm.es

biopsia renal y proteinuria en orina de 24 horas mayor a 1 g fueron incluidos. Todos ellos recibieron tratamiento durante al menos 24 meses, 27 en el grupo 1 (irbesartán) y 23 en el grupo 2 (IECA). En los dos grupos encontramos una reducción significativa (p < 0,001) de la proteinuria (49,2% en el grupo 1 y 44,8% en el grupo 2) desde el tercer mes, que se confirma a los 12 y 24 meses de seguimiento (58,1% y 62,7% en el grupo 1, y 56,8% y 55,4% en el grupo 2, respectivamente), aunque no se observaron diferencias significativas entre los dos grupos. No encontramos diferencias respecto al control tensional. En ninguno de los dos grupos encontramos un descenso significativo del filtrado glomerular, sin embargo, éste fue mayor en el grupo tratado con EICA (2,98 ± 7,77 vs *1,64 ± 6,84 ml/min/año) aunque sin diferencia significativa respecto a irbesartán, mientras que tres pacientes inicialmente tratados con IECA mostraron intolerancia (tos). Como conclusión, en nuestro estudio irbesartán mostró un efecto antiproteinúrico y nefroprotector similar a los IECA en pacientes con glomerulonefritis crónica, siendo además segura su administración.*

Palabras clave: ***Irbesartán. Proteinuria. Nefroprotección. Glomerulonefritis.***

INTRODUCTION

Most of renal diseases progress to end-stage renal failure irrespective of the initial lesion.[1,2] This is particularly true in all renal diseases that present with increased glomerular permeability to macromolecules and that, finally, result in an increased urinary excretion of proteins. For the last two decades, many evidences have suggested that, in glomerular diseases, baseline albumin excretion rate correlates with the decrease in glomerular filtration rate observed in non-diabetic renal diseases[3] and also in insulin-dependent diabetes mellitus.[4] These data have led to consider that proteinuria is one of the most reliable predictors of renal disease progression,[5] and many studies have demonstrated that limitation of proteins glomerular ultrafiltration, either with diet or with anti-hypertensive medication, slows renal disease progression.[3,6]

There are clinical evidences showing that renin-angiotensin system (RAS) blockade with angiotensin converting-enzyme inhibitors (ACEI) or with angiotensin II AT1 receptors antagonists slows renal damage progression in diabetic nephropathy and chronic proteinuric non-diabetic nephropathies,[7-10] and, moreover, this renoprotective effect goes beyond the simply reduction of blood pressure levels. In type 2 diabetes, two recent studies with losartan[7] and irbesartan[8] have demonstrated protection from renal function deterioration in patients with established nephropathy, likely independently from their anti-hypertensive effect. This has led to allowance for considering RAS blockers drugs (ACEI and ARAII) as first option agents for the treatment of patients with chronic disease, both diabetic and non-diabetic.

In our study, we decided to evaluate the renoprotective effectiveness of an AT1 receptors antagonists (irbesartan) in non-diabetic proteinuric chronic renal disease compared with ACEIs (captopril, enalapril, lysinopril), with demonstrated renoprotective effect.

MATERIAL AND METHODS

Patients

For inclusion in the study, patients were required to be older than 18 years, having chronic glomerulonephritis ascertained by renal biopsy and confirmed proteinuria in 24-hour urine sample greater than 1 g, and having ruled out other treatments (steroids, immunosuppressants) or the latter having been ineffective. It was required that treatment had to be kept for at least two years and the patients having being followed at the outpatient clinic for that period of time.

Study Design

This is a mixed study, retrospective until 1999, and prospective until data gathering, in patients diagnosed by renal biopsy between October 1995 and December 2001, and done in the Cartegena Health Area, with a 24-month follow-up in each patient.

Patients were on ACEIs treatment from 1995 until the time of randomization. From 1999, patients that gave their informed consent were randomly assigned into two groups. Group 1 received irbesartan treatment 150-300 mg daily. Group 2 (which includes the retrospective section) were treated with angiotensin-con-

verting enzyme inhibitors (captopril 75-100 mg/day, enalapril 10-20 mg/day, or lysinopril 20 mg/day). Variations in drug doses were stratified according to antiproteinuric response (50% reduction of baseline values) and/or blood pressure control, which is defined as being lower than 130/85. Three patients initially assigned to group 2 showed intolerance to the prescribed drug (cough) and were included in group 1.

Efficacy and safety objectives

In both groups, primary efficacy variable was the ability to significantly reduce proteinuria in 24-h urine sample.

Blood pressure control, and creatinine clearance and annual reduction rate of the inverse of plasma creatinine were designated as secondary efficacy variables.

Control times of the following variables were initially and at 3, 12 and 24 months: blood pressure, 24-h urine proteinuria, plasma creatinine, and creatinine clearance.

Safety was assessed in both groups, as well, by analyzing potassium and plasma creatinine at the second week after beginning of pharmacological treatment, and clinical adverse events in the first month and at the laboratory control time points previously referred.

Statistical analysis

Statistical analysis was done with SPSS software version 11.0 (SPSS, Chicago, Inc.). The results are expressed as mean and standard deviation for age, time of follow-up, blood pressure, proteinuria, inverse of plasma creatinine, and creatinine clearance. Gender, type of glomerulonephritis, patients receiving antihypertensive pharmacological combinations, and proteinuria reduction are expressed as frequencies and percentages.

The Student's t test is used for mean comparison between groups for independent samples and for related-samples within the same group assessment, and Chi-squared test and Fisher's exact test for dependent and independent variables.

RESULTS

Sample analysis

Group 1 of treatment with irbesartan comprises 27 patients, and 23 patients received ACEIs treatment.

Table I. Baseline characteristics of patients included in the study

Parameter	Irbesartan group	ACEI group	Significance level
Age (years)	46.59 ± 15.15	41.52 ± 16.43	0.308
Gender			
Male	81.48%	69.57%	0.508
Female	18.52%	30.43%	
Type of glomerulonephritis			
IgA	48.15%	52.17%	
Mesangiocapilar	22.22%	17.39%	0.967
Membranous	14.81%	17.39%	
Mesangial Proliferative IgM	14.81%	13.05%	
Blood pressure (mmHg)			
Systolic	139.74 ± 21.06	135.96 ± 16.55	0.426
Diastolic	84.11 ± 11.43	83.22 ± 6.81	0.315
Proteinuria (grams in 24 hours)	5.28 ± 3.98	4.26 ± 2.81	0.296
Inverse of creatinine (mg/dL)	0.80 ± 0.24	0.92 ± 0.31	0.126
Creatinine clearance (mL/min)	79.92 ± 30.64	86.53 ± 29.15	0.439

Three patients from group 1 were initially assigned to group 2, shifting groups within the first month because of clinical intolerance. No patient from group 1 had previously received anti-hypertensive treatment (before 1999) with ACEI or ARAII. Baseline data fro age, gender, time of follow-up, type of glomerulonephritis, blood pressure, proteinuria, creatinine clearance, and inverse of plasma creatinine are shown in Table I. There are no significant differences in baseline characteristics of patients included in both groups.

Effect on proteinuria

As shown in Figure 1, in both groups there is a significant reduction ($p < 0.001$) of proteinuria (49.2% in group 1, and 44.8% in group 2), from the third month of follow-up, which is confirmed in the next control points (58.1% and 62.7% in group 1, 56.8% and 55.4% in group 2, at 12 and 24 months, respectively), although no significant differences were observed between groups (fig. 2 and table III).

Effect on blood pressure

We did not observe significant differences in blood pressure control between groups at any of the control points, being at the end of follow-up SBP 128.19 ± 16.78 for irbesartan group, and 125.26 ± 14.73 for ACEI group, and DBP 78.89 ± 11.99 for group 1 and 76.17 ± 8.39 for group 2.

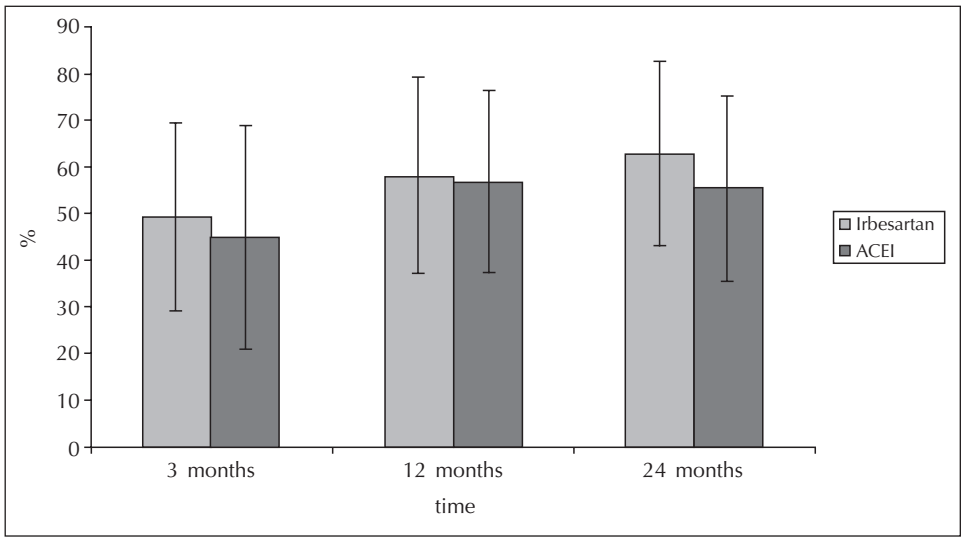

Fig. 1.—% of proteinuria reduction.

There are no significant differences either between groups in the number of patients that required a drug combination (calcium channel blockers, diuretics, and beta-blockers) to maintain the target blood pressure, being 8 (29.6%) patients in group 1 and 6 (26.1%) in group 2.

Effect on glomerular filtration

With regards to renal function, in no group we observed significant changes in glomerular filtration measured as creatinine clearance (CrCl) (fig. 3) and as the inverse of plasma creatinine (1/Cr) (Table III), the annual reduction rate of 1/Cr for irbesartan group 0.025 ± 0.074, and for ACEI group 0.038 ± 0.13 (p = 0.106). The annual reduction rate of creatinine clearance (mL/min/year) was 1.64 ± 6.84 for group 1, and 2.98 ± 77.77 for group 2 (p = 0.114).

The correlation slope of 1/Cr over time of follow-up is not perform since data on five previous plasma creatinine determinations were lacking in some patients.

Safety

Three patients initially assigned to ACEI group presented clinical intolerance within the first month (two had cough and one erectile dysfunction), so that they assigned to group 1 by second intention.

One patient in each group (3.7% and 4.3% for groups 1 and 2, respectively) had symptomatic blood pressure levels decrease, in both cases transient. One patient (4.3%) in group 2 had mild hypokalemia, corrected by dietary management.

No other adverse effect attributable to pharmacological treatment was found in our study. In this sense, we highlight the lack of significant worsening of renal function in any patient.

DISCUSSION

The role of angiotensin II in renal disease progression has been the focus of a number of investigations,[12,13] having incriminated hemodynamic and non-hemodynamic mechanisms. The increase

Table II. Proteinuria progression throughout the study

Proteinuria*	Irbesartan group	p	ACEI group	p
Basal	5.28 ± 3.95		4.26 ± 2.81	
3 months	2.68 ± 2.42	< 0.001	2.35 ± 1.83	< 0.001
12 months	2.21 ± 2.04	< 0.001	1.84 ± 1.50	< 0.001
24 months	1.97 ± 2.01	< 0.001	1.9 ± 1.52	< 0.001

* grams is 24-hour urine.

Table III. Renal function progression measured by invrse of creatinine (mg/dL)

1/Cr	Grupo irbesartán	p	Grupo IECA	p
Basal	0.80 ± 0.24		0.92 ± 0.43	
3 months	0.79 ± 0.24	0.456	0.85 ± 0.31	0.205
12 months	0.76 ± 0.22	0.105	0.82 ± 0.29	0.122
24 months	0.75 ± 0.24	0.121	0.84 ± 0.33	0.242

in intraglomerular pressure derived from AII vasoconstrictor effect on the efferent arteriole leads to a permselectivity impairment of the glomerular membrane, which is, among others, one of the determinant mechanisms or proteinuria occurrence. The abnormal protein traffic through the glomerular capillaries may contribute to renal disease progression, so that proteinuria is considered a renal damage marker, and that decrease in protein excretion is one of the main therapeutic goals in proteinuric renal diseases.[2,6,14]

Multicenter studies undertaken with regards to blockade of the renin-angiotensin system by angiotensin II AT1 receptor blockers have been done in patients with diabetic nephropathy,[7-9,19], and in patients non-diabetic proteinuric renal disease.[11] One of the major outcomes of our study has been that administration of angiotensin II AT1 receptor blocker, irbesartan, to patients with non-diabetic proteinuric renal disease produces a decrease in proteinuria similar to that shown by angiotensin-converting enzyme inhibitors. Theses results are in agreement with those notified by Brenner *et al*.[7] and Lewis *et al*.[8], where losartan and irbesartan use, respectively, in patients with type 2 diabetic nephropathy led to a significant decrease in proteinuria, independently of blood pressure control. Also, in our series, irbesartan or ACEI use decreased blood pressure levels. Similar results have been observed in non-diabetic proteinuric renal diseases,[15] where in patients with IgA nephropathy, the use of enalapril and irbesartan induced a similar decrease of proteinuria. Proteinuria decrease is observed early (from the third month of treatment), which is in agreement with results from Perico.[15]

Since proteinuria is considered one of the major markers of progression to renal failure, as previously discussed, we analyzed the renoprotective effect by studying creatinine clearance and the inverse of plasma creatinine, and we observed no significant decrease in glomerular filtration throughout the study in both groups; although we did find that in the irbesartan-treated group this decrease in glomerular filtration was milder than that in ACEI-treated group, although without any significant differences. The results are in agreement with those published for type 2 diabetic nephropathy, where the use of ACEI has not always shown a renoprotective effect associated to the decrease in proteinuria,[16,17] which has been demonstrated with angiotensin II receptor antagonists such as losartan[7] and irbesartan.[9] Similarly, reduction rate in glomerular filtration with irbesartan (1.6 mL/min/year) coincides with that notified for ACEI ramipril in non-diabetic disease,[10] particularly if we compare with more prolonged follow-up times,[18] where filtration decrease was close to 1 mL/min/year.

Recent studies by Barnett *et al*.[19] in patients with type 2 diabetes mellitus have shown that telmisartan use is not inferior to enalapril in long-term Reno-

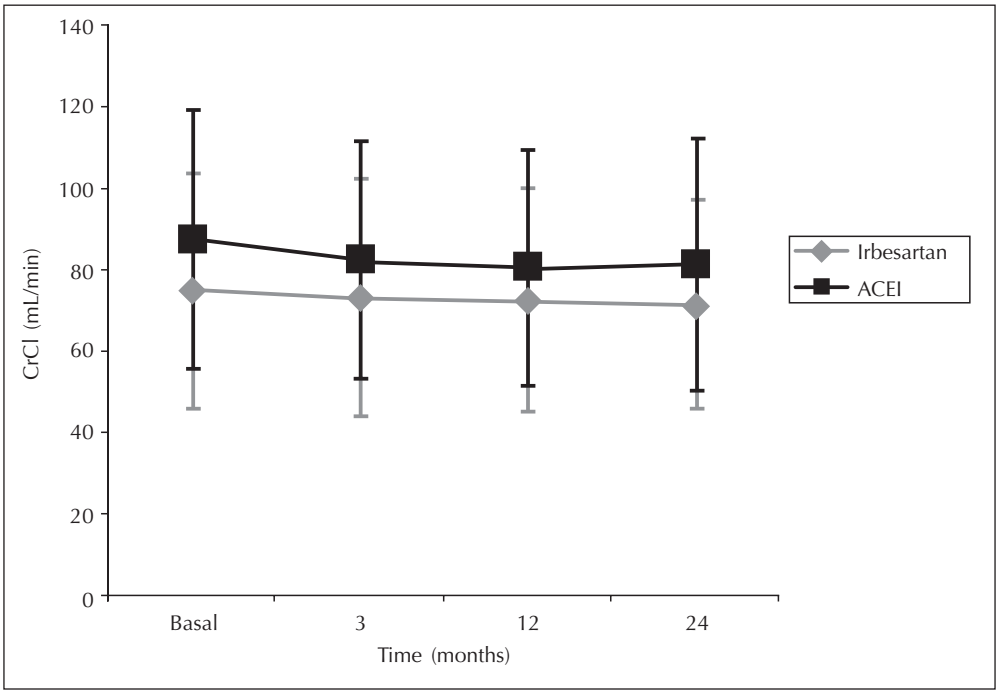

Fig. 2.—Creatinine clearance progression.

protection, our results being comparable to these ones.

The clinical implication that we may suggest from our study, similarly to previously published data, is that both irbesartan and ACEI (captopril, enalapril and lysinopril) are able to decrease proteinuria without decreasing glomerular filtration in non-diabetic chronic proteinuric renal disease, which leads us to think that long-term treatment with ARAII slows renal failure progression, although more long-term studies and with larger samples are needed to endorse this hypothesis. From a practical perspective, the choice of one or the other type of treatment should be guided by potential tolerability differences and by adverse effects, lesser in the case of AT1 receptor blockers.

To conclude, in our study the renin-angiotensin system blockade with irbesartan has shown an antiproteinuric and renoprotective effect similar to that with ACEI; therefore, we suggest that its use would be indicated as a first-option drug in proteinuric renal diseases where ACEI show adverse effects.

REFERENCES

1. Remuzzi G, Ruggenenti P, Benigni A: Understanding the nature of renal disease progression. *Kidney Int* 51: 2-15, 1997.
2. Taal MW, Brenner BM: Renoprotective benefits of RAS inhibition: from ACEI to angiotensin II antagonists. *Kidney Int* 57: 1803-1817, 2000.
3. Peterson JC, Adler S, Burkanrt JM y cols.: for de Modification of Diet in Renal Disease (MDRD) Study Group: blood pressure control, proteinuria and the progression of renal disease. *Ann Intern Med* 123: 754-762, 1995.
4. Breyer JA, Bain RP, Evans JK y cols.: and The Collaborative Study Group: predictors of the progression of renal insuficiency in patients with insulin-dependent diabetes and overt diabetic nephopaty. *Kidney Int* 50: 1651-1658, 1996.
5. Keane W: Proteinuria: its clinical importance and role in progressive renal disease. *Am J Kidney Dis* 35: S97-S105, 2000.
6. Jafar TB, Stark PC, Schmid CH y cols.: Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 60: 1131-1140, 2001.
7. Brenner BM, Cooper ME, DeZeeuw D y cols.: for the Renal Study Investigators: effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861-869, 2001.
8. Parving HH, Lehnert H, Bröchner-Mortensen J y cols.: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870-878, 2001.
9. Lewis EJ, Hunsicker LG, Clarke WR y cols.: for the Collabortive Study Group: renorpotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851-860, 2001.
10. The GISEN Group: Randomised placebo-controlled trial of effect of ramipril on declining in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropahy. *Lancet* 349: 1857-1863, 1997.
11. Praga M, Andrade CF, Luño J y cols.: Antiproteinuric efficacy of losartan in comparison with amlodipine in no diabetic proteinuric renal diseases: a double-blind, randomized clinical trial. *Nephrol Dial Transplant* 18 (9): 1806-13, 2003.
12. Aros C, Remuzzi G: The renin-angiotensin system in progresion, remision and regresion of chronic nephropathies. *J Hyperten* 20 (Supl. 3): S45-S53, 2002.
13. Schieppati A, Remuzzi G: The future of renoprotection: frustratio and promises. *Kidney Int* 64: 1947-1955, 2003.
14. Praga M: Slowing the progression of renal failure. *Kidney Int* 61 (Supl. 80): S18-S22, 2002.
15. Perico N, Remuzzi A, Sangalli F y cols.: The Antiproteinuric Effect of Angiotensin Antagonism in Human IgA Nephropathy is Potenciated by Indomethacin. *J Am Soc Nephrol* 9: 2308-2317, 1998.
16. Sano T, Hotta N, Kawsamura T y cols.: Effect of long-term enalapril treatment on persistent microalbuminuria in normotensive type2 diabetic patients: result of 4-year, prospective randomized study. *Diabetic Med* 13: 120-124, 1996.
17. Hsueh WA: Treatment of type 2 diabetic nephropathy by blockade of the renin-angiotensin system: a comparison of angiotensin-converting enzyme inhibitor and angiotensin receptor antagonists. *Cur Opinion Pharmacol* 2: 182-188, 2002.
18. Ruggeneti P, Perna A, Gheradi G y cols.: Renal function and requirement for dialysis in chronic nehropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 354: 359-364, 1998.
19. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J: Diabetics Exposed to Telmisartan and Enalapril Study Group: Angiotensin-receptor blockade *versus* converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 351 (19): 1934-6, 2004.