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Irbesartan in hypertensive non-diabetic advanced chronic kidney disease. Comparative study with ACEI

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SUMMARY

Angiotensin-converting enzyme inhibitors (ACEI) have proved an antihypertensive and renoprotective effect with reduction of proteinuria in diabetic and non diabetic nephropathy, but not exempt of side effects in advanced chronic kidney disease (ACKD) patients. Angiotensin receptor blockers (ARB) have emerged as antiproteinuric, renoprotective and cardioprotective therapy. Only a few reports have been published studying ARB effects on non-diabetic ACKD patients. Our aim is to study Irbesartan (ARB) on non-diabetic ACKD patients and compare its effects with ACEI. Patients and methods: *Forty three non-diabetic patients at ACKD stage IV NKF-DOQI (CrCl < 30 ml/min) were enrolled in a prospective study. Group I: 21 received Irbesartan monodose 150-300 mg/day (63 ± 17 y/o, 12F, 9M, ClCr 22.1 ± 8 ml/m.), Group II: 22 received ACEI (65 ± 13 y/o, 8F, 14M, CrCl 22.3 ± 7 ml/m). Parameters studied: blood pressure (BP), pulse pressure (PP), renal function (CrCl), proteinuria (in patients with proteinuria ≥ 0.5 g/d), serum K+ and serum uric acid, at month 0, 3, 6, 9 & 12.* Results: *At 12 months, BP was controlled in 57% of Group I* vs *39% of Group II. Mean systolic BP was decreased from 154/85 to 138/77 in G I, and from 146/85 to 133/77 in GII, with a decrease in 10.7% of mean BP in GI and 8.5% in GII (NS). Irbesartan reduced PP in 7.2%* vs *8.3% with ACEI (NS). CrCl reduction with Irbesartan was 0.23* vs *0.21 ml/min/month with ACEI (NS). The antiproteinuric effect was higher with Irbesartan (from 2.1 to 1.3 g/day) vs. ACEI (from 1.35 to 1.33 gr /day), being statistically significant the reduction percentage between the two groups (p = 0.041). Serum K+ level do not change in Irbesartan group and increased 10% in ACEI group (p < 0.001). Uric acid was decreased by Irbesartan in 17% and increased in 4% by ACEI (p < 0.001).* Conclusions: *Irbesartan in non-diabetics patients with advanced chronic renal disease, compared with ACEI showed similar blood pressure control and similar effect on chronic kidney disease progression, with higher antiproteinuric effect. On the other side, Irbesartan showed a reduction of serum uric acid, and did not increase serum K+ levels.*

Key words: *Angiotensin-converting enzyme inhibitors. Angiotensin receptor blockers. Irbesartan. Chronic kidney disease. Proteinuria. Hypertension.*

RESUMEN

Los inhibidores del enzima de conversión de angiotensina (IECAs) han demostrado un efecto antihipertensivo, renoprotector y antiproteinurico en pacientes con nefropatía diabética y no diabética, aunque deben administrarse con precaución en la enfermedad renal crónica avanzada (ERCA). Los antagonistas de los receptores de angiotensina II (ARA II) muestran un perfil similar a los IECA en la nefropatía diabética con buena tolerancia clínica, pero existen pocos estudios sobre su efecto en la ERCA de etiología no diabética. ***Objetivo:*** **Estudiar la acción del Irbesartan (ARA II) sobre la TA, proteinuria y evolución de la función renal en pacientes con ERCA de etiología no diabética y comparar sus efectos con pacientes de las mismas características tratados con IECAs.** ***Pacientes y métodos:*** **Estudio longitudinal, prospectivo, no aleatorizado, con 43 pacientes no diabéticos en situación de ERCA estadio IV de NKF-DOQI (CLCR < 30 ml/min). Grupo I (G I): 21 pacientes (63 ± 17 años; CLCR 22,1 ± 8 ml/min) con Irbesartan en monodosis de 150-300 mg/día. Grupo II (G II): 22 pacientes (65 ± 13 años; CLCR 22,3 ± 7 ml/min) con IECAs. Se compara la evolución de la TA, función renal, proteinuria (en pacientes con proteinuria > 0,5 g/día), potasio y ácido úrico en 12 meses.** ***Resultados:*** **En el 57% de los pacientes en el GI y el 39% del G II se obtuvo un buen control de la TA a los 12 meses. La TA sistólica se redujo de 154/85 a 138/77 en el GI y de 146/85 a 133/77 en el G II, con un descenso de la tensión arterial media del 10,7% en G I y 8,5% en el G II (NS). La presión de pulso descendió un 7,2% con Irbesartan y un 8,3% con IECAs (NS). La disminución de la función renal fue igual en los dos grupos (Irbesartan 0,23** ***vs*** **0,21 ml/min/mes con IECAs): El efecto antiproteinúrico fue mayor con Irbesartan (2,1 a 1,3 g/día) que con IECAs (1,35 a 1,33 g/día), siendo significativa la reducción porcentual entre los dos grupos (p = 0,041). Los niveles de K sérico no se modificaron con Irbesartan y aumentaron un 10% con IECAs (p < 0,001). Se observó un descenso del ácido úrico del 17% en los pacientes con Irbesartan, mientras que con IECAs se aprecio un incremento del 4% (p < 0,001).** ***Conclusiones:*** **El empleo de Irbesartan en pacientes no diabéticos con ERCA muestra un control de la TA similar al obtenido con IECAs, así como una acción semejante sobre la progresión de la función renal. En estos pacientes Irbesartan produce una mayor reducción de la proteinuria que los IECAs, sin incremento del potasio sérico y con un efecto favorable sobre los niveles de ácido úrico.**

Palabras clave: Inhibidores del enzima de conversión de angiotensina. Antagonistas de receptores de angiotensina. Irbesartan. Enfermedad renal crónica avanzada. Proteinuria. Hipertensión arterial.

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INTRODUCTION

Chronic renal disease is accompanied in most of the cases by arterial hypertension (AHT) and is an important morbidity and mortality factor in these patients. Several drugs may be used to control it, and some of them have shown their potential for decreasing or slowing the progression of renal failure and/or proteinuria. Angiotensin converting enzyme inhibitors (ACEIs) have been successfully used in patients with AHT and nephropathy of both diabetic and non-diabetic origin, reducing proteinuria and with a favorable effect on renal failure progression.[1-5] Some adverse effects have been described among which persistent cough is one of the most common ones, and an added problem in stage IV advanced chronic renal disease (ACRD 4)[6] is that ACEIs may contribute to renal function worsening expressed by serum creatinine increase by 30-35% and produce hyperkalemia.[7,8] Angiotensin-II receptor antagonists (ARA II) have also shown their effect on proteinuria and progression of renal function in patients with diabetic nephropathy,[9-12] with less adverse affects than ACEIs, although there are few clinical trials about their efficacy on hypertension, proteinuria, renal function progression in patients with no-diabetic nephropathy[13,14] or with established ACRD of non-diabetic origin.[15,16]

Irbesartan is a drug belonging to the ARA II family that has shown its effectiveness in the management of AHT, even in patients with ACRD o on dialysis.[15,17] It is a rapidly absorbed drug after oral administration, being mainly cleared through the liver (78%) and in lower amounts through the kidney (22%), with a half-life of 11-15 h,[18] with no dose adjustment required in ACRD.[19] Irbesartan has shown anti-proteinuric effects and slowing progression of diabetic nephropathy.[9,11]

In this work we undertook a study on the effect of Irbesartan therapy in non-diabetic ACRD patients, analyzing its antihypertensive efficacy, its action on proteinuria and progression of renal disease, and its effects on some biochemical, as compared to ACEIs therapy in the same type of patients and with the same degree of renal impairment.

PATIENTS AND METHODS

Patients

In this longitudinal non-randomized study we prospectively included for one year 43 patients with non-diabetic stage IV ACRD of NKF-DOQI (creatinine clearance (CrCl) < 30 mL/min). Twenty-one patients (group I) were treated with Irbesartan at starting doses of 150 mg/day, increasing up to 300 mg/day (once daily) as needed to improve BP management. In those patients not achieving appropriate BP control with full doses of Irbesartan (300 mg/day), other non-ARA-II non-ACEIs drugs were added. The mean age was 63[17] years, 12 women and 9 men, with mean CrCl at the beginning of the therapy of 22.1 (8.0) mL/min. Group II was comprised by 22 patients treated with ACEIs (enalapril in 9, captopril in 7, perindopril in 6), starting at daily doses of 5 mg, 50 mg, and 2 mg, respectively, and going up to maximal doses of 20 mg, 100 mg, and 4 mg of enalapril, captopril and perindopril, respectively. Those patients not achieving BO control at those doses were added other non-ARA-II non-ACEIs drugs. The mean age of group II patients was 65[13] years, 8 women and 14 men, with baseline CrCl of 22.3 (7.0) mL/min. Baseline epidemiological data for both groups are shown in Table I, with no statistical differences between the groups. Patients on dialysis therapy or with suspicion of renal artery stenosis were not included in any of the groups. The causes of renal disease for both groups are shown in table II.

In no one of the groups the patients had previously received antihypertensive medication with ACEIs or ARA II, nor medications with ionic exchange resins or non-steroidal anti-inflammatory drugs during the study. Two patients (one in each group) were on allopurinol before the study beginning, which was continued throughout the study. Three patients (14%) in group I and four (18%) in group II received diuretics and 14% in GI and 13.6% in GII received dihydropiridinic calcium-channel blockers as added antihypertensive medication throughout the study.

Methods

The study design did not include randomization or calculation of the sample size since a limited number of patients with the characteristics required attend our outpatient clinic, considering this a limitation of the study, and thus an observer-dependent bias, carrying out the daily clinical practice according to clinical guidelines.

One-year follow-up was done with a baseline control including physical examination, BP measurement in the morning in a seated position, pulse pressure measurement, and laboratory work-up. During the first month, fortnightly BP controls with antihypertensive medication adjustments were done. At months 3, 6, 9, and 12 the same schedule as baseline visit was done. The increase of Irbesartan or ACEIs doses to maximal doses was based on the achievement of systolic blood pressure ≤ 140 mm Hg and diastolic BP < 90 mm Hg. The laboratory work-up included creatinine, serum uric acid and potassium, and 24-hour urine creatinine and proteinuria (proteinuria follow-up was undertaken only in those patients with baseline proteinuria ≥ 0.5 g/day at baseline visit). The progression rate of renal

Table I. Baseline descriptive statistics in both groups

	Group I (ARA II)		Group II (ACEI)	
	Mean	St. dev.	Mean	St. dev.
Age (years)	63.57	17.04	65.09	13.66
Weight (kg)	61.57	9.70	68.45	7.20
Hematocrit	36.84	5.40	37.00	3.28
Hb (g/dL)	12.57	1.87	12.52	1.14
Serum creatinine mg%	2.99	1.33	3.35	1.46
CrCl (mL/min)	22.11	7.73	22.34	7.14
Potassium (mEq/L)	4.52	0.72	4.50	0.50
SBP (mmHg)	153.76	28.04	145.68	11.26
DBP (mmHg)	85.24	18.27	85.23	8.38
MBP (mmHg)	108.08	19.99	105.28	8.77
Pulse pressure (mmHg)	68.52	19.55	60.45	7.39
Proteinuria (g/24 h)	1.51	1.50	0.95	0.98

Table II. Causes of renal disease in both groups

	Group I		Group II	
	Frequency	Percentage	Frequency	Percentage
PRD[a]	2	9.5	3	13.6
NAS	9	42.9	9	40.9
TIN	3	14.3	6	27.3
CGN	6	28.6	4	18.2
Unknown	1	4.8	0	0.0
	21	100.0	22	100.0

[a]PRD: polycystic renal disease; NAS: nephroangiosclerosis; TIN: tubulointerstitial nephropathy; CGN: chronic glomerulonephritis.

failure was calculated in mL/min/month of CrCl in both groups. Treatment tolerability was checked by means of occurrence of adverse events or laboratory changes, at each visit.

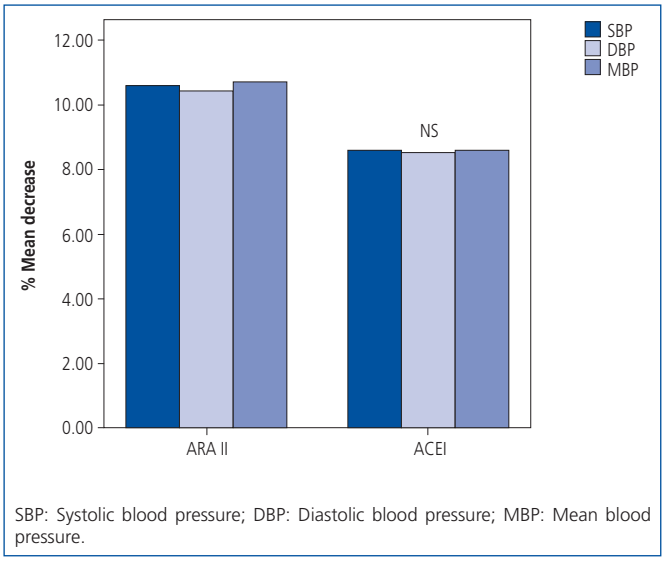
The statistical analysis was done with SPSS 11.5 (Chicago, Ill.). Baseline results were compared with those obtained at 12 months of follow-up by using Student's t test, Chi-squared test, and Mann-Whitney test, as required. The null hypothesis was rejected when $p < 0.05$.

RESULTS

All patients completed 12 months of treatment, with no one of them being included in dialysis during the study period. At 12 months of follow-up, BP was controlled in 57% of the patients in group I only using Irbesartan versus 39% of the patients in group II only treated with ACEIs; however, the goal of BP control established at the study beginning was obtained in both groups with no significant differences for SBP, DBP, and mean blood pressure (MBP), as shown in Fig. 1. At 12 months with Irbesartan, mean SBP was reduced from 154 to 138 mm Hg and DBP from 138 to 77 mm Hg. With ACEIs a decrease in SBP from 146 to 133 mm Hg and in DBP from 85 to 77 mm Hg was observed. MBP was reduced by 10.7 % with Irbesartan and by 8.5 % with ACEIs. Similarly, the pulse pressure decreased in the Irbesartan group and in the group treated with ACEIs, with no differences between them (7.2% *vs* 8.3%). Figure 2 shows the behavior of serum K levels, which are not changed from baseline values in group I, and with a 10% increase in group II ($p < 0.001$). Uric acid increased by 4% from baseline in the group treated with ACEIs, whereas it was reduced by 17% in the patients treated with Irbesartan ($p < 0.001$) (fig. 2). We did not observe differences in renal function decrease, which progressed similarly in both groups. The CrCl decrease throughout the study was 0.23 mL/min/month in group I and 0.21 mL/min/month in group II (NS).

Mean 24-h protein excretion decreased at 12 months in patients treated with Irbesartan from 2.1 g/day to 1.3 g/day, the difference being significant as compared with the ACEIs group, in which proteinuria is slightly reduced from 1.35 g/day to 1.33 g/day ($p = 0.041$).

Treatment with Irbesartan and with ACEIs has been well tolerated by the patients, with no patient being withdrawn from the study for adverse reactions, important biochemical changes, or reaching CrCl values requiring inclusion into dialysis. Moderate increases in serum K levels at some analytical checkpoint did not oblige to patient withdrawal in any case. One patient from group II who months before had been treated with captopril, which was discontinued because of persistent cough, and who remained coughing in spite of medication discontinuation, was assigned to the enalapril group at the study beginning; the cough persisted without being able to ascertain the cough with ACEIs therapy. Two other patients from group II had mild cough and decided to keep on taking the medication. SBP < 100 mm Hg was observed at some measurement in 2 patients from group I and in 1 from group II,



SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure.

Figure 1. Mean decrease of blood pressure in both treatment groups: Irbersartan (ARA II) and ACEIs. NS: Not significant.

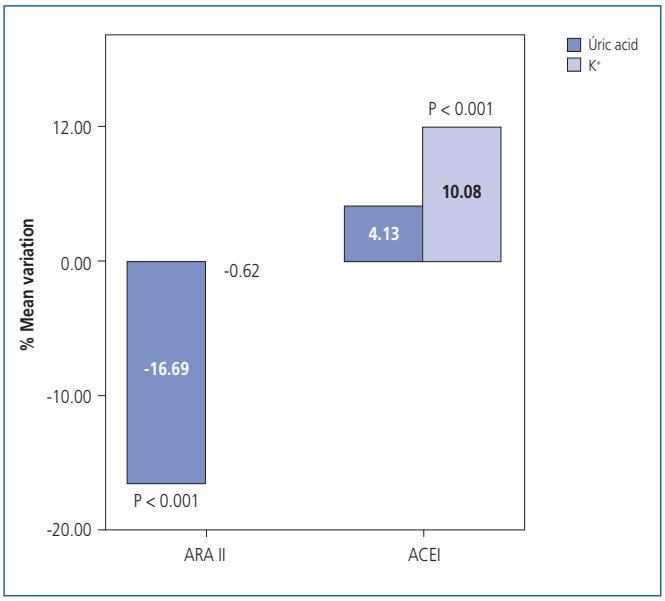


Figure 2. Percentage variation of serum K^+ and uric acid at 12 months of treatment, comparing Irbesartan (ARA II) with ACEIs.

with no clinical repercussion obliging study medication discontinuation.

DISCUSSION

Most of the studies done with ARA II among hypertensive patients with renal impairment have been carried out in diabetic nephropathy.[9-12] The outcomes on AHT control as well as on proteinuria and renal disease progression have been successful, as those reported with ACEIs in diabetic and non-diabetic patients.[1-5] In our work, the antihypertensive efficacy of an intermediate half-life ARA II, such as Irbesartan, has been shown in non-diabetic with mild to moderate hypertension and advanced chronic renal disease, followed at a specific outpatient clinic, with similar results to those obtained in patients on ACEIs and with similar characteristics; better effect on serum uric acid and potassium levels, and on proteinuria has been shown in the former as compared with the latter. In one of the few published studies including a subgroup of patients with ACRD of non-diabetic origin and followed-up for 3 months, outcomes similar to ours are obtained for BP control and decrease of proteinuria, even when used as monotherapy.[15]

Our study was carried out at a single center, with patients coming from the advanced chronic disease clinic, which implies the difficulty on recruiting ACRD patients near to be included into dialysis techniques and that may be followed for a long time in order to assess the efficacy of an antihypertensive therapy; so are the study limitations. In spite of these limitations, the 12-month follow-up period has allowed us analyzing the progression of renal failure and verifying that this is not different when using ACEIs or Irbesartan (-0.21 and -0.23 mL/min/month, respectively), and similar to what has been published. Renal disease progression rates of -0.46 mL/min/month of CrCl have been described in patients with non-diabetic chronic renal disease treated with standard antihypertensive medication.[20] This progression rate is reduced down to -0.23/mL/min/month when in a random way patients are treated with drugs such as captopril or nifedipine.[20] Our results seem to indicate that the reduction in the progression of renal disease achieved with ACEIs or an ARA II such as Irbesartan also occurs when renal disease is at advanced stages, as is the case in the patients included in this study in which dialysis therapy was not required in any one during the 12-month follow-up period. It is likely that the lack of a difference in renal disease progression in between the groups is related with the low number of sample patients.

Irbesartan has shown to have an anti-proteinuric effect in diabetic nephropathy in large studies such as IRMA[9] or IDNT,[11] similarly to other ARA II such as Losartan (RENAAL study)[10] o valsartan (MARVAL study).[12] In non-diabetic nephropathy, smaller studies have shown this same effect on proteinuria with Losartan.[14,21] All of these studies included patients with mild degrees of renal failure and in most of them the benefit on renal function was independent of blood pressure control.[10,12,14,21] The higher effect on proteinuria with Irbesartan as compared with ACEIs observed in our patients has the peculiarity to occur in non-diabetic patients with ACRD. In a group of patients with the same characteristics, assessed at three months, De Rosa et al.[15] describe proteinuria decrease with Irbesartan as compared with baseline values.

The known effect of the increase in serum potassium levels in some patients with renal failure treated with ACEIs has been extended to ARA II due to inhibition of the renin-angiotensin system that occurs with both drug families.[8] Our results show the different behavior of serum potassium by using ACEIs or Irbesartan in ACRD patients, observing a 10% increase with the former as compared with sustained potassium levels with the ARA II agent. Bakris et al.[22] have described similar results when comparing Lysinopril (ACEIs) with Valsartan (ARA II) in patients with glomerular filtration rate < 60 mL/min, relating the significant lysinopril-induced increase in serum potassium with a relatively lower reduction in plasma aldosterone produced by the ARA II agent. We do not know whether this hypothesis would be applicable to our patients with higher renal function impairment. The ACEIs and ARA II doses used in our patients are the usual ones, not too high due to their degree of renal disease, although there already exist studies using high doses of candersartan (5 times higher than the maximal usual ones) in chronic renal disease, without observing changes in baseline serum potassium levels.[23] Another finding in our study was the reduction with time in serum uric acid levels with Irbesartan that is not obtained in the group treated with ACEIs. There are several works describing the decrease in uric acid using Losartan.[24-26] This action of Losartan seems to be transient and related with its uricosuric effect. In a study comparing Losartan with enalapril in healthy subjects, ACEIs showed no effects on fractional clearance of uric acid, by contrast with the ARA II agent.[24] The comparison of the uricosuric effect of Losartan as compared with other ARA II drugs yields controversial results, so that in the work by Wurzner et al.[25] with hyperuricemic patients comparing Losartan with Irbesartan, a decrease in uric acid is obtained only with the former. In another study[26] in patients with mild to moderate AHT, Losartan, as compared with Eprosartan, increased uric acid urinary excretion but none of them produced changes in serum levels of uric acid. Our study does not include data on uric acid renal excretion that may clear the mechanism of uric acid serum levels reduction when using Irbesartan, although the follow-up of our patients has been longer than in the above-mentioned studies and than in patients with important renal function impairment.

To conclude, our results (considering the mentioned limitations) show that while keeping similar antihypertensive efficacy and behavior in the progression of renal function, Irbesartan reduces proteinuria at a higher degree than ACEIs, whit no increase in serum potassium and with a significant decrease in uric acid levels in patients with advanced chronic renal disease of non-diabetic origin.

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