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Original Investigation

Effect of Dual Blockade of the Renin-Angiotensin System on the Progression of Type 2 Diabetic Nephropathy: A Randomized Trial

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Background: Blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers has been shown to lessen the rate of decrease in glomerular filtration rate in patients with diabetic nephropathy.

Study Design: A multicenter open-label randomized controlled trial to compare the efficacy of combining the angiotensin-converting enzyme inhibitor lisinopril and the angiotensin II receptor blocker irbesartan with that of each drug in monotherapy (at both high and equipotent doses) in slowing the progression of type 2 diabetic nephropathy.

Setting & Population: 133 patients with type 2 diabetic nephropathy (age, 66 ± 8 years; 76% men) from 17 centers in Spain.

Intervention: Patients were randomly assigned (1:1:2) to lisinopril (n = 35), irbesartan (n = 28), or the combination of both (n = 70).

Outcomes: The primary composite outcome was a >50% increase in baseline serum creatinine level, end-stage renal disease, or death.

Results: Baseline values for mean estimated glomerular filtration rate and blood pressure were 49 ± 21 mL/min/1.73 m^2 and 153 ± 19/81 ± 11 mm Hg. Mean geometric baseline proteinuria was protein excretion of 1.32 (95% CI, 1.10-1.62) g/g creatinine. After a median follow-up of 32 months, 21 (30%) patients in the combination group, 10 (29%) in the lisinopril group, and 8 (29%) in the irbesartan group reached the primary outcome. HRs were 0.96 (95% CI, 0.44-2.05; P = 0.9) and 0.90 (95% CI, 0.39-2.02; P = 0.8) for the combination versus the lisinopril and irbesartan groups, respectively. There were no significant differences in proteinuria reduction or blood pressure control between groups. The number of adverse events, including hyperkalemia, was similar in all 3 groups.

Limitations: The study was not double blind. The sample size studied was small.

Conclusions: We were unable to show a benefit of the combination of lisinopril and irbesartan compared to either agent alone at optimal high doses on the risk of progression of type 2 diabetic nephropathy.

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INDEX WORDS: Type 2 diabetic nephropathy; ACE inhibitor; angiotensin receptor blocker; dual blockade; renal progression.

Blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) has been shown to lessen proteinuria and the rate of decrease in glomerular filtration rate (GFR) in patients with diabetic nephropathy. In the seminal study by Lewis et al[1] of 409 patients with type 1 diabetic nephropathy, therapy with ACE inhibitors led to a 50% reduction in risk of doubling of serum creatinine level, requiring dialysis, or death. In 2 other major studies, IDNT (Irbesartan Diabetic Nephropathy Trial)[2] and RENAAL (Reduction in End Points in Non–Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan),[3] the risk of doubling of serum creatinine level, requiring dialysis, or death was significantly lower in patients with type 2 diabetic nephropathy treated with an ARB than in patients who received placebo.

Several studies have demonstrated that the antiproteinuric effect of RAS blockers is dose dependent. Therefore, to maximize this effect, it is necessary to titrate up to the highest tolerated dose.[4-10] Proteinuria is a surrogate of kidney disease progression, and in nondiabetic patients, uptitration of RAS blockade

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therapy to reduce proteinuria conferred further benefit on kidney outcomes.[9] The effects of ARBs and ACE inhibitors are not equivalent, but some studies suggest that the efficacy of these drugs could be similar,[10-13] although none has been performed in patients with established diabetic nephropathy.

To improve the renoprotective effects of RAS blockers, combining an ACE inhibitor and an ARB could be useful.[14-16] A number of recent publications have described a more marked antiproteinuric effect of dual blockade of the RAS compared with ACE inhibitors or ARBs in monotherapy despite a similar effect on blood pressure (BP).[17] However, to our knowledge, no controlled study has compared dual blockade of the RAS with ACE inhibitors or ARBs in monotherapy on progression of type 2 diabetic nephropathy.

The purpose of this study was to compare the efficacy of combining the ACE inhibitor lisinopril and the ARB irbesartan with that of each drug in monotherapy (at both high and equipotent doses) in slowing the progression of kidney disease in patients with type 2 diabetic nephropathy. A secondary objective was to evaluate the safety of treatment with high doses of ACE inhibitors or ARBs and combined treatment in these patients.

METHODS

Study Design

We performed a multicenter (17 centers throughout Spain) open-label clinical trial (2006-2011) in which patients were randomly assigned 1:1:2 to receive lisinopril (40 mg), irbesartan (600 mg), or the combination of lisinopril, 20 mg, plus irbesartan, 300 mg. We assessed progression of type 2 diabetic nephropathy. The planned study duration was 4 years. Median follow-up was 32 (25th-75th percentile, 18-48) months and the enrollment period was 18 months. The randomization sequence was created using SPSS statistical software (IBM-SPSS Statistics, www.ibm.com/SPSS_Statistics) and stratified by center using random block sizes of 8 patients within strata with a 1:1:2 allocation. The allocation sequence, generated by an investigator with no clinical involvement in the trial, was concealed in opaque sealed envelopes from the researcher enrolling and assessing participants. All patients provided written informed consent. The protocol fulfilled the criteria of the Declaration of Helsinki and was approved by the regulatory authorities and local ethics committees.

Patients

From 189 patients screened, we enrolled 133 patients older than 35 years with type 2 diabetes and a clinical diagnosis of diabetic nephropathy, stage 2 or 3 chronic kidney disease, and a urine protein-creatinine ratio (UPCR) >300 mg/g on a morning urine spot sample on 2 separate occasions. Other inclusion criteria included potassium level <5.5 mEq/L, glycosylated hemoglobin value <10%, proteinuria with protein excretion <10 g/24 h, or blood albumin level >2 g/dL. All patients had hypertension, with BP at rest <180/95 mm Hg. Exclusion criteria were myocardial infarction, cerebrovascular stroke, heart failure, or myocardial revascularization in the last 3 months or any condition that could restrict long-term survival.

Intervention

During a 4-week washout period, patients continued to receive their standard antihypertensive therapy. If they had been using ARBs or ACE inhibitors, these medications were discontinued and replaced by alternative open-label medications to control BP. After the 4-week washout period, patients were randomly assigned to receive once-daily doses of lisinopril (10 mg), irbesartan (150 mg), or the combination (lisinopril, 5 mg, plus irbesartan, 75 mg), along with conventional antihypertensive therapy.

The dose was titrated up to the maximum recommended study dosage after 8 weeks (lisinopril, 40 mg; irbesartan, 600 mg; and lisinopril [20 mg] + irbesartan [300 mg]). The treatment was continued while patients were in the study. The dose was reduced if hypotension or hyperkalemia appeared. Throughout the study, patients received the standard of care for the treatment of diabetes. Hyperkalemia was controlled when necessary by means of a hypokalemic diet and cation exchange resins. Visits were scheduled every 4 months to monitor BP, use of concomitant medication, adherence measured by counting pills at each visit, and laboratory values and assess whether adverse events had occurred or end points had been reached.

Follow-up Assessment

Median follow-up was 32 (25th-75th percentile, 18-48) months. Systolic and diastolic BP were measured with an OMRON automatic BP monitor (OMRON Health Care, www.omron-healthcare.com) and previous cardiovascular diseases were recorded. Serum creatinine, measured by the kinetic Jaffé blank correction method and standardized for all laboratories from a program accredited (ISO 9000:2008) of the Spanish Society of Clinical Biochemistry; hemoglobin level; and other laboratory values, including levels of serum cholesterol (total lipoprotein, high-density lipoprotein, and low-density lipoprotein), triglycerides, and glycosylated hemoglobin, were measured immediately when received. UPCR was measured in a central laboratory.

C-Reactive protein (CRP), serum albumin, aldosterone, and 25-hydroxyvitamin D levels were checked at baseline and 4 and 12 months after treatment. The 4-variable MDRD (Modification of the Diet in Renal Disease) Study equation was used to estimate GFR (eGFR), measured at baseline and at 6, 12, 24, 36, and 48 months after RAS blockade treatment.

Routine clinical and biochemical variables were measured by standardized methods on autoanalyzers. Highly sensitive CRP plasma level was measured with a latex-based turbidimetric immunoassay on a Hitachi analyzer (Sigma Chennai Co, www.sigmaaldrich.com). Urinary protein excretion was measured with an immunonephelometric method. Aldosterone was measured by radioimmunoassay, and 25-hydroxyvitamin D, by chemiluminescent immunoassay.

Outcome Measures

The primary efficacy measure was time to the first event of the composite end point (50% increase in serum creatinine concentration), end-stage renal disease (ESRD), or death. The 50% increase in serum creatinine concentration was defined as the first serum creatinine value that was 50% higher than the baseline value, confirmed by a second serum creatinine value a month later. ESRD was defined as the need for long-term dialysis therapy or kidney transplant. Death and hospitalization due to any cause were recorded. The information reviewed by physicians always included study hospitalization records, and in the case of an out-of-hospital death, family members were interviewed by telephone to better ascertain the circumstances surrounding the death. Secondary end points were change in UPCR and the tolerance and safety of each treatment schedule. Adverse events were recorded during follow-