Hong Kong Study Using Valsartan in IgA Nephropathy (HKVIN): A Double-Blind, Randomized, Placebo-Controlled Study

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• ***Background:*** **Previous studies showed that angiotensin-receptor blocker (ARB) therapy decreased proteinuria and possibly slowed the rate of renal function decline in patients with chronic proteinuric nephropathies. We performed a double-blind, randomized, placebo-controlled, multicenter study on the ARB valsartan in the treatment of patients with immunoglobulin A (IgA) nephropathy.** ***Methods:*** **From 6 centers, we recruited 109 patients with IgA nephropathy who had either: (1) proteinuria with protein greater than 1 g/d and serum creatinine level less than 2.8 mg/dL (<250 μmol/L), or (2) serum creatinine level of 1.4 to 2.8 mg/dL (120 to 250 μmol/L) regardless of degree of proteinuria. Patients were randomly assigned to administration of either valsartan, 80 mg/d (titrated up to 160 mg/d for blood pressure control), or placebo for 104 weeks. Additional antihypertensive therapy was allowed to achieve a target blood pressure of 140/90 mm Hg. The primary end point was doubling of serum creatinine level or dialysis-dependent renal failure. Secondary outcomes included change in proteinuria and decrease in glomerular filtration rate (GFR).** ***Results:*** **There were 54 patients in the treatment group and 55 patients in the placebo group. Baseline clinical characteristics were similar between groups, although the treatment group had a marginally greater baseline GFR (87 ± 36 versus 78 ± 38 mL/min/1.73 m^2 [1.45 ± 0.60 versus 1.30 ± 0.63 mL/s/1.73 m^2];*P* = 0.29) and less proteinuria (protein, 1.8 ± 1.2 versus 2.3 ± 1.7 g/d; *P* = 0.21) than the placebo group. Average blood pressures during the study were 92.7 ± 10.6 mm Hg in the treatment group and 100.9 ± 9.1 mm Hg in the placebo group (*P* < 0.001). During the study period, 4 patients in the placebo group and 1 patient in the treatment group reached the primary end point (log-rank test, *P* = 0.18). Proteinuria decreased significantly in the treatment group (protein, 1.8 ± 1.2 to 1.2 ± 1.2 g/d; *P* = 0.03), but did not change in the placebo group. With multiple linear regression models, valsartan treatment resulted in a 33.0% decrease in proteinuria (95% confidence interval, 10.9 to 55.1) after adjusting for other confounding factors. There was a significant decrease in mean rate of GFR decrease in the valsartan-treated group (−5.62 ± 6.79 mL/min/y [−0.09 ± 0.11 mL/s/y]) compared with the placebo group (−6.98 ± 6.17 mL/min/y [−0.12 ± 0.10 mL/s/y]) throughout the study period after adjustment for average blood pressure and proteinuria (*P* = 0.014).** ***Conclusion:*** **Valsartan significantly decreases proteinuria and slows renal deterioration in patients with IgA nephropathy after adjustment for confounding factors, notably blood pressure. The long-term benefit of valsartan needs to be confirmed with additional studies.** ***Am J Kidney Dis*** **47:751-760.**

INDEX WORDS: Glomerulonephritis; proteinuria; renal failure; angiotensin-receptor blocker.

IMMUNOGLOBULIN A (IgA) nephropathy causes a progressive decrease in renal function, with a 20% incidence of end-stage renal disease in 10 years.[1,2] In addition to being the most common glomerular disease in the world[3] and a major cause of end-stage renal disease, there currently is no definite cure for IgA nephropathy.[4] Furthermore, there is no concrete evidence on the benefit of angiotensin-converting enzyme (ACE) inhibitors.[5] The role of angiotensin II-receptor blockers (ARBs) is not yet firmly established, although their antihypertensive, renopro-

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tective, and antiproteinuric effects appear to be of benefit. In this respect, amelioration of glomerular injury or fibrosis by valsartan was shown in animal models of IgA nephropathy.[6] In humans, inhibition of angiotensin II action was shown to decrease urinary transforming growth factor β1 levels in patients with IgA nephropathy, thus ameliorating extracellular matrix protein accumulation.[7,8] ARB treatment was effective in decreasing proteinuria in the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease Study, which had a substantial number of patients with IgA nephropathy.[9] However, prospective controlled studies of the clinical benefit of ARBs in the treatment of IgA nephropathy are lacking.

To examine the therapeutic role of the ARB valsartan in patients with IgA nephropathy, we conducted a multicenter, randomized, double-blind, placebo-controlled study of 109 Chinese patients with IgA nephropathy.

METHODS

Study Patients

Patients with biopsy-confirmed IgA nephropathy (defined using standard morphological and immunohistochemical criteria) were recruited between June 2000 and June 2003. Inclusion criteria were age of at least 18 years and either: (1) proteinuria with protein of at least 1 g/d and serum creatinine level less than 2.8 mg/dL (<250 μmol/L), or (2) serum creatinine level between 1.4 and 2.8 mg/dL (120 and 250 μmol/L) irrespective of the magnitude of proteinuria. Patients were eligible for our study irrespective of their blood pressure, but those with accelerated or malignant hypertension were considered not eligible. Other exclusion criteria were expected survival less than 2 years; secondary IgA nephropathy, including Henoch-Schönlein purpura; pregnant or lactating women; clinically significant hepatic disease; known allergy or reactions to ARBs; and recent treatment (within 4 weeks of enrollment) with ACE inhibitors or ARBs.

The study was approved at all participating centers by the appropriate institutional review boards. Written informed consent was obtained from all patients.

Study Design

Eligible patients were randomly assigned to administration of valsartan, 80 mg/d (treatment group), or placebo (placebo group). The appearance, packaging, and labeling of the active medication and placebo were identical. Individuals were randomly assigned by means of a computer-generated list using a 1-to-1 ratio in permuted blocks stratified by center. The randomization list was used for packaging of tablets and then maintained by a third party who was not involved in conduction of the study. Marked drug packs were designated for each patient. Patients were not stratified by any baseline characteristics during randomization.

After randomization, patients' usual antihypertensive medications were continued. Target blood pressure control was set at less than 140/90 mm Hg. If target blood pressure was not achieved after a 4-week treatment period, the study medication dosage was doubled (valsartan, 160 mg/d, or equivalent placebo). Additional new antihypertensive medications (β-blocker, calcium channel blocker, or thiazide diuretics, followed by any appropriate additional agent if blood pressure remained high) were allowed after 8 weeks at the discretion of the attending physicians. Study medication was continued for 104 weeks. Neither study personnel nor patients were aware of treatment assignments.

Safety evaluations, which included all reports of adverse events and clinical laboratory tests, were conducted throughout the study. Serum and urinary samples were collected at each visit and analyzed for biochemistry and proteinuria. Renal function was assessed by concentrations of urea, creatinine, and glomerular filtration rate (GFR), estimated by using the abbreviated Modification of Diet in Renal Disease Study equation, which was detailed in the National Kidney Foundation Practice Guidelines.[10] At each clinic visit, systolic and diastolic blood pressures were measured after 5 minutes of rest in a sitting position, with the average of 2 measurements recorded. Patients were evaluated every 4 weeks during the first 12 weeks and every 12 to 16 weeks thereafter. Clinical data, including blood pressure, urinary protein excretion, estimated GFR, and serum biochemical test result, were recorded at enrollment and continued throughout the study period. For each patient, blood pressure control during the study period was represented by the average of all clinic blood pressure measurements while on study medication (ie, 4 to 104 weeks). An independent data and safety monitoring committee oversaw the study. The funding source had no role in the collection, analysis, or interpretation of data or the decision to submit the manuscript for publication.

Statistical Analysis and Outcome Measures

Sample size was estimated before the study by using the Power Analysis and Sample Size for Windows software (PASS 2000; NCSS, Kaysville, UT). Calculation of sample size was based on the primary end point. Based on previous studies of the treatment effect of ACE inhibitors on patients with chronic renal insufficiency,[11,12] it was expected that approximately 60% of patients administered placebo and 20% of the treatment group would develop the primary end point within 2 years. Fifty-five patients on each arm were required to detect the anticipated difference with 80% power at a 5% α level (2 sided), assuming a dropout rate of 10%.

The statistical package MIXREG (University of Illinois at Chicago, Chicago, IL, http://tigger.uic.edu/~hedeker/mix.html) was used for fitting the linear mixed-effects regression model, whereas all other analysis was performed using the Statistical Package for Social Sciences for Windows software, version 11.0 (SPSS Inc, Chicago, IL).[13] Means and SDs were calculated for continuous variables, and frequencies and percentages were calculated for categorical variables. Because the distribution of proteinuria values was