Cover page

Official title

A randomized, double blinded, placebo-controlled, multicenter, Phase III study to evaluate the efficacy and safety of Losartan in Early Immunoglobulin A nephropathy (IgAN) patients: study protocol for a randomized controlled trial (BEST-IgAN-1)

Date of the document

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Study protocol

Hypothesis

Treatment with losartan will prevent the development of a significant proteinuria, defined as random urine protein-to-creatinine ratio (UPCR) ≥ 1.0 g/g creatinine. Compared with placebo-treated patients, the incidence of significant proteinuria will be lower in losartan-treated patients.

Study design

This is a multi-center, prospective, randomized, double-blinded, placebo controlled, phase 3 study. This study is an investigator-initiated clinical trial. The study algorithm is described in Fig. 1. After enrollment, clinical follow-up will be performed 144 weeks after interventional drugs application.

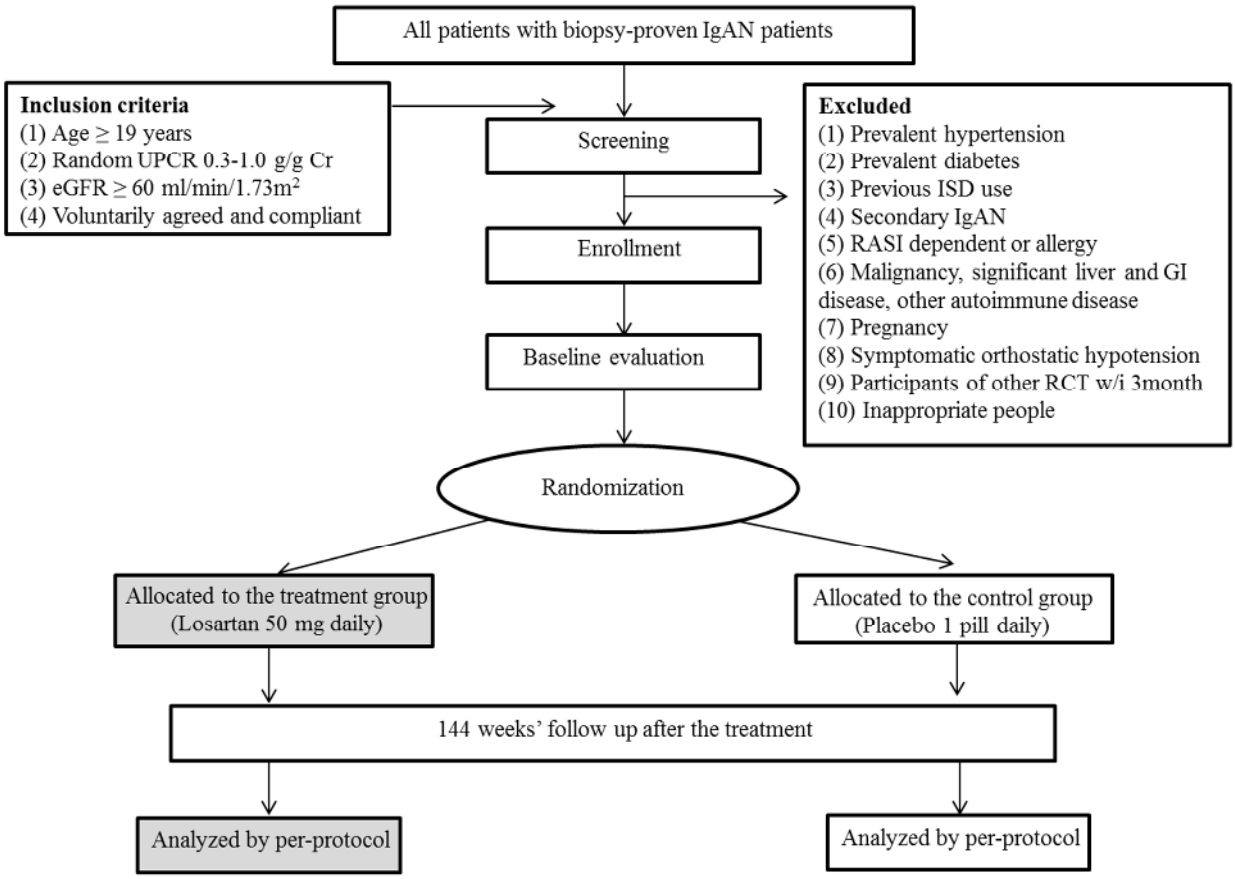

Figure 1. Study algorithm. IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio; eGFR, estimated glomuerular filtration rate; ISD, immunosuppressive drugs; RASI, renin-angiotensin-aldosterone system inhibitor; RCT, randomized clinical trials;w/i, within.

Study participants and measurements

Biopsy-proven IgAN patients aged ≥ 19 years will be screened. The following will be conducted at the initial visit: (1) a questionnaire regarding socioeconomic status, past medical history, current medication history, and smoking status; (2) a physical examination of all systems; (3) height and weight measurements; (4) blood pressure and pulse rate measurements. Participants who meet all of the inclusion and exclusion criteria and provide

written, informed consent are eligible for this study (Table 1). Hypertension is defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, physician diagnosis of hypertension, or using antihypertensive drugs. Diabetes is defined as fasting glucose ≥126 ml/dL, physician diagnosis of diabetes, or using insulin or oral anti-diabetic drugs. Dependency to renin-angiotensin-aldosterone system inhibitor (RASI) is condition which cannot stop RASI including ischemic or congestive heart failure. The estimated glomerular filtration rate (eGFR) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. [1]

Table 1. Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Biopsy-proven IgAN	Prevalent hypertension
Age ≥ 19 years	Prevalent diabetes
Random UPCR ≥ 0.3 g/g Cr and < 1.0 g/g Cr at visit 1	Previous ISD use to treat IgAN
eGFR ≥ 60 mL/min/1.73 m^2 at visit 1	Secondary IgAN
People who voluntarily agreed to participate	RASI dependent or hypersensitive condition
People who are compliant	Other chronic diseases: malignancy within 5 years, significant liver and GI disease, and other autoimmune disease
	Pregnancy
	Symptomatic orthostatic hypotension
	Participants of other interventional studies or

	taking interventional durgs w/i 3month Inappropriate people ascertained by investigator

IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate; ISD, immunosuppressive drugs; IgAN, immunoglobulin A nephropathy; RASI, renin-angiotensin-aldosterone system inhibitor, GI, gastrointestinal. Biopsy-proven IgAN is defined as dominant or co-dominant deposits of mesangial IgA in immunofluorescence stain. Hypertension is defined as systolic blood pressure ≥140 mmHg and ≥90 mmHg, previous physician diagnosis of hypertension, or taking anti-hypertensive drugs. Diabetes is defined as fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, taking insulin or anti-diabetic drugs, or previous physician diagnosis of diabetes. RASI dependent condition is congestive heart failure, ischemic heart disease, and others.

Randomization

A research coordinator will conduct the randomization and deliver the study drug. The participants and investigators will be blinded to the treatment assignment. A list of random numbers will be generated by an independent statistician. Eligible participants will be randomly assigned 1:1 to either the treatment group or the control group in accordance with the predefined randomization list with a block size of four.

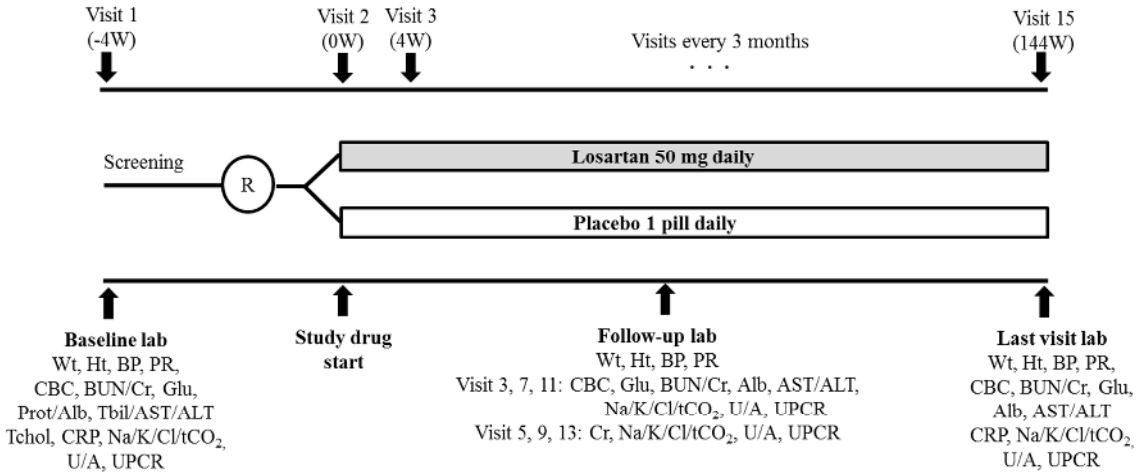

Figure 2. Study schedule. W, week; R, randomization; Wt, weight; Ht, height; BP, blood pressure; PR, pulse rate; CBC, complete blood cell counts; BUN, blood urea nitrogen; Cr, creatinine; Glu, glucose; Prot, protein; Alb, albumion; Tbil, total bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; Tchol, total cholesterol; CRP, c-reactive protein;tCO2, total CO2; U/A, urinalysis; UPCR, urine protein-to-creatinine ratio.

Treatment

An ARB, losartan , which is clinically available, will be used in this study. At visit 1, informed consent will be taken from patients who are suitable for inclusion criteria, and baseline lab will be analyzed. After 4 weeks' screening, patient who did not have exclusion criteria will start study drug at visit 2 after randomization (Fig 2). The losartan and placebo tablets will be provided by Yuhan Corporation (Seoul, Korea). After randomization, the participants will take either a losartan 50mg daily (treatment group) or placebo (control group) pill for 144 weeks. The tablet shapes and packaging of the placebo pills are identical to those of the losartan pills. The prescription and administration of the study drugs will be conducted in a double-blind manner during 144 weeks' clinical follow-up period. Investigators or research coordinators will evaluate drug compliance by counting pills.

Outcome measures

The primary outcome of interest is the development of a significant proteinuria at 144 weeks after study drug started, where significant proteinuria is defined as random UPCR ≥ 1.0 g/g creatinine two consecutive times. The secondary outcomes will include development of incident hypertension, eGFR decline ≥ 40% from the baseline, and induction of proteinuria remission. Induction of proteinuria remission is defined as random UPCR < 0.2 g/g creatinine two consecutive times.

Clinical and laboratory evaluations

The physical examination and medication reviews will be conducted on every visits. Laboratory evaluations will be performed on every odd visits (Fig 2); the laboratory evaluations will include a complete blood count; measurements of the levels of hemoglobin, electrolytes, blood urea nitrogen, serum creatinine, fasting glucose, total protein, albumin, total bilirubin, alanine transaminase, aspartate aminotransferase, total cholesterol, C-reactive protein, urinalysis with microscopy and UPCR.

Safety issues

Major safety issues are hyperkalemia, symptomatic hypotension, and abrupt decline of eGFR. Any occurrence of musculoskeletal pain, loin pain, lower extremity pain, dizziness, upper respiratory tract infection, and sinusitis will be recorded during treatment with losartan/ placebo. All adverse events, including serious adverse events, will be recorded and followed up during the study period or until resolution. All serious adverse events will be graded and reported to investigators and the ethics committee.

Sample size calculation

No previous study has evaluated the effect of a losartan on the development of significant proteinuria. The investigators expect that the incidence of significant proteinuria development will be 33 % in patients with early IgAN and that treatment with a losartan could reduce this incidence by 13%. The investigators calculated the required sample size for an estimated dropout rate of 20 %, a one-sided level of significance of $\alpha = 5$ %, and a power of 80 % and found that 87 participants will be needed in each group to find a significant difference using a $\chi 2$ test. A total of 174 participants will be included in the analysis.

Statistical analysis

Statistical analyses will be conducted on per protocol (PP) primarily, but intention-to treat (ITT) will also be conducted. For the PP analysis, all participants who completed the study will be included to evaluate the primary and secondary outcomes. For the ITT analysis, all participants who were enrolled and randomized to one of the two groups will be included. The baseline characteristics and laboratory data will be presented as the means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. The incidence of a significant proteinuria development, incident hypertension, and proteinuria remission will be compared between the two groups using a $\chi 2$ test. The differences in changes in eGFR will be analyzed using Student's t-test or the Mann-Whitney U test. A value of $P < 0.05$ will be considered statistically significant. All analyses will be performed using SPSS Statistics software version 22.0 (IBM Corporation, Armonk, NY, USA).

References

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* May 5 2009;150(9):604-612.