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Original Investigation

Angiotensin Blockade and Progressive Loss of Kidney Function in Hemodialysis Patients: A Randomized Controlled Trial

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Background: Glomerular filtration rate (GFR) declines during long-term dialysis treatment. In peritoneal dialysis, blockade of the renin-angiotensin-aldosterone system reduces GFR decline. Observational studies suggest that similar treatment may preserve kidney function in hemodialysis (HD).

Study Design: A multicenter, randomized, placebo-controlled, double-blinded trial, with 1-year follow-up.

Setting & Participants: Adult HD patients with urine output > 300 mL/24 h, HD vintage less than 1 year, and cardiac ejection fraction > 30%. Patients were included from 6 HD centers.

Intervention: Patients were randomly assigned to placebo or the angiotensin II receptor blocker irbesartan, 300 mg daily. Target systolic blood pressure (BP) was 140 mm Hg.

Outcomes & Measurements: Primary outcomes were change in GFR measured as the mean of creatinine and urea renal clearance together with urine volume. Secondary outcomes were change in albuminuria, renin-angiotensin II-aldosterone hormone plasma levels, and time to anuria.

Results: Of 82 patients randomly assigned (41 patients in each group), 56 completed 1 year of treatment. The placebo and irbesartan groups were comparable at baseline in terms of sex balance (26 vs 30 men), mean age (62 vs 61 years), median HD vintage (137 vs 148 days), mean HD time (10 vs 11 h/wk), median urine volume (1.19 vs 1.26 L/d), and mean GFR (4.8 vs 5.7 mL/min/1.73 m^2). The target BP level was reached in both groups and BP did not differ significantly between groups over time. Adverse-event rates were similar. GFR declined by a mean of 1.7 (95% CI, 1.2-2.3) and 1.8 (95% CI, 1.1-2.4) mL/min/1.73 m^2 per year in the placebo and irbesartan groups, respectively. Mean difference (baseline values minus value at 12 months) between groups was −0.0 (95% CI, −0.8 to 0.8). In each group, 4 patients became anuric.

Limitations: GFR decline rates were lower than expected, reducing the power.

Conclusions: At equal BP levels, we found that irbesartan treatment did not affect the decline in GFR or urine volume significantly during 1 year of treatment in HD patients. Irbesartan treatment was used safely in the studied population.

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INDEX WORDS: Adult; albuminuria; aldosterone; angiotensin II; angiotensin II receptor blocker; anuria; double-blinded; glomerular filtration rate (GFR); GFR decline; hemodialysis (HD); investigator-initiated; irbesartan; multicenter study; placebo; preservation of residual renal function; randomized controlled trial; renin; residual renal function; SAFIR (Saving Residual Renal Function in Hemodialysis Patients Receiving Irbesartan) trial; urine volume.

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All-cause mortality among dialysis patients is 6.7-8.5 times higher than in the general population in the United States.[1] Observational studies in dialysis patients have reported that full loss of glomerular filtration rate (GFR) is associated with increased mortality.[2,3] Even small values of GFR are important, and 1 unit per week greater renal urea clearance (Kt/V_{urea}) has been reported to be associated with a significantly lower risk of death in hemodialysis (HD) patients.[4] Preserved kidney function offers HD patients several advantages. Apart from a lower dialysis dose and more liberal fluid intake, less ultrafiltration requirement leads to smaller changes in fluid homeostasis and lower risk of hypotensive episodes. Furthermore, middle- and large-sized uremic toxins are cleared

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better and the endogenous production of erythropoietin is maintained to some degree.[5]

Among Asian peritoneal dialysis (PD) patients, 2 randomized studies showed that GFR is preserved by both angiotensin-converting enzyme (ACE)-inhibitor and angiotensin II receptor blocker (ARB) treatment.[6,7] In HD patients, observational studies indicate that blockade of the renin-angiotensin-aldosterone system (RAAS) may preserve GFR,[8,9] but to date, no randomized controlled trials have been published.

The aim of the SAFIR (Saving Residual Renal Function in Hemodialysis Patients Receiving Irbesartan) Study was to investigate whether RAAS blockade with the ARB irbesartan resulted in better preservation of GFR and urine volume, and a decrease in albuminuria, compared to placebo in HD patients.

METHODS

Overview of Study

The study design has been described previously.[10] In brief, the SAFIR Study is a double-blinded, multicenter, randomized, placebo-controlled, parallel-group trial initiated by the investigators. Patients were recruited from 6 Danish HD centers. Inclusion criteria were reasonably good general condition, diuresis at last measurement >300 mL/24 h, stable HD treatment (no planned transfer to PD treatment and recovery of kidney function not anticipated), HD vintage less than 1 year, and 18 years or older. After inclusion and before randomization, urine volume was measured and had to be >300 mL/24 h and left ventricular ejection fraction had to be $>30\%$ on echocardiography. If either of these parameters was not met, the patient was excluded. Patients were followed up for 1 year. The study was conducted between April 2009 and December 2012.

Intervention

Original tablets (irbesartan, 150 mg, or placebo) were delivered to the Pharmacy Department at Aarhus University Hospital, Denmark, by Sanofi Denmark (Slotsmarken 13) and were identical apart from irbesartan content. Investigators, study nurses, and patients were kept blinded throughout the study.

If a participant was receiving an ACE inhibitor, ARB, or renin antagonist at inclusion, this treatment was discontinued 1 week before the baseline visit. After the baseline visit, 1 tablet daily of study drug was prescribed. If well tolerated (no hypotension or hyperkalemia), the dose was increased to 2 tablets daily after 2 weeks. This dose was unchanged throughout the study unless adverse events occurred. Treatment adherence was monitored by counting residual tablets monthly. To reach equal blood pressure (BP) levels in the 2 treatment groups, investigators were encouraged to achieve a predialytic systolic BP of 140 mm Hg in all patients by adjusting dry weight and by use of all classes of antihypertensive drugs apart from RAAS-blocking agents.

Randomization

The Pharmacy Department at Aarhus University Hospital, Denmark, randomly assigned patients 1:1, stratified by diabetes. A permuted-block randomization was applied.

Outcomes

The prespecified primary outcome measure was slope of GFR decline over time. Secondary outcomes included albuminuria; time to anuria, defined as absence of daily urine voiding; change in plasma levels of RAAS hormones; and occurrence of adverse events.

Glomerular Filtration Rate

GFR was assessed as the mean of creatinine and urea clearance values based on 24-hour urine collections.[11] GFR was assessed at baseline and repeated after 1 week to elucidate acute effects of irbesartan, and then every 3 months for 1 year. All visits were carried out in the morning 2 days after the last HD session. Plasma creatinine and urea were measured after dialysis 2 days before visits and at the start of dialysis on the visit day. To minimize the urea and creatinine postdialysis rebound effect, postdialysis blood samples were drawn 10 minutes after termination of the blood pump. A linear increase in plasma creatinine and urea levels between dialysis sessions was assumed and the values used were estimated corresponding to halfway through the urine collection.[10] Creatinine was measured in 6 different laboratories. All methods used were calibrated to the isotope-dilution mass spectrometry reference. Urine was collected during the last 24 hours of the interdialytic interval.

RAAS Hormones

To ensure separation of the 2 groups in terms of RAAS hormone levels, radioimmunometric assay was used to determine plasma concentrations of renin (Cisbio Bioassays; Siemens Healthcare Diagnostics; reference range, 1-59 pg/mL), angiotensin II (after extraction from plasma by commercial cartridges[12]; reference range, 3-30 pg/mL), and aldosterone (Coat-A-Count; Siemens Healthcare Diagnostics; reference range, 1-31 ng/dL).

BP and Hydration

Predialytic ambulatory BP measurements and adverse events were registered after 1 week, 2 weeks, 1 month, 6 weeks, and 2 months and then each month. BP was measured in a standardized manner as previously described.[10] Intradialytic hypotension was defined as symptomatic hypotension requiring intravenous fluid resuscitation or preterm ending of the dialysis session and was registered each month. Clinical hydration status was based on clinical observation of BP, edema, and dialysis tolerability and was assessed monthly on a 4-step scale: dehydration, normal hydration, slight overhydration, or severe overhydration.

Ethics

All patients provided written informed consent. The study was conducted in accordance with good clinical practice and the ethical standards described in the Declaration of Helsinki. The Central Denmark Region Committees on Biomedical Research Ethics, the Danish Health and Medicines Authority, and the Danish Data Protection Agency approved the study protocol. A local independent good clinical practice unit monitored all sites.

Sample Size

When we were planning the study, no exact data were available regarding GFR decline in HD patients during the first 2 years after commencing dialysis therapy. In a study in PD patients, the annual decline was 3 mL/min/1.73 m^2 without ARB treatment.[6] An expected faster GFR decline in incident HD patients led us to assume an annual decline of 4 mL/min/1.73 m^2. Using type I error level $= 0.05$, power $= 0.80$, estimated standard deviation $= 1.725$, and minimal relevant difference $= 1.4$ mL/min/1.73 m^2 (reduction in GFR decline $= 35\%$), 24 patients were needed in each group (2-sample comparison of means). Expecting a considerable dropout rate (eg, adverse events and transplantation), we decided to include a minimum of 80 patients.

Statistical Methods

Results are presented as numbers for categorical variables and mean $\pm$ standard deviation for continuous normal distributed variables. Normality was checked with QQ plots and equal