Prevention of Transition From Incipient to Overt Nephropathy With Telmisartan in Patients With Type 2 Diabetes

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To date, evidence for long-term renoprotection with angiotensin receptor blockers (ARBs) has come almost exclusively from Caucasian patients (1–3), despite Japanese people being at high risk of diabetic nephropathy and very susceptible to end-stage renal disease (4–6). We conducted the INNOVATION Study (Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy; ClinicalTrials.gov Identifier NCT00153088) to evaluate the efficacy of an ARB in preventing transition from microalbuminuria to overt nephropathy in Japanese patients (7). This study is the first large-scale clinical study to investigate prevention of overt diabetic nephropathy using an ARB in normotensive as well as in hypertensive Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The randomized, multicenter, double-blind, placebo-controlled trial was performed in patients aged from 30 to 74 years old with type 2 diabetes and urinary albumin-to-creatinine ratio (UACR) 100–300 mg/g and serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women). Exclusion criteria included type 1 diabetes, age of diabetes onset <30 years, seated systolic blood pressure/diastolic blood pressure (SBP/DBP) ≥180/100 mmHg, and definable chronic kidney disease other than diabetic nephropathy. A total of 527 patients out of 1855 screened were randomized to telmisartan 80 or 40 mg, or placebo; the starting dose was 20 mg, titrated to 40 mg after 2 weeks or to 80 mg after a further 2 weeks. Minimum treatment period was 1 year each patient. Primary efficacy end point was the transition rate from incipient to overt nephropathy (UACR >300 mg/g and increase ≥30% from baseline at two consecutive 4-week visits). Secondary end point was microalbuminuria remission (UACR <30 mg/g). Frequency and severity of adverse events were also assessed. The Kaplan-Meier method was used to determine transition rates to overt nephropathy; log-rank test was used for pair-wise comparison between treatment groups. Effect of blood pressure reduction on transition rate was estimated using Cox’s proportional hazard model. The protocol conformed to the principles of the Declaration of Helsinki and was approved by the institutional review boards at the 142 study centers (7). Patients provided written, informed consent before enrollment.

RESULTS

Of the 527 randomized patients (mean age 61.7 years), 13 were excluded from primary analysis because of suspected type 1 diabetes or UACR measurements being missing during treatment. Mean duration of follow-up was 1.3 ± 0.5 years (maximum 2.3 years). Transition rates to overt nephropathy were telmisartan 80 mg (n = 168) 16.7%, telmisartan 40 mg (n = 172) 22.6%, and placebo (n = 174) 49.9% (both telmisartan doses versus placebo, P < 0.0001) (Fig. 1a). In addition, 163 normotensive patients were included in the study. Transition rates in normotensive patients were telmisartan 80 mg (n = 51) 11.0%, telmisartan 40 mg (n = 58) 21.0%, and placebo (n = 54) 44.2% (both telmisartan doses versus placebo, P < 0.01) (Fig. 1b). After adjustment for changes in SBP, telmisartan still decreased the transition rate to overt nephropathy. Telmisartan 80 and 40 mg reduced mean UACR at final observation by 58.8 and 37.9 mg/g, respectively, and placebo increased UACR by 40.9 mg/g (both telmisartan doses versus placebo, P < 0.0001). Microalbuminuria remission at final observation occurred in 21.2% with telmisartan 80 mg, 12.8% with telmisartan...
40 mg, and 1.2% with placebo (both telmisartan doses versus placebo, \( P < 0.001 \)). One or more adverse event was recorded in >90% of patients in each treatment group; most event were mild or moderate in intensity. Regarding the decrease of blood pressure, SBP/DBP fell from 138/78 mmHg to 128/72 mmHg with telmisartan 80 mg, from 137/78 mmHg to 128/72 mmHg with telmisartan 40 mg, and from 137/77 mmHg to 132/74 mmHg with placebo (each blood pressure change at 1 year from baseline \( P < 0.01 \)).

**CONCLUSIONS**

Patients with type 2 diabetes and microalbuminuria receiving telmisartan 80 or 40 mg achieved superior renoprotection, demonstrated by lower transition rates to overt nephropathy, compared with placebo. Achievement of microalbuminuria remission was superior with telmisartan 80 or 40 mg than with placebo. Remission is a key goal for renoprotection, as well as cardiovascular protection (8). Remission rates compare very favorably with those reported in Caucasian hypertensive patients with type 2 diabetes and microalbuminuria treated with irbesartan (3). Telmisartan also reduced transition to overt nephropathy in normotensive patients, suggesting telmisartan had a blood-pressure–independent effect. Further evidence for this is that differences in transition rates with respective treatments were maintained when adjustment was made for SBP reduction. The beneficial effects of telmisartan were dose-dependent.

Overall, telmisartan reduced transition from incipient to overt nephropathy, and induced remission of albuminuria in Japanese type 2 diabetic patients.
REFERENCES


Figure 1—Kaplan-Meier curves for transition from incipient to overt nephropathy in patients treated once daily with telmisartan 80 mg, telmisartan 40 mg, and placebo.

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