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Original article

Efficacy and safety of a 60-week treatment with candesartan in Japanese patients with mild to moderate chronic heart failure

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ABSTRACT

Background: Chronic heart failure (CHF) is an increasingly common cardiovascular disease despite recent advances in its diagnosis and management.
Methods and results: A multicenter, open-label study was designed to assess the efficacy and safety of 60-week treatment with candesartan in Japanese patients with mild to moderate CHF. Primary efficacy endpoints were changes from baseline in plasma brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), end-diastolic dimension, and New York Heart Association (NYHA) functional class. Two hundred and eighty-nine eligible patients were divided into 2 groups based on the daily dose at the end of treatment: high-dose (HD, 8 mg, $N = 170$) and low-dose (LD, 2 or 4 mg, $N = 119$). Neither plasma BNP levels nor LVEF changed from the baseline to the end of treatment in the LD group, whereas BNP significantly improved from 61.6 to 50.1 pg/mL ($p = 0.0005$) and LVEF from 57.2 to 60.1% ($p = 0.0005$) in the HD group. The changes in NYHA functional class were comparable between groups: 21.2% improved and 76.3% unchanged in the LD group and 20.6% improved and 79.4% unchanged in the HD group. No safety concerns were observed in either group.
Conclusions: HD candesartan was more effective in improving plasma BNP levels and cardiac function than LD in Japanese CHF patients. Both LD and HD candesartan were well tolerated in CHF patients.

Introduction

Chronic heart failure (CHF) is an increasingly common cardiovascular disease and is the major cause of morbidity and mortality throughout the world [1–3]. Patients with CHF are at high risk for death and hospitalization for worsening HF. In Japan, approximately 1–2 million adults have CHF and more than 180,000 patients die of heart diseases each year with a death rate of approximately 140 per 100,000 persons [4].

For the treatment of hypertension and HF, angiotensin-converting-enzyme (ACE) inhibitors have been widely used as first-line drugs [1,2]. Angiotensin II receptor blockers (ARBs) have emerged as an alternative for inhibiting the renin–angiotensin–aldosterone system by selectively blocking the angiotensin II type 1 receptor. Candesartan is an ARB having a long-acting antihypertensive effect due to its lower dissociation rate from the angiotensin type 1 receptor [5].

A randomized, double-blind, placebo-controlled Assessment of Response to Candesartan in HF in Japan (ARCH-J) study evaluating the efficacy and safety of 6-month treatment with candesartan 8 mg once daily in patients with congestive HF demonstrated that the incidence of confirmed progression of congestive HF was significantly lower in the candesartan group, especially in the subgroup of patients previously treated with ACE inhibitors, than in the placebo group (7.4% vs. 22.2%) with a risk reduction of 66.7% and a risk difference of −14.8% ($p < 0.001$) [6]. Based on these results, an additional indication for candesartan for the treatment of mild to moderate CHF in patients for whom treatment with ACE inhibitors is inappropriate was approved in Japan in 2005.

In order to collect and analyze data on the frequency and background factors of dose escalation/reduction in a clinical setting, we conducted a study to assess the efficacy and safety of 60-week treatment with candesartan in Japanese patients with mild to moderate CHF.

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Subjects and methods

Study design

The study design is shown in Fig. 1. This study was a multicenter, open-label study consisting of a 4-week run-in period and a 60-week treatment period. The starting dose of candesartan for the treatment of CHF was 4 mg once daily, which could be increased up to 8 mg once daily as needed. An alternative starting dose of 2 mg once daily was recommended for a period not exceeding 4 weeks for patients who had systolic blood pressure (SBP) of <120 mmHg, renal dysfunction, severe HF, or those given diuretics concomitantly. All patients received candesartan, starting at a dose of either 2 or 4 mg once daily, which was increased to 8 mg once daily by week 12 as tolerated and needed. Dose escalation/reduction was decided upon as needed during the treatment period. Patients visited the study sites every 2–4 weeks (every 4 weeks in principle) from week −4 to week 60. Throughout the study period, concomitant medication for HF was allowed except for ACE inhibitors and ARBs.

Study patients

Japanese outpatients with mild to moderate CHF who met the following inclusion criteria were enrolled: age ≥ 20 years; previously treated with ACE inhibitors regardless of duration; considered unsuitable by the investigators for treatment with ACE inhibitors; and New York Heart Association (NYHA) functional class II–III. The main exclusion criteria included: unstable angina; serious ventricular arrhythmia; serious valvular stenosis; hypertrophic obstructive cardiomyopathy; acute myocardial infarction within 4 weeks before the start of treatment; cerebrovascular disease, coronary-artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within 12 weeks before the start of treatment; CABG or PCI implemented or scheduled after the start of the study; cardiogenic shock or SBP < 80 mmHg; serious respiratory disease; renal artery stenosis; hyperkalemia; pregnant or nursing women or women suspected of being pregnant; or patients considered ineligible by the investigators.

The study was performed at 50 centers in Japan between June 2006 and July 2008 in accordance with the Declaration of Helsinki, the International Conference on Harmonization and the Harmonized Tripartite Guidelines on Good Clinical Practice (GCP), and was approved by the Institutional Review Board at each study site. All patients provided written informed consent.

Study protocol

NYHA functional class, vital signs, adverse events (AEs), and the medication adherence were examined every 4 weeks throughout the study period. Echocardiography, a resting 12-lead electrocardiogram (ECG), and other laboratory tests were performed and assessed every 12 weeks.

Study endpoints

The primary efficacy endpoints were the changes from baseline in plasma brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVDd), and NYHA functional class at the end of treatment, using last observation carried forward data analysis. Other efficacy measures included the changes from baseline in left ventricular end-systolic dimension (LVDs), 12-lead ECG findings, and body weight at the end of treatment. The following outcome measures were assessed: adverse drug reactions, cardiovascular events, death from cardiovascular events, hospitalization or death due to HF deterioration, nonfatal myocardial infarction, and addition or dose escalation of concomitant medications for HF (continuous oral medication over 2 weeks). Reasons for considering ACE inhibitor treatment inappropriate, and dose escalation/reduction or continuation of the same dose were also recorded.

Statistical analysis

To allow for possible withdrawals/discontinuations, we planned to enroll 300 patients in the clinical study. For the primary efficacy endpoints, the mean, standard deviation (SD), and the two-sided 95% confidence interval (CI) were calculated by applying a one-sample *t* test. The distributions of the data of changes in plasma BNP were highly skewed by outliers. Therefore, the geometric means and the two-sided 95% CIs were calculated by converting the means of log-transformed BNP values and the two-sided 95% CIs back to the original scale using back transformation for these indices. For these variables, a one-sample *t* test was performed by using log-transformed values. Eligible patients were divided into 2 groups based on the candesartan dose at the end of treatment: low-dose (LD, 2 or 4 mg) and high-dose (HD, 8 mg). To compare the 2 groups, analysis of covariance (ANCOVA) was performed using

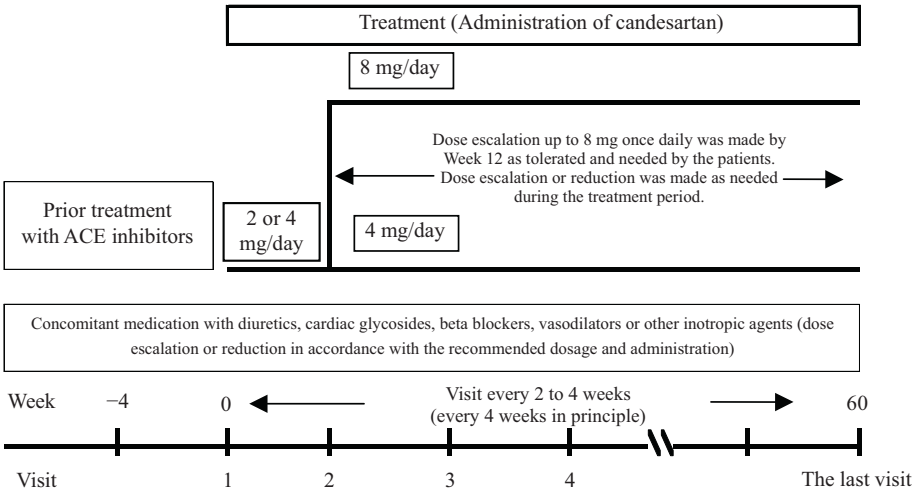

Fig. 1. Study design. ACE, angiotensin-converting enzyme.