Randomized Trial of Effect of Urate-Lowering Agent Febuxostat in Chronic Heart Failure Patients with Hyperuricemia (LEAF-CHF)

Study Design

Takashi Yokota,1 MD, Arata Fukushima,1 MD, Shintaro Kinugawa,1 MD, Takahiro Okumura,2 MD, Toyoaki Murohara,3 MD and Hiroyuki Tsutsui,3 MD

Summary

Hyperuricemia is an independent predictor of mortality in patients with chronic heart failure. The aim of the study is to determine whether a urate-lowering agent febuxostat, an inhibitor of xanthine oxidase, may improve the clinical outcomes in chronic heart failure patients with hyperuricemia when compared to conventional treatment. This multicenter, prospective, randomized, open-label, blinded endpoint study with a follow-up period of 24 weeks will enroll 200 Japanese chronic heart failure patients with hyperuricemia. The eligibility criteria include a diagnosis of chronic heart failure (New York Heart Association functional class II-III with a history of hospitalization due to worsening of heart failure within the last 2 years), reduced left ventricular systolic function (left ventricular ejection fraction < 40%) and increased plasma natriuretic peptide [plasma B-type natriuretic peptide (BNP) ≥ 100 pg/mL or N-terminal pro BNP (NT-proBNP) ≥ 400 pg/mL] and hyperuricemia (serum uric acid >7.0 mg/dL and ≥ 10 mg/dL) at the screening visit. The primary outcome is the difference in the plasma BNP levels between the baseline and 24 weeks of treatment. The plasma BNP levels are measured in the central laboratory in a blinded manner. This study investigates the efficacy and safety of febuxostat in chronic heart failure patients with hyperuricemia.

Key words: BNP, Oxidative stress, Xanthine oxidase inhibitor

Hyperuricemia is a common finding in patients with chronic heart failure (CHF) and is a known independent predictor of mortality and rehospitalization due to worsening heart failure (HF).2-4 The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) reported that 56% of CHF patients had hyperuricemia with a higher incidence of all-cause and cardiac death, and rehospitalization due to worsening HF.5,6 In addition, hyperuricemia is closely linked to the occurrence of atrial fibrillation, which can be a trigger of worsening HF.7 The mechanism by which hyperuricemia is associated with worse clinical outcomes in CHF patients may be explained by the detrimental effects of uric acid (UA) on the vascular endothelium through the activation of inflammatory cytokines.8 In patients with CHF, xanthine oxidase (XO) is highly activated, and increased reactive oxygen species (ROS) emission from XO in the vascular endothelium can cause endothelial dysfunction in the peripheral vessels, leading to increased cardiac afterload.9 UA is produced via XO and, thus, it can be a useful marker for systemic oxidative stress in patients with CHF. Emerging evidence has drawn more attention to the effects of XO inhibitors on clinical outcomes.

Previous studies have shown that allopurinol, a widely used XO inhibitor for patients with hyperuricemia, may be effective in the treatment of cardiovascular disease.10,11 High-dose allopurinol has been reported to reduce HF-related death in CHF patients.12 In addition, previous studies have shown that in patients with CHF, allopurinol decreases B-type natriuretic peptide (BNP) levels,13 which is known as a strong predictive biomarker of HF-related death.14 However, a randomized trial to investigate the effect of oxypurinol, a metabolite of allopurinol, in patients with CHF did not improve clinical outcomes,15 and a recent clinical trial using allopurinol also failed to improve clinical status, exercise capacity, quality of life, or cardiac function in hyperuricemic HF patients.16

Febuxostat, a novel urate-lowering agent for treatment against gout and hyperuricemia, inhibits XO via a different pathway from allopurinol. Febuxostat has demonstrated superiority to allopurinol in XO inhibition in vitro studies15,16 and lowering serum UA in clinical studies.17 Since febuxostat is finally eliminated via not only renal but also via hepatic pathways, it can be safely and
efficiently used even in patients with mild to moderate renal dysfunction. A randomized trial reported that febuxostat demonstrated superiority to allopurinol in reducing oxidative stress and in improving cardiac and renal function in patients with hyperuricemia who underwent cardiac surgery. Accordingly, febuxostat is expected to have a stronger inhibitory effect than allopurinol on XO.

The aim of the randomized LEAF-CHF (Effect of urate-Lowering Agent Febuxostat in Chronic Heart Failure patients with hyperuricemia) study is to determine whether febuxostat may improve morbidity and mortality in patients with HF with reduced ejection fraction (HFrEF) and hyperuricemia. BNP levels are evaluated as a primary endpoint of this study, with a follow-up period of 24 weeks to assess the efficacy of febuxostat in CHF patients. All the subjects receive the general lifestyle guidance for hyperuricemia recommended by the Japanese Society of Gout and Nucleic Acid Metabolism throughout the study period.

Methods

Study design: LEAF-CHF is a multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) study that investigates whether the urate-lowering agent, febuxostat, reduces plasma BNP levels in CHF patients with hyperuricemia. This study is approved by the institutional ethics committee at each participating site and is conducted in accordance with the ethical principles described in the Declaration of Helsinki (2013 revised version). Written informed consent is provided by all the enrolled patients prior to any study-related procedures. The study has been registered at the University Hospital Medical Information Network (UMIN ID: 000013330).

Patient population: The inclusion and exclusion criteria are listed in the Table. We enroll a total of 200 ambulatory or admitted HF patients with hyperuricemia, who do not meet any exclusion criteria. Briefly, eligible patients have New York Heart Association (NYHA) functional class II or III and left ventricular ejection fraction (LVEF) < 40% with elevated plasma BNP and hyperuricemia (serum UA levels > 7.0 mg/dL and ≤ 10.0 mg/dL). The LVEF is calculated from the apical four- and two-chamber views based on the modified Simpson’s method by echocardiography.

Randomization: After providing written informed consent, eligible patients are randomly assigned to the febuxostat group or the control group in a 1:1 ratio through a Web-based randomization system. Patient allocation is performed by the minimization method according to the following baseline variables: age, serum UA, plasma BNP or NT-proBNP, and LVEF. Since eligible participants have asymptomatic hyperuricemia as shown by the serum UA levels > 7.0 mg/dL and ≤ 10.0 mg/dL, all the subjects are provided lifestyle guidance aimed at decreasing the UA levels.

In the febuxostat group, the investigators prescribe the febuxostat preparation (Feburic tablets, Teijin Pharma, Tokyo, Japan) per the dosage schedule listed in the protocol (Figure 1), and the control group is also followed. The data on the dosing condition in the febuxostat group and concomitant therapies in both groups are followed from the time of enrollment until the completion of the study or withdrawal from the study.

Study protocol: Figure 1 and Figure 2 summarize the study schema and the visit schedule. The duration of the study is 24 weeks, which includes a 12-week titration phase of stepwise dose increases and a 12-week dose-maintenance phase, defined by the previous finding of the BNP-lowering effect of allopurinol at 12 weeks. Prelimi-
nary screening for trial eligibility is based on clinical information from a review of medical records by investigators at or before the baseline visit. The initial dose of febuxostat is 10 mg/day.

The dose is up-titrated to 20 mg/day at the 4-week visit, then, increased to 40 mg/day at the 8-week visit to reach the target dose of 60 mg/day at 12 weeks, unless the serum UA < 2.0 mg/dL. The target dose of 60 mg/day is maintained until the end of the study (24 weeks) after randomization. If the serum UA is < 2.0 mg/dL, the dosage is reduced by 20 mg from the previous dose. The target dose of 60 mg was determined to exert the maximum inhibitory effect of febuxostat on UA levels and ROS emission via the potent suppression of XO.

Patient demographic data such as age, gender, height and body weight, etiology of HF, and medical history are recorded at the baseline in all the patients. Signs and symptoms of HF, NYHA functional class, systolic and diastolic blood pressure, and heart rate are monitored at the baseline and every 4 weeks. Chest X-ray and echocardiography are performed at the baseline and at 24 weeks. To ensure objectivity, the plasma BNP levels are measured at a central laboratory under blind conditions at the baseline and every 4 weeks. Plasma oxidized low-density lipoprotein cholesterol (ox-LDL), serum high-sensitivity C-reactive protein (hs-CRP), and urinary 8-isoprostanes and 8-hydroxydeoxyguanosine (8-OHdG) are all measured in a central laboratory at the baseline and at 24 weeks. In addition, the following blood examinations are measured at the baseline and every 4 weeks: hemoglobin (Hb), serum UA, and serum creatinine. The estimated glomerular filtration rate (eGFR) is calculated from serum creatinine value and age using the Japanese equation as follows: 

\[ eGFR = 194 \times (\text{serum creatinine in mg/dL}) - 1.094 \times (\text{age in years}) - 0.287 \times (0.739 \text{ if female}) \]

**Study endpoints:** The primary endpoint is the change in plasma BNP concentration from the baseline to 24 weeks. Plasma BNP is an established surrogate marker that strongly predicts death and cardiovascular events in HF patients,\(^{21,22}\) and previous studies have shown the reducing effect of allopurinol on plasma BNP concentration.\(^{21,22}\) For between-group comparison of the change in log-transformed BNP levels, the analysis of covariance will be performed using the baseline BNP levels as the covariate. The secondary endpoints include: (1) LV EF and E/e', the ratio of peak early transmural ventricular filling velocity to early diastolic tissue Doppler velocity, measured at the baseline and at 24 weeks; (2) NYHA functional class, eGFR, serum UA, Hb, and the plasma BNP concentration during the study period; and (3) all-cause mortality or major cardiovascular events.

The independent Endpoint Evaluation Committee will centrally review the events reported by the investigators per the event adjudication criteria in a blinded manner. The exploratory endpoint is to determine the effect of febuxostat on the following: (1) markers of inflammatory activation (hs-CRP), (2) oxidative stress (ox-LDL, 8 isoprostanes, and 8-OHdG), and (3) renal function (ratio of urine albumin and creatinine).

**Sample size calculation:** The sample size of the present study is assumed on the basis of a previous study by Gavin, et al.\(^{11}\) In that randomized, double-blinded, placebo-controlled trial, 50 patients with CHF were randomly assigned to 3 months of treatment with allopurinol (300 mg/
day) or placebo. The BNP levels in the allopurinol group were 14.5 pmol/L (51 pg/mL) before treatment and 11.9 pmol/L (42 pg/mL) after treatment, whereas those in the placebo group were unaltered. Based on those results, it is presumed that the difference in the change in log-transformed BNP levels is 0.2 and that the standard deviation is twice as large as the change in log-transformed BNP levels.

To detect the between-group difference by analyzing covariance under conditions of two-sided $\alpha = 0.05$, $\beta = 0.9$, and allocation ratio = 1.0, the sample sizes of the needed patient populations were calculated to be 86 for HF and 86 for controls. Estimating a 15% loss due to withdrawals and dropouts, we set the target population size as 100 patients in each group (total 200 patients).

**Efficacy endpoints will be analyzed primarily by using the full analysis set (FAS), which includes all the enrolled and randomized subjects, and eliminating subjects who do not respond to treatment after enrollment.** The per-protocol set (PPS) of patients meeting all the inclusion and exclusion criteria will be also analyzed for reference. Safety endpoints will be evaluated using the safety analysis population, which comprises all the enrolled and randomized patients.

As a primary analysis, the summary statistics of the BNP levels at the baseline and at 24 weeks, as well as the ratio of the BNP levels at the baseline to the levels at 24 weeks, will be calculated for each treatment group. For the between-group comparison of the change in the log-transformed BNP levels from the baseline to 24 weeks, analysis of covariance will be performed using dummy variables that represent the treatment groups, as well as the log-transformed BNP levels at the baseline as the covariates. If the study is terminated before 24 weeks, the BNP levels at the termination of the study will be used instead of those at 24 weeks in the primary analysis. In addition, the paired $t$-test will be conducted to compare the change in the log-transformed BNP levels from the baseline to 24 weeks in each treatment group.

As a secondary analysis, the paired $t$-test will be performed to compare the LVEF, E/E', serum UA, eGFR, hemoglobin, and each exploratory endpoint from the baseline to 24 weeks or study termination. The analysis of covariance will be performed for the comparison of the between-group change in those variables from the baseline to 24 weeks. The changes of the NYHA class from the baseline to 24 weeks will be analyzed within groups by the Wilcoxon signed-rank test and are compared among groups by the Wilcoxon rank-sum test. Furthermore, the Kaplan-Meier method will be used to estimate the event rate throughout 24 weeks for each treatment group, and the log-rank test will be used to compare those event rates.

The differences are considered statistically significant when $P < 0.05$. The same analysis will be performed using PPS to confirm the robustness of the results. An interim analysis is not scheduled during the study.

**Role of the sponsor and the authors:** The LEAF-CHF study is being supported by the sponsor (Teijin Pharma Ltd., Tokyo, Japan), which will not participate in the data collection, the event evaluation, and the data analysis. The study was designed by the authors in collaboration with the sponsor and the contract research organization (CRO; Hubitgenomix Co., Tokyo, Japan). The study is conducted by the LEAF-CHF investigators with the assistance with the CRO. The first draft of the manuscript was written by Go Ichien (Hubitgenomix Co.), and was fully reviewed and revised by all the authors. The authors had final re-
sponsibility for the decision to submit for publication.

Discussion

The LEAF-CHF study is designed to test the hypothesis that the inhibition of XO by febuxostat, when added to optimal HF therapy, may be beneficial clinically in patients with HFrEF. It will not compare the efficacy of febuxostat with that of allopurinol, although febuxostat is expected to exert a stronger effect of XO inhibition than allopurinol, based on the previous studies.15-18 It compares the changes in the plasma BNP levels as well as clinical outcomes between the febuxostat group and the control group in patients with HFrEF.

The total study period for the LEAF-CHF is 24 weeks; the patients assigned to the active treatment group will receive febuxostat 60 mg/day as a target dose for 12 weeks after titration, with stepwise dose increases for 12 weeks. A previous study revealed a significant decrease in the BNP levels after allopurinol treatment for 12 weeks in patients with CHF.11 In addition, the administration of 60 mg/day of febuxostat for 6 months, including the dose-escalation period, has been reported to lower serum UA significantly more than allopurinol 300 mg/day and to have a superior inhibitory effect on oxidative stress in patients with hyperuricemia who underwent cardiac surgery.11 Taken together, the study period and the target dose in the present trial appears to be sufficient to evaluate the efficacy of febuxostat in CHF patients.

For this study, the range of serum UA in the inclusion criteria is > 7.0 mg/dL to ≤ 10 mg/dL. Although no universally accepted definition of hyperuricemia exists, we employed the definition of hyperuricemia as serum UA > 7.0 mg/dL, based on the Guideline for the Management of Hyperuricemia and Gout 2010 of the Japanese Society of Gout and Nucleic Acid Metabolism.19 While the guideline recommends the initiation of pharmacotherapy at a serum concentration of UA ≥ 9.0 mg/dL in patients with asymptomatic hyperuricemia,19 and in particular, the risk of gout increases at a serum concentration of UA ≥ 10.0 mg/dL. Thus, patients allocated to the control group will be withdrawn from the study and subsequently receive appropriate therapy if their serum UA levels increase and exceed 10.0 mg/dL during the study period.

We determined the primary endpoint of this study as the difference in plasma BNP levels between the baseline and 24 weeks of treatment, since the absolute value of plasma BNP is influenced by the left ventricular hypertrophy and renal dysfunction. BNP is widely used as a clinically relevant diagnostic and predictive marker for HF and is a powerful predictor of short- and long-term prognosis and rehospitalization due to worsening HF in CHF patients.11,23 A meta-analysis of studies in patients with CHF has shown that each 100 pg/mL rise in BNP levels is associated with a 35% increase in the relative risk of death.20 To ensure objectivity, the BNP levels will be measured in a central laboratory in a blinded manner.

Secondary endpoints include all-cause death, cardiovascular events, including cardiovascular death, rehospitalization due to worsening HF, NYHA class, LVEF, E/e', absolute values of plasma BNP, eGFR, hemoglobin (Hb), and serum UA. As a parameter of left ventricular (LV) function, E/e' will be measured to assess LV diastolic function and LVEF will be used to assess LV systolic function. Previous studies have shown that elevated serum UA inversely correlates with the LV diastolic function.21 In the LEAF-CHF study, we will evaluate eGFR and Hb because the JCARE-CARD has reported that chronic kidney disease and anemia are powerful and independent prognostic factors in CHF patients.22,23

Plasma ox-LDL, and urinary 8-isoprostanes and 8-OHdG will be measured at the baseline and at 24 weeks of treatment to assess the inhibitory effect of febuxostat on systemic oxidative stress in CHF patients. Growing evidence suggests that oxidative stress is a key to the pathogenesis and development of HF.23 In addition, serum UA levels are not necessarily associated with the cardiac function and the severity of HF.24 Our hypothesis is that febuxostat treatment may improve clinical outcomes via reduced ROS emission originating from XO rather than lowered serum UA. In accordance with this hypothesis, the dosage of febuxostat is increased stepwise up to 60 mg/day even after serum UA level reaches 7.0 mg/dL or less (except for < 2.0 mg/dL). In previous studies, febuxostat was administered targeting serum UA ≤ 6.0 mg/dL.17,18 Until now, there is no report of the harmful effect of febuxostat in a concentration-dependent manner.

LEAF-CHF Study has already begun enrollment in August 2014. The enrollment of patients will be completed in December 2017 and the follow-up of the enrolled patients will be finished in June 2018. This study may provide evidence for a novel therapeutic approach to CHF patients targeting the reduction of not only the serum UA levels but also XO-induced ROS emission.

Acknowledgments

The authors thank all the enrolled patients, participating cardiologists and other medical professionals who contributed substantially to this cooperative study.

Disclosures

Conflicts of interest: T.Y., A.F., and S.K. have no conflict of interest that should be declared. T.O has received research grants from Ono Pharmaceutical, Bayer Yakuhin, and Daiichi-Sankyo; scholarship funds from Mitsubishi Tanabe Pharma. T.M. has received speakers’ bureau/honorarium from Teijin Pharma and Pfizer Japan; scholarship funds from Teijin Pharma and Pfizer Japan. H.T. has received speakers’ bureau/honorarium from Astellas Pharma, Otsuka Pharmaceutical, Takeda Pharmaceutical, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Teijin Pharma, Nippon Boehringer Ingelheim, Novartis Pharma K.K, Bayer Yakuhin, and Bristol-Myers Squibb; honorarium for writing promotional material for Medical Review; research grants from Actelion Pharmaceuticals Japan; scholarship funds from Astellas Pharma and Daiichi-Sankyo.
Appendix

Study organization: The study is managed by the principal investigator (Hiroyuki Tsutsui) and the Steering Committee as an investigator-initiated clinical study. The Independent Data Monitoring Committee and the Event Evaluation Committee are organized independently from the study group. A study statistician (Koji Oba, Tokyo University) contributes to ensure statistical accuracy.

Steering committee: Hiroyuki Tsutsui (chair, Kyusyu University), Toyoaki Murohara (vice chair, Nagoya University Graduate School of Medicine), Mitsuaki Isobe (Sakakibara Heart Institute), Hiroshi Itó (Okayama University), Takayuki Inomata (Kitasato University Kitasato Institute Hospital), Koichiro Kinugawa (Internal Medicine, University of Toyama), Issei Komuro (The University of Tokyo Hospital), Yoshiniko Saito (Nara Medical University), Yasushi Sakata (Osaka University Graduate School of Medicine), Yasuhiko Sakata (Tohoku University Graduate School of Medicine), Hiroaki Shimonawa (Tohoku University Graduate School of Medicine), Ichiro Hisatome (Graduate School of Medical Science, Tottori University), Satoru Masuyama (Hyogo College of Medicine), Shinichi Momomura (Jichi Medical University Saitama Medical Center), Masafumi Yano (Yamaguchi University Graduate School of Medicine), Kazuhiko Yamamoto (Tottori University Faculty of Medicine), and Michihiro Yoshimura (The Jikei University School of Medicine).

Independent data monitoring committee: Hitonobu Tonomiike (chair, Sakakibara Heart Institute), Yutaka Kiyohara (Asahikawa Medical University) (Kurume University Medical Center), and Naoyuki Hasebe (Asahikawa Medical University)

Research institute: Kyusyu University Hospital, Hokkaido University Hospital, Nagoya University Hospital, Tokyo Medical and Dental University, Okayama University Hospital, Kitasato University Hospital, The University of Tokyo Hospital, Nara Medical University Hospital, Osaka University Hospital, Tohoku University Hospital, Hyogo College of Medicine, Jichi Medical University Saitama Medical Center, Yamaguchi University Hospital, Tottori University Hospital, The Jikei University School of Medicine, Sapporo Medical University Hospital, Heart sounds Mori Clinic, Tosei General Hospital, Nishio Municipal Hospital, Osaka General Medical Center, Sakurabashi Watanabe Hospital, National Cerebral and Cardiovascular Center, Sakakibara Heart Institute, Toranomon Hospital, St. Marianna University School of Medicine, Nagoya City University Hospital, Hiroshima University, Osaka Medical College Hospital, Medical Corporation JR Hiroshima Hospital, Masao Fujii Memorial Hospital, Hiroshima Prefectural Hospital, Otaru Kyokai Hospital, Showa University Hospital, Sapporo City General Hospital, Tokuyama Central Hospital, Graduate School of Medicine, and Faculty of Medicine Kyoto University, Saiseikai Yamaguchi hospital, and Yamaguchi Prefectural Grand Medical Center.

References