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Original article

Rationale, design, and baseline characteristics of a study to evaluate the effect of febuxostat in preventing cerebral, cardiovascular, and renal events in patients with hyperuricemia

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ABSTRACT

Background: Since uric acid is associated with cardiovascular and renal disease, a treatment to maintain blood uric acid level may be required in patients with hyperuricemia. This study aims to evaluate preventive effects of febuxostat, a selective xanthine oxidase inhibitor, on cerebral, cardiovascular, and renal events in patients with hyperuricemia compared to conventional treatment.
Methods and results: This study is a prospective randomized open-label blinded endpoint study. Patient enrolment was started in November 2013 and was completed in October 2014. The patients will be followed for at least 3 years. The primary endpoint is a composite of cerebral, cardiovascular, and renal events, and all deaths including death due to cerebral, cardiovascular, and renal disease, new or recurring cerebrovascular disease, new or recurring non-fatal coronary artery disease, cardiac failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, new atrial fibrillation, and all deaths other than cerebral or cardiovascular or renal disease. These events will be independently

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evaluated by the Event Assessment Committee under blinded information regarding the treatment group. The study was registered at ClinicalTrials.gov with the identifier NCT01984749.
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Introduction

Hyperuricemia may be viewed as a clinically important risk factor for various cardiovascular diseases. Hyperuricemia has been paid attention to since the close association between hyperuricemia and coronary artery disease and hypertension was demonstrated in 1965 [1–6]. Similarly, in Japan, a report by Tomita et al. documented hyperuricemia as being associated with a significantly higher incidence in such conditions as cardiac disease, cerebrovascular disease, and renal failure [7]. The association between serum uric acid and the onset of cardiovascular events has also been reported in numerous epidemiological studies conducted in individuals with lifestyle-related diseases, such as hypertension, diabetes mellitus, and dyslipidemia, or high-risk patients with ischemic heart disease, renal impairment, or other risk factors [8,9]. Furthermore, a recent study suggested that hyperuricemia may be a major determinant of increased cardiovascular risk among high-risk hypertensive patients [10]. Results of a meta-analysis also showed that hyperuricemia was significantly associated with stroke and mortality [11]. Among patients who experienced acute myocardial infarction (AMI), subsequent high serum uric acid concentrations were suggested to be related to progression of cardiac failure, and uric acid level was shown to be a suitable marker for predicting future adverse events after AMI [12]. High serum uric acid concentrations in hyperuricemic patients are hypothesized to cause vascular endothelial dysfunction, resulting in complications of cardiac dysfunction [13]. Therefore, hyperuricemia may be a risk factor for cerebral, cardiovascular, and renal diseases, and the significance of aggressive uric acid lowering is widely noted [14].

Febuxostat is a novel urate-lowering agent approved in January 2011 in Japan for the treatment of gout and hyperuricemia. The compound inhibits xanthine oxidase (XO) through a different mechanism from allopurinol, which is a drug that blocks uric acid production. Febuxostat has been shown in vitro to be superior in inhibiting the production of XO-derived reactive oxygen species compared with allopurinol [15,16]. Clinical data also demonstrated more potent serum uric acid lowering effects with febuxostat compared with allopurinol [17]. Because of elimination via both hepatic and renal pathways, febuxostat has been shown to be efficacious and safe even in patients with mild to moderate renal impairment [18]. A randomized controlled study in hyperuricemic patients who underwent cardiac surgery reported that febuxostat significantly improved renal function, oxidative stress, and cardiac function compared with allopurinol [19,20]. Based on these results, febuxostat is expected to exert more potent XO-inhibitory effects than allopurinol.

Despite the increasing recognition of the need to treat hyperuricemia, data have been limited on the beneficial effect of treating hyperuricemia on the occurrence of cerebral or cardiorenovascular events. We, therefore, planned to conduct a clinical study as the FREED (Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy). This study aims to evaluate the effect of febuxostat on preventing cerebral or cardiorenovascular events in elderly patients with hyperuricemia at risk for cerebral or cardiorenovascular disease compared to conventional therapy.

Methods

Study design

This study is a multicenter, prospective, randomized, open-label, blinded endpoint (PROBE), two-arm parallel treatment groups study. This study is conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. The institutional review board at each participating hospital approved this trial. This study was registered at ClinicalTrials.gov with the identification number NCT01984749.

Patient screening and enrollment

The eligible patients invited must fulfill all of the inclusion criteria and must not meet any of the exclusion criteria to be enrolled in this study (Tables 1 and 2). The investigators identified candidate patients on the basis of clinical information from routine medical care. The investigators recorded all potential candidate patients presumed to be eligible for this study, and provided candidate patients with explanations about study objectives, study protocol, possible adverse reactions of the study drugs, privacy protection method, and study withdrawal. All patients for the study provided their written informed consent to the study investigators after receiving explanations. The investigators also determined the eligibility of individual patients who provided consent to participate in this study. For enrollment of each patient, the investigators completed the "Enrollment Form" with all necessary data on the basis of screening results, using an electronic data capture (EDC) system for clinical studies or fax.

Patient enrollment was started on November 1, 2013 and was completed on October 31, 2014. The study period starts from the time of enrollment to the time of either completion (i.e. 36 months after enrollment) or withdrawal from the study.

Randomization

Randomization of the patient to a study treatment group occurred after a patient was registered. Patients were randomized to either the febuxostat or non-febuxostat group at a 1:1 ratio by a

Table 1
Inclusion criteria.

(1) Ambulatory patients aged 65 years or older at the time of enrollment.
(2) Patients with hyperuricemia as shown by serum uric acid >7.0 mg/dL and ≤9.0 mg/dL within 2 months prior to enrollment.
(3) Patients at risk for cerebral or cardiorenovascular disease as defined by the presence of any of the following (1) to (4):
(1) Prior history of or active hypertension.
(2) Prior history of or active type 2 diabetes mellitus.
(3) Renal disorder (as shown by eGFR ≥30 to <60 mL/min/1.73 m^2 within 3 months prior to enrollment).
(4) Prior history of cerebrocardiovascular disease occurring >3 months prior to enrollment (i.e., stroke [cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage], coronary artery disease, vascular disease, or cardiac failure).
(4) Patients who provided written informed consent in person to participate in this study.

eGFR, estimated glomerular filtration rate.

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