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Original article

Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD)

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ABSTRACT

Background: The NU-FLASH trial demonstrated that febuxostat was more effective for hyperuricemia than allopurinol. This time, we compared these medications in patients with chronic kidney disease (CKD) from the NU-FLASH trial.

Methods and results: In the NU-FLASH trial, 141 cardiac surgery patients with hyperuricemia were randomized to a febuxostat group or an allopurinol group. This study analyzed 109 patients with an estimated glomerular filtration rate (eGFR) $\leq$60 mL/min/1.73 m^2, and also analyzed 87 patients with stage 3 CKD. The primary endpoint was the serum uric acid level. Secondary endpoints included serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein, eicosapentaenoic acid/arachidonic acid ratio, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and high-sensitivity C-reactive protein.

Among patients with an eGFR $\leq$ 60 mL/min/1.73 m^2, uric acid levels were significantly lower in the febuxostat group than the allopurinol group from 1 month of treatment onward. The serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein, eicosapentaenoic acid/arachidonic acid ratio, and high-sensitivity C-reactive protein were also significantly lower in the febuxostat group. Similar results were obtained in the patients with stage 3 CKD.

Conclusion: In cardiac surgery patients with renal dysfunction, febuxostat reduced uric acid earlier than allopurinol, had a stronger renoprotective effect than allopurinol, and also had superior antioxidant and anti-inflammatory effects.

Introduction

While the short-term results of cardiac surgery are generally good [1], appropriate treatment for frequent complications such as diabetes, hypertension, hyperlipidemia, chronic kidney disease (CKD), and hyperuricemia is necessary to obtain a favorable remote outcome. Among these complications, hyperuricemia is reported to be associated with the onset and progression of CKD [2]. There has been an increasing number of reports about the association between hyperuricemia and other lifestyle-related diseases such as hypertension, hyperlipidemia, arteriosclerosis, obesity, and CKD [3,4]. Allopurinol has long been regarded as a first-line drug for the treatment of hyperuricemia. However, adverse reactions such as renal dysfunction, hepatic dysfunction, Stevens-Johnson syndrome, and hypersensitivity vasculitis have been reported with allopurinol, and its efficacy is insufficient in some cases [5,6]. In addition, the dose that can be administered is limited in CKD patients.

Febuxostat was developed in Japan for the treatment of hyperuricemia. It became available in the USA from 2009, Europe from 2010, and Japan from 2011. A potent uric acid-lowering effect of this drug has been reported [7]. We previously conducted a comparative study of febuxostat and allopurinol (the Nihon University working group study of Febuxostat and usuaL

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Allopurinol therapy for patientS with Hyperuricemia: NU-FLASH study), and reported that "In addition to reducing uric acid (UA) to a significantly lower level than allopurinol, febuxostat showed a renoprotective effect, inhibited oxidative stress, displayed anti-atherogenic activity, had an antihypertensive effect, and prevented vascular endothelial damage in cardiac surgery patients with hyperuricemia" [8]. However, that study did not compare the two drugs in patients with CKD, so we analyzed the CKD patients from the NU-FLASH trial in the present study.

Methods

Study protocol

The subjects were patients with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 before treatment from among the patients enrolled in the previous NU-FLASH trial (University Hospital Medical Information Network study ID: UMIN000005964) that compared febuxostat (Teijin Pharma Ltd., Tokyo, Japan) with allopurinol (GlaxoSmithKline K.K., Tokyo, Japan) for hyperuricemia.

Endpoints: The primary endpoint was the serum UA level after treatment. The secondary endpoints were as follows: serum creatinine (s-Cr), eGFR, urinary albumin, cystatin-C, oxidized low-density lipoprotein (O-LDL), eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio, total cholesterol (T-cho), triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), high-sensitivity C-reactive protein (hs-CRP), and adverse reactions.

UA, s-Cr, T-cho, TG, LDL, and HDL were measured before the start of treatment as well as after 1, 3, and 6 months of treatment, while urinary albumin, cystatin-C, O-LDL, and the EPA/AA ratio were measured before treatment and after 3 and 6 months of treatment. Adverse reactions were classified as acute attacks of gout, skin reactions, renal dysfunction (increase of s-Cr by ≥50%), hepatic dysfunction (increase of aspartate aminotransferase/alanine aminotransferase by ≥50%), gastrointestinal symptoms, and allergic reactions. The target serum uric acid level was ≤6.0 mg/dL, and the dose of each test drug was increased up to a maximum of 60 mg/day for febuxostat or 300 mg/day for allopurinol. In patients with an eGFR ≤ 30 mL/min/1.73 m^2, the maximum daily dose was 40 mg for febuxostat and 200 mg for allopurinol. eGFR was calculated according to the methods proposed for Japanese persons by the Japanese Society of Nephrology (men: $194 \times sCr^{-1.094} \times age^{-0.287}$, women: $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$) [9].

Statistical analysis

For parametric data, results were expressed as the mean ± standard error of the mean (SEM). For time-course analysis, repeated measures ANOVA with Fisher's protected least squares difference test was used. Comparisons between the febuxostat group and the allopurinol group were done with the *t*-test. In all analyses, $p < 0.05$ was considered statistically significant.

Results

Out of the 141 patients enrolled in the NU-FLASH study, 109 patients had an eGFR ≤ 60 mL/min/1.73 m^2 and 87 patients had stage 3 CKD (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. None of the subjects was taking losartan, which has been reported to reduce uric acid levels [10]. All patients were stable with no changes in oral medications and dietary therapy at 1 year or more after cardiac surgery, and none of them commenced a new diet and/or exercise regimen.

Patients with an eGFR ≤ 60 mL/min/1.73 m^2

Primary endpoint

UA (Fig. 2): There was no significant difference in UA between the 2 groups before the start of treatment (8.73 ± 0.90 mg/dL in the febuxostat group vs. 8.63 ± 1.00 mg/dL in the allopurinol group,

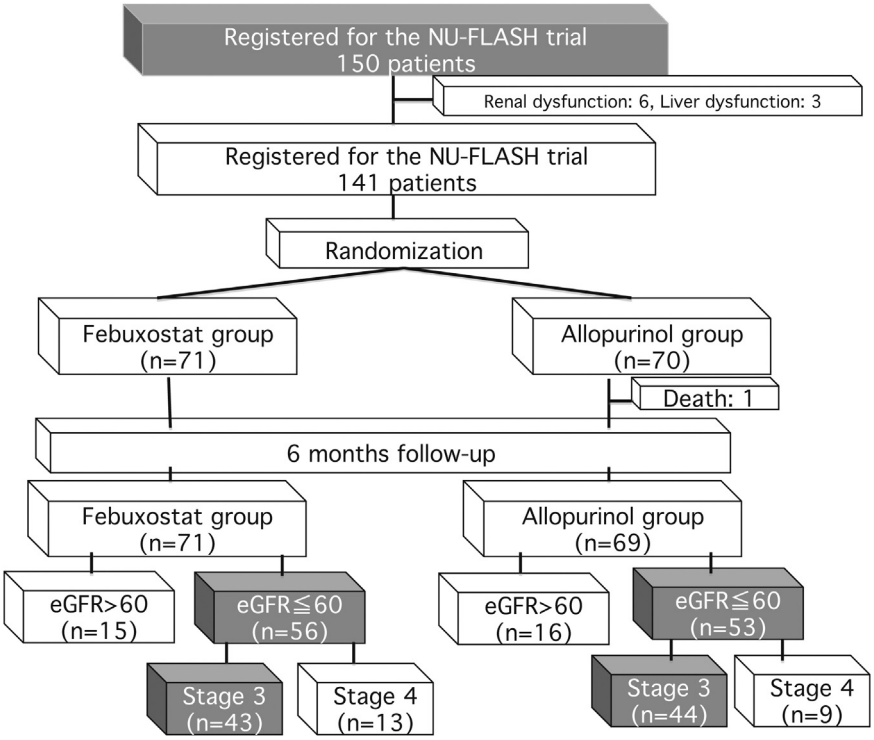

Fig. 1. Study population. NU-FLASH, Nihon University working group study of Febuxostat and usuaL Allopurinol therapy for patientS with Hyperuricemia; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2).