The Urate-lowering Efficacy and Safety of Febuxostat in Korean Patients with Gout

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Objective. To compare the urate-lowering efficacy and the safety of febuxostat, allopurinol and placebo in Korean patients with gout for 4 weeks.

Methods. Subjects (n=182) with gout were randomized to febuxostat (40, 80, 120 mg), allopurinol 300 mg, or placebo group. The primary end point was the proportion of subjects whose serum urate concentration fell to less than 6.0 mg/dL after the 4-week treatment.

Results. The primary end point was reached at 25.7%, 80.0% and 83.3% of patients receiving 40, 80 and 120 mg of febuxostat, respectively, 58.3% of those receiving 300 mg of allopurinol and none of the placebo (p<0.001: each febuxostat dose or allopurinol group versus placebo group, p=0.0484 and p=0.0196: febuxostat 80 and 120 mg compared with allopurinol, respectively). The number and proportion of subjects who developed adverse events (AEs) were 13 subjects (37%), 14 (39%) and 18 (50%) in the febuxostat of 40, 80 and 120 mg group, respectively, 21 (57%) in the allopurinol 300 mg group and 17 (46%) in the placebo group. No statistically significant differences in the incidence rates of adverse events were observed between the groups. There was no significant difference in gout flare-up incidence.

Conclusion. Febuxostat, 80 mg or 120 mg, was more effective than allopurinol (300 mg) or placebo, when lowering the serum urate. The safety of febuxostat and allopurinol was comparable.

Key Words. Gout, Febuxostat, Urate-lowering efficacy, Korean patients

Introduction

Febuxostat is a new uric acid synthesis inhibitor. It is a 2-arylthiazole derivative, which was chemically engineered, as a novel xanthine oxidase/xanthine dehydrogenase (XO) inhibitor. Febuxostat is being used for the management of hyperuricemia in patients with gout (1-3), and is already approved for marketing in major countries including EU, USA and Japan.

For over 30 years, allopurinol is the only uric acid synthesis inhibitor that is being used for hyperuricemia and gout. Uric acid is the last product of purine metabolism, by a process catalyzed by XO, through which, subsequent intermediate products are generated from hypoxanthine to xanthine, and finally to uric acid. Allopurinol, whose chemical structure is similar to that of purine, acts as an inhibitor of xanthine oxidase. Oxipurinol, a major metabolite of allopurinol, also inhibits other enzymes in the process of purine metabolism (4,5). Oxipurinol is mainly ex-
creted via the urine and its excretion is delayed in patient with renal dysfunction. Continued high serum level of oxipurinol in patients with renal problems is worrisome (5). Febuxostat is a new uric acid synthesis inhibitor, which has a totally different chemical structure from that of allopurinol. It selectively inhibits XO, without acting on the other major enzymes that are related to purine metabolism. It has been confirmed to be a potent selective xanthine oxidase/xanthine dehydrogenase (XO) inhibitor in vitro and have strong effects on lowering the serum and urinary uric acid concentrations in animals, such as rats and chimpanzees (6,7). Several randomized controlled clinical trials (RCTs) have shown febuxostat’s (in daily doses from 80 to 240 mg) superiority in urate-lowering efficacy, when compared to that of placebo or allopurinol at 300 mg daily. Moreover, febuxostat was more efficacious than allopurinol and was equally safe for subjects with hyperuricemia and gout complicated by mild and moderate renal impairment (8-11). The small number of severe cardiovascular (CV) AEs, was encountered in febuxostat/allopurinol comparative RCTs. However safety of febuxostat and allopurinol, including CV safety, was comparable at doses of 40 mg or 80 mg of febuxostat (8).

In a phase II study involving gout patients, the proportion of subjects achieving a serum urate concentration of <6.0 mg/dL, after 4 weeks of treatment, with febuxostat 40 mg QD, febuxostat 80 mg QD and febuxostat 120 mg QD were 56%, 76% and 94%, respectively (12). The mean serum uric acid reduction from baseline at day 28 was 2% in the placebo group, 37% in the 40 mg febuxostat group, 44% in the 80 mg febuxostat group and 59% in the 120 mg febuxostat group. The difference in urate level reduction was statistically significant between the placebo group and each of the febuxostat treatment groups (febuxostat 40 mg, 80 mg and 120 mg). These previous results suggested that a 4-week trial is acceptable in demonstrating the urate lowering efficacy of febuxostat.

This was a randomized, multi-centered, double-blinded, allopurinol-controlled, placebo-controlled study, which is undertaken to evaluate the urate-lowering effect of febuxostat in the Korean population with hyperuricemia and gout.

Materials and Methods

Study population

Subjects with the age of 18 to 85 years, with a diagnosis of gout (based on the preliminary criteria of the American College of Rheumatology for acute arthritis of gout (13)) were enrolled in the study. Serum uric acid of ≥8.0 mg/dL and serum creatinine of ≤1.5 mg/dL were eligible for the study.

Exclusion criteria included; subjects with hypersensitivity to allopurinol, thiazide diuretic therapy, aspirin >325 mg/day, prednisolone >10 mg/day, alcohol intake ≥14 drinks/week, other urate-lowering therapy, and hepatic dysfunction (both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >1.5 times the upper limit of normal).

Study method

This study was conducted at 10 centers in Korea and was approved from the institutional review boards of each respective institution based on the Declaration of Helsinki. All subjects gave written informed consent.

Subjects that passed the screening evaluation were then randomly assigned to one of the five treatment regimens; febuxostat 40 mg, 80 mg, 120 mg, placebo or allopurinol 300 mg QD based on their serum urate level at baseline (1) ≥8 mg/dL, <9 mg/dL, 2) ≥9 mg/dL, <10 mg/dL, 3) ≥10 mg/dL. The stratified randomization was used to keep the balance of serum urate concentration between groups and done by the central coordinator to maintain the blindness. The patient visiting schedule was as follows; day -14 or day -1 screening visit (day -14 for subjects taking allopurinol or uricosuric agents prior to this study, or Day -1 for subjects not receiving allopurinol or uricosuric agents), day -1 visit, day 1 visit and the 28-day treatment period. Colchicine 0.6 mg QD was given to minimize the risk of gout flare-ups, acute gout response manifesting red, hot or swollen joint with pain, during the washout/run-in period, and during the double blind study period. The medication which could impact on the serum urate concentration and interact with the study medication was prohibited; chronic use (>100 consecutive days) of NSAIDs, salicylate-containing medication, probenecid, benz-bromarone, thiazide diuretics, predisone, azathioprine, mercaptopurine, dicumarol, cyclophosphamide, trimethoprim-sulfamethoxazole and so on. Low dose aspirin (<325 mg/day) and acetaminophen were allowed as required.

Efficacy endpoint

The primary end point was the proportion of subjects whose serum urate concentration fell to less than 6.0 mg/dL after 4 weeks of treatment. The secondary end point was the percent reductions in serum urate levels from the baseline to the end of the study (day 28).

Demographic information and medical history

All data were collected from the patients regarding body mass index (BMI), alcohol use and coexisting conditions, according to each treatment group.