

Febuxostat: A Novel Non-Purine Selective Inhibitor of Xanthine Oxidase for the Treatment of Hyperuricemia in Gout

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Abstract: Febuxostat is a novel non-purine selective inhibitor of xanthine oxidase being developed for the management of hyperuricaemia in patients with gout. To critically review the clinical trial data, safety profile, pharmacology, and role of febuxostat for the treatment of hyperuricemia and gout.

A review of the literatures on febuxostat was performed. All available human studies describing the pharmacology of febuxostat were included; including pharmacodynamics, efficacy, and safety of febuxostat. Available studies, patents and abstracts were identified through PubMed (1990-December 2006), Delphion, Cochrane Databases, and the American College of Rheumatology and European League Against Rheumatism Web sites. Key search terms were febuxostat, TMX-67, and TEI-6720. Febuxostat has been used at a dose of 80 to 120 mg for the management of hyperuricemia in gout. The drug is mainly metabolized by the liver and therefore mild-moderate renal impairment does not appear to impede its effect. However, given the limited long-term liver function safety data, failure of a large percentage of patients taking febuxostat to achieve the primary end point of serum urate levels less than 6.0 mg/dL, and higher drop out rate in the Febuxostat group in the clinical trials, the exact role of febuxostat as a urate-lowering therapy remains uncertain. Febuxostat is a promising alternative to allopurinol for the treatment of gout and hyperuricemia. The optimal length of colchicines prophylactic therapy for chronic gout, clinical significance of abnormal liver function tests results during therapy, and safety in patients with moderate or severe hepatic and renal insufficiency warrant further investigation. A post-market surveillance is also needed to address the safety issue of long-term febuxostat treatment.

Keywords: Febuxostat, gout, hyperuricemia, uric acid, allopurinol, treatment.

INTRODUCTION

Gout is an increasingly common rheumatic disease. Global studies have found an increase in mean serum urate in both genders during the past four decades [1-3]. Gout affects more than five million Americans. The underlying cause of gout is hyperuricemia, or levels of urate in the serum greater than 6.8 mg/dL (405 $\mu\text{mol/L}$). It is the most common form of arthritis in men over the age of 40, and though women are less commonly affected, the prevalence of gout may be rising among postmenopausal women. In addition to treating acute attacks of arthritis, the management of chronic gout includes control of the serum urate level. The optimal management of chronic gout entails therapy to maintain serum urate levels below the solubility threshold for deposition of urate crystals. Allopurinol, a purine-analogue inhibitor of xanthine oxidase, has long been the main therapy for the management of chronic gout in many countries. Although quite efficacious when prescribed in doses sufficient to achieve the targeted lower levels of serum urate, rare occurrences of serious hypersensitivity reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis and a variety of drug interactions that restrict its use in some patients limit its widespread use. Febuxostat (TEI-6720; TMX-67), a novel non-purine selective inhibitor

of xanthine oxidase, is being developed by Teijin, with licensees Ipsen and TAP Holdings, for the treatment of hyperuricemia in gout. The drug is the first new medication aimed at reducing urate levels since allopurinol was approved in 1964. In February 2005, it was reported that launch in Japan was expected to be delayed for several years due to the need for additional clinical trials; in May 2005, an EU filing was expected by the end of 2005 [4]. This article aims to critical review the clinical trial data, safety profile, pharmacology, and the role of febuxostat for the treatment of hyperuricemia in gout.

MATERIALS AND METHODS

A review of the literatures on febuxostat was performed. All available human studies describing the pharmacology of febuxostat were included; including pharmacodynamics, efficacy, and safety of febuxostat. Available studies and abstracts published in English were identified through PubMed (1990-December 2006), Cochrane Central Register of Randomised Controlled Trials, and the American College of Rheumatology and European League Against Rheumatism Web sites. Key search terms were febuxostat, TMX-67, and TEI-6720. The reference lists of identified articles were checked for any additional articles that might have been missed in the original search. Furthermore, a systematic review and critical appraisal of the literatures regarding febuxostat was performed. Patents discussing the preparation of these compounds which are helpful in treating gout and hyperuricemia has been mentioned [5-10]. This work further discusses this drug's clinical implications and provides

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further discussion before its marketing approval by the FDA of United States.

RESULTS

All clinical studies were funded by TAP Pharmaceuticals, the maker of febuxostat. TAP Pharmaceutical Products Inc., located in Lake Forest, Illinois, is a 50-50 joint venture between Abbott, headquartered in Abbott Park, Illinois, and Takeda Pharmaceutical Company Limited, of Osaka, Japan. TAP licensed febuxostat from Teijin Pharma Limited, based in Tokyo, Japan. Results from a Phase III clinical trial (Febuxostat versus Allopurinol Control Trial, FACT) showed that daily oral febuxostat (80 or 120 mg) is efficacious in reducing the level of serum urate in subjects with gout and hyperuricemia compared to allopurinol 300 mg per day [11]. In this randomized, controlled, 52-week study, 762 patients with gout and with serum urate concentrations of at least 8.0 mg/dL (480 μ mol/L) were randomized to receive either febuxostat (80 mg or 120 mg) or allopurinol (300 mg) once daily for 52 weeks; 760 patients received the study drug. During weeks 1 through 8, patients also received naproxen or colchicine for prophylaxis against gout flares. The main outcome measure was a serum urate concentration of less than 6.0 mg/dL (360 μ mol/L) at the last 3 monthly measurements, and the secondary outcomes included reduction in the incidence of gout flares and in tophus area. The primary end point was achieved in 53% (136/255) of patients receiving 80 mg of febuxostat, 62% (154/250) of those receiving 120 mg of febuxostat, and 21% (53/251) of those receiving allopurinol. Although the incidence of gout flares diminished with continued treatment, the overall incidence during weeks 9 through 52 was similar in all groups: 64% of patients receiving 80 mg of febuxostat, 70% of those receiving 120 mg of febuxostat, and 64% of those receiving allopurinol. Similar reductions in gout flares and tophus area occurred in all treatment groups. The median reduction in tophus area was 83% in patients receiving 80 mg of febuxostat and 66% in those receiving 120 mg of febuxostat, as compared with 50% in those receiving allopurinol. More patients in the high-dose febuxostat group discontinued the study than did those in the allopurinol group ($P = 0.003$) or in the low-dose febuxostat group. Four of the 507 patients (0.8%) in the two febuxostat groups but none of the 253 patients in the allopurinol group died. However, blinded investigators determined that all deaths were from causes judged to be unrelated to the study drugs. Based on results from this clinical trial [11], TAP Pharmaceutical Products Inc. have submitted an application seeking FDA approval for febuxostat in the management of hyperuricemia in gout patients. From rheumatologist point of view, the investigation suggest that Febuxostat is very encouraging because it shows that febuxostat was superior or equal at lowering serum uric acid levels compared to allopurinol. But clinical outcomes - incidence of gout flares and the size of the tophi - did not differ in the randomized, controlled trial of the two medications. It is of noted that as 300 mg per day is routinely the starting dose of allopurinol, with most patients who tolerate the medication requiring higher doses to achieve normalization of serum urate levels. Based on previous research, Dr. Becker and colleagues noted, they expected between half and 60% of the participants taking allopurinol to reach the primary endpoint;

in fact, only 21% did so. One possible explanation is that baseline urate levels in this study were higher than those commonly seen when allopurinol was first studied. A second explanation is that allopurinol is usually titrated to find the effective dose; in this study, the dose was fixed at 300 milligrams daily to avoid compromising the blinding of the investigators. Furthermore, the study limitations include failure of a large percentage of patients taking febuxostat to achieve the primary end point of serum urate levels less than 6.0 mg/dL; large numbers of dropouts for reasons that are not clearly defined; use of a fixed daily dose of allopurinol; lack of details about the degree, duration, and reversibility of liver enzyme elevation; and exclusion of patients with severe renal insufficiency. Febuxostat, at a daily dose of 80 mg or 120 mg, was more efficacious than allopurinol at the commonly used fixed daily dose of 300 mg in lowering serum urate [11], although similar reductions in gout flares and tophus area occurred in all treatment groups. The study does not show conclusively that febuxostat is more effective at lowering urate levels than allopurinol. It is likely that allopurinol would have been more effective at lowering urate levels if the dose had been titrated as recommended in the allopurinol package insert. A high percentage of febuxostat patients at each dose still did not reach the primary endpoint and suggested that further research should investigate both whether higher doses can be given safely and if such higher doses would be effective. This work also reviews two other clinical trials data of Febuxostat [12-15], which including one not yet published data [12].

The two additional clinical studies also show significantly higher percentage of patients achieved reduced serum urate levels with febuxostat than those who took allopurinol. One not yet published study, which was presented at the American College of Rheumatology Annual Scientific Meeting in November 2005 (San Diego) [12], assessed 1067 patients, who had gout and serum urate levels of at least 8.0 mg/dL, over a 28-week period. They were an average of 52 years old and had had gout for an average of 11 years. Almost all of the subjects (94%) were men, and the majority (78%) are white. The average baseline serum level exceeded 10 mg/dL in 39% of subjects, and the average serum urate level was 9.85 mg/dL; 20% of the subjects had tophi. In addition to gout, 47% of subjects had hypertension; 33% had hyperlipidemia; and 13% had cardiovascular disease. Nearly two thirds were obese and consumed alcohol (62% and 66%, respectively). In this randomized, placebo-controlled trial, there were five treatment groups, three treatment groups were given febuxostat 80 mg/day, 120 mg/day and 240 mg/day respectively. Another treatment group received 100 (for patients with serum creatinine 1.6-2.0 mg/dl) or 300 mg of allopurinol (for patient with serum creatinine 1.5 mg/dL) depending on the serum creatinine levels, and another group received a placebo treatment. The main outcome measure was a serum urate concentration of less than 6.0 mg/dL (360 μ mol/L) at the last 3 monthly measurements. The study showed a reduction of the uric acid level to less than 6 mg/dL at the last three monthly visits in 48% (126/262) of patients who received 80 mg/day of febuxostat; 65% (175/269) of patients who received 120 mg/day of febuxostat; and 69% (92/134) of patients who took 240 mg/day of febuxostat. In comparison, only 22%

(60/268) of patients taking 100-300 mg/day of allopurinol achieved the primary endpoint target reduction and none (0/134) of the patients in the placebo group achieved the reduction (Table 1). When a single visit at week 28 was evaluated, those patients whose uric acid level was reduced to <6 mg/dL was 76% taking febuxostat 80 mg/day, 87% taking 120 mg/day, and 94% taking 240 mg/day, compared to 41% taking allopurinol and 1% of patients taking placebo. The study also included 40 subjects who had moderately impaired renal function (serum creatinine level ranging from 1.6 to 2.0 mg/dL) so that they could assess the safety of the highest dose of febuxostat, 240 mg daily. Of the subjects with moderate renal impairment, four of the nine (44%) patients receiving the 80-mg febuxostat dose achieved a serum urate level of less than 6 mg/dL in each of the last three visits, as did five (45%) of the 11 subjects receiving the 120-mg febuxostat dose and three (60%) of the five subjects receiving the 240-mg febuxostat dose; none of those subjects on allopurinol or placebo achieved the target. Through the first eight weeks of the study, the rate of patients having gout flares that required treatment ranged from 20% in the placebo group to 46% in the group receiving 240 mg of febuxostat. The initial reduction of serum urate is associated with a temporary increase in gout flares. In the last three weeks of the study, the rate of flares ranged from 7% in the 240-mg group to 20% in the placebo group. The investigators concluded that the study result showed that when compared to allopurinol, febuxostat is at least twice as effective in reducing serum uric acid level. However, allopurinol was in a fixed dosage of 100 or 300 mg/day. Additionally, the trial was meant to determine the safety of febuxostat. Adverse events, which included digestive disturbances, headache and liver function abnormalities, were similar across all treatment groups, and of the 34 serious adverse events across all treatment groups, most were cardiac disorders in patients with pre-existing cardiovascular disease. The investigators concluded that Febuxostat was well tolerated, and the majority of treatment-related adverse events were transient and mild-to-moderate in severity. No dose adjustment appears to be necessary in those with renal insufficiency or mild-to-moderate hepatic impairment. Treatment-related adverse events consisted of elevated liver enzymes, headache, nausea and vomiting, abdominal pain, and dizziness, and occurred at similar rates across the treatment groups: 16% in the allopurinol subjects, 18% of those in the 120-mg febuxostat group, 21% of those in the 80-mg febuxostat group, 23% of those receiving placebo, and 29% of those in the 240-mg febuxostat group. Diarrhea, the most common adverse event, occurred in 4% of those receiving placebo, 3% of those on allopurinol, and in the febuxostat groups at rates of 2% in the 80-mg group, 7% in the 120-mg group, and 1% in the 240-mg group. Subjects with renal insufficiency had similar rates of adverse events as the other subjects, even at the highest dose of febuxostat. Of the subjects experiencing serious adverse events, primarily cardiovascular events, 33 were not considered treatment-related because of the subjects' medical histories. However, numbers of dropouts and details about the liver enzyme elevation results was not available from Web searching.

Another four-week, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial

examining safety and efficacy in patients with gout has been published in March 2005 issue of Arthritis and Rheumatism [13], which was presented at the American College of Rheumatology (ACR) Annual Scientific Meeting in November 2004 [14] and the American College of Rheumatology (ACR) Annual Scientific Meeting in November 2002 [15]. The authors conducted a phase II, randomized, double-blind, placebo-controlled trial in 153 patients (ages 23-80 years). Subjects received febuxostat (40 mg, 80 mg, 120 mg) or placebo once daily for 28 days and colchicine prophylaxis for 14 days prior to and 14 days after randomization. The primary end point was the proportion of subjects with serum urate levels <6.0 mg/dl on day 28. The targeted serum urate level was attained on day 28 in 0% of those taking placebo and in 56% of those taking 40 mg, 76% taking 80 mg, and 94% taking 120 mg of febuxostat. The majority of subjects in each febuxostat group attained the targeted serum urate concentrations as early as day 7. The mean serum urate reduction from baseline to day 28 was 2% in the placebo group and 37% in the 40-mg, 44% in the 80-mg, and 59% in the 120-mg febuxostat groups. Gout flares occurred with similar frequency in the placebo (37%) and 40-mg febuxostat (35%) groups and with increased frequency in the higher dosage febuxostat groups (43% taking 80 mg; 55% taking 120 mg). During colchicine prophylaxis, gout flares occurred less frequently (8-13%). Incidences of treatment-related adverse events were similar in the febuxostat and placebo groups [13]. In this report, liver function tests abnormalities occurred in four subjects (4/115) in the febuxostat groups and none (0/38) in the placebo group. Treatment related abnormalities in liver function test results were observed in a total of 4 febuxostat subjects (two taking 40 mg, 1 taking 80 mg, 1 taking 120 mg). The authors described that abnormalities in liver function test were temporally associated with administration of colchicines, either alone or with febuxostat. In all instances, liver function test values returned to normal limits after discontinuation of colchicines [13]. From this point one may wonder that if the study was double blinded.

DOES FEBUXOSTAT HAS MORE ADVANTAGES OVER ALLOPURINOL FOR HYPERURICEMIA IN GOUT PATIENTS

Hyperuricemia, defined as a serum urate concentration of 6.8 mg/dL or higher, predisposes individuals to gout, which manifests itself as acute gouty arthritis, chronic tophaceous gout, uric acid urolithiasis, acute uric acid nephropathy, and monosodium urate gouty nephropathy. The most frequently used pharmacologic urate-lowering drugs involve use of a uricosuric agent or a xanthine oxidase inhibitor. In term of lowering serum urate level to therapeutic level, all kinds of urate-lowering drugs are equal effective. Allopurinol at an average dose of 300 mg (range, 100-800 mg daily) is one of the commonly prescribed of these agents. Febuxostat has been used at a dose of 80 to 120 mg for the management of hyperuricemia in gout. With febuxostat 10-120 mg, the pharmacokinetics are linear. Febuxostat 10-120 mg/day rapidly and sustainably reduces serum uric acid by 25-70% in uric acid under-excretors and overproducers [16,17]. Both drugs inhibit xanthine oxidase and thereby prevent the formation of uric acid, although they are metabolized differently. Febuxostat is mainly metabolized by the liver

Table 1. Demographic Data of Febuxostat Treated Patients in Double-blind Randomize-Controlled Clinical Trials

Clinical trial (Phase)	1 (II)	2 (III)	3 (III)
Published	Arthritis Rheumatism ¹³	NEJM ¹¹	not yet ¹²
Case number	153	760	1067
Year	–	July 2002 – Aug 2004	Feb 2003 – Sep 2004
Treatment group (n)	Febuxostat 40 mg (38) Febuxostat 80 mg (37) Febuxostat 120 mg (40) Placebo (38)	F 80 mg (257) F 120 mg (251) Allop 300 mg (254)	F 80 mg (262) F 120 mg (269) F 240 mg (134) Allop 100-300 mg (268) Placebo (134)
Treatment duration	4 weeks	52 weeks	28 weeks
Primary endpoint achieved (% of serum urate < 6.0 mg/dL)	Febuxostat 40 mg: 56% Febuxostat 80 mg: 76% Febuxostat 120 mg: 94% Placebo: 0%	F 80 mg: 53% F 120 mg: 62% Allop 300 mg: 21%	F 80 mg: 48% F 120 mg: 65% F 240 mg: 69% Allop 100-300 mg: 22% Placebo: 0%
Secondary endpoint			
Gout flare	35%:43%:55%:37%	64%:70%:64%	not yet published
Tophus area decrease	not done	83%:66%:50%	not yet published
Lost to follow-up (n)	none	25:18:21	not yet published
Discontinued treat (n)	2:1:3:2	88:98:66	
Liver function test abnormality (%)	5%:3%:3%:0%	4%:5%:4%	not yet published
Death (n)	none	2:2:0 (unrelated)	none

Allop: allopurinol; F: Febuxostat; n: case number.

and therefore mild-moderate renal impairment does not appear to impede its effect. No dose adjustment appears to be necessary in those with renal insufficiency or mild-to-moderate hepatic impairment [18-20]. Febuxostat is a potential alternative to allopurinol for patients with hyperuricemia and gout. In the clinical trials [11-15] and animal study [21,22], Febuxostat is more potent and more selective than allopurinol, and might have less allergenic potential than allopurinol. Febuxostat may be a useful alternative for subjects who cannot take allopurinol or other drugs used to treat gout and may be particularly useful in the 5-10% of people who react adversely to allopurinol and to those with kidney impairment that may preclude adequate allopurinol dosing. However, in those previous studies [11-13,18,19], patients with severe renal impairment were excluded from the study and the effectiveness and safety of febuxostat among these patients is not well known. This will require additional study.

One of the advantages of febuxostat is that it might be less allergenic than allopurinol. We need a drug that can lower uric acid without the adverse reactions associated with allopurinol. A major obstacle to the treatment of hyperuricemia in patients allergic to allopurinol and renal function impairment is the limited availability of suitable, equally effective, alternative, urate-lowering drugs. Some gout

patients suffered from allopurinol allergy and unresponsiveness or contraindications to uricosuric agents, in these patients febuxostat would be an alternative.

PHARMACOKINETICS, AND PHARMACODYNAMICS OF FEBUXOSTAT

Uric acid is a product of purine metabolism generated during the enzymatic degradation of hypoxanthine and xanthine. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, and of xanthine to uric acid (Fig. 1). Hyperuricemia occurs either through overproduction or underexcretion of uric acid or a combination of the two. The concentration of urate in plasma depends on de novo purine synthesis, dietary intake, and uric acid elimination by the proximal renal tubules and intestine. The liver enzyme, xanthine oxidase (XO) produces uric acid during purine catabolism. The kidney is important in the elimination of uric acid, with two-thirds of daily production of uric acid being excreted by the kidney and the remaining third being eliminated by the gastrointestinal tract. Uricosuric drugs (benzbromarone, probenecid, and sulfapyrazone) increase urinary uric acid excretion by inhibiting renal tubular urate reabsorption. Allopurinol and febuxostat are xanthine oxidase inhibitor. Unlike allopurinol, febuxostat is not purine-like in structure (Table 2). Additionally, febuxostat inhibits xanthine oxidase, but, unlike allopurinol, febuxostat does not

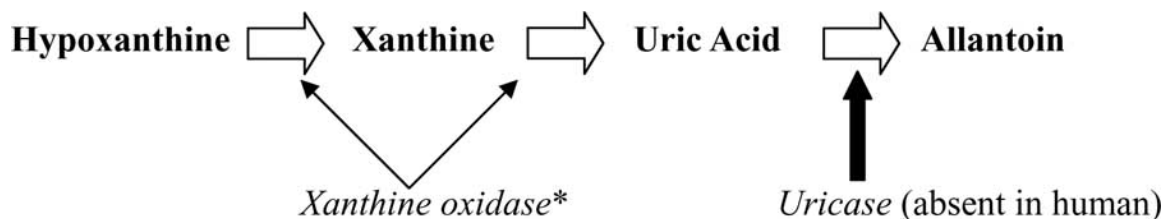


Fig. (1). Uric acid metabolism and sites of action of allopurinol and febuxostat (xanthine oxidase inhibitor*).

Table 2. Comparison of Two Xanthine Oxidase Inhibitors: Allopurinol and Febuxostat

Drug	Febuxostat	Allopurinol
Chemical structure	Non-purine	Purine analog
Xanthine oxidase inhibition	Selective inhibition	Nonselective inhibition*
Route	Oral	Oral
Dosage (usual)	40–240 mg (80–120 mg)	100–800 mg (300 mg)
Half-life	1.3 to 15.8 hours	Allopurinol: 1 to 3 hours Oxipurinol: 17 to 40 hours**
Excretion	Liver	Kidney
Dosage adjustment in mild to moderate renal dysfunction	Not	Yes
Drug interaction	There have been no documented major drug interactions with febuxostat	Azathioprine, 6-mercaptopurine, cyclophosphamide
Severe side effect	Unknown	Hypersensitivity syndrome

* Uric acid is an end product of purine metabolism generated during the enzymatic degradation of hypoxanthine and xanthine by the xanthine oxidase. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, and of xanthine to uric acid. Febuxostat differs from allopurinol in chemical structure, as it is not a purine analogue, and it is a selective inhibitor of xanthine oxidase. However, both allopurinol and oxipurinol inhibit at least five enzymes in the purine and pyrimidine pathway other than xanthine oxidase (non-selective).

** Oxipurinol is the chief active metabolite of allopurinol.

XO: xanthine oxidase

inhibit any other enzymes in the purine and pyrimidine pathways and it is not incorporated in nucleotides. Furthermore, febuxostat is mainly metabolized by the liver, so, unlike allopurinol is excreted by the kidney, thus it may not require dosage adjustments in renal failure. Allopurinol, its major active product, oxypurinol, and their respective metabolites inhibit other enzymes involved in purine and pyrimidine metabolism. Febuxostat (TEI-6720, TMX-67) displayed potent mixed-type inhibition of the activity of purified bovine milk XO indicating inhibition of both the oxidized and reduced forms of XO. At concentrations up to 100 μ M, febuxostat had no significant effects on the activities of the following enzymes of purine and pyrimidine metabolism: guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, purine nucleoside phosphorylase, orotate phosphoribosyltransferase and orotidine-5'-monophosphate decarboxylase [23]. Febuxostat (2-[3-cyano-4-(2-methylpropoxy)-phenyl]-4-methylthiazole-5-carboxylic acid) is an orally administered selective inhibitor of xanthine oxidase that is not a purine analog. The mechanism of febuxostat inhibition of the enzyme is mixed inhibition, contrasting with the competitive kinetics exhibited by allopurinol. This difference in kinetic mechanism is consistent with the findings that febuxostat blocks substrate

access to the molybdenum-pterin moiety of xanthine oxidase by occupying a channel in the enzyme leading to the active site, and that febuxostat inhibits both the oxidized and reduced forms of xanthine oxidase [24]. In animal studies [21,22] febuxostat was shown to provide more potent and longer lasting hypouricemic activity than allopurinol, and has minimal effects on other enzymes that are involved in purine and pyrimidine metabolism [23]. TEI-6720 (2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid) is an extremely potent inhibitor of xanthine oxidoreductase. In a phase I, dose-escalation study [25], febuxostat was studied in dose groups (10, 20, 30, 40, 50, 70, 90, 120, 160, 180 and 240 mg) of 12 subjects each (10 febuxostat plus 2 placebo). In all groups, subjects were confined for 17 days and were administered febuxostat once daily on day 1, and days 3-14. During the course of the study, blood and urine samples were collected to assess the pharmacokinetics of febuxostat and its metabolites, and its pharmacodynamic effects on uric acid, xanthine and hypoxanthine concentrations after both single and multiple dose administration. Orally administered febuxostat was rapidly absorbed with a median time to reach maximum plasma concentration following drug administration of 0.5-1.3 hours. The pharmacokinetics of febuxostat were not time dependent (day 14 vs.

day 1) and remained linear within the 10-120 mg dose range, with a mean apparent total clearance of 10-12 L/h and an apparent volume of distribution at steady state of 33-64 L.

DISCUSSIONS

Gout is a disorder of the purine metabolism or the renal excretion of uric acid, which is the final product of endogenous and dietary purine metabolism in human. Urate-lowering drugs are of equal effectiveness, aim to reduce serum urate level to below the solubility limit, i.e. 6.8 mg/dl, and are usually set at < 6.0 mg/dl. Almost all currently available urate-lowering agents may have side effects, which are sometimes severe and life-threatening. Although the risk is very low, it exists and continuously happens [26-28]. Choosing the most appropriate urate-lowering agent for a patient may avoid unnecessary complication. Generally, uricosuric drugs such as probenecid, sulfipyrazone, or benzbromarone, are safer than allopurinol. Whether febuxostat, a nonpurine selective inhibitor of xanthine oxidase, is safer than allopurinol requires large scale post-marketing surveillance or before-market study. Current options for treating hyperuricemia in chronic gout are limited. The purine analogue, allopurinol, has been in clinical use for more than 40 years as an inhibitor of xanthine oxidase in the treatment of hyperuricemia and gout [29]. Allopurinol is a xanthine oxidase inhibitor that blocks the conversion of hypoxanthine to xanthine, and xanthine to uric acid. Allopurinol is converted to oxypurinol via xanthine oxidase, with oxypurinol being a strong inhibitor of the conversion of hypoxanthine and xanthine to uric acid. By blocking xanthine oxidase, allopurinol decreases uric acid levels in both the blood and urine while increasing the excretion of uric acid precursors hypoxanthine and xanthine. Allopurinol is metabolized in the liver and has a half-life of 1 to 3 hours, but oxypurinol, which is the active metabolite of allopurinol and is excreted in the urine, has a half-life of 17 to 40 hours. Allopurinol thus can be used at doses from 100 to 800 mg per day in a once-daily dosing schedule. Side effects of allopurinol are infrequent and generally mild. A severe hypersensitivity reaction to allopurinol is rare but potentially life-threatening. The allopurinol hypersensitivity syndrome is characterized by fever, skin rash, hepatitis, leukocytosis with eosinophilia, and worsening renal function. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia and gout. The investigative agent febuxostat is more efficacious for the management of gout than allopurinol in 300 mg/day. Febuxostat significantly reduces uric acid levels within 2 weeks after initiation of therapy. Approximately 60% of patients achieved the primary goal of serum uric acid less than 6 mg/dL during the last 3 months following once-daily administration of febuxostat 80 mg or 120 mg for at least 52 weeks. It may be a useful alternative for subjects who cannot take allopurinol or other agents used to treat gout. When and whether febuxostat will be FDA approved is not known but it would be the first new medication for gout in more than 40 years.

CURRENT & FUTURE DEVELOPMENTS

Febuxostat is a promising alternative to allopurinol for the treatment of gout and hyperuricemia. The optimal length of prophylactic colchicines therapy for chronic gout, clinical

significance of abnormal liver function tests results during long-term therapy, and safety in patients with moderate or severe hepatic and renal insufficiency warrant further investigation. A post-market surveillance is also needed to address the safety issue of long-term febuxostat treatment.

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