Expert Opinion

Febuxostat: a non-purine, selective inhibitor of xanthine oxidase for the management of hyperuricaemia in patients with gout

H Ralph Schumacher Jr
University of Pennsylvania, Chief of Rheumatology, VA Medical Center, Philadelphia, USA

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase being developed for the management of hyperuricaemia in patients with gout. With febuxostat 10 – 120 mg, the pharmacokinetics are linear. No dose adjustment appears to be necessary in those with renal insufficiency or mild-to-moderate hepatic impairment. Febuxostat 10 – 120 mg/day rapidly and sustainably reduces serum uric acid by 25 – 70% in uric acid underexcretors and overproducers. Prophylaxis with colchicine or a non-steroidal anti-inflammatory drug can mitigate the gout-flare risk from the rapid urate lowering after febuxostat initiation. Febuxostat is well tolerated, the majority of treatment-related adverse events are transient and mild-to-moderate in severity. Febuxostat can broaden the therapeutic options for urate-lowering therapy in those with gout.

Keywords: febuxostat, hyperuricaemia, gout, non-purine, xanthine oxidase inhibitor

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1. Introduction

Gout is a disease characterised by recurrent episodes of acute joint inflammation resulting from the crystallisation and deposition of monosodium urate (MSU) crystals. It is the most common cause of acute monoarticular arthritis. It has been estimated that ≤ 5 million Americans suffer from gout. Men carry the major burden of gout prevalence with an 8.6% cumulative incidence. There is a 1% overall incidence in the general population [1,2]. The increasing rate of obesity, ageing of the general population, increased incidence of concurrent diseases, the greater use of medications that reduce uric acid excretion and consumption of foods and beverages high in purines have been cited as factors resulting in an increasing incidence of gout [3].

Hyperuricaemia is the critical biochemical precursor for the development of gout. It is best defined as a serum uric acid (sUA) > 6.8 mg/dl, a level at which urate is likely to crystallise in tissues and lead to gout. Hyperuricaemia is the result of a reduction in the renal excretion of uric acid and/or an excessive rate of uric acid production. In humans, uric acid is the end product in the cascade of hypoxanthine metabolism to xanthine and then to uric acid, with each of these metabolic steps catalysed by xanthine oxidase. Under normal conditions, uric acid is excreted to maintain uric acid levels below those precipitating crystallisation. However, in those who are either underexcretors or overproducers of uric acid, the total body pool of urate rises, resulting in hyperuricaemia. At a critical threshold, with or without other factors (e.g., temperature, local tissue changes, dehydration and so on), the sUA level is saturated and crystal precipitation occurs. These crystals can trigger the acute inflammatory response with the synthesis and release of inflammatory mediators, culminating in painful, inflamed joint/s that are characteristic of an acute flare of gout [4].

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The natural course of hyperuricaemia and gout is divided into four stages: asymptomatic hyperuricaemia; acute gout flares; intercritical segments; and advanced gout with the duration of each stage being variable and dependent on the cause and severity of the hyperuricaemia [5]. An acute gout flare is characterised by the rapid development, often at night, of a warm, swollen, erythematous and exquisitely painful joint. The majority of initial acute gout attacks are monoarticular with ≤ 50% of these occurring in the first metatarsophalangeal joint (termed podagra). Left untreated, the acute gout attack may resolve within several hours or persist for ≤ 2 weeks. This is followed by variable periods of time (from months to years) between episodes. Attacks or flares can recur at unpredicatable intervals but tend to occur more frequently over time in individuals with uncontrolled hyperuricaemia [6]. Of the patients with an initial episode of gout, ~ 80% will have a recurrent attack in ≤ 2 years [7]. The asymptomatic period between acute gout episodes is termed the intercritical segment. It is likely that the persistent hyperuricaemia in these individuals continues to result in crystal deposition in the joint and possibly other clinically silent pathology. As the intercritical phases become shorter, the attacks may become polyarticular, more severe, longer lasting and accompanied by fever. Advanced gout from long-standing hyperuricaemia can result in chronic, persistent, destructive and crippling arthritis and visible deposits of urate crystals in the soft tissues called tophi [8].

2. Overview of gout treatment options

The treatment of gout is highly dependent on the stage of the disease. Treatment of those with asymptomatic hyperuricaemia is generally not recommended although some recent evidence suggests that it may be a risk factor for other disorders including cardiovascular disease [9-11].

In those with an acute flare of gout, treatment goals are to reduce the exquisite pain and inflammation that is characteristic of these attacks. This is best accomplished with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or colchicine, which address the underlying inflammatory process [12–15], along with adjunctive therapy such as resting the inflamed joint and the application of ice on the affected area for some patients [16,17].

The definitive treatment required, especially for those with recurrent gout flares, is to reverse the metabolic aetiology of gout, that is, the hyperuricaemia, and prevent the progression of the disease (e.g., recurrent attacks and tophus formation). The optimal management of these patients is the sustained lowering of total body pool of uric acid and attainment of sUA levels to ≤ 6 mg/dl (357 μM) [6,18]. Results of a recent study found that virtually 100% of the patients with sUA levels of ≥ 10 mg/dl have recurrent attacks of gout. On the other hand, those whose average sUA is ≤ 6 mg/dl have a < 20% annual incidence of recurrence (**Figure 1**) [6]. In those with tophi, resorption may require a sUA reduction of < 5 mg/dl 19]. In a study examining urate crystal persistence in the knee joints of 57 patients, those with sUA levels > 6 mg/dl (n = 38), despite 1 year of allopurinol therapy, experienced more gout attacks (mean of six attacks/year) compared with those with sUA levels ≤ 6 mg/dl (n = 19, mean of 1 attack/year) [18]. Among the patients who consented to knee aspiration, MSU crystals were still found in 14 of 16 patients with sUA levels > 6 mg/dl and in 7 of the 16 with levels ≤ 6 mg/dl [18].

The primary classes of antihyperuricaemic agents currently available are the uricosurics (e.g., probenecid, sulfinpyrazone, and, in some countries, benzbromarone) that enhance renal excretion of uric acid and the inhibitors of xanthine oxidase/xanthine dehydrogenase (i.e., allopurinol). In general, uricosurics are indicated in patients who are underexcretors of urate; however, the clinical use of these agents (probenecid and sulfinpyrazone) is limited by their potential for renal-stone formation, the need for sustained hydration, and diminished efficacy in those with impaired renal function [14]. Several additional drugs, including losartan, fenofibrate and high-dose aspirin, also have mild uricosuric effects [20–23].

Allopurinol, a purine-like structure developed in the early 1960s, is the only commercially available xanthine oxidase/xanthine dehydrogenase inhibitor and is widely regarded as the mainstay of long-term gout management. It can be effective in reducing the total body pool of uric acid-resorbing tophi and decreasing flares. Allopurinol can produce serious and life-threatening adverse events that include vasculitis, toxic epidermal necrolysis, eosinophilia, hepatitis, reduced renal function and bone-marrow suppression (collectively known as the allopurinol hypersensitivity syndrome [AHS]) [24,25]. Postulated mechanisms for the adverse-event profile of allopurinol include its non-selective inhibition of other enzymes involved in purine and pyridine metabolism that may result in the impairment of suppressor T-cell function [26-29] and its effects on immunological reactions that enhance toxicity, inflammation and allergic reactions [26]. Allopurinol has been associated with bone-marrow depression, possibly as a result of purine and pyrimidine synthesis inhibition [30-32].

There is a recognised need for more effective treatment to reduce the total body pool of uric acid, regardless of its pathogenesis, with an enhanced tolerability and safety profile. This review presents information on febuxostat, the first compound in the non-purine selective inhibitor of the xanthine oxidase class of agents. Febuxostat is currently in late-stage development for the treatment of hyperuricaemia in patients with gout.

3. Febuxostat: a non-purine selective inhibitor of xanthine oxidase

3.1 Chemical and physical properties

The active component of febuxostat (TMX-67, a 2-arylthiazole derivate) is 2-(3-cyano-4-[2-methylpropoxy]phenyl)-4-methylthiazole-5-carboxylic acid. Febuxostat has a molecular weight of 316.38 and its chemical structure (**Figure 2**) is notable and dissimilar to the purine-like

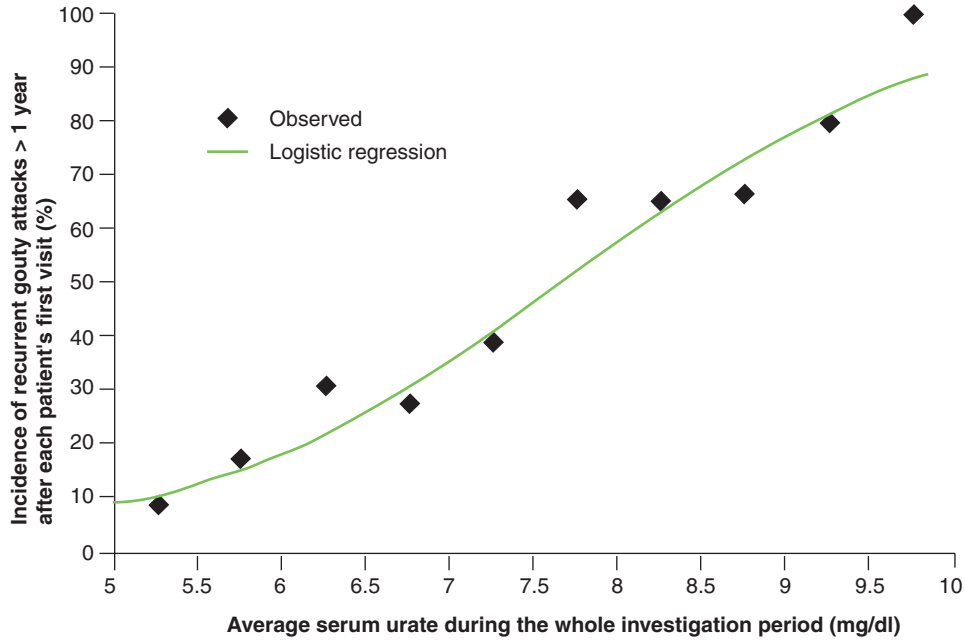

Figure 1. Target for serum urate as a function of recurrent gout attack incidence. A clear relationship was displayed between the average serum uric acid concentration and the percentage of patients who experienced at least one recurrent gouty attack during the observation period. A total of 86% (71/81) of the patients who had a serum uric acid of < 6 mg/dl did not experience an acute gout flare during the study period. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc., from SHOJI A, YAMANAKA H, KAMATANI N: A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum.* (© 2004) **51**(3):321-325.

structure of allopurinol. It has an empirical formula of $C_{16}H_{16}N_2O_3S$.

Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide, soluble in dimethylsulfoxide, sparingly soluble in ethanol, slightly soluble in methanol and acetonitrile, and practically insoluble in water.

3.2 Pharmacodynamics of febuxostat

3.2.1 Mechanism of action

Febuxostat is a potent inhibitor of xanthine oxidase with an *in vitro* inhibition (K_i) value of < 1 nM ($1.2 \pm 0.05 \times 10^{-10}$) [33]. It is a potent inhibitor of both the oxidised and reduced forms of xanthine oxidase [31–36]. Unlike allopurinol, febuxostat does not inhibit the other enzymes involved in purine or pyrimidine metabolism (e.g., guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase) (**Figure 3**) [27,29,37-41]. In an animal study, no bone-marrow depression effects were observed with febuxostat [42].

3.2.2 Pharmacokinetics and metabolism in healthy subjects

A Phase I, multiple-dose, placebo-controlled, dose-escalation study of febuxostat in 154 healthy adults found the pharmacokinetics of febuxostat to be neither time nor dose dependent at doses of 10 – 120 mg/day [43]. Following oral administration, the absorption of febuxostat is fairly complete (≥ 84%) and rapid (time to maximum concentration [t_{max}] being ~ 1 h). Daily doses in the range of 10 – 120 mg produced dose-proportional increases in maximum febuxostat plasma concentrations (C_{max}) and area under the plasma concentration versus time curves (AUC) [43]. At higher doses of febuxostat (120 – 240 mg/day), a greater than dose-proportional increase in the AUC was observed due to a possible decrease in the renal clearance of the conjugated febuxostat and subsequent increase in its biliary excretion and enterohepatic recirculation (**Table 1**) [43,44]. Febuxostat is highly (99.2%) bound to plasma proteins (primarily albumin) [45,46].

Febuxostat is extensively metabolised by conjugation via uridine diphosphate glucuronosyltransferase and oxidation via the cytochrome P450 (CYP) system. Oxidation of the parent compound leads to the formation of pharmacologically active hydroxyl metabolites (primarily 67M-1, 67M-2 and 67M-4) [44,45,47].

Febuxostat and its metabolites are eliminated in the urine [44,47]. On average, < 5% of the febuxostat dose is excreted as unchanged drug in the urine over 24 h [44,47].

3.2.3 Pharmacokinetics and pharmacodynamics of febuxostat in subjects with renal or hepatic impairment

Results of several studies indicate that febuxostat is unlikely to require any dosage adjustment when used in those with mild,

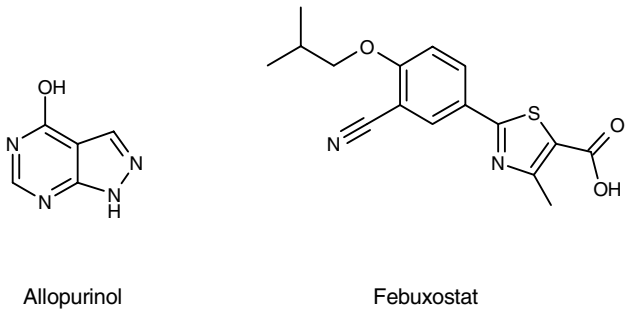

Figure 2. Chemical structures of febuxostat and allopurinol. Unlike allopurinol, which is an analogue of the purine hypoxanthine, febuxostat has a non-purine-like structure.

moderate or even severe renal impairment or those with mild or moderate hepatic impairment. No studies of febuxostat have been performed in subjects with severe hepatic impairment (Child-Pugh class C); therefore, one cannot advise about the use of this agent in these patients.

A single dose of febuxostat 20 mg p.o. administered to 15 subjects with normal (creatinine clearance [CrCl] ≥ 80 ml/min), mild (CrCl ≥ 50 and < 80 ml/min), or moderate (CrCl ≥ 30 and < 50 ml/min) impairment of renal function caused a less than twofold difference in the AUC of plasma-unchanged febuxostat among the renal function groups (mean AUCs of 2644, 2338 and 4005 ng·hr/ml in those with normal, mild and moderate renal impairment, respectively) [48]. In a separate study of subjects with mild (CrCl 50 – 80 ml/min/1.73 m^2), moderate (CrCl 30 – 49 ml/min/1.73 m^2), or severe (CrCl 10 – 29 ml/min/1.73 m^2) renal insufficiency, the t_{max} and C_{max} values of unbound febuxostat following multiple 80-mg doses were similar to values observed in those with normal (CrCl > 80 ml/min/1.73 m^2) renal function [44]. The values of 24-h AUC (AUC_{24}) of unbound febuxostat and apparent elimination half-life increased with decreasing renal function, an effect that is likely to be related to a decrease in the renal clearance of conjugated febuxostat and a subsequent increase in biliary excretion and enterohepatic recirculation. Plasma exposure to febuxostat and its metabolites was generally higher in those with diminished renal function. The mean sUA concentration decreased to a similar extent in all renal function groups with reductions of 55 – 64% from baseline observed by day 7 [44]. Among the different renal-function groups, febuxostat was well tolerated. Therefore, it was concluded that febuxostat 80 mg/day does not appear to require any dose adjustment based on renal function [44].

Administration of febuxostat 80 mg/day for 7 days to 16 subjects with mild (Child-Pugh class A, n = 8) or moderate (Child-Pugh class B, n = 8) hepatic impairment produced no significant differences in unbound C_{max} or AUC, or in t_{max} of febuxostat or its metabolites compared with values observed in 12 subjects with normal hepatic function [49]. No clinically significant differences were observed in the percentage decrease in sUA concentration between subjects with mild or moderate hepatic impairment (49 and 48%, respectively) and subjects with normal hepatic function (62%).

3.2.4 Effect of age and gender on pharmacokinetics and pharmacodynamics

A pharmacokinetic–pharmacodynamic study evaluating the effect of age and gender found that elderly (between 65 and 76 years of age) subjects administered multiple-dose febuxostat exhibited no significant changes compared with younger subjects (between 19 and 40 years of age) in C_{max} (27 ± 9 ng/ml versus 28 ± 12 ng/ml) or AUC_{24} (61 ± 20 versus 56 ± 19 ng.hr/ml) values for unbound febuxostat [45]. The percentage decreases from baseline in sUA were similar in elderly (56 ± 9%) and younger (55 ± 8%) subjects.

In the same study, differences in selected pharmacokinetic parameters were observed between males and females following multiple oral doses of febuxostat. Unbound febuxostat C_{max} and AUC values were statistically significantly ($p \leq 0.05$) higher in females than in males [45]. However, after inclusion of weight as a covariate, the differences were not statistically significant ($p > 0.05$). The difference between genders for percentage decrease in sUA concentrations was not clinically significant (59% in females and 52% in males).

3.2.5 Drug–drug and drug–food interactions

In vitro metabolism data showed that febuxostat had no significant effect on the activity of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 (K_i values > 100 µM). However, these data indicated a weak inhibitory effect of febuxostat on CYP2D6 *in vitro* (K_i = 40 µM). Co-administration of febuxostat with desipramine, a CYP2D6 substrate, in 18 CYP2D6 extensive-metaboliser subjects produced a slight increase in the C_{max} (16%) and AUC (22%) of despiramine that was associated with a 17% decrease in the 2-hydroxydespiramine to despiramine metabolic ratio [50]. These findings suggest that febuxostat may cause mild inhibition of the CYP2D6 isoenzyme; however, this effect does not appear to be clinically significant. Other drug–drug interaction investigations with febuxostat are currently being performed.

Administration of febuxostat with magnesium hydroxide and aluminum hydroxide antacids or a high-fat meal appears to delay its absorption [51]. Unlike the antacids, which produced no effect on AUC, giving febuxostat with a high-fat meal caused decreases in AUC by 16 – 19%. However, it was shown that the decrease in AUC following multiple dosing with febuxostat 80 mg was not associated with any clinically significant change in the pharmacodynamic effects (i.e., percentage decrease in sUA concentration) of febuxostat [51].

3.3 Pharmacodynamics

In a Phase I study, escalating once-daily oral doses of febuxostat 10, 20, 30, 40, 50, 70, 90, 120, 160, 180 and 240 mg were administered for 13 days to groups of subjects (n = 12 in each dose group) [43,52]. Once-daily doses of febuxostat 300 mg were also administered to 10 healthy subjects for 1 week. Urine and

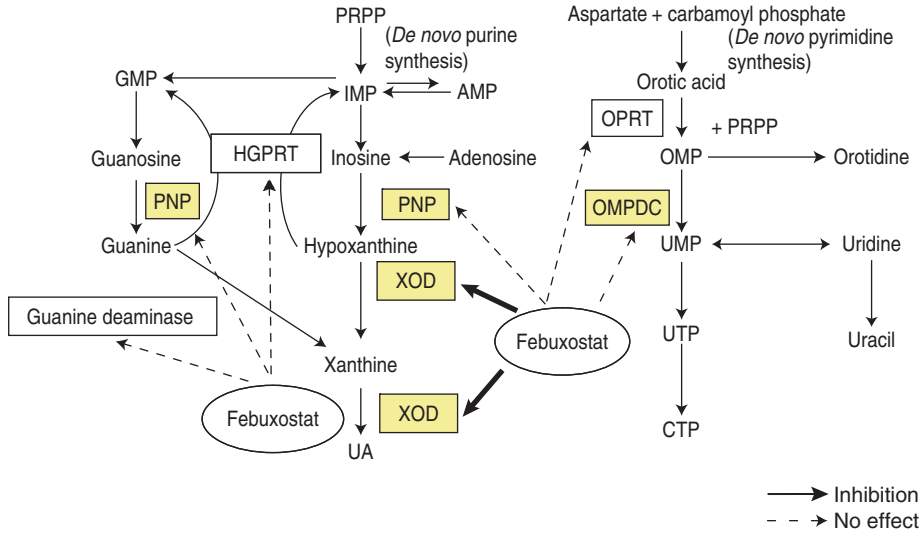

Figure 3. Mechanism of inhibitory action of febuxostat. This non-purine selective inhibitor of xanthine oxidase inhibits both the oxidised and the reduced forms of the enzyme, but not other enzymes in purine and pyrimidine metabolism. Thus, febuxostat reduces the formation of xanthine and uric acid. The enzymes in shaded boxes have been shown to be inhibited by allopurinol, oxypurinol or their metabolites. Reprinted from *Life Sci.* (**76**): TAKANO Y, HASE-AOKI K, HORIUCHI H *et al.*: Selectivity of febuxostat, a novel non-purine inhibitor of xanthine oxidase/xanthine. 1835-1847 © (2005), with permission from Elsevier.

AMP: Adenosine monophosphate; CTP: Cytidine 5′-triphosphate; GMP: Guanosine 5′-monophosphate; HGRTP: Hypoxanthine guanine phosphoribosyl transferase; IMP: Inosine 5′-monophosphate; OMP: Orotidine monophosphate; OMPDC: Orotidine monophosphate decarboxylase; OPRT: Orotate phosphoribosyl transferase; PNP: Purine nucleoside phosphorylase; PRPP: 5-Phosphoribosyl-1-pyrophosphate ; UA: Uric acid; UMP: Uridine 5′-monophosphate; UTP: Uridine 5′-triphosphate; XOD: Xanthine oxidase dehydrogenase.

blood sampling were performed to assess the pharmacodynamic effects on uric acid, xanthine and hypoxanthine. Daily doses of febuxostat in the range of 10 – 120 mg produced dose-linear mean sUA reductions that ranged from 25 to 70% [43,52]. A dose-linear response relationship was also observed for increases in 24-h mean serum xanthine concentrations in the febuxostat 10 – 90 mg dose range [43,52]. These effects appeared to plateau at febuxostat doses higher than 90 and 120 mg/day for serum xanthine and uric acid concentrations, respectively. A decrease in total daily urinary uric acid excretion and a substantial increase in total daily urinary xanthine excretion were observed [43,52].

In Phase III clinical studies (reviewed in Section 4) performed in Japanese subjects, the effects of febuxostat on sUA were found to be comparable in subjects whose pathogenesis of hyperuricaemia was due to underexcretion (uric acid clearance/CrCl ≤ 5.5; including mixed type with underexcretion and overproduction) or non-underexcretion [53,54].

4. Clinical efficacy

4.1 Phase I studies

The results of Phase I studies of febuxostat are presented in Sections 3.2 and 5.

4.2 Phase II studies

4.2.1 Dose-ranging urate-lowering efficacy studies

In a placebo-controlled, 8-week, randomised, multi-centre, double-blind study performed in Japan, the efficacy and safety of febuxostat 10, 20 and 40 mg/day for 6 weeks was evaluated in 128 subjects with gout or hyperuricaemia (baseline sUA ≥ 8 mg/dl) [55]. A total of 32 subjects were randomised to each of the four treatment groups and were treated for 2 weeks with placebo (those randomised to placebo) or a 10-mg lead-in dose of febuxostat (those randomised to febuxostat 10, 20 or 40 mg) prior to the commencement of the 6-week study period. Dose-dependent reductions in sUA and the percentages of patients who attained a sUA level ≤ 6 mg/dl were observed in the treatment groups. Mean percentage decreases in sUA from baseline were 20.1, 31.5 and 41.9% in those treated with febuxostat 10, 20 and 40 mg, respectively. The proportions of subjects with sUA ≤ 6 mg/dl were 22, 63 and 78% in those treated with febuxostat 10, 20 and 40 mg, respectively. Patients treated with placebo exhibited a 0.1% mean percentage decrease in sUA and no placebo-treated patient attained a sUA ≤ 6 mg/dl.

A placebo-controlled 4-week, randomised, multi-centre, double-blind study performed in the US evaluated the dose-response efficacy of febuxostat 40, 80 and 120 mg/day in 153 patients with hyperuricaemia (baseline sUA ≥ 8 mg/dl) and gout [56]. Significantly greater proportions of febuxostat-treated than placebo-treated subjects achieved sUA ≤ 6 mg/dl at each visit ($p < 0.001$ for each comparison). At day 28, sUA < 6 mg/dl was achieved in 56, 76 and 94% of those treated with febuxostat 40, 80 and 120 mg/day, respectively, compared with 0% of the patients treated with placebo.

The urate-lowering efficacy of febuxostat is sustainable, even with extended treatment [57,58]. In an ongoing extension of a Phase II, 4-week study [57], 116 subjects were given febuxostat

Table 1. Selected pharmacokinetic parameters of febuxostat in healthy subjects.

		AUC (μg·h/ml)*‡		C_{max} (μg/ml)‡		t_{max} (h)‡		$t_{½}$ (h)§	
Dose	***Number***	***Single***	***Multiple***	***Single***	***Multiple***	***Single***	***Multiple***	***Single***	***Multiple***
40 mg/day	10	4	4.3	1.53	1.82	1.4	1.2	3.8	6.3
50 mg/day	20	4.41	4.38	1.97	1.79	0.8	1.1	4.5	6.7
70 mg/day	10	6.93	6.95	3.08	2.69	1	1.1	4.7	8.5
80 mg/day	11		7.5 ± 2.68		2.87 ± 1.25		1¶		4.71
90 mg/day	10	9.09	9.65	3.48	4.06	1	1	6.8	10
120 mg/day	10	11.31	11.96	4.47	5.31	1	1.1	9.1	11.9

*AUC refers to AUC_{∞} and AUC_{24} after single and multiple oral dosing, respectively. ‡Harmonic mean. §Presented as arithmetic mean. ¶Presented as median.
Data for 40, 50, 60, 90 and 120 mg/day from [43]. Data for 80 mg/day dose from [44].
AUC: Area under curve; C_{max}: Maximum plasma concentration; $t_{½}$: Half-life; t_{max}: Time to maximum concentration.

80 mg/day, titrated to 40 or 120 mg/day based on sUA and occurrence of adverse events. Between 74 and 81% of the subjects at each treatment visit had sUA values < 6 mg/dl with the mean percentage reduction from baseline in sUA at each visit ranging from 45 to 48%. Most of the patients (72%) were maintained on febuxostat 80 mg/day with 20% given 120 mg/day and 9% given 40 mg/day. It is not clear whether even higher percentages would achieve serum urates < 6 mg/dl if more patients were given 120 mg.

4.2.2 Gout flare

In a Phase II, placebo-controlled, 4-week trial reviewed in Section 4.2.1 [56], 153 patients were given colchicine prophylaxis for 14 days prior to and 14 days following febuxostat 40, 80 and 120 mg once-daily treatment initiation. During the period of colchicine prophylaxis, the incidences of gout flare were 11, 8, 8 and 13% in those randomised to placebo, febuxostat 40, 80 and 120 mg, respectively. As expected, higher incidences of gout flare occurred when colchicine prophylaxis was discontinued. The incidences of gout flare were 34, 30, 40 and 42% when placebo, febuxostat 40, 80 and 120 mg were administered alone, respectively.

In the ongoing extension of this study [57,58] discussed in Section 4.2.1, colchicine prophylaxis was administered to the 116 subjects treated initially with febuxostat 80 mg/day and titrated to 40 or 120 mg based on sUA and adverse events. Gout-flare incidence was lower during colchicine prophylaxis (10% at 1 month). Cessation of colchicine was associated with an increase in gout flare (58% at 3 months) that gradually declined with continued febuxostat treatment (35% at 6 months, 26% at 1 year and 17% at 2 years) [58]. This long-term lowering of sUA can decrease gout flares.

4.2.3 Febuxostat use in allopurinol-intolerant patients

Results of a Phase II open-label extension study discussed in Section 4.2.1 indicate that long-term treatment with febuxostat maintains its sUA-lowering efficacy and is well tolerated, even in those patients with a history of allopurinol intolerance. A total of eight patients who had been allopurinol intolerant (defined as a history of a reaction precluding rechallenge) with gout and persistent hyperuricaemia (baseline sUA ranged from 8.2 to 11.1 mg/dl) entered an open-label extension study following the completion of a double-blind Phase II study [59]. Subjects were treated with febuxostat 80 mg/day, titrated to 40 or 120 mg/day based on sUA levels and occurrence of adverse events. During the open-label treatment period, sUA was maintained near or < 6 mg/dl. Treatment with febuxostat was well tolerated in these patients, with 75% (six of eight) of the patients continuing febuxostat treatment for ≥ 2 years.

4.3 Phase III studies

4.3.1 Comparison with allopurinol and placebo with serum uric acid < 6 mg/dl as the end point

The uric acid-lowering efficacy and safety of febuxostat was compared with that of allopurinol in a multi-centre study performed in the US and Canada [60]. A total of 760 patients (96% males) were randomised to 52 weeks of treatment with febuxostat 80 mg/day (n = 256), febuxostat 120 mg/day (n = 251) or allopurinol 300 mg/day (n = 253). The mean sUA at baseline was 9.84 ± 1.26 mg/dl, with 40% of the patients having baseline sUA values > 10 mg/dl. The majority of subjects were obese (62%), reported the use of alcohol (66%), with substantial percentages having hypertension (44%), impaired renal function (CrCl < 80 ml/min) and/or hyperlipidaemia (34%). The primary efficacy end point was the percentage of patients reaching a sUA level of < 6 mg/dl at the last three monthly visits. Significantly ($p < 0.05$) greater percentages of patients treated with febuxostat 80 or 120 mg/day attained and maintained sUA levels of < 6 mg/dl (53% [136/255] and 62% [154/250], respectively) compared with patients treated with allopurinol 300 mg (21% [53/251]) (**Figure 4**). At the final 52-week visit, 81% (129/159) and 82% (119/145) of those treated with febuxostat 80 and 120 mg/day, respectively, had a sUA of < 6 mg/dl compared with 39% (70/178) of those treated with allopurinol 300 mg ($p < 0.05$ for the comparisons between febuxostat 80 and 120 mg versus allopurinol 300 mg).

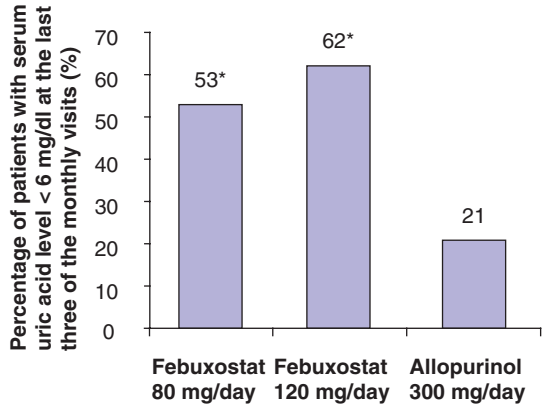

Figure 4. Percentage of patients with serum uric acid levels < 6 mg/dl during the last three of the monthly visits from a Phase III US study enrolling patients with serum uric acid ≥ 8 mg/dl at baseline. In this US study, > 40% of the patients had baseline serum uric acid values > 10 mg/dl. The mean serum uric acid among all of the patients was 9.8 ± 1.26 mg/dl. Febuxostat 80 or 120 mg/day produced percentages of patients (53 and 62%, respectively) with serum uric acid < 6 mg/dl that were significantly ($p < 0.001$) greater than that observed with allopurinol (21%). Adapted from [63].

In two double-blind, multi-centre, placebo- or allopurinol-controlled trials conduced in Japan, the efficacy and safety of febuxostat in subjects with gout or hyperuricaemia (baseline sUA ≥ 8mg/dl) were evaluated [53,54]. In the placebo-controlled study [53], subjects were randomised to placebo or febuxostat 10 mg/day during a 2-week introductory phase, followed by treatment with either placebo or febuxostat 20 or 40 mg during the 6-week treatment phase. In the allopurinol-controlled study [54], 256 subjects were treated with allopurinol 100 mg/day or febuxostat 10 mg/day during a 12-day introductory phase, followed by treatment with allopurinol 100 mg b.i.d. or febuxostat 40 mg/day during the 44-day treatment phase. Significantly higher percentages of patients treated with febuxostat attained sUA levels of ≤ 6 mg/dl as compared with those treated with placebo or allopurinol (**Figure 5A** and **5B**). In both studies, the percentage decreases from baseline in sUA were comparable in those subjects whose hyperuricaemia was due to underexcretion or non-underexcretion (overproducers and normal) [53,54]. The percentage decreases in sUA for underexcretors and non-underexcretors treated with febuxostat were 41.3 and 41.4%, respectively, compared with 34.7 and 34.4%, respectively, observed in those patient subgroups treated with allopurinol [49].

Comparing and contrasting the results from the US and Canada study [60] with those of the Japanese studies [53,54] highlights several interesting observations. In the Japanese studies, higher percentages of patients achieved the target sUA end point with lower doses of febuxostat as compared with the findings observed in the US and Canada trial [60]. This may be due to differences in the baseline characteristics of the patients as well as the efficacy evaluation end point. The Japanese often use lower doses of many drugs. Although all of the studies enrolled patients with baseline sUA levels of ≥ 8 mg/dl, > 40% of those in the US and Canada trial had sUA levels > 10 mg/dl (mean 9.8 mg/dl) at baseline whereas the mean baseline sUA level data, which was not stated by the Japanese investigators, may have been lower.

4.4 Comparison with allopurinol: gout flares and tophi reduction end points

In the Phase III US and Canada clinical trial described in Section 4.3.1, patients randomised to febuxostat 80 or 120 mg or allopurinol 300 mg were given co-therapy with colchicine 0.6 mg/day or naproxen 250 mg b.i.d. for the first 8 weeks of the study to reduce the risk of acute gout flare [60]. Significantly higher percentages of patients in each febuxostat group attained sUA levels of < 6 mg/dl at the last three of the monthly visits as well as at the 52-week visit compared with those in the allopurinol group ($p < 0.05$ for each comparison). Overall, the subjects who achieved an average post-baseline sUA level of < 6 mg/dl had fewer gout flares requiring treatment (6 versus 14%) and a greater median reduction in tophus area (75 versus 50%) at week 52 compared with those who did not.

5. Tolerability

To date, clinical reports indicate that febuxostat 10 – 300 mg/day is well tolerated with a safety profile that is comparable with that of placebo and allopurinol. In the nearly 1200 patients enrolled in the Phase II double-blind and open-label extension studies and Phase III double-blind studies described in Sections 4.2 and 4.3, febuxostat treatment was well tolerated with adverse events being mild-to-moderate in severity and transient in nature. In the long term Phase II extension study of 116 subjects [58], the most common treatment-related adverse events were diarrhoea (9%, n = 10) with five subjects having an alternate aetiology of colchicine administration and headache (4%, n = 5). Five subjects (4%) also had abnormal liver function tests that were possibly associated with concomitant colchicine administration. Among the eight subjects with a history of allopurinol intolerance entered into a Phase II extension study [59], one subject experienced possibly related abdominal and truncal rashes during treatment. The study drug was stopped and resumed without rash recurrence. A second subject developed a transient facial rash that lasted for 6 days and resolved while on the study drug without treatment. In the large (n = 760) Phase III double-blind trial [60], in which patients were given febuxostat 80 or 120 mg, or allopurinol 300 mg with colchicine or naproxen prophylaxis for the first 8 weeks, the most frequent treatment-related adverse events listed were liver function abnormalities (4, 5 and 4% in each treatment group, respectively), diarrhoea (3% in each group), headaches (1, 2 and 3%), joint-related signs and symptoms (< 1, 2 and 2%), and musculoskeletal/connective tissue signs

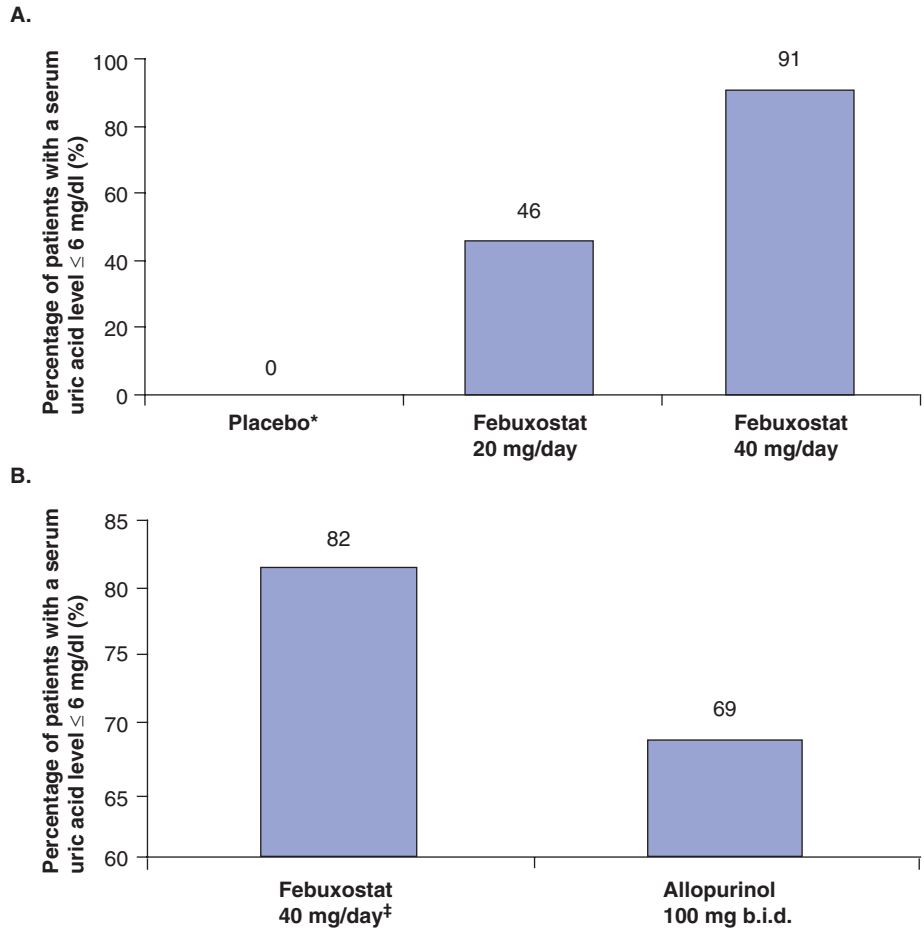

Figure 5. Proportions of subjects with serum uric acid levels ≤ 6 mg/dl by treatment group from two Phase III studies in Japan enrolling patients with serum uric acid ≥ 8 mg/dl at baseline. A. Febuxostat 20 and 40 mg produced a dose-dependent decrease from baseline serum uric acid level with the reductions produced by each dose being significantly greater than placebo ($p \leq 0.006$). The reductions in serum uric acid produced by febuxostat were comparable in those with gout or hyperuricaemia.
B. The proportion of subjects that attained the critical threshold of serum uric acid ≤ 6 mg/dl was significantly greater in febuxostat-treated versus allopurinol-treated patients (82 versus 69%, $p = 0.019$). Febuxostat also produced a percentage decrease in serum uric acid from baseline that was significantly greater than that produced by allopurinol (-40.5 versus 33.9%, respectively; $p < 0.001$). Adapted from [54] and [56], respectively.
*$p < 0.001$ placebo compared with febuxostat 20 mg/day, $p = 0.006$ placebo compared with febuxostat 40 mg/day. ‡$p = 0.019$ febuxostat 40 mg/day versus allopurinol 100 mg b.i.d.

and symptoms (2, 1 and 2%). Overall, 5 – 6% of the patients in each treatment group exhibited abnormalities in liver function tests that were associated with the administration of colchicine either alone or in combination with febuxostat or allopurinol. These liver function test abnormalities returned to normal either during continued study drug administration, after withdrawal of colchicine or at the completion of the study period.

Three Phase I studies have reported similar adverse events and incidences. In a Phase I study involving 154 healthy volunteers [59] treated with single- and multiple-dose febuxostat at doses ranging from 10 to 240 mg/day, the most common treatment-related adverse events were headache, nausea, flushing or vasodilation, and dizziness, with all of the adverse events being self limited. A total of nine subjects withdrew from the study due to an adverse event (fever, myalgia, confusion, asthenia, abdominal pain and tachycardia). No deaths or serious adverse events occurred. In a Phase I study of the effects of age and gender on febuxostat pharmacodynamics and pharmacokinetics [45], the most common adverse events were headache and constipation with the overall incidence of adverse events being lower in men versus women (13 versus 54%), and in those between 19 and 40 compared with those between 65 and 76 years of age (25 versus 42%). In a four-period, placebo-controlled, active-comparator (moxifloxacin) crossover Phase I study [61] designed to assess the effect of febuxostat on the QT interval, the most common adverse events were diarrhoea, abdominal pain, nausea, vomiting, hot flushes and headache. Administration of febuxostat at doses of 80 or

300 mg/day for 4 days did not produce any prolongation of the QT interval.

6. Conclusions

The primary treatment goal for patients with gout is to reverse its pathogenesis, that is, hyperuricaemia, and thereby prevent progression of the disease. Febuxostat is the first compound from what may be an emerging class of antihyperuricaemic agents, the non-purine selective inhibitors of xanthine oxidase. It displays dose-linear pharmacokinetics, and in studies of 80 mg/day, does not appear to require dose adjustment in those with moderate renal insufficiency or hepatic impairment. The results of Phase II and III clinical studies of febuxostat are promising, it produces a substantial reduction in sUA that is sustainable with long-term treatment. The effects of febuxostat are consistent regardless of whether the hyperuricaemia is due to uric acid overproduction or underexcretion. Febuxostat is well tolerated with the majority of treatment-related adverse events being mild-to-moderate in severity and transient in nature.

7. Expert opinion

It has been > 40 years since clinicians have had a new oral treatment for patients with chronic gout. Febuxostat is the first agent in a proposed class of non-purine selective inhibitors of xanthine oxidase. In clinical studies, febuxostat was found to produce reliable reductions in sUA. It may be that the unique non-purine structure of febuxostat will result in a favourable tolerability and safety profile. In clinical trials, febuxostat 80 or 120 mg/day was shown to be as or more effective than allopurinol 300 mg in reducing sUA levels to below the threshold of 6 mg/dl that is critical for ultimately reducing the risk of acute gout flares as well as tophus size reduction. Doses of febuxostat, as with allopurinol, should be titrated to achieve serum urates of < 6 mg/dl. Febuxostat can broaden the pharmacological armamentarium for the safe management of patients with chronic gout. It may be of most immediate value in those with allopurinol hypersensitivity and with renal disease, in whom allopurinol use has been difficult. As febuxostat can quickly and dramatically lower sUA, colchicine or other prophylaxis will be important for the first months after its initiation to reduce gout flares.

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Affiliation

H Ralph Schumacher Jr, MD
University of Pennsylvania and VA Medical Center, Philadelphia, Pennsylvania, USA
E-mail: schumacr@mail.med.upenn.edu