

Febuxostat in the management of hyperuricemia and chronic gout: a review

Miao Hu
Brian Tomlinson

Division of Clinical Pharmacology,
Department of Medicine
and Therapeutics, The Chinese
University of Hong Kong, Prince
of Wales Hospital, Shatin,
New Territories, Hong Kong SAR,
China

Abstract: Febuxostat is a novel, potent, non-purine selective xanthine oxidase inhibitor, which in clinical trials demonstrated superior ability to lower and maintain serum urate levels below 6 mg/dL compared with conventionally used doses of allopurinol. Febuxostat was well tolerated in long term treatment in patients with hyperuricemia including those experiencing hypersensitivity/intolerance to allopurinol. Dose adjustment appears unnecessary in patients with mild to moderate renal or liver insufficiency or advanced age. The most common adverse reactions reported were abnormal liver function tests, headache, and gastrointestinal symptoms, which were usually mild and transient. However, whether hepatotoxicity becomes a limitation in the use of febuxostat needs to be determined in further studies. An increased frequency of gout flares occurs for a prolonged period after treatment initiation, as with any aggressive lowering of serum urate, and prolonged prophylaxis with colchicine or NSAIDs is usually required. Febuxostat has been granted marketing authorization by the European Commission in early 2008 for the treatment of chronic hyperuricemia and gout. Febuxostat is the first major treatment alternative for gout in more than 40 years and is a promising alternative to allopurinol, although continued long-term surveillance on safety and efficacy is required.

Keywords: febuxostat, TEI-6720, TMX-67, gout, hyperuricemia, xanthine oxidase inhibitor

Introduction

Gout occurs as an acute arthritis that appears when there is a sudden onset of inflammation in response to the accumulation of crystals of monosodium urate in or around a joint (Schlesinger 2004), which is closely associated with hyperuricemia. With persistent urate crystal deposition, gout may progress from acute episodic attacks to a disabling chronic deforming arthropathy, with destructive deposits of urate crystals (tophi) in bones, joints, subcutaneous tissue, and other organs (Becker 1988; Becker et al 2005b; Tomlinson 2005). Renal damage may occur due to interstitial urate crystal deposition and urinary tract stones composed entirely or partly of monosodium urate and uric acid crystals (Becker 1988; Schlesinger 2004).

The development of gout can be divided into four stages: asymptomatic hyperuricemia, the gouty attack, the intercritical period, and chronic gouty arthritis. It has been recognized that hyperuricemia may exist for many years before the first clinical attack of gout (Falasca 2006). Hyperuricemia has been thought to be the fundamental pathogenic biochemical aberration upon which various etiological factors predispose to the expression of the clinical disorder of gout (Teng et al 2006). Moreover, hyperuricemia is also associated with chronic renal damage (Iseki et al 2004), some metabolic disturbances and risk factors for atherosclerotic cardiovascular disease including hypertension, overweight, insulin resistance, and hyperlipidemia (Slot 1994), which may occur together as the metabolic syndrome. This may explain the recognized association between gout and cardiovascular disease (Abbott et al 1988; Krishnan et al 2006; Choi and Curhan 2007), although there are no studies to show

Correspondence: Brian Tomlinson
Division of Clinical Pharmacology,
Department of Medicine and
Therapeutics, The Prince of Wales
Hospital, Shatin, Hong Kong
Tel +852 2632 3139
Fax +852 2632 3139
Email btomlinson@cuhk.edu.hk

whether lowering plasma urate will reduce the cardiovascular risk in humans (Kim et al 2003; Wortmann 2005).

Multiple epidemiological studies from a diverse range of countries suggest that gout has increased in prevalence and incidence in the past few decades and the profile of clinical gout is becoming more complex (Roddy et al 2007). The established risk factors for gout include genetic factors, excess alcohol consumption, purine-rich diet, metabolic syndrome, use of diuretics, and chronic renal failure (Roddy et al 2007). Trends in lifestyle and dietary factors may partly explain the changes in the epidemiology of gout (Hak and Choi 2008). Furthermore, suboptimal management also contributes to the rising prevalence of clinically symptomatic chronic gout (Roddy et al 2007).

Conventional dietary recommendations for gout have emphasized the restriction of purine intake. There are two main approaches: the traditional low purine, low protein, alcohol-restricted diet, and more recently, a weight-reducing, purine-unlimited, calorie- and carbohydrate-restricted diet, with increased proportional intake of both protein and unsaturated fats. However, a rigid purine restricted diet is of dubious therapeutic value and there are also no long-term studies of the efficacy of either approach (Fam 2002).

The treatment for an acute attack of gout is usually either colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs). For chronic gout, prophylactic therapy to reduce the serum urate level is thought to be appropriate in patients who have more than two gout flares a year or in individuals with gouty complications, and this could reduce the likelihood of recurrent gout by 80% (Emmerson 1996; Choi et al 2005; Bruce 2006). The physiochemical properties of monosodium urate cause crystals to precipitate in body fluids if the concentration is greater than 6.8 mg/dL (400 μ mol/L). Hence the target of urate lowering therapy is to reduce the serum urate concentration to below 6.0 mg/dL (353 μ mol/L), which should prevent the recurrence of gouty attacks or at least reduce their frequency substantially and allow the remission in size of gouty tophi (Wortmann 2005).

It was previously considered that it may be useful to divide subjects with hyperuricemia into those who are urate overproducers from those who are underexcretors, based on the 24-hour uric acid excretion (Wortmann 2002). Underexcretors may be candidates for uricosuric drugs such as probenecid or benzbromarone, but probenecid has limited efficacy and/or safety in patients with renal impairment or prior urolithiasis, and the more potent uricosuric agent benzbromarone was associated with several cases

of fulminant hepatic failure and is not generally available (Emmerson 1996; Li-Yu et al 2001; Becker et al 2005b).

The urate-lowering therapy allopurinol, a xanthine oxidase (XO) inhibitor, has been the mainstay of prophylactic treatment for gout and conditions associated with hyperuricemia for many years (Wortmann 2002). It is the treatment of choice for urate overproducers, tophaceous gout, nephrolithiasis, or urate nephropathy, and in patients with renal insufficiency (Teng et al 2006). In theory allopurinol should be effective in almost every patient with hyperuricemia if a sufficient dose is taken, but achieving normal serum urate levels may be difficult in patients with impaired renal function or in transplant recipients (Schlesinger 2004). In practice approximately 20% of patients report side effects with allopurinol and 5% discontinue medication (Wortmann 2005). There is a rare but serious hypersensitivity reaction to allopurinol, which involves fever, rash, eosinophilia, hepatitis, and progressive renal insufficiency (Schlesinger 2004; Wortmann 2005). This appears to be dose- or plasma concentration-dependent and can cause up to 20% mortality (Teng et al 2006). Patients with renal insufficiency or receiving diuretic therapy are at increased risk of adverse effects (Wortmann 2005). It has been found that severe cutaneous adverse reactions, which include the drug hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis are strongly associated with the HLA-B*5801 allele in Han Chinese patients, which could be developed as a screening test to identify the risk before commencing therapy (Hung et al 2005). As a result of frequent failure to reach target serum urate levels, or the intolerance to allopurinol in some patients, the development of an alternative potent serum urate lowering treatment has been a desirable goal. Febuxostat is a novel potent selective inhibitor of XO that appears to be well tolerated in all groups of patients, including those who are sensitive to allopurinol.

Pharmacology

Febuxostat, {TEI-6720, TMX-67, 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methyl- thiazole-5-carboxylic acid}, is a non-purine compound with the empiric chemical formula $C_{16}H_{16}N_2O_3S$ and molecular weight of 316.38 (Bruce 2006). It is a selective inhibitor of XO that has been developed for the treatment of hyperuricemia and gout, as it was found to have a potent inhibitory activity for XO/xanthine dehydrogenase (XDH) during evaluation of a range of newly synthesized molecules (Komoriya et al 1993). In humans, the xanthine oxidoreductase (XOR) enzyme catalyzes the last two steps in uric acid synthesis, the oxidation of hypoxanthine to xanthine

and of xanthine to uric acid (hypoxanthine → xanthine → uric acid). Humans and the great apes lack the enzyme uricase which converts uric acid into allantoin (Osada et al 1993). Some non-enzymatic conversion of uric acid to allantoin does take place and the ratio of serum urate to allantoin has been considered as a potential marker of oxidative stress (Benzie et al 1999).

XOR is synthesized as XDH, which in mammals can easily be converted to XO by oxidation of sulfhydryl residues or by proteolysis (Okamoto et al 2003). Febuxostat was shown to inhibit both the oxidized and reduced forms of XO, unlike allopurinol and oxypurinol, each of which binds only to one form of the enzyme (Okamoto et al 2003; Takano et al 2005). The molecular mechanism of inhibition of XO activity by febuxostat (Adenuric[®], Ipsen, Paris, France) is by high affinity binding to the enzyme in a molecular channel leading to the molybdenum-pterin active site, whereas allopurinol exerts relatively weak competitive inhibition on activity of only the oxidized form of XO (Okamoto et al 2003; Takano et al 2005). In contrast to allopurinol and oxypurinol, febuxostat does not structurally resemble purines or pyrimidines and has no significant effect on the activities of other enzymes involved in purine and pyrimidine metabolism, which might relate to some of the adverse effects caused by allopurinol and its metabolites (Takano et al 2005).

More recently, Okamoto and Nishino have reported that XOR inhibitors can be categorized into different types according to the crystal structure of the various inhibitors binding to XOR (Okamoto and Nishino 2008). Febuxostat has numerous hydrogen bonds, salt bridges, and hydrophobic interactions with amino acids in the active site and almost completely fills the narrow channel leading to the molybdenum center of the enzyme, which is considered as a structure-based inhibitor, whereas allopurinol and oxypurinol are thought to be mechanism-based inhibitors (Okamoto and Nishino 2008). The XO inhibitory activity and hypouricemic effect of febuxostat compared to allopurinol have been studied *in vitro* and in a variety of animal models (Komoriya et al 1993; Osada et al 1993; Horiuchi et al 1999). All these studies demonstrated that febuxostat had a greater potency than allopurinol in reducing serum urate levels and/or allantoin levels. Furthermore, the pleiotropic effects of febuxostat dependent on its hypouricemic effect have also been investigated and these studies provided a foundation for later evaluations in humans (Sanchez-Lozada et al 2008a, b, c; Zhao et al 2008).

As increased fructose consumption is associated with hyperuricemia, the metabolic syndrome, and renal damage,

Sanchez-Lozada et al evaluated whether febuxostat could alleviate some of the features of the metabolic syndrome as well as the renal hemodynamic alterations and afferent arteriopathy induced by a high-fructose diet in rats. They found that a high-fructose diet was associated with hyperuricemia, hypertension, as well as increased plasma triglycerides and insulin. Febuxostat treatment in rats on a high-fructose diet resulted in significant lowering of blood pressure, serum urate, triglycerides, and insulin ($p < 0.05$ for all comparisons) compared with those without treatment, and it also significantly reduced glomerular pressure, renal vasoconstriction, and afferent arteriolar area relative to those without treatment. However, febuxostat treatment in rats on a normal diet had no significant effects (Sanchez-Lozada et al 2008a).

Considering the close association between prolonged hyperuricemia and renal disease, Sanchez-Lozada et al evaluated the effect of febuxostat on progressive renal disease in a 5/6 nephrectomy (5/6 Nx) model in Wistar rats with and without hyperuricemia induced by the uricase inhibitor oxonic acid (OA) (Sanchez-Lozada et al 2008b). The 5/6 Nx rats given OA and placebo developed hyperuricemia, renal vasoconstriction and glomerular hypertension in association with further aggravation of afferent arteriopathy compared with those without OA-induced hyperuricemia. Febuxostat prevented OA-induced hyperuricemia and in 5/6 Nx rats with or without OA-induced hyperuricemia it ameliorated proteinuria, preserved renal function and prevented glomerular hypertension. Functional improvement was accompanied by preservation of afferent arteriolar morphology and reduced tubulointerstitial fibrosis. These results suggested that febuxostat prevented renal injury in 5/6 Nx rats with and without coexisting hyperuricemia and due to its effect on preserving preglomerular vessel morphology, normal glomerular pressure was maintained even in the presence of systemic hypertension (Sanchez-Lozada et al 2008b).

Using different animal models, the same group of researchers also examined the effect of febuxostat on hyperuricemia-induced hypertension and renal damage (Sanchez-Lozada et al 2008c). They found that in OA-induced hyperuricemic rats, febuxostat lowered uric acid and ameliorated systemic and glomerular hypertension as well as mesangial matrix expansion and the development of preglomerular arteriolar disease as indicated by a reduction of the arteriolar area and media-to-lumen ratio. In normal rats, febuxostat tended to lower uric acid but had no effect on blood pressure, renal hemodynamics, and afferent arteriole morphology. The authors suggested that febuxostat merits further evaluation

for the treatment of hypertension and renal alterations induced by hyperuricemia (Sanchez-Lozada et al 2008c).

More recently, Zhao et al (2008) reported the effects of chronic XO inhibition by febuxostat or allopurinol on the progression of chronic heart failure (CHF) induced by left coronary artery ligation in rabbits, which have low intrinsic myocardial XO activity similar to humans. One day after coronary ligation, rabbits were assigned to early treatment with vehicle or febuxostat for 49 days or to delayed-treatment with vehicle for 21 days followed by either febuxostat or allopurinol for 28 days. Treatment with febuxostat initiated shortly after myocardial infarction delayed or prevented the onset of CHF, but XO inhibition with either drug initiated after establishment of the disease had no cardiac protection effects (Zhao et al 2008).

Pharmacokinetics

After oral administration, about 85% of febuxostat is absorbed rapidly with a time (t_{\max}) to reach peak plasma concentrations (C_{\max}) of approximately 1 hour in healthy human subjects (Bruce 2006). In a phase I study in which oral febuxostat doses of 40, 70, and 120 mg were given to healthy male and female adults ($n = 154$), C_{\max} values of 1.53, 3.08, and 4.47 $\mu\text{g/mL}$ occurred at t_{\max} of about 1 hour, with area under the plasma concentration-time curve (AUC) values of 4.00, 6.93, and 11.31 $\mu\text{g}\cdot\text{h/mL}$, respectively. The elimination half-life ($t_{1/2}$) values tended to increase (from 3.8 to 9.1 hours) with increasing doses and were longer after multiple doses (6.3 to 11.9 hours) compared with single doses (Becker et al 2004a). Escalating dose pharmacokinetic studies of single and multiple doses of febuxostat in healthy volunteers have

shown that C_{\max} and AUC exhibit an approximately linear relation with single doses of 10 to 240 mg and 10 to 120 mg, respectively, and nearly dose proportional increases were noted for both C_{\max} and AUC after multiple oral doses with a mean apparent total clearance of 10 to 12 L/h and an apparent volume of distribution at steady state of 33 to 64 L (Becker et al 2004a; Khosravan et al 2006b). The AUC increased more than proportionally between the groups receiving 120 and 240 mg daily suggesting some enterohepatic recirculation (Becker et al 2004a; Khosravan et al 2006b) (Table 1).

Febuxostat is highly bound to albumin in blood (~99%) and appears to have a low to medium apparent volume of distribution at steady state of approximately 0.7 L/kg (Mayer et al 2005). The metabolism of febuxostat occurs predominantly in the liver by glucuronidation to produce the acyl-glucuronide metabolite (22%–44% of the dose), and to a much lesser extent (2%–8%), to produce oxidative metabolites, 67M-1, 67M-2, and 67M-4 (Figure 1) by cytochrome P450 enzymes (Khosravan et al 2006b). Approximately 25% to 45% of the drug was excreted in urine mainly as the conjugate with only about 1% to 6% being eliminated as the unchanged drug. An additional 2% to 8% of the dose was excreted as oxidative metabolites, either unchanged or as conjugates. Age and gender did not have statistically or clinically significant effects on the pharmacokinetics, pharmacodynamics or safety of febuxostat in healthy individuals after daily oral dosing with febuxostat at 80 mg for 7 days, which suggested that no dose adjustment should be necessary when administering febuxostat based on age or gender (Khosravan et al 2008b). Patients with gout and/or hyperuricemia treated

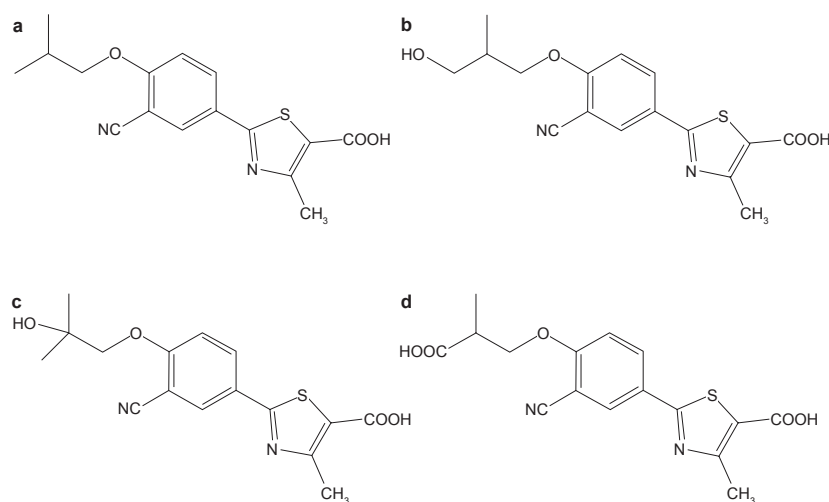


Figure 1 Chemical structures of (a) febuxostat and metabolites (b) 67M-1, (c) 67M-2, and (d) 67M-4. Adapted with permission from Khosravan R, Grabowski BA, Wu JT, et al. 2006b. Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin Pharmacokinet*, 45:821–41. Copyright © 2006 Wolters Kluwer.

with oral febuxostat at 10 mg daily for 2 weeks, then 20 mg daily for a further 4 weeks had similar AUC and C_{\max} values for febuxostat after the last dose as those reported for the same dose in healthy male adults (Komoriya et al 2003).

Renal impairment

Although renal clearance may only contribute to a small degree to the total systemic clearance of febuxostat, the effects of renal impairment on the pharmacokinetics and pharmacodynamics of febuxostat have been evaluated considering this is of clinical importance as many patients with gout may have impaired renal function. A clinical study was conducted to examine the pharmacokinetics and pharmacodynamics of febuxostat in individuals ($n = 15$) with mild (creatinine clearance [Cl_{cr}] 50–80 mL/min) or moderate (Cl_{cr} 30–50 mL/min) impairment in renal function, compared with healthy ($Cl_{cr} \geq 80$ mL/min) participants (Hoshide et al 2004). The difference in plasma AUC for unchanged febuxostat after single oral doses of 20 mg febuxostat was less than 2-fold across the groups, indicating that renal impairment had little clinical impact on the pharmacokinetic profile. Changes in plasma urate levels from pre-dose levels were not significant in this study (Hoshide et al 2004).

Another parallel-group, open-label, multiple-dose study compared the safety, pharmacokinetics, and pharmacodynamics of febuxostat (80 mg/d), administered orally for 7 days, in individuals with normal renal function ($Cl_{cr} > 80$ mL/min/1.73 m; $n = 11$), or mild (Cl_{cr} 50–80 mL/min/1.73 m; $n = 6$), moderate (Cl_{cr} 30–49 mL/min/1.73 m; $n = 7$), or severe (Cl_{cr} 10–29 mL/min/1.73 m; $n = 7$) renal impairment. Mean unbound febuxostat t_{\max} and C_{\max} values in subjects with various degrees of renal impairment were similar to those in subjects with normal renal function, whereas the mean $AUC_{(24\text{h})}$ unbound and $t_{1/2z}$ ($t_{1/2}$ obtained by a non-compartment analysis from the terminal slope of the concentration-time curve) values tended to increase with increasing renal impairment. For the C_{\max} and $AUC_{(24\text{h})}$ values for the quantifiable active metabolites 67M-1, 67M-2, and 67M-4, with the exception of C_{\max} for 67M-1, regression analyses indicated a significant linear relationship with Cl_{cr} , suggesting that plasma exposure to the metabolites as well as febuxostat was generally increased in proportion to the degree of renal impairment. Although plasma exposure to febuxostat and its metabolites was generally higher in subjects with increasing degrees of renal impairment, the percentage reductions in serum urate were comparable, with a mean value of 55% to 64% by day 7 irrespective of renal function. The 80-mg once-daily dose of febuxostat was safe

and well tolerated and the investigators concluded that no dose adjustment is required based on differences in renal function (Mayer et al 2005).

Hepatic impairment

As hepatic metabolism plays an important role in febuxostat elimination the effects of hepatic impairment on the pharmacokinetics, pharmacodynamics, and safety of febuxostat were investigated in a phase I study in individuals with normal ($n = 11$), mildly impaired (Child-Pugh class A; $n = 8$) or moderately impaired (Child-Pugh class B; $n = 8$) hepatic function. Subjects took oral febuxostat 80 mg daily for 7 days. There were smaller reductions in serum urate in the patients with hepatic impairment than in those with normal hepatic function but no differences in the pharmacokinetic parameters of febuxostat or its metabolites, suggesting the dosage may not need to be reduced in patients with mild or moderate hepatic dysfunction (Khosravan et al 2006a). However, the safety and efficacy of febuxostat in patients with severe hepatic impairment has not been studied. Liver toxicity was not reported in any of the animal studies.

Drug interactions

Febuxostat is highly bound to albumin in blood and is mainly metabolized by UDP-glucuronosyltransferase (UGT) 1 and 2 families and to a lesser extent by cytochrome P450 (CYP) enzymes. In vitro studies showed the presence of ibuprofen or warfarin did not change the plasma protein binding of febuxostat and febuxostat did not influence the plasma protein binding of ibuprofen or warfarin, suggesting that febuxostat was unlikely to cause a drug-drug interaction by displacement of protein binding (Mukoyoshi et al 2008). Examination of the inhibitory effect of febuxostat on CYP enzymes suggested that it had minimal inhibitory effect on the activities of any CYP (Mukoyoshi et al 2008). Based on the in vitro study that showed febuxostat had a weak inhibitory effect on CYP2D6, but no effect on CYP1A2, CYP2C9, CYP2C19 or CYP3A4, Khosravan et al (2005b) examined the effect of multiple doses of febuxostat 120 mg daily on the pharmacokinetics of desipramine, a substrate for CYP2D6. A small increase in total exposure to desipramine was found suggesting that CYP2D6-mediated metabolism was mildly inhibited, but this was considered clinically insignificant (Khosravan et al 2005b). The potential interactions between febuxostat and other medications which might be concurrently used in patients with hyperuricemia and gout have been evaluated in some studies.

Four phase I, two-period, crossover studies were performed in healthy male and female subjects to evaluate

Table 1 Pharmacokinetics of febuxostat

Reference	Subjects	Dose	Results
(Becker et al 2004a; Khosravan et al 2006b)	Male and female healthy volunteers (n = 142)	Different doses (10, 20, 30, 40, 50, 70, 90, 120, 160, 180, and 240 mg) with 12 subjects each group for 2 weeks	A linear PK and dose-response (% decrease in sUA) relationship for febuxostat dosages within the 10–120 mg range
(Komoriya et al 2004)	Patients with gout and/or hyperuricemia (n = 10)	10 mg daily for 2 weeks then 20 mg daily for 4 weeks	Oxidative metabolites 67M-1, 67M-2, and 67M-4 had similar C_{max} and t_{max} as parent drug and 40% of drug was excreted in urine as glucuronic acid conjugate 67-Glu. Data were similar to those reported in healthy male adults
(Hoshide et al 2004)	Healthy subjects and individuals with mild or moderate impairment in renal function (n = 15)	Single dose of 20 mg	The difference in plasma AUC for unchanged febuxostat across the groups was less than 2-fold indicating that renal impairment had little clinical impact on the PK of the drug. Changes in sUA levels from pre-dose levels were not significant
(Mayer et al 2005)	Male and female subjects with normal renal function (n = 11) and with mild (n = 6), moderate (n = 7), or severe renal impairment (n = 7)	80 mg daily dose for 7 days	Plasma exposure to febuxostat and its metabolites was generally higher in subjects with increasing degrees of renal impairment, but the % decrease in sUA were comparable regardless of the renal function group. No dose adjustment needed for febuxostat treatment based on differences in renal function
(Khosravan et al 2006a)	Subjects with normal hepatic function (n = 11) and mild (n = 8) and moderate (n = 8) hepatic impairment	80 mg daily dose for 7 days	No statistically or clinically significant differences in the plasma PK and PD parameters were observed between subjects with mild or moderate hepatic impairment and those with normal hepatic function. No dose adjustment needed in subjects with mild to moderate hepatic impairment
(Khosravan et al 2006c)	Male and female healthy volunteers, study 1 (n = 26); study 2 (n = 24)	In study 1, subjects received febuxostat 80 mg once daily, indomethacin 50 mg twice daily, or both for 5 days. In study 2, subjects received febuxostat 80 mg, naproxen 500 mg twice daily, or both for 7 days	Febuxostat had no effect on the plasma PK of indomethacin and naproxen. Indomethacin had no effect on the plasma PK of febuxostat. Although naproxen caused an increase in plasma exposure to febuxostat, this increase is not expected to be clinically significant
(Khosravan et al 2008a)	Male and female healthy volunteers (n = 92)	Single 40 mg (n = 24), or multiple 80 mg (n = 24), or single 120 mg (n = 20) in fasting and non-fasting conditions, or single 80 mg (n = 24) doses alone or with antacid	Food caused a decrease in the rate and extent of absorption of febuxostat, but this decrease was not associated with a clinically significant change in febuxostat PD effect. Despite a decrease in the absorption rate of febuxostat, antacid had no effect on the extent of febuxostat absorption
(Khosravan et al 2008b)	Healthy male and female subjects (aged 18–40 years or ≥ 65 years) (n = 96)	80 mg daily dose for 7 days	Age or gender had no clinically significant effect on the PK, PD, or safety of febuxostat

Abbreviations: AUC, area under the plasma concentration-time curve; PD, pharmacodynamic; PK, pharmacokinetic; sUA, serum uric acid.

the effect of food and antacid on the pharmacokinetics and/or pharmacodynamics of febuxostat. Food decreased rate and extent of absorption of febuxostat, but this decrease was not associated with a clinically significant change in the pharmacodynamic effect. With antacid there was a

decrease in the absorption rate of febuxostat, but no effect on the total extent of febuxostat absorption. These findings suggested that febuxostat can be taken with food or antacid without a significant effect on the response (Khosravan et al 2008a).

Grabowski et al (2005) reported that a single dose of hydrochlorothiazide 50 mg did not alter the pharmacokinetics of febuxostat, but caused a slightly higher serum uric acid concentration that was not considered to be clinically significant. Khosravan et al evaluated the potential drug interactions between febuxostat and other medication for treatment or prevention of acute gout attacks, including colchicine, indomethacin and naproxen (Khosravan et al 2005a, 2006c). Febuxostat had no effect on the plasma pharmacokinetics of colchicine, indomethacin, and naproxen and none of these medications had clinically significant effects on the pharmacokinetics of febuxostat. Therefore, based on the plasma pharmacokinetic data in healthy subjects,

febuxostat can be administered with colchicine, indomethacin or naproxen with no dose adjustments.

Safety and efficacy in clinical trials

The in vitro and animal studies with febuxostat showed it was more potent than allopurinol in reducing serum urate levels without any major additional adverse effects (Tomlinson 2005). A series of clinical trials from phase I to phase III have been carried out to evaluate the safety and efficacy of febuxostat in humans (Table 2).

A phase I, multiple-dose, placebo-controlled, dose-escalation study was conducted in healthy male and female adults in the United States with a majority of Caucasian

Table 2 Efficacy of febuxostat in phase III and long term clinical trials

Reference	Patients	Study design	Treatment	Outcomes
(Kamatani et al 2004)	256 (Japanese)	R, DB, MC, 8 weeks	FBX 40 mg, ALO 100 mg BD	82% of patients in the FBX arm achieved sUA levels of ≤ 6.0 , compared with 69% in the ALO arm
(Becker et al 2005a) FACT	762 (77% Caucasian)	R, DB, MC, 52 weeks	FBX 80 mg, 120 mg, ALO 300 mg	53%, 62%, and 21% of patients in FBX 80 mg, 120 mg, and ALO 300 mg groups achieved sUA < 6 mg/dL, respectively ($p < 0.001$ for the comparison of each febuxostat group with the allopurinol group) The overall incidence of gout flares was 64% 70%, and 64% for FBX 80 mg, 120 mg, and ALO 300 mg groups, respectively
(Schumacher et al 2005) APEX	1067 (78% Caucasian) including 40 with moderately impaired renal function	R, PC, 28 weeks	Placebo, FBX 80 mg, 120 mg, 240 mg, ALO 300 mg/100 mg (depend on renal function)	48%, 65%, 69%, 22%, and 0% of patients in FBX 80 mg, 120 mg, 240 mg, ALO 300/100 mg, and placebo groups achieved sUA < 6 mg/dL at each of the last 3 visits, respectively ($p < 0.05$ for all comparison between groups) and 44%, 45%, 60%, 0%, 0% for subjects with moderate renal impairment for each groups
(Wortmann et al 2006) EXCEL	1086 (79% Caucasian)	R, OL, LT, (an extension study of 2 phase III trials above)	FBX 80 mg, 120 mg, 240 mg, ALO 300 mg/100 mg (depend on renal function)	The incidence of gout flares decreased gradually from 1.4, 1.72, and 1.49 flares per year in the 1st year to 0.19, 0.0, and 0.11 flares per year in the 3rd year for febuxostat 80 mg, 120 mg, and allopurinol 300/100 mg groups, respectively
(Schumacher et al 2006) FOCUS	116 (85% Caucasian) with 61 subjects on continued treatment with ≥ 48 months	OL, LT	FBX 40 mg, 80 mg, 120 mg	Across all doses, the proportion of subjects with sUA < 6.0 mg/dL were 78%, 76%, 84%, and 90% at year 1, 2, 3, and 4, respectively. Overall incidence of gout flares requiring treatment declined markedly by 2 years and continued over 4 year of febuxostat treatment. After the 1st year of stable dose, subjects, on average, had < 1 gout flare/year

Abbreviations: ALO, allopurinol; DB, double blind; FBX, febuxostat; LT, long term; MC, multicenter; OL, open label; PC, placebo controlled; R, randomized; sUA, serum uric acid.

subjects ($n = 142$) (Becker et al 2004a; Khosravan et al 2006b). Febuxostat was given orally for 2 weeks in daily doses in the range of 10 to 240 mg. Febuxostat resulted in significant decreases in serum and urinary urate concentrations and increases in serum and urinary xanthine concentrations. The percentage decreases in serum urate concentrations ranged from 27% to 76% (net change: 1.34–3.88 mg/dL), which were proportional to dosage for 10 to 120 mg doses but higher doses (>120 mg) did not appear to have a greater effect. Percentage decreases in serum uric acid were 27%, 35%, 37.5%, 40%, 47%, 50%, 60%, 69%, 70%, 72%, and 76% for the 10, 20, 30, 40, 50, 70, 90, 120, 160, 180, and 240 mg doses, respectively. Proportional increases in serum xanthine concentrations, decreases in urinary uric acid excretion, and increases in urinary xanthine and hypoxanthine excretion were also observed for doses of 10 mg to 120 mg. Adverse events were mild or moderate and self-limited, but not uncommon. The incidence of adverse events tended to be higher with higher doses of febuxostat. No deaths or serious adverse events were observed (Khosravan et al 2006b).

Based on the results from the above phase I study, the doses for phase II studies were selected and tested in patients with gout. A phase II double-blind, placebo-controlled, multicenter study included 153 patients, aged 23 to 80 years, with gout and baseline serum urate ≥ 8.0 mg/dL (Becker et al 2005b). Subjects were randomized to febuxostat (40 mg, 80 mg, 120 mg) or placebo once daily for 28 days with colchicine (0.6 mg twice daily) prophylaxis for 14 days prior to and 14 days after randomization. The subjects achieving the primary outcome of serum urate <6.0 mg/dL on day 28, were 0%, 56%, 76%, and 94% for placebo, 40 mg, 80 mg, and 120 mg dose febuxostat groups, respectively ($p < 0.001$ for each treatment group vs. placebo). Compared with baseline, decreases in serum urate at day 28 were 2%, 37%, 44%, and 59% for placebo, 40-, 80-, and 120-mg dose groups, respectively ($p < 0.001$ for each treatment group vs placebo). 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% with 80 mg; 55% with 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 (Becker et al 2005b).

A long-term, open-label extension of the above 4-week double-blind phase II study included 116 patients and 69 patients continued for at least 2 years (Schumacher et al 2004; Wortmann et al 2004). Subjects were initially given febuxostat 80 mg/day with titration to either 40 or 120 mg

based on serum urate and adverse events, achieving a stable dose after 28 weeks. Colchicine (0.6 mg twice daily) prophylaxis was implemented during the initial phase of treatment. Most patients (74%–81%) maintained serum urate levels of <6.0 mg/dL throughout the study period. Any treatment-related adverse events were mild-to-moderate with the most common being diarrhea, headache, and abnormal liver function test results. No serious adverse event was considered to be related to febuxostat. Analysis of a small number of patients ($n = 9$) in this extension study with gouty tophi revealed that tophus volume increased in patients with serum urate >6.0 mg/dL and decreased in patients with serum urate <6.0 mg/dL (Becker et al 2004c). Febuxostat was also efficacious, safe and well tolerated in a subgroup of allopurinol-intolerant patients included in the trial extension ($n = 8$) (Becker et al 2004b). More recently, the investigators further reported the data from 61 subjects with long-term treatment with febuxostat for at least 4 years (FOCUS) (Schumacher et al 2006). Across all doses, the proportion of subjects with serum urate <6.0 mg/dL were 78%, 76%, 84%, and 90% at year 1, 2, 3, and 4, respectively. The overall incidence of gout flares requiring treatment declined markedly by 2 years and continued over 4 years of febuxostat treatment. After the first year of stable dose, subjects, on average, had <1 gout flare per year. 26 subjects entered the study with a palpable tophus; 20 (77%) of these subjects had no tophus detectable at the examinations during the study. The most common treatment-related adverse events for all febuxostat groups were diarrhea, gastrointestinal motility disorders, headache, abnormal liver function tests, and hyperlipidemia. This longest clinical study of febuxostat therapy to date showed that long-term treatment with febuxostat reducing and maintaining serum urate <6.0 mg/dL was accompanied by beneficial clinical outcomes, including reduction in gout flares and tophus volume (Schumacher et al 2006). They also found that 4 years treatment with febuxostat was safe, effective, and well tolerated in 6 allopurinol-intolerant patients, and 3 subjects with tophi identified at the time of enrollment had disappearance of their tophi by the fourth year of febuxostat treatment (Becker et al 2006).

The Febuxostat versus Allopurinol Controlled Trial (FACT), a phase III, randomized, double-blind, 52-week, multicenter trial, compared the safety and efficacy of febuxostat with allopurinol in adult subjects with gout (Becker et al 2005a). A total of 762 patients with chronic gout and serum urate levels ≥ 8.0 mg/dL were randomized to receive once-daily doses of either 80 or 120 mg febuxostat or 300 mg allopurinol for 52 weeks and 760 received at

least one dose of the study drug during the study period. Naproxen (250 mg twice daily) or colchicine (0.6 mg once daily) was provided for gout flare prophylaxis during the 2-week washout period and first 8 weeks of the study. The primary endpoint of serum urate <6.0 mg/dL at all the last three measurements at monthly intervals up to 52 weeks was reached in 53%, 62%, and 21% of the febuxostat 80 mg and 120 mg and allopurinol 300 mg groups, respectively ($p < 0.001$ for the comparison of each febuxostat group with the allopurinol group). Although the incidence of gout flares gradually decreased 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. The median reduction in tophus area was 83% and 66% in patients receiving 80 mg or 120 mg of febuxostat and 50% in those receiving allopurinol ($p > 0.05$). More patients in the high-dose febuxostat group than in the allopurinol group ($p = 0.003$) or the low-dose febuxostat group discontinued the study. The investigators concluded that febuxostat 80 mg or 120 mg daily was more effective than allopurinol 300 mg daily in reducing serum urate (Becker et al 2005a).

Another large phase III study, the APEX study, involving 1067 subjects (78% Caucasians) with gout and serum urate levels ≥ 8.0 mg/dL compared the safety and efficacy of febuxostat to allopurinol and placebo (Schumacher et al 2005). This study included 40 subjects with moderately impaired renal function (serum creatinine 1.6 to ≤ 2.0 mg/dL) and a high dose of febuxostat for safety evaluation. Subjects were randomized to receive placebo, febuxostat 80 mg, 120 mg, or 240 mg (safety dose) or allopurinol once daily in a 1:2:2:1:2 ratio for 28 weeks. No dose adjustments based on renal function were made in the febuxostat treatment groups, but subjects randomized to allopurinol received 300 mg/day if serum creatinine was ≤ 1.5 mg/dL and 100 mg/day for serum creatinine 1.6 to ≤ 2.0 mg/dL. The primary endpoint of the proportion of subjects with serum urate <6.0 mg/dL at each of the last 3 visits was achieved in 48%, 65%, 69%, 22%, and 0% in febuxostat 80 mg, 120 mg, 240 mg, allopurinol 300/100 mg, and placebo groups, respectively ($p < 0.05$ for the comparison of each febuxostat group with the allopurinol group and placebo group) and 44%, 45%, 60%, 0%, and 0%, respectively, for subjects with moderate renal impairment for each group. After 28 weeks, 76%, 87%, 94%, 41%, and 1% of patients in febuxostat 80 mg, 120 mg, 240 mg, allopurinol 300/100 mg, and placebo groups had

serum urate <6.0 mg/dL ($p < 0.05$ for the comparison of each febuxostat group with the allopurinol group and placebo group). Adverse events including liver function abnormalities, headache, nausea and vomiting, abdominal pain, and dizziness, were similar in incidences across treatment groups. There were no increases in adverse events in subjects with moderate renal insufficiency including those receiving febuxostat 240 mg daily. These results suggested that febuxostat (80 mg, 120 mg, or 240 mg) demonstrated superior efficacy compared with placebo and allopurinol (300 or 100 mg) in reducing and maintaining serum urate <6.0 mg/dL. Febuxostat was generally safe and well tolerated at all doses (Schumacher et al 2005).

Clinical benefits of long-term urate-lowering therapy with febuxostat have been evaluated in the EXCEL trial, which is an extension study of 2 Phase III trials mentioned above (FACT and APEX) (Wortmann et al 2006). This long-term open-label study was designed to determine if subjects treated with febuxostat or allopurinol maintaining serum urate <6.0 mg/dL was associated with reduction in gout flare frequency and tophus resolution. A total of 1086 subjects completing the above two phase III trials were enrolled. At the time of interim analysis, 75% (815/1086) of subjects completed ≥ 16 months in EXCEL; the durations of exposure to initial treatment were 492, 428, and 271 days, respectively, for febuxostat 80 mg, 120 mg, and allopurinol 300/100 mg. The incidence of gout flares decreased gradually from 1.4, 1.72, 1.49 flares per year in the first year to 0.19, 0.0, and 0.11 flares per year in the third year for febuxostat 80 mg, 120 mg, and allopurinol 300/100 mg groups, respectively. The most common febuxostat treatment-related adverse events were abnormal liver function tests, headache, hypertension, diarrhea, and arthralgia/stiffness, whereas the most common treatment-related adverse events for allopurinol were abnormal liver function tests and rash (Wortmann et al 2006).

The effects of lower doses of febuxostat were evaluated in Japanese subjects compared to placebo or allopurinol in some studies (Kamatani et al 2003, 2004). A phase II, multicenter, double-blind study was conducted to assess the efficacy and safety of doses of febuxostat in 128 patients with gout or hyperuricemia (serum urate levels ≥ 8.0 mg/dL). Participants were randomized to receive once-daily doses of placebo or febuxostat (10 mg, 20mg, or 40 mg; $n = 32$, per group). Patients assigned to the febuxostat groups were administered 10 mg febuxostat for the first 2 weeks, followed by 10 mg, 20 mg, or 40 mg for a subsequent 6-week treatment period, while individuals assigned to the placebo group

received placebo throughout the 8-week trial. Serum urate levels of <6.0 mg/dL were achieved in 0%, 22%, 31.5%, and 41.9% of patients with placebo, 10 mg, 20 mg, and 40 mg febuxostat groups, respectively. There was no significant difference in response rate between gout and hyperuricemia patients or between urate overproducers or underexcreters. Febuxostat was safe and well tolerated at all doses (Kamatani et al 2003).

A further phase III study compared the safety and efficacy of febuxostat with allopurinol in 256 Japanese subjects with gout or hyperuricemia with serum urate levels ≥ 8.0 mg/dL (Kamatani et al 2004). In this randomized, multicenter, double-blind study, patients received either febuxostat (10 mg once daily) or allopurinol (100 mg once daily) for a 12-week introductory phase before doses were increased for a further 44 days of treatment with febuxostat (40 mg once daily) or allopurinol (100 mg twice daily). The decrease in serum urate levels after 8 weeks of treatment was significantly ($p < 0.001$) greater in the febuxostat group (40.5%), compared with the allopurinol group (33.9%). Furthermore, 82% of patients in the febuxostat arm achieved serum urate levels of ≤ 6.0 , compared with 69% in the allopurinol arm ($p < 0.05$). Adverse reactions were reported in 11% of patients in the allopurinol group and 8.6% in the febuxostat group. The majority of adverse events were transient and mild in severity (Kamatani et al 2004).

Summary

Febuxostat has been shown to be safe and effective in lowering serum urate according to the available clinical data. Doses of 80 mg of febuxostat are more effective in lowering serum urate than doses of 300 mg of allopurinol. Febuxostat has shown to be well tolerated in long term treatment in patients experiencing hypersensitivity/intolerance to allopurinol.

Dose adjustment does not seem to be necessary in patients with mild to moderate renal/liver insufficiency or advanced age according to data from these particular groups of subjects. The most common adverse reactions reported were abnormal liver function tests, headache, and gastrointestinal symptoms, which were usually mild and transient. Hepatotoxicity was not a feature in the animal studies, but whether it becomes a limitation in the clinical use of febuxostat needs to be determined in further studies. As with other urate-lowering therapies, the rapid decrease in serum urate associated with initiation of treatment with febuxostat caused a number of patients to experience acute gout flares. This appeared to be more frequent with the more potent serum urate-lowering

effects of higher doses of febuxostat, but this increased incidence of gout attacks tended to decline with ongoing treatment and could be attenuated with concomitant prophylaxis during the initiation of febuxostat therapy. In February 2008, 80 mg and 120 mg of febuxostat film-coated tablets (Adenuric[®]) were granted marketing authorization by the European Commission for the treatment of chronic hyperuricemia in conditions in which urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis), which is the first major treatment alternative for gout in more than 40 years (CHMP 2008; Ipsen 2008). A concern on potential serious cardiovascular adverse events was noted in the European Commission statement, but this was not apparent in the published clinical trial reports.

In summary, febuxostat is a promising urate-lowering therapy as an alternative to allopurinol for the treatment of hyperuricemia and gout, although further observation on post-marketing safety and efficacy of long term treatment with febuxostat in patients with gout or hyperuricemia and with other complications is required.

Disclosures

The authors have no conflicts of interest to disclose.

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