

Management of Chronic Hyperuricemia with Febuxostat

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Abstract: Gout is a common and painful rheumatologic disorder affecting 1 to 2 percent of adults in developed countries. Allopurinol remains the most commonly prescribed agent for gout in the United States. Unfortunately, many patients treated with allopurinol do not achieve target serum uric acid (sUA) levels, possibly due to the need for dosage adjustment in patients with renal insufficiency and the perceived intolerability to allopurinol in doses greater than 300 mg per day. Febuxostat, an oral non-purine inhibitor of xanthine oxidase, was recently approved by the US Food and Drug Administration for chronic management of hyperuricemia in patients with gout. The purpose of this manuscript is to review the data with febuxostat compared with allopurinol and to discuss their relative place in therapy.

Keywords: hyperuricemia, uric acid, gout, gouty arthritis, febuxostat, allopurinol

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Introduction

Gout is a common rheumatologic disorder affecting 1 to 2 percent of adults in developed countries.¹ Epidemiologic evidence demonstrates that the incidence of gout has more than doubled in the US and the UK from the 1970's to the 1990's.³ These findings may result from an increased aging population, rising rate of obesity, and widespread use of thiazide diuretics and low dose aspirin, all of which promote hyperuricemia, the precursor to gout.³ Serum uric acid is a waste product resulting from degradation of purines, from the diet and cell metabolism, by the enzyme, xanthine oxidase (see Fig. 1). Febuxostat is a novel, non-purine inhibitor of xanthine oxidase for chronic management of hyperuricemia in patients with gout. In clinical studies, febuxostat demonstrates substantial reductions in serum uric acid levels and improvements in the overall management of gout. The clinical profile of febuxostat in the management of hyperuricemia and gout serves as the focus for this review.

Pathophysiology and Risk Factors

Gout is a disease of acute and chronic manifestations caused by the deposition of urate crystals in articular and extra-articular tissues. In the joints, deposition of urate crystals may precipitate symptoms of acute gouty flare that includes severe localized joint pain, warmth, redness, and limited range of motion.⁴ Chronic uncontrolled hyperuricemia result in painful, destructive development of 'tophi', which are collections of urate crystals that deposit in soft tissues, bones, and tendons. Criteria for diagnosis of primary gout involves evidence of monosodium urate crystals in the synovial fluid and/or tophi confirmed with crystal examination (Table 1).⁵

Development of urate crystals & gouty complications is largely determined by the level of hyperuricemia. Normal serum uric acid (sUA) in men (≤ 7 mg/dl) and women (≤ 6 mg/dl) are already near the limits of urate solubility (6.8 mg/dl at 37 °C).⁶ The greater sUA levels exceed their plasma saturation point, the greater



Figure 1. Purine metabolism and role of xanthine oxidase in uric acid production.

Table 1. ACR preliminary criteria for the classification of the acute arthritis of primary gout.⁵

1. More than one attack of acute arthritis
2. Maximum inflammation developed within 1 day
3. Monoarthritis attack
4. Redness observed over joints
5. First metatarsophalangeal joint painful or swollen
6. Unilateral first metatarsophalangeal joint attack
7. Unilateral tarsal joint attack
8. Proven or suspected tophus
9. Hyperuricemia
10. Asymmetric swelling within a joint on x-ray
11. Subcortical cysts without erosions on x-ray
12. Monosodium urate monohydrate microcrystals in joint fluid during an attack
13. Joint fluid culture negative for organisms during an attack

the likelihood of acute gouty arthritic attacks.^{6,7} While not all patients with hyperuricemia will develop acute gout flares or chronic gouty complications,⁷ sUA levels in excess of 10 mg/dl promote ubiquitous formation of tophaceous deposits that may develop 10 years from the initial gouty attack.^{2,8} Conversely, acute flares of gouty arthritis can occur in the presence of normal uric acid levels.⁹

Causes of gout can be classified as sources for overproduction or under excretion of uric acid (see Table 2). Risk factors and causes for gout can be found in the dietary, medical, and medication history,

Table 2. Etiology of hyperuricemia.

Pathophysiology	Causes
Decreased uric acid excretion	Primary idiopathic, hypertension, renal impairment, lead nephropathy, preeclampsia, sarcoidosis, metabolic abnormalities (hypothyroidism, starvation or diabetic ketosis, lactic acidosis, Bartter's syndrome), drugs (alcohol, diuretics, low-dose aspirin, levodopa, ethambutol, pyrazinamide, cyclosporine)
Uric acid overproduction	Primary idiopathic, obesity, purine-rich diet, psoriasis, lymphoproliferative/myeloproliferative disorders, drugs (alcohol, nicotinic acid, warfarin, chemotherapy [tumor lysis syndrome]), inherited enzyme defects (HPRT deficiency, increased PRPP synthetase)

Abbreviations: HPRT, hypoxanthine-guanine phosphoribosyltransferase; PRPP, phosphoribosyl pyrophosphate.



as well as alcohol intake. Uric acid is the end product of purine metabolism. In the United States, higher consumption of purine rich foods and increased alcohol intake are directly associated with higher urate levels and incidence of gout.^{11,12} Medications, particularly thiazide diuretics and low dose aspirin, are often associated with gout.¹³ When gout is linked to diuretics, it is recommended to stop the diuretic and switch to an alternative regimen when possible.¹⁴ Additional medications sources of gout are summarized in Table 2. Medical conditions associated with increased incidence gout or gouty flares include hypertension, diabetes, renal insufficiency, hypertriglyceridemia, hypercholesterolemia, and obesity.¹⁵

Current Treatment Strategies

Management of chronic gout includes prevention of acute gouty arthritis and tophaceous deposits, and treatment of pre-existing tophi and their complications. These outcome measures can be improved in patients who achieve reductions in sUA levels to 6 mg/dl or lower.⁸ Initiation of urate lowering therapy (ULT) is most beneficial in patients with severe established gout including tophi, radiographic evidence of joint damage, and urate nephrolithiasis.¹⁴ In addition, ULT has demonstrated a cost savings in patients with at least 2 gouty attacks a year.¹⁷

Urate lowering medications can be categorized as uricosuric agents, which promote renal excretion; uricostatic agents, which decrease urate formation; and uricolytic agents, which increase urate degradation. The selection of hypouricemic medication in gout is determined by medication tolerance, cost, patient comorbidities, and the cause of hyperuricemia.¹⁶

Uricosuric medications directly treat the predominant source of hyperuricemia (90% of patients), renal urate underexcretion.¹⁸ Probenecid, sulfinpyrazone, and benzbromarone are the three uricosuric agents marketed in Europe, while only probenecid is available in the US. Although probenecid and sulfinpyrazone are effective in reducing gouty flares, both medications demonstrate less sUA lowering ability than allopurinol.¹⁴ Probenecid has a tolerable side effect profile, but loses hypouricemic effects in patients with evidence of renal insufficiency (ie, CrCL < 60 ml/min).¹⁹ Sulfinpyrazone can impair platelet function, increasing the risk of gastric bleed, and has been rarely been associated with

bone marrow suppression.¹⁹ Benzbromarone is the most potent of uricosuric agents, possessing efficacy in patients with mild to moderate renal insufficiency (CrCL > 25 ml/min). However, the potential for fatal hepatotoxicity in patients receiving high dose benzbromarone have limited its use.¹⁹

Uricolytic agents provide uricase, an enzyme not found in humans, which stimulates formation of allantoin and reduce urate levels. Rasburicase (Elitek[®]) is a recombinant form of uricase indicated for management of expectant hyperuricemia in pediatric patients with leukemia, lymphomas, or solid organ tumors likely to experience tumor lysis syndrome.²⁰ Rasburicase rapidly and greatly lowers sUA levels but requires biweekly or monthly intravenous administration. Repeated injections of uricase agents result in formation of anti-uricase antibodies in 7% to 14% of patients, leading to diminished efficacy with continued use.¹⁶ Potential for antigenicity, intravenous administration, cost, and limited long term assessment make the role of uricase agents in chronic gout uncertain.

Allopurinol, an uricostatic agent, is the most commonly prescribed medication for reduction of hyperuricemia and long term management of gout.²¹ Acceptance of allopurinol is attributable to low cost, once daily dosing, and therapeutic efficacy regardless of hyperuricemic origin. Allopurinol possesses a predictable sUA lowering effect, with a reduction of 1 mg/dL for every 100 incremental dose, allowing clinicians to achieve therapy goals by titrating doses from 100 to 800 mg daily.¹⁴ However, in the US and Europe, allopurinol doses commonly do not exceed 300 mg daily,^{13,21} despite fewer than 50% of patients achieving sUA levels less than 6 mg/dL.²¹

Physicians reluctance to titrate allopurinol doses to therapeutic goals may result from several concerns. First, allopurinol may induce gouty flares secondary to rapid urate lowering effects, resulting in noncompliance and treatment failure. Acute reductions in sUA concentrations may destabilize synovial microtophi, which could precipitate gouty arthritis.¹⁶ After an acute episode of gout, these events may be diminished by waiting 6 to 8 weeks to begin urate lowering therapy, by slowly titrating doses of allopurinol (ie, 100 mg every few weeks), and by prophylaxis with concurrent use of colchicine until sUA levels are normalized.²²



Second, while allopurinol promotes mild, reversible adverse events in 20% of patients, about 5% of patients are unable to tolerate therapy.¹⁹ Clinicians may be apprehensive of dosing escalation due to possible allopurinol hypersensitivity syndrome, a rare adverse event, affecting 0.4% of patients, but associated with a mortality of about 20%.^{6,23} This hypersensitivity syndrome may be attributable to accumulation of a metabolite, oxypurinol, which occurs more readily in renal insufficiency.¹⁶ Failure to achieve goal sUA concentrations in patients receiving allopurinol affords opportunity for newer, alternative urate lowering therapy. Novel urate lowering therapy should possess predictable sUA lowering effects regardless of hyperuricemic etiology, prove safe and effective in renal insufficiency, and provide convenient administration in the management of chronic gout.

Pharmacology

Febuxostat has a similar mechanism of action as oxypurinol, the active and oxidized form of allopurinol, in that it lowers sUA concentrations by inhibiting xanthine oxidase in the purine metabolism pathway (Fig. 1).²⁴ Since the potency of febuxostat (in vitro inhibition constant, K_i , less than 1 mM) is comparable to oxypurinol ($K_i = 0.5$ mM), advantages of this newer agent are primarily related to its alternate molecular structure and mechanism of enzyme inhibition.^{24,25} Oxypurinol covalently binds with the reduced molybdenum center of xanthine oxidase and has weak competitive inhibition of the oxidized form of the enzyme. Within hours of administration, the pharmacologic effects of oxypurinol can be eradicated due to reoxidation of the molybdenum cofactor, a process that can displace the drug and can only be overcome by administering allopurinol multiple times a day.²⁴ Febuxostat requires no conversion to an active form and, since it is structurally unrelated to purine or pyrimidines, is more selective for xanthine oxidase; it therefore does not interfere with other enzymes in the purine metabolism pathway.^{25,26} Febuxostat inhibits both the reduced and oxidized forms of xanthine oxidase by binding with high affinity in a narrow channel leading to the molybdenum center of the enzyme and essentially obstructing substrate binding.²⁴ This enhanced mechanism produces more sustained reductions in sUA levels compared to allopurinol.

Pharmacokinetics and Pharmacodynamics

When administered orally, the absolute bioavailability of febuxostat is thought to approximate 84%.²⁷ Absorption occurs rapidly and maximum plasma concentrations (C_{max}) are reached within 1 hour.^{28,29} Febuxostat is 99% protein bound to albumin and has a volume of distribution of 0.7 L/kg.^{27,29–31} Dose escalation studies in healthy volunteers demonstrate proportional increases in area under the plasma concentration-time curve (AUC) and C_{max} for dose ranges of 10–120 mg and 10–240 mg respectively. However, the pharmacodynamic effects of febuxostat in healthy individuals appear to reach maximum benefit at doses of 120 mg, with no additional decreases in sUA attained beyond this dose.^{28,29}

Febuxostat has a half-life of 5–8 hours and is primarily cleared via the hepatic system with only 1%–6% of the drug being excreted unchanged in the urine.^{28,29} The major pathways of elimination are conjugation (up to 45% of febuxostat) to the acyl-glucuronide metabolite, via uridinediphosphate-glucuronyl transferase (UDPGT) enzymes, and oxidation (up to 8% of parent drug) at cytochrome (CYP) P450 isoenzymes 1A2, 2C8 and 2C9 to active metabolites. These metabolites undergo enterohepatic circulation and biliary excretion.^{28,29}

Special populations

Few studies have evaluated the pharmacokinetic and pharmacodynamic effects of febuxostat in patients with renal or hepatic impairment. Data from two studies suggest that dose adjustments are unnecessary in patients with mild, moderate, or severe renal impairment. Although renal dysfunction can increase the half-life and AUC of febuxostat, no statistically significant differences in C_{max} or mean changes in sUA concentrations have been documented.^{32,33} It has been hypothesized that a higher degree of conjugated drug undergoes enterohepatic recycling and excretion via the biliary route to compensate in patients with renal dysfunction.³³

Similarly, a study of febuxostat in patients with normal hepatic function compared to patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic dysfunction demonstrated an increased C_{max} , AUC, and half-life in patients with hepatic dysfunction; however, this finding was not



statistically significant.³⁰ Percent reductions in sUA levels were significantly less substantial in patients with hepatic dysfunction; however, this finding was not considered clinically significant since the decrease in sUA levels in patients with hepatic impairment was comparable to reductions observed in previous studies of healthy subjects. Again, it was hypothesized that compensatory changes in clearance of febuxostat occur in the presence of organ dysfunction; in this case, excretion of unchanged drug and glucuronidation would increase as oxidative metabolism and biliary excretion decreases. It should be noted that febuxostat has not been studied in patients with end stage renal disease (ESRD), severe hepatic impairment, or combined renal and hepatic impairment.

One study has evaluated whether febuxostat has pharmacokinetic and pharmacodynamic differences in males compared to females and in patients aged 18–40 years compared to patients aged 65 years or older.³⁴ There were no differences in C_{max} , AUC, or percent reductions in sUA levels between age groups. Female patients did have significantly higher C_{max} and AUC of unbound drug compared to males. This translated into significantly larger percent decreases in mean sUA concentrations in the female group.³⁴ These gender differences were attributed to weight discrepancies between the two groups and were not considered to be clinically significant. Based on the results of this analysis, dosage adjustments are not recommended based on patient age or gender.

Efficacy

Febuxostat has been studied in over 3800 patients with hyperuricemia due to gout. Clinical trials ranging from 4 weeks to 5 years have been conducted to assess the safety and efficacy and are summarized in Table 3.

A multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response study assessed the efficacy and safety of febuxostat in 153 patients with gout.³⁵ Subjects were randomized to febuxostat 40 mg/d ($n = 37$), 80 mg/d ($n = 40$), or 120 mg/d ($n = 38$) or matching placebo ($n = 38$) for 4 weeks. All included subjects met the American College of Rheumatology criteria for gout and had a serum uric acid level ≥ 8.0 mg/dL.⁵ Subjects were excluded if they had significant renal (defined as SCr > 1.5 mg/dL

or CrCl < 50 ml/min) or hepatic dysfunction, were pregnant or lactating, concurrently receiving urate lowering agents, azathioprine, 6-mercaptopurine, aspirin (> 325 mg/d) or other salicylates, or had a history of alcohol abuse. Efficacy outcome measures included the proportion of patients with sUA < 6 mg/dL on day 28; the proportion of patients with sUA levels < 6 mg/dL at weeks 1, 2, and 3; the percent reduction in sUA level from baseline at each visit; and the percent reduction in daily uric acid excretion from baseline to day 28. Colchicine prophylaxis, 0.6 mg twice daily, was provided during the 2 week washout period and initial 2 weeks of the trial. Acute gout flares occurring following the prophylaxis period were treated at the investigator's discretion.

A greater proportion of patients in the febuxostat groups achieved sUA < 6 mg/dL at each visit compared with subjects receiving placebo ($P < 0.001$ for all comparisons).³⁵ The majority of patients receiving febuxostat reached the goal sUA level < 6 mg/dL as early as day 7, and maintained targeted levels < 6 mg/dL at each visit. The mean percentage reductions from baseline were significantly greater in febuxostat-treated patients compared with subjects receiving placebo ($P < 0.001$ for all comparisons). Finally, the percent reduction in daily uric acid excretion from baseline was significantly greater in febuxostat groups (mean change from 44%–47%) compared with placebo (5.9% increase; $P < 0.001$ for all comparisons).³⁵ The authors concluded that febuxostat at all doses studied resulted in prompt and persistent reduction of serum uric acid levels significantly more often than placebo-treated subjects.

A phase III, multicenter, double-blind, randomized, active-control study evaluated febuxostat versus allopurinol in the treatment of hyperuricemia due to gout. The Febuxostat versus Allopurinol Controlled Trial (FACT)³⁶ enrolled 760 adult subjects who were randomized to receive either allopurinol 300 mg/day ($n = 253$), febuxostat 80 mg/day ($n = 256$) or febuxostat 120 mg/day ($n = 251$) for 28 weeks. All patients met the ACR preliminary criteria for acute gout and had a baseline sUA level > 8.0 mg/dL.⁵ Similar exclusion criteria were used as reported previously. The primary efficacy endpoint was sUA concentration < 6.0 mg/dL at each of the last three monthly measurements. Additional efficacy endpoints included the proportion of patients



Table 3. Summary of clinical trial results with febuxostat.

Reference	Design	Treatment regimen	Patients with serum uric acid level < 6 mg/dL	Serum uric acid level change from baseline	Gout flares requiring treatment	Effects on tophi
Becker ³⁵	Phase II, randomized, double-blind, multicenter, 28 days	Febuxostat 40 mg/d (n = 37) Febuxostat 80 mg/d (n = 40) Febuxostat 120 mg/d (n = 38) Placebo (n = 38)	55% ^a 76% ^a 94% ^a 0%	-35% to -59% (all febuxostat groups) ^a 1.6-2.2%	35% 43% 55% 37%	Not reported
Becker ³⁶	Phase III, randomized, double-blind, multicenter, 52 weeks (FACT)	Febuxostat 80 mg/d (n = 256) Febuxostat 120 mg/d (n = 251) Allopurinol 300 mg/d (n = 253)	At last 3 visits: 53% ^b 62% ^b 21%	-45% ^b -52% ^b -33%	Day 1-Week 8: 22% 36% ^c 21% Week 9-Week 52: No difference	Similar decrease in number and size of tophi among all groups (P = NS)
Schumacher ³⁷	Phase III, randomized, double-blind, multicenter, 28 weeks (APEX)	Febuxostat 80 mg/d (n = 267) Febuxostat 120 mg/d (n = 269) Febuxostat 240 mg/d (n = 134) Allopurinol 300 mg/d (n = 268) ^d Placebo (n = 134)	At last 3 visits: 48% ^{a,b} 65% ^{a,b,e} 69% ^{a,b,e} 22% ^a 0%	-45% ^f -52% ^f -66% ^f -34% ^h -3%	Day 1-Week 8: 28% 36% ^g 46% ^g 23% 20% Week 9-Week 28: No difference	Median tophus size reduced in all groups (P = NS) Mean number of tophi decrease significant only in Febuxostat 120 mg/d (P < 0.05 vs. placebo)
Becker ³⁹	Phase III, open-label, multicenter, 3 years (EXCEL)	Febuxostat 80 mg/d (n = 650) Febuxostat 120 mg/d (n = 291) Allopurinol 300 mg/d (n = 145)	After 1 month: 81% ^h 87% ^h 46% ^h After 1 year: 87% ^h 85% ^h 82% ^h	-47% ^h -53% ^h -32% ^h	From baseline until 18 months: 5%-25% ^h From 18 months to end of study: 4% ^h	Mean tophus size and number decreased in all treatment groups (P = NS)
Schumacher ³⁸	Phase III, open-label, multicenter, 5 years (FOCUS)	Febuxostat 80 mg/d (n = 606) Febuxostat 120 mg/d (n = 388) Allopurinol 300 mg/d (n = 92)	At final visit: 100% ^h 82% ^h 81% ^h	-49.2% ^h -47.1% ^h -50.7% ^h	During entire study: 75% ^h 47% ^h 41% ^h	69% (18/26) patients with palpable tophi at baseline had complete resolution of index tophus
Becker ⁴⁰	Phase III, randomized, double-blind, multicenter, 6 months (CONFIRMS)	Febuxostat 40 mg/d (n = 757) Febuxostat 80 mg/d (n = 756) Allopurinol 300 mg/d (755)	45% 67% ⁱ 42%	Not reported	Day 1-Week 8: 10-15% ^h	Not reported

Notes: ^aP < 0.001 vs. placebo; ^bP < 0.001 vs. allopurinol; ^cP < 0.001 vs. allopurinol and febuxostat 80 mg/d; ^dPatients with renal insufficiency received Allopurinol 100 mg/d; ^eP < 0.001 vs. febuxostat 80 mg/d; ^fP < 0.05 vs. allopurinol and placebo; ^gP < 0.001 vs. febuxostat 40 mg/d and allopurinol.



with sUA levels < 6 mg/dL at each visit, the overall percent reduction from baseline in sUA concentration, the percentage change in tophus area, change in number of tophi, and the proportion of subjects requiring treatment for acute gout flares during weeks 9 through 52.

Significantly more patients in the febuxostat groups achieved the primary efficacy endpoint relative to subjects receiving allopurinol ($P < 0.001$ for all comparisons).³⁶ Compared with allopurinol, the proportion of patients with sUA levels < 6.0 mg/dl at each visit was significantly higher in groups receiving febuxostat ($P < 0.001$), and these differences were maintained through week 52 ($P < 0.001$). The mean percentage reduction in sUA level from baseline ranged from -33% to -52% and was significantly greater in both febuxostat groups ($P < 0.001$). In both allopurinol and febuxostat groups a similar decrease in size and number of tophi was seen ($P = \text{NS}$). Similar proportion of patients experienced acute gout flares requiring treatment during weeks 9 through 52: 64% of the allopurinol cohort; 64% of febuxostat 80 mg cohort; and 80% of the febuxostat 120 mg cohort ($P = \text{NS}$). Acute gout flares were highest during the initial 8 weeks, gradually decreased over the course of the study with the incidence of flare ranging from 6% to 8% for febuxostat patients to 11% for allopurinol subjects during the final three weeks of the trial.³⁶ The authors concluded that febuxostat 80 mg to 120 mg per day was more effective in lowering sUA levels than fixed dose allopurinol (300 mg/day).

The Allopurinol- and Placebo-controlled, Efficacy study of febuXostat (APEX) was a phase III, multicenter, randomized, double-blind trial over 28 weeks.³⁷ This trial enrolled 1,072 subjects who were then randomized to febuxostat 80 mg/day ($n = 267$), febuxostat 120 mg/day ($n = 269$), febuxostat 240 mg/day ($n = 134$), allopurinol 300 mg/day ($n = 268$), or placebo ($n = 134$). Adult patients of either sex between 18 to 85 years of age with gout defined by ACR criteria,⁵ hyperuricemia (sUA ≥ 8.0 mg/dL) and serum creatinine < 2.0 mg/dL were considered eligible. Subjects were excluded if they were intolerant of allopurinol, naproxen, or colchicine; drank > 14 alcoholic beverages per week; had evidence of hepatic dysfunction with AST and ALT > 1.5 times the upper limit of normal; had evidence of renal calculi; or had any other significant medical condition.

Following a 2 week washout period, patients were randomized to study drug stratified by renal function. Patients defined as moderate renal insufficiency (SCr > 1.5 to ≤ 2.0 mg/dL) received allopurinol 100 mg/day ($n = 10$), but there was no dosage adjustment in the febuxostat treatment groups. The primary efficacy endpoint was the proportion of patients with sUA concentration < 6.0 mg/dL at each of the last three monthly measurements. Additional endpoints included the proportion of patients with sUA levels < 6 mg/dL at each visit, the percent reduction in sUA concentration from baseline at each visit, the proportion of subjects requiring treatment for acute gout flares during weeks 8 through 28, and the percentage change in tophus size and reduction in number of tophi from baseline.

Compared with allopurinol- or placebo-treated subjects, a significantly greater proportion of patients receiving febuxostat achieved the target sUA level < 6.0 mg/dL at the last 3 monthly visits ($P < 0.001$ vs placebo and allopurinol).³⁷ A significantly higher proportion of subjects receiving febuxostat 120 mg or 240 mg achieved the primary endpoint compared to patients receiving febuxostat 80 mg ($P < 0.001$ for both comparisons). A significantly greater proportion of subjects receiving allopurinol achieved the primary endpoint compared with placebo-treated patients ($P < 0.001$). In patients with moderate renal impairment, a significantly higher proportion of febuxostat-treated patients at all doses (12 of 25; 48%) studied achieved the primary endpoint compared with allopurinol (0 of 10 patients; $P < 0.05$ for all comparisons). Patients receiving febuxostat at any dose had greater percentage decrease in sUA levels compared with allopurinol or placebo ($P < 0.05$). Although a significantly greater proportion of subjects receiving febuxostat 120 mg or 240 mg ($P < 0.05$ versus febuxostat 80 mg, allopurinol or placebo) experienced a gout flare requiring treatment during the initial 8 weeks, there were no significant differences in subjects requiring treatment for acute gout flare between treatment groups during the predefined study period from weeks 9 to 28 following the prophylaxis period. No significant differences in tophi size or number were appreciated with the exception of a mean percent decrease in number of tophi between febuxostat 120 mg (-1.2) and placebo (-0.3) at week 28 ($P < 0.05$).³⁷ The authors concluded that



febuxostat, at any dose, effectively lowered and maintained target sUA levels relative to allopurinol or placebo. These differences were apparent in patients with normal or moderately impaired renal function.

The results of two long-term, open-label, extension studies are also available. The Febuxostat Open-label Clinical trial of Urate-lowering efficacy and Safety (FOCUS) was a 5-year extension of the phase II trial discussed previously. A total of 116 patients were enrolled and dosage titrations to 40 mg, 80 mg or 120 mg were allowed within the initial 24 weeks, but a stable dose was maintained after week 24 until study completion.³⁸ The fEbuXostat/allopurinol Comparative Extension Long-term study (EXCEL) was an open-label extension of the 2 phase III trials discussed previously.³⁹ A total of 1,086 patients were randomized in a 2:2:1 ratio to febuxostat 80 mg (n = 650), febuxostat 120 mg (n = 291) or allopurinol 300 mg (n = 145). As in APEX, subjects with moderate renal insufficiency receiving allopurinol (n = 8) received an adjusted dose of allopurinol, 100 mg per day. Treatment regimens could be modified by the investigators during the initial 6 months, and any patients with sUA level > 6 mg/dL after 6 months were withdrawn from the study. The primary efficacy outcome measure for both studies was the proportion of study participants who achieved and maintained a sUA level < 6 mg/dL at each visit. Additional efficacy outcomes reported included: the percent reduction in sUA level from baseline; the proportion requiring treatment for an acute gout flare; and changes tophi from baseline.

In the FOCUS study, exactly half of all patients withdrew from the study with only 58 subjects completing the trial. The major reasons for discontinuation were listed as personal reasons (n = 22), adverse events (n = 13), gout flare (n = 8), lost to follow-up (n = 5), protocol violation (n = 1), and other reasons (n = 9). Of the subjects completing the trial, 93% (n = 53) achieved the primary endpoint and the mean percent reduction in sUA levels in patients receiving febuxostat for > 2 years was nearly 50% from baseline. Sixty-nine percent (18/26) patients with palpable tophi at baseline had complete resolution of the index tophus during the study. The only statistically significant finding reported was that more Caucasian subjects achieved sUA < 6 mg/dL than non-Caucasian subjects at the final visit (87% vs. 65%; $P = 0.025$).³⁸

The authors concluded that febuxostat was effective in maintaining sUA < 6 mg/dL in most patients and resulted in decreased frequency of gout flares with long-term treatment.

Patient withdrawal from EXCEL was also significant as 39% of patients (422 of 1086) withdrew before the end of the 3-year trial. Reported reasons for withdrawal included: lost to follow-up (n = 90); personal reasons (n = 78); adverse effects (n = 78); treatment failures (n = 70); protocol violation (n = 12); gout flare (n = 5); and other (n = 85). Following 1 month of initial treatment, 81% of febuxostat 80 mg and 87% of febuxostat 120 mg subjects had achieved sUA < 6 mg/dL; however, only 46% of allopurinol patients had achieved this sUA level. For the remainder of the study, the percentage of febuxostat-treated subjects with sUA level maintained ≤ 6 mg/dL remained above 80%.³⁹ As allopurinol patients failing to meet the goal urate level were switched to febuxostat, the percentage of allopurinol subjects maintaining sUA < 6 mg/dL rose to 82% by the end of the first year. For the remainder of the study, the goal sUA level was maintained by 75 to 100% of remaining subjects regardless of treatment group at each visit. Overall, the mean tophus size and number decreased in all treatment groups with long-term maintenance of the goal sUA range.³⁹ Although statistical measures were described in the methods section, no statistically significant findings were reported from the study. The authors concluded that sustained maintenance of the goal sUA range with either febuxostat or allopurinol resulted in improvements in tophi and near elimination of gout flares over time.

The Confirmation of Febuxostat in Reducing and Maintaining Serum Urate (CONFIRMS) trial was a phase III, multicenter, randomized, double-blind trial over 6 months.⁴⁰ This study enrolled 2,269 subjects from 324 sites in the US who were then randomized to febuxostat 40 mg/day (n = 757), febuxostat 80 mg/day (n = 756), or allopurinol 300 mg/day (n = 755). Subjects with moderate renal impairment (defined as CrCl 30 to 59 ml/minute, estimated by the Cockcroft-Gault formula) received allopurinol 200 mg/day. Of the total cohort, 276 had previously completed either the 3-year or 5-year open label trial with either febuxostat or allopurinol.^{38,39} Adults aged 18 to 85 with a diagnosis of gout meeting ACR preliminary criteria and baseline sUA level > 8 mg/dL



were eligible for inclusion. Exclusion criteria included severe renal impairment ($\text{CrCl} < 30$ ml/minute); consumption of more than 14 alcoholic beverages per week or history of alcoholism or drug abuse; evidence of hepatic dysfunction with AST and ALT > 1.5 times the upper limit of normal; secondary hyperuricemia; xanthinuria; or had any other significant medical condition. Prophylaxis for gout with colchicine 0.6 mg daily or naproxen 250 mg twice daily was allowed throughout the trial and during the washout period for subjects receiving prior ULT. The primary efficacy endpoint was the proportion of subjects with sUA < 6 mg/dL at the final visit. Additional endpoints included the proportion of subjects with mild or moderate renal impairment with final sUA < 6 mg/dL, and the proportion of subjects with sUA < 6 mg/dL, 5 mg/dL, and 4 mg/dL at each visit.

The proportions of patients achieving a sUA < 6 mg/dL at the final visit were 45.2%, 67.1%, and 42.1% in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups, respectively. Although the difference in febuxostat 40 mg and allopurinol was not significant, the response rate in the febuxostat 80 mg group was statistically significant ($P < 0.001$).³⁹ Similar findings were evident when comparing patients with mild or moderate renal impairment and any sUA endpoint (< 6 mg/dL, < 5 mg/dL, or < 4 mg/dL) with significantly more patients in the febuxostat 80 mg group compared with allopurinol or febuxostat 40 mg ($P < 0.001$ for each comparison). Additionally, in subjects with renal impairment, significantly more subjects in the febuxostat 40 mg group reached a final sUA < 6 mg/dL compared with allopurinol 300/200 mg group ($P = 0.021$).⁴⁰ Overall the authors concluded that febuxostat 80 mg was more effective in lowering sUA relative to febuxostat 40 mg or allopurinol 300/200 mg. In patients with mild or moderate renal impairment, both febuxostat doses were more efficacious than allopurinol.

Safety and Tolerability

In clinical trials to-date in patients with gout and hyperuricemia, febuxostat was generally well tolerated with most treatment-related adverse events of mild to moderate severity. Compared with patients with normal renal function, there has been no increase in frequency of adverse events in patients with mild

to moderate renal impairment, although use in these patients has been limited.

When data from the three phase III controlled studies is combined, the most commonly reported adverse effects with febuxostat were liver function test abnormalities (5.4%), rash (1.2%), nausea (1.0%), and arthralgias (0.8%).^{36,37,40} No significant differences were found in the frequency of adverse events between febuxostat at FDA-approved doses (40 mg and 80 mg) and placebo.

A higher rate of cardiovascular thromboembolic events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) was observed at a higher rate with febuxostat (0.74/100 patient-years) relative to allopurinol (0.6/100 patient-years). Although a direct causal relationship has not been established, and these differences were not statistically different. Based on these data, the FDA required an additional study (CONFIRMS) prior to approval to evaluate the thromboembolic risk of febuxostat compared to allopurinol. The rate of adjudicated Antiplatelet Trialists Collaboration (APTCL) events were 0.0%, 0.4%, and 0.4% in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups ($P = \text{NS}$). One death occurred in each febuxostat group and three occurred in the allopurinol group.⁴⁰

Although no dose-response relationship has been identified, transaminase elevations greater than 3 times the upper limit of normal have been observed in clinical trials. The manufacturer recommends routine liver function monitoring at 2 and 4 months after starting febuxostat, and periodically thereafter.²⁷

Place in Therapy

Currently, there are few therapies available for the management of hyperuricemia and gout. Allopurinol remains the most commonly prescribed medication presumably due to a favorable safety and efficacy profile, convenient once-daily dosing, and low cost. Allopurinol demonstrates a predictable urate lowering effect of 1 mg/dL with every 100 mg incremental dose. Unfortunately, allopurinol is unable to achieve sUA levels less than 6 mg/dL in approximately half of all patients treated, and many physicians are reluctant to titrate the dose above 300 mg per day.²¹

Febuxostat is a viable therapeutic option for the management of hyperuricemia due to gouty arthritis.

**Table 4.** Comparison of allopurinol and febuxostat.

Structure	Allopurinol	Febuxostat
	Purine-based	Non-purine based
Mechanism of action	Inhibits xanthine oxidase, the enzyme responsible for conversion of hypoxanthine to xanthine to uric acid	
Indication	<ul style="list-style-type: none"> • Prevention of gouty arthritis flare • Prevention/treatment of secondary hyperuricemia during treatment of tumors or leukemia • Prevention of recurrent calcium oxalate calculi 	<ul style="list-style-type: none"> • Chronic management of hyperuricemia in patients with gout
Dosing	Initiate at 100 mg/d; titrate weekly to maximum of 800 mg/d; doses > 300 mg/d should be given in divided doses	Initiate at 40 mg/d; may increase to 80 mg/d if sUA > 6 mg/dL after 2 weeks
Adjustment for renal impairment	Adjustment required due to accumulation of allopurinol and metabolites	No adjustment required if CrCl > 30 ml/min; insufficient data with severe impairment (CrCl < 30 ml/min)
Adjustment for hepatic impairment	Adjustment recommended with severe hepatic impairment	No adjustment needed for mild-moderate impairment; not recommended with severe hepatic impairment
Adverse effects	LFT abnormalities, rash (including Stevens-Johnson), diarrhea, nausea	LFT abnormalities, rash, arthralgias
Pregnancy category	C	C

It lowers serum uric acid levels rapidly and predictably. Febuxostat is generally well tolerated with the most common adverse effects being increased liver function tests, rash, nausea, and diarrhea.²⁷ Few drug-drug or drug-food interactions exist; however, febuxostat should not be used concomitantly with azathioprine, mecaptopurine, didanosine, or theophylline on the basis of known interactions with allopurinol.^{41–43} In the US, the recommended starting dose is 40 mg daily with the option to increase the dose to 80 mg if the sUA level is not reduced below 6 mg/dL after a minimum of two weeks of therapy.²⁷ Table 4 provides a brief comparison of allopurinol and febuxostat.

Conclusion

Febuxostat is the first medication approved for hyperuricemia and gout by the US FDA since allopurinol was approved in 1966. Allopurinol and febuxostat share the same mechanism of action, and their efficacy and safety has been compared in several well controlled trials.

The available data shows that febuxostat increased the percentage of patients with sUA levels below the target of 6 mg/dL in patients more frequently than in allopurinol-treated patients. While in the short-term this increased the frequency of gout flares as mobilization of urate crystals occurs, the frequency of flares

decreased over time as total body stores of urate is reduced. Febuxostat is generally well tolerated with approximately 10% of patients discontinuing therapy due to side effects. In closing, febuxostat represents a reasonable alternative for patients with gout who are unable to take allopurinol due to lack of efficacy, hypersensitivity, or intolerance.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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