Febuxostat: A Novel Agent for Management of Hyperuricemia in Gout

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Bisht and Bist: Febuxostat: Novel Drug for Gout

Gout is a metabolic disorder characterized by elevated uric acid levels in the body, associated with painful arthritis, tophi and nephropathy. The most frequently used pharmacologic urate lowering strategies involve reducing urate production with a xanthine oxidase inhibitor and enhancing urinary excretion of uric acid with a uricosuric agent. Urate lowering agents are limited in number, availability and effectiveness. The emergence of a new medication, febuxostat, to lower serum urate levels is welcome as no new drug have been approved since the introduction of allopurinol, in 1964, and the drugs that are available have limitations owing to inefficacy or toxicity. Febuxostat is a novel, nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia and gout.

Key words: Gout, hyperuricemia, xanthine oxidase inhibitor

Gout is the most common form of inflammatory arthritis in men and is caused by the deposition of monosodium urate crystals in tissues[1]. The condition generally occurs after years of sustained high uric acid concentrations and it is estimated to affect approximately 5.1 million people in the United States, according to the most recent National Health and Nutrition Examination Survey (NHANES III)[2]. Prevalence of gout and/or hyperuricemia during the past 10 years has been increasing, possibly because of an increase in the prevalence of two important risk factors for hyperuricemia, namely, obesity and aging[1,3]. Acute and chronic arthritis, tophi and renal diseases are manifestations of gout that reflect the magnitude and duration of hyperuricemia, which is the biological hallmark of gout[4].

Treatment of an acute attack of gout differs from treatment aimed at preventing attacks and other manifestations by reducing the serum urate level. The drugs available for the treatment of hyperuricemia in patients with gout are uricosuric agents (e.g. probenecid, sulfinpyrazone), which increase the excretion of uric acid, and xanthine oxidase inhibitor (e.g. allopurinol and its metabolite oxypurinol), which inhibit the oxidation of xanthine to uric acid. Use of the uricosuric drugs is limited by their inefficacy in patients whose creatinine clearance is less than 50 ml per min per 1.73 m^2 of body surface area; this excludes most patients older than 60 years of age. Xanthine oxidase inhibitors are effective in patients with renal insufficiency, but these patients may require a reduction in dose because its clearance is primarily by renal mechanisms. Allopurinol is the most commonly used antihyperuricemic agent because of its efficacy regardless of the cause of hyperuricemia and because of the convenience of once daily dosing[5]. The introduction of febuxostat provided clinicians with an additional hope for the treatment of hyperuricemia and gout in patients who are non responsive to allopurinol. This article reviews pharmacological aspects of febuxostat.

Febuxostat is a novel, orally administered antihyperuricemic drug[6]. Chemically, febuxostat is (2-[3-cyano-4-(2-methylpropoxy)-phenyl]-4-methylthiazole-5-carboxylic acid). It is a non purine analogue inhibitor (fig. 1) of both the oxidized and reduced forms of xanthine oxidase; in contrast, allopurinol an hypoxanthine analog, weakly inhibits the oxidized form[4,6]. It acts as a potent inhibitor of xanthine oxidase and was found to be more than 10-30 times potent than allopurinol in animal

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studies[7]. The ki value of febuxostat is 0.7 nM as compared to allopurinol which is 0.7 μM[8]. It has minimal effects on other enzymes involved in purine and pyrimidine metabolism[6].

Febuxostat is rapidly absorbed after oral administration with a time to reach peak concentration (t_{max}) of approximately 1 h. The drug is highly bound to albumin in blood (~99%) and appears to have a low to medium apparent volume of distribution of approximately 0.7 l/kg[9]. The pharmacokinetics of febuxostat appears to be linear in the 10 mg to 120 mg once-daily dose range[9]. It is mainly metabolized to its acylglucuronide metabolite via uridine diphosphate glucuronosyltransferase (UGT) enzymes and to a lesser extent to its active oxidative metabolites 67M-1, 67M-2, and 67M-4 via cytochrome P450 enzymes[10]. Less than 6% of the administered dose is excreted in the urine as unchanged drug[10]. The mean half-life is 4 to 9 h.

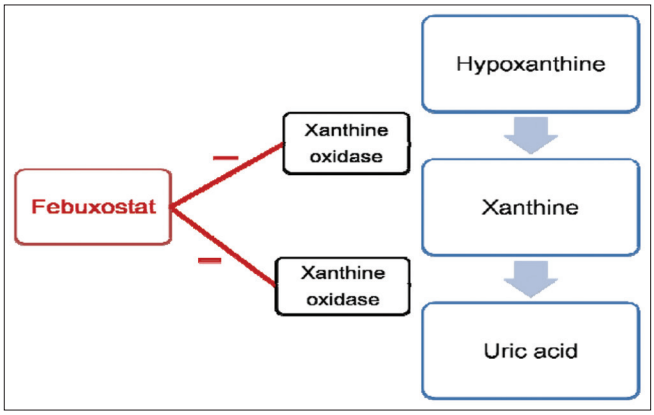

Fig. 1: Mechanism of action of febuxostat

Febuxostat was found to be well tolerated. The most common adverse events include abnormal liver function test results, abdominal pain, diarrhea, headache, joint related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms[11]. All adverse events were of mild intensity. The overall incidence of adverse events during dosing was higher for subjects in the moderate hepatic impairment (75%) and mild hepatic impairment (63%) groups as compared to subjects in the normal hepatic function group (25%)[10]. There were no serious adverse events or clinically significant changes from baseline in laboratory values, physical examination, vital signs, or ECG readings during the study period.

TABLE 1: SUMMARY OF CLINICAL TRIALS CONDUCTED TO ASSESS EFFICACY OF FEBUXOSTAT

Study	Study design/ duration	Number of patient	Drug compared	Outcome (Serum uric acid concentration < 6 mg/dL)	Reference
Phase II trial	Multicenter, double-blind, placebo controlled Study. 42 days	103	Placebo Febuxostat 20 mg Febuxostat 40 mg	0% 45.7% 91.2%	14
Phase II trial	Placebo-controlled, dose response study. 36 days	128	Placebo Febuxostat 20 mg Febuxostat 40 mg	0% 31.5% 41.9%	15
Phase II trial	Randomized, double-blind, placebo-controlled, dose response study. 28 days	153	Placebo Febuxostat 40 mg Febuxostat 80 mg Febuxostat 120 mg	0% 56% 76% 94%	16
Phase III trial -Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat [APEX]	Randomized controlled, double-blind. 28 weeks	1,072	Placebo Febuxostat 80 mg Febuxostat 120 mg Febuxostat 240 mg Allopurinol 300 mg	1% 72% 79% 92% 39%	17
Phase III trial	Multicenter, randomized controlled, double-blind, double dummy. 56 days	256	Febuxostat 40 mg Allopurinol 200 mg	82% 69%	18
Phase III trial -Febuxostat vs Allopurinol Controlled Trial [FACT]	Randomized controlled, double-blind. 52 weeks	760	Febuxostat 80 mg Febuxostat 120 mg Allopurinol 300 mg	74% 80% 36%	11
Phase III trial	Randomized controlled, double-blind. 24 weeks	2,269	Febuxostat 40 mg Febuxostat 80 mg Allopurinol 300 mg	45% 67% 42%	19

Febuxostat is indicated for the long-term management of hyperuricemia in patients with gout. It was found to be more effective in the doses of 40-120 mg per day in lowering serum urate levels than the fixed daily dose of 300 mg of allopurinol. The results of various clinical trials conducted for assessing the uric acid lowering effect of febuxostat is summarized in Table 1. The reduction in the frequency of gout flares and decrease in the size or number of tophi was similar to allopurinol. It is a potential alternative to allopurinol for patients with hyperuricemia and gout. The relative costs of allopurinol and febuxostat may influence the decision of use of these agents. The ability of febuxostat was not altered in patients with mild to moderate renal insufficiency[12]. Comparative features of the common antihyperuricemic agents are given in Table 2. However, further studies are needed to define long term safety profile of febuxostat, especially when it is administered in patients with secondary hyperuricemia, renal insufficiency, or in those with other coexisting conditions or receiving medications that may cause hepatotoxicity[13].

Febuxostat is contraindicated in patients being treated with the xanthine oxidase substrates azathioprine, mercaptopurine, and theophylline. Like allopurinol, febuxostat is not effective for the treatment of acute gouty attacks and may even precipitate them during the first 6 months of therapy. Prophylactic therapy with nonsteroidal anti-inflammatory drug or colchicine is advised to prevent the same. However, discontinuation of febuxostat is not necessary if a gout flare occurs[10]. Periodic liver function tests are advised for patients receiving febuxostat as transaminase elevations greater than 3 times the upper limit of normal were observed in patients treated with febuxostat in clinical trials[10]. A higher rate of cardiovascular thromboembolic events was observed in patients treated with febuxostat. Although a causal relationship has not been established, it is recommended that patients be monitored for signs and symptoms of myocardial infarction and stroke[10]. Caution is advised with the use of febuxostat in patients with severe renal or hepatic impairment because of a lack of data in this population[10].

Coadministration of febuxostat with xanthine oxidase substrate drugs (azathioprine, mercaptopurine or theophylline) could increase plasma concentrations of these drugs, since these drugs are metabolized by xanthine oxidase, resulting in severe toxicity; hence their concomitant use is contraindicated. Since febuxostat does not inhibit or induce cytochrome P450 enzymes it lacks significant drug interactions with other drugs metabolized of these enzymes.

TABLE 2: COMPARISION OF COMMONLY USED ANTIHYPERURICEMIC AGENTS WITH FEBUXOSTAT

Agent	Advantages	Disadvantages
Allopurinol	Efficacy in both overproducers and underexceretors of uric acid. Single daily dosing. Can be used cautiously in renal insufficiency. FDA approved for use in secondary hyperuricemia and recurrent urinary calculi patient with increased uric acid excretion	Potentially serious adverse effects. Drug interactions e.g. warfarin, azathioprine. Inconsistent achievement of target serum urate level.
Probenecid	No fatal adverse effect. Useful in underexcretors of uric acid.	Multiple drug interactions. Renal insufficiency is a problem. Risk of nephrolithiasis. Multiple daily dosing. Inconsistent achievement of target serum urate level
Febuxostat	Well tolerated. Better uric acid lowering effect. Metabolised mainly in liver	Long term adverse effects not known. Clinically not superior or cost effective compared with allopurinol increased as required to control uric acid levels (up to 900 mg) Efficacy in secondary hyperuricemia and recurrent urinary calculi patient with increased uric acid excretion not known

Febuxostat is an orally active drug found to be effective in the dosage of 40-120 mg/day. The pharmacokinetics of the drug allows it to be suitable for once a day dosing. The recommended starting dosage of febuxostat is 40 mg once daily, if the patients do not achieve the target serum uric acid concentration (<6 mg/dl) after 2 weeks then the dose is increased to 80 mg once daily. Although febuxostat is metabolized mainly in liver, but no dosage adjustment is necessary for patients with mild to moderate hepatic impairment, however caution is required in severe hepatic impairment as there is lack of data in this population[10]. No dose adjustment required for mild to moderate renal failure but caution is required for severe impairment[10]. Febuxostat is

pregnancy category C drug, and therefore its use in pregnancy is recommended only if the potential benefit outweighs the potential risk to the fetus. Human breast milk excretion data is not known hence caution is advised if febuxostat is administered to women who are breast-feeding. Safety and effectiveness have not been established in children therefore it should not be used in them[10].

Febuxostat, is the latest drug for the treatment of hyperuricemia and gout developed after a gap of nearly 40 years. It has been approved by European medicines agency and US. Availability of febuxostat provides an alternative to the patients not tolerating or having inadequate reduction in serum uric acid level with allopurinol,

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