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Study of Febuxostat for the Management of Hyperuricemia in Gout

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ABSTRACT

The past decade has seen an exponential increase of novel therapeutic modalities for a variety of rheumatic disorders, including gout. Gout is the common inflammatory arthritis in an elderly population and can be challenging because its typical appearances are more common in elderly. The management of hyperuricemia in elderly with gout requires special consideration in terms of co-medication, contraindications and risk of adverse reactions. So the Urate-lowering agents including allopurinol and uricosuric agents are also used sensibly in the elderly. The novel therapeutic agent recently approved by USFDA for the treatment of rheumatic disorders in gout is **Febuxostat**, a nonpurine selective xanthine oxidase inhibitor. This review presents its pharmacokinetics and pharmacodynamics, efficacy and safety profile and its usefulness in gout patients. Febuxostat can be used in patients with mild-to-moderate renal or hepatic impairment.

INTRODUCTION

Gout is a metabolic disorder characterized by hyperuricemia (normal plasma urate 2-6 mg/dl). Uric acid, a product of purine metabolism, has low water solubility, especially at low pH. When blood levels are high, it precipitates and deposits in joints, kidney and subcutaneous tissue.

Chronic gout- When pain and stiffness persist in a joint between attacks, gout has become chronic.[1] Pain is a designation for a spectrum of sensations of highly divergent characters and intensity ranging from unpleasant to intolerable.[2,3] Other cardinal features are hyperuricemia, tophi (chalk like stones under the skin in pinna, eyelids, nose, around joints and other places) and urate stones in the kidney. In majority of patients, hyperuricemia is due to under secretion of uric acid, while in few it is due to over production. Chronic gouty arthritis may cause progressive disability and permanent deformities.[1] Gout is the collective name for several disorders that are characterized by formation and deposition of monosodium urate (MSUr) crystals. The condition is associated with recurrent episodes of acute joint pain due to deposition of MSUr crystals in the synovial fluid. In addition to the effects observed in joints, skin/subcutaneous tissue and kidneys may also be affected by tophaceous deposits, cellulitis, urate nephropathy, and/or kidney stones, respectively. In most cases, no identifiable underlying cause of gout is present, but evident factors are usually present that may contribute to increases in urate (uric acid) levels, which may include reduced renal function, obesity and the use of diuretics. Hyperuricemia may exist for several years to decades before the first symptoms of gout attacks appear; therefore it is a disease associated and correlated with aging. Gout is one of the most common inflammatory arthritis affecting the elderly; however in general it appears to be poorly managed.[4-6] The incidence and prevalence of gout in the elderly is increasing. This appears related to improved lifespan leading to similar increases in age-related diseases (e.g, cardiovascular diseases) and their associated adverse effects of treatment (e.g, diuretics and low-dose salicylates) which can increase the risk of gout. “Elderly onset gout” differs from “classical” gout found in middle-aged men in several respects: no male predominance but an equal gender distribution, polyarticular presentation with upper-extremity joint involvement, fewer acute gouty episodes, indolent clinical course, and an increased incidence of tophi.[7-9] This review will focus on Febuxostat for the management of gout in the elderly.

Gout pathophysiology

Uric acid is formed from nucleic acid either endogenously from cell breakdown or exogenously from metabolism of food. Cooling and acidification of the microenvironment, which can result in acute formation of urate crystals, reduce the solubility of MSUr. The gut excretes one-third of urate and two-third amount gets excreted through urine. Renal urate transport is typically explained by a 4-component model: glomerular filtration, a near-complete reabsorption of filtered urate, subsequent secretion, and post secretory reabsorption in the remaining proximal tubule. Recently, several new urate transporters have been identified which play key roles in urate homeostasis, including URAT-1 and Glut-9. The regulation of serum uric acid levels is under a strong genetic control. A recent meta-analysis of genome-wide association scans shows that common DNA variants at 9 different loci are associated with uric acid concentrations. Excessive consumption of alcohol (particularly beer), sweetened soft drinks, fructose, meat, and seafood can also increase levels of serum urate (sUr). Inhibition of urate transporters can be achieved by uricosurics, and production of uric acid can be inhibited using xanthine oxidase inhibitors, such as allopurinol. Febuxostat is a new selective inhibitor of xanthine oxidase. Uric acid deposits can also be lysed by the enzyme uricase, the coding gene for which became defective in humans in the Miocene because of an evolutionary mutation. The combined absence of uricase and almost total reabsorption of filtered urate explains that humans (and the greater apes) have 10-fold higher sUr levels than other mammals.[10]

Drug-induced hyperuricemia

Chronic diuretic therapy is associated with reduced excretion of uric acid. Mechanisms are increased uric acid reabsorption in the proximal tubule secondary to volume depletion, and competition between the diuretic and uric acid for the organic acid secretory mechanism in the proximal tubule. Low-dose diuretic therapy in hypertensive patients does not seem to alter serum urate levels significantly.[11,12] Indeed, the requirement for anti-gout therapy in hypertensive patients is doubled for thiazide doses of ≥25 mg/day (in hydrochlorothiazide equivalents); no significant increase in risk is seen for lower doses. Similarly, low-dose therapy with a loop diuretic is not associated with hyperuricemia.[13,14]

Treatment strategies for gout

Several approaches to the treatment of gout are available depending on the patient's disease status. Optimal treatment often requires a combination of pharmacological intervention and lifestyle changes. Treatment should be tailored to the patient's prognostic factors (high sUr, previous attacks, and radiographic signs), the clinical phase of disease (acute, recurrent, tophaceous) and general risk factors, such as obesity, alcohol consumption, renal impairment, use of diuretics or other risk factors for secondary hyperuricemia. Primary prevention of gout often involves changes in lifestyle, such as a low-purine/weight reducing diet or restricting alcohol intake.[15] Acute gout is usually treated by reducing the inflammation of the affected joint with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and cooling.[16,17]

Primary prevention of gout

Primary prevention of gout involves changes in lifestyle, such as changes to diet (low-purine/weight-reducing diet) and restricting alcohol consumption. No randomized studies have been conducted evaluating the effect of lifestyle changes on the incidence of attacks in patients with gout. Nevertheless, experts agree that lifestyle changes may have some effect. Physicians in daily practice also give lifestyle advice, when gout symptoms appear. However, fewer than 20% of patients with gout seeking medical advice are prepared to make long term changes in lifestyle.[18] Recently, the negative role of meat, seafood and beer consumption, and the protective role of dairy products in the development of gout were demonstrated in a prospective study over a 12-year period among a population of around 47,000 healthy male subjects.[19]

FEBUXOSTAT

Febuxostat pharmacology

The active substance is a new chemical entity designated as 2-[3-cyano-4-(2-methlypropoxy) phenyl]-4-methlythiazole-5-carboxylic acid (Figure 1).

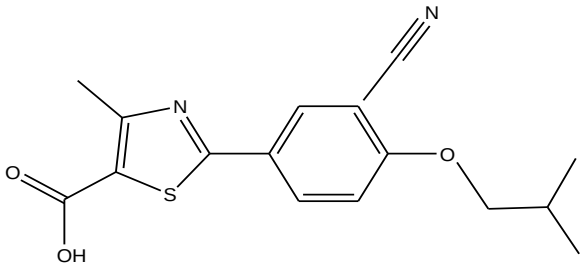

Fig.1 Chemical structure of Febuxostat

It is a non-purine, selective xanthine oxidase/xanthine dehydrogenase inhibitor. It is available in a dosage of 80 or 120 mg Febuxostat.

Febuxostat 10 to 120 mg/day dose-dependently reduced mean sUr levels from baseline by 25% to 70% in healthy volunteers; 24-hour urinary uric acid excretion at day 8 was decreased by 46% to 66% relative to placebo. Both effects seemed to plateau at dosages >120 mg/day. Age (18 to 40 years versus ≥65 years) and sex had no clinically significant effect on the pharmacokinetic and pharmacodynamic properties of oral Febuxostat 80 mg/day in healthy volunteers.[20-21] Absorption of Febuxostat is rapid, with a time to C_{max} of ≈1 hour. Febuxostat can be administered regardless of food or antacid intake.[22] Pharmacokinetic values are linear in the range of 10 to 120 mg. Febuxostat is highly (>98%) bound to human plasma proteins, mainly at the diazepam binding site. Elimination half-life of Febuxostat is approximately 12 hours. Febuxostat is mainly eliminated by glucuronidation in the liver. Also, some quantifiable active metabolites 67M-1, 67M-2, and 67M-4 were found. No dosage adjustments are recommended in patients with mild to moderate renal impairment. Febuxostat inhibits cytochrome P450 isoenzyme 2D6, but interactions with CYP2D6 are not considered clinically significant.[23-25]

Clinical efficacy

In a phase II dose-response study the efficacy of 40 mg, 80 mg, and 120 mg/day. Febuxostat was evaluated in 153 patients with hyperuricemia (baseline sUr ≥0.48 mmol/L) and gout.[26] Patients were aged 23 up to 80 years. Subjects received Febuxostat (40 mg, 80 mg, 120 mg) or placebo once daily for 28 days and colchicine prophylaxis for 14 days prior to and 14 days after randomization. Significantly more patients receiving Febuxostat than placebo achieved a sUr level of ≤0.36 mmol/L) at each visit (P <0.001 for each comparison). The target sUr level (≤0.36

mmol/L) was achieved at study end in 0% of patients in the placebo group and 56%, 76% and 94% of patients in the 40 mg, 80 mg, and 120 mg Febuxostat groups, respectively. Subjects who completed this study were entered into a 5-year open-label extension study (FOCUS) and initially received Febuxostat 80 mg daily. Between weeks 4 and 24, dosing was adjusted to Febuxostat 40 or 120 mg. All subjects received gout flare prophylaxis during the first 4 weeks. Gout flares were recorded and treated throughout the study, and sUr, baseline tophi and safety were monitored. Among 116 subjects initially enrolled, dose adjustments were made for 44 (38%) subjects. As a result, 8 subjects received Febuxostat 40 mg, 79 received 80 mg, and 29 received 120 mg daily maintenance dose. At 5 years, 93% (54/58) of the remaining subjects had sUr <6.0 mg/dL (<0.36 mmol/L). Fifty-eight subjects (50%) discontinued prematurely; 38 did so in the first year. The primary reasons for discontinuation were: personal reasons 22 (19.0%), adverse event 13 (11.2%), gout flare 8 (6.9%), lost to follow-up 5 (4.3%), protocol violation 1 (<1%), other 9 (7.8%). Sustained reduction of sUr was associated with nearly complete elimination of gout flares. In 26 subjects with a tophus at baseline, resolution was achieved in 69% (18/26) by last visit on study drug at any point during the study. There were no deaths reported during the study. Long-term treatment with Febuxostat resulted in durable maintenance of sUr <6.0 mg/dL for most subjects. There was nearly complete abolition of gout flares in patients completing the study. Baseline tophi resolved in a majority of subjects.[27]

In the phase III FACT trial, 762 patients with gout and with serum urate concentrations of at least 8.0 mg/dL (0.48 mmol/L) were randomly assigned to receive either Febuxostat (80 mg or 120 mg) or allopurinol (300 mg) once daily for 52 weeks; 760 patients received the study drug.[28] Prophylaxis against gout flares with naproxen or colchicines was provided during weeks 1 through 8. The primary endpoint was a target sUr <6.0 mg/dL (0.36 mmol/L) at the last 3-monthly measurements. The secondary endpoints included reduction in the incidence of gout flares and in tophus area. The primary endpoint was reached in 47% to 59% of patients receiving 80 mg of Febuxostat, 44% to 74% of those receiving 120 mg of Febuxostat, and 8% to 40% of those receiving 300 mg allopurinol (P <0.001 for comparison of each Febuxostat group with the allopurinol group). The rates of discontinuation due to adverse events were higher in both the 80-mg Febuxostat group and the 120-mg Febuxostat group than in the allopurinol group. Categories and frequencies of treatment-related adverse events were not linked to discontinuation, but only published for all reported treatment-related adverse events. Febuxostat was concluded, at a daily

dose of 80 mg or 120 mg, to be more effective than 300 mg Allopurinol in lowering sUr. Febuxostat reduced the median tophus area by 83% and 66% in patients in the 80-mg and 120-mg groups compared with 50% in patients receiving allopurinol. Similar reductions in gout flares occurred in all treatment groups: 64% and 70% in the 80-mg and 120-mg Febuxostat groups, and 64% of patients receiving allopurinol. It was considered that an 8-week period of prophylaxis against gout flares due to urate mobilization probably was too short, as many gout attacks were noticed in the first weeks afterwards in all groups. This might be one of the reasons that no differences in reduction of gout flares were seen. Another point of discussion is the dose limit of allopurinol of 300 mg/day in this study, which is often considered as the "safe" maximum dosage.[29,30] It is known that dosages up to allopurinol 600 mg/day are more effective, and the licensed maximum dosage is 800 mg/day (or 900 mg/day in some countries).[31] In the APEX trial, 1072 patients with gout, including persons with impaired renal function, and with sUr concentrations of at least 0.48 mmol/L were randomy assigned to receive either Febuxostat (80 mg or 120 mg or 240 mg) versus allopurinol (300 mg or 100 mg) once daily for 28 weeks versus placebo.[32] Significantly higher percentages of subjects treated with Febuxostat 80 mg (48%), 120 mg (65%), and 240 mg (69%) attained the primary endpoint of at least 3 monthly sUr levels <0.36 mmol/L compared with allopurinol (22%) and placebo (0%). A significantly higher percentage of patients with impaired renal function treated with Febuxostat 80 mg (4 out of 9 = 44%), 120 mg (5 out of 11 = 45%), and 240 mg (3 out of 5 = 60%) achieved the primary endpoint compared with those treated with 100 mg allopurinol (0 out of 10 = 0%). Serious adverse events occurred similarly in all groups, although diarrhea and dizziness were more frequent in the 240 mg Febuxostat group. Primary reasons for withdrawal were similar across groups except for gout flares, which occurred more frequent with Febuxostat than with allopurinol. Schumacher et al concluded that at all doses studied Febuxostat more effectively lowered and maintained serum urate levels <0.36 mmol/L than did allopurinol or placebo in subjects with hyperuricemia and gout, including in those with mild to moderate impaired renal function.[32] Subjects who completed the FACT or APEX trial were invited to enroll in an open-label extension study and assigned to fixed-dose daily ULT with Febuxostat (80 mg or 120 mg) or allopurinol (EXCEL).[33] The majority of subjects were male, Caucasian, and in the age rabge of 45 to 65 years. ULT reassignment was permitted during months 1 to 6 to achieve sUr concentrations of 3.0 to 6.0 mg/dL (0.18 to 0.36 mmol/L). Flares requiring treatment, tophus

size, safety, and sUr levels were monitored during up to 40 months of ULT maintenance. After 1 month of initial treatment, >80% of subjects receiving either Febuxostat dose, but only 46% of subjects receiving allopurinol, achieved sUr <6.0 mg/dL (<0.36 mmol/L). After ULT reassignment, >80% of all remaining subjects maintained the primary efficacy endpoint of sUr <6.0 mg/dL at each visit. More subjects initially randomized to allopurinol required ULT reassignment to achieve sUr <6.0 mg/dL compared with subjects receiving Febuxostat. Maintenance of sUr <6.0 mg/dL resulted in progressive reduction to nearly 0 in proportion of subjects requiring gout flare treatment. Baseline tophus resolution was achieved by 46%, 36%, and 29% of subjects maintained on Febuxostat 80 mg, Febuxostat 120 mg, and allopurinol, respectively. Overall adverse event rates (including cardiovascular adverse event rates), adjusted for 10-fold greater Febuxostat than allopurinol exposure, did not differ significantly among treatment groups. Durable maintenance of goal range sUr level with either dose of Febuxostat or in smaller numbers of subjects with allopurinol resulted in near elimination of gout flares and improved tophus status over time.[34]

Febuxostat tolerability and safety

In terms of safety, to date, results from clinical trials have shown that Febuxostat is well tolerated with a safety profile comparable to that of placebo and allopurinol. The most commonly reported adverse drug reactions (investigator assessment) are liver function abnormalities (3.5%), diarrhea (2.7%), headache (1.8%), nausea (1.7%), and rash (1.5%).[35] In both the double-blind and extension phases, liver function test abnormalities were associated with colchicine administration.[24] Diarrhea, nausea, and vomiting are more frequent in patients concomitantly treated with colchicine. Some serious rashes were reported with Febuxostat in the APEX study. Since allopurinol can cause life-threatening cutaneous reactions (Stevens-Johnson syndrome) in rare cases, special attention to this serious adverse event is necessary.[30,35]

CONCLUSION

According to the above studies the Febuxostat can be regarded as a useful, novel, nonpurine selective potent inhibitor of xanthine oxidase. The pharmacokinetic data available for Febuxostat gives the linear response at 10 to 120 mg daily rapidly and sustainably reduces serum uric acid by 25% to 70%. Elderly onset of gout has distinct clinical features in comparison to gout in

middle aged men, and therefore co-medication and co-morbidity should be carefully evaluated. When the preventive treatment is to be considered in such population, the potential benefits should prevail over the risk.

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