

Treatment of Gout—A new Approach

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Abstract: Since a long time back allopurinol has been constantly used to subsidize uric acid level in blood by competitive and suicidal inhibition of xanthine oxidase. Barring a few side effects there was never felt any emergency for invention of an alternative. But a dire research was going on to bring into light an alternative which is better than allopurinol in some aspects. Now a non-purine xanthine oxidase Febuxostat is a new non-purine xanthine oxidase inhibitor that is more potent than allopurinol 300 mg daily. Febuxostat was more effective than allopurinol in the subset with impaired renal function. Long-term extension studies at different levels confirmed the efficacy and tolerability of Febuxostat. In patients who achieved the Serum uric acid level of 6 mg/dl (360 μ mol/l), the incidence of gout flares fell steadily and tophi resolved in many patients. The incidence of adverse events such as dizziness, diarrhoea, headache and nausea with Febuxostat was similar to allopurinol. The incidence of cardiovascular side-effects was numerically higher with Febuxostat than with allopurinol, but this was not statistically significant. Co-administration of Febuxostat with AZA or 6-mercaptopurine is not recommended. Prophylaxis (colchicines and/or NSAIDs) against acute attacks should be used for at least the first 6 months, since early mobilization flares were observed in the clinical trials. In conclusion, Febuxostat is more effective than allopurinol 300 mg daily in reducing uric acid level 6 mg/dl (360 μ mol/l), the target recommended long term option for treatment of gout.

Key words: Gout, Urate lowering capacity, Febuxostat, Clinical studies, Serum uric acid, Adverse effects.

I. Introduction

Gout is a form of inflammatory arthritis, associated with hyperuricaemia, in which the formation of Uric acid is the final product of purine metabolism in human beings. Despite the fact that uric acid was first identified approximately 2 centuries ago, certain pathophysiologic aspects of hyperuricaemia are still not clearly understood. For years, hyperuricaemia has been identified with or thought to be the same as gout, but uric acid has now been identified as a marker for a number of metabolic and hemodynamic abnormalities. Unlike allantoin, the more soluble end product found in lower animals, uric acid is a poorly soluble end product of purine metabolism in humans. Human beings have higher levels of uric acid, in part, because of a deficiency of the hepatic enzyme, uricase, and a lower fractional excretion of uric acid. Approximately two thirds of total body urate is produced endogenously, while the remaining one third is accounted for by dietary purines. Approximately 70% of the urate produced daily is excreted by the kidneys, while the rest is eliminated by the intestines. However, during renal failure, the intestinal contribution of urate excretion increases to compensate for the decreased elimination by the kidneys.

The blood levels of uric acid are a function of the balance between the breakdown of purines and the rate of uric acid excretion. Theoretically, alterations in this balance may account for hyperuricaemia, although clinically defective elimination accounts for most cases of hyperuricaemia. Sodium monosodium urate crystals in the joints and periarticular tissues cause acute inflammatory attacks as well as long-term tissue damage. The strategy for the long-term management of gout is to lower the serum urate (sUA) level and hence the level in the tissues, and maintain it below the saturation point (6.8 mg/dl or 410 μ mol/l) so that existing monosodium urate crystals dissolve and no further crystals form. A target level for sUA of \leq 6 mg/dl (360 μ mol/l) is recommended recently. For many years, allopurinol has been the most widely used urate-lowering agent in gout patients. It is recommended that allopurinol be initiated at a low dose of 100 mg, which is then titrated upwards in 100 mg increments every few weeks to achieve the therapeutic target [2]. However, this is rarely done in clinical practice, for reasons that are unclear, and the vast majority of physicians give allopurinol at the standard dose of 300 mg/day without titration. Moreover, there is increasing evidence to show that the 300 mg dose is relatively ineffective in achieving the target sUA level and that higher doses (or combination therapy) may be needed to attain this [3, 4]. There has never been a systematic evaluation of the use of higher doses of allopurinol nor has a controlled clinical trial been carried out comparing fixed dosing with titration to achieve a target sUA. Side-effects including rashes occur in a small proportion of patients receiving allopurinol, and a more severe reaction described as allopurinol hypersensitivity syndrome is believed to affect around 1 in 300 treated patients [2]. Characterized by symptoms such as severe skin rash, fever and deterioration in renal function [5], allopurinol hypersensitivity syndrome is potentially life-threatening, and is associated with significant mortality and morbidity. Oxypurinol, which is the main metabolite of allopurinol and is responsible for most of its urate-lowering effects, is excreted predominantly by the kidneys and hence it has been recommended that the dosage

of allopurinol be reduced in patients with renal impairment. It has become increasingly obvious that alternative therapeutic options may have a significant impact on the future of successful gout management, especially in those patients with renal impairment or who are unresponsive or intolerant to allopurinol. Febuxostat is a new oral non-purine xanthine oxidase (XO) inhibitor that has recently been approved in Europe for the treatment of chronic hyperuricaemia and gout. It has been evaluated in an extensive clinical trials programme, and results have shown that it is an effective therapy for lowering sUA levels. This article reviews the evidence to show that Febuxostat is a valuable treatment option that may provide considerable benefits for patients with gout and hyperuricaemia.

Pharmacodynamics

Febuxostat is structurally different from allopurinol and lacks the purine ring (Fig. 1). It is a more selective and potent inhibitor of XO than allopurinol and has no effect on other enzymes involved in purine or pyrimidine metabolism. Febuxostat showed potent mixed-type inhibition of XO from purified bovine milk, with K_i and K_i' values of 0.6 and 3.1 nM, respectively, suggesting that both the oxidized and reduced forms of XO were inhibited [7]. The onset of action of Febuxostat is sufficiently fast that sUA levels can be re-tested within 2 weeks of initial dosing [8].

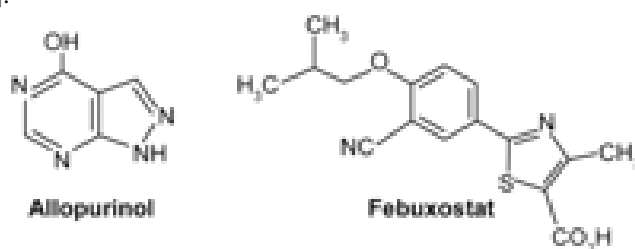


FIG. 1.

Unlike allopurinol, Febuxostat is a non-purine XO inhibitor.

Pharmacokinetics

Febuxostat is well absorbed after oral administration (84% oral bioavailability). The effects of food or antacids on absorption are not considered to be clinically relevant and Febuxostat can be given without regard to food intake [9]. Febuxostat is almost completely bound to plasma proteins (99% binding), primarily albumin. The active metabolites of Febuxostat are 82–91% protein bound [8]. The main route of elimination of Febuxostat is metabolism in the liver followed by excretion of metabolites in the urine and faeces. It is metabolized via the uridine diphosphate glucuronosyltransferase system and oxidized by the cytochrome P450 system. The pharmacokinetics of Febuxostat are unaffected in subjects with mild-to-moderate hepatic impairment (Child-Pugh Classes A and B) [10]. Less than 5% of the dose of Febuxostat is excreted unchanged in the urine. The safety and efficacy of Febuxostat have not been fully evaluated in patients with creatinine clearance <30 ml/min. Neither age nor gender had any significant effect on the pharmacokinetics, Pharmacodynamics or safety profile of Febuxostat [12].

Drug interactions

Studies of drug interactions between Febuxostat and a variety of other medicinal agents have reported that Febuxostat can be co-administered with colchicines (0.6 mg b.i.d.), certain NSAIDs (naproxen and indometacin), hydrochlorothiazide, warfarin and desipramine or other CYP2D6 substrates, without any dose adjustment, and without any clinically significant effects on the pharmacokinetics of either agent [8]. No drug interaction studies have been undertaken with AZA or 6-mercaptopurine, but since these drugs are metabolized by XO, co-administration with Febuxostat is not recommended.

Phase II studies and dose selection

A Phase II randomized double-blind dose-response study in 50 patients with gout compared Febuxostat 40, 80 and 120 mg/day with placebo over 28 days, with colchicines prophylaxis in all groups [13]. The study population was predominantly male (89%) with mean baseline sUA >8.0 mg/dl (480 μ mol/l). The primary endpoint was the proportion of patients reaching the target sUA level of <6 mg/dl (<360 μ mol/l) on Day 28. The proportion of patients successfully achieving the endpoint was significantly greater with 40, 80 and 120 mg Febuxostat (56, 76 and 94% of patients, respectively) than with placebo (0% of patients; $P < 0.001$ for each comparison).

Based on the results of the Phase II study, doses of 80 and 120 mg were selected for evaluation in the Phase III programme.

The trials showed that Febuxostat was significantly more effective than the conventional dose of 300 mg/day allopurinol in lowering sUA, as shown by the higher proportion of patients achieving the primary endpoint of

sUA <6 mg/dl (<360 μ mol/l) at the last three visits (Fig. 2). Significantly more Febuxostat-treated patients met the primary endpoint in both studies compared with those receiving allopurinol 300 mg

There was no significant difference in the incidence of gout flares between the patients. Immediately after the end of prophylaxis, the incidence of acute gout attacks requiring treatment was higher in patients with lower sUA levels, probably reflecting continued mobilization of pre-existing urate crystals and implying that a longer period of prophylaxis was required.

The study which included a small subset of patients with significantly impaired renal function (serum creatinine >1.5 to \leq 2.0 mg/dl); Febuxostat was safe and well tolerated in this population. It was effective in controlling sUA in this renal impaired population: Febuxostat was also very effective in patients aged >65 years. The primary endpoint of sUA level <6 mg/dl (360 μ mol/l) at the last three visits was achieved in >75% of febuxostat-treated patients (72% at 80 mg and 78% at 120 mg) compared with 46% with allopurinol ($P \leq 0.01$). Treatment was well tolerated in this population [16].

Long-term open-label extension studies

Patients not achieving a reduction in sUA level <6 mg/dl (360 μ mol/l) were permitted to switch therapy from allopurinol to Febuxostat, or vice versa, within the first 6 months of the study. The switch from allopurinol to Febuxostat resulted in successful lowering of sUA level for 67% of the patients, whereas only 9% of the patients who switched from Febuxostat to allopurinol lowered their sUA level <6 mg/dl.

In both the long-term extension study and in the double-blind trials, there was a relatively high incidence of acute gout flares in the first few weeks after the initiation of Febuxostat and after the end of the prophylactic colchicines/naproxen treatment. The number of flares then declined to very low numbers over the period of treatment. The early acute gout attacks represented mobilization flares which are precipitated at any time the sUA levels rapidly increase or decrease. In studies of urate-lowering therapies, the frequency of acute flares following the institution of treatment directly parallels the effectiveness of the drug to dramatically or rapidly lower sUA levels. This can be partially prevented by using a longer duration of prophylaxis.

Tolerability and adverse events

The most commonly reported adverse drug reactions (investigator assessment) were liver function abnormalities (3%), diarrhea (3%), headache (1%), nausea (2%), and dizziness and/or altered taste (2%). The percentage of patients with mild liver function test abnormalities was similar in the Febuxostat and allopurinol treatment arms (3 vs. 4%, respectively). The incidence of adverse events such as dizziness, diarrhea, headache and nausea with Febuxostat was similar to allopurinol in the combined Phase III trials and the long-term follow-up [3, 14, 20].

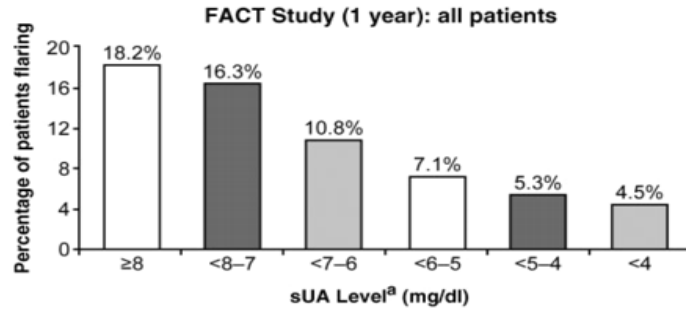
II. Conclusions

Febuxostat reduced and maintained sUA levels <6 mg/dl (360 μ mol/l) for up to 40 months, and was significantly more effective than allopurinol at the usual dose of 300 mg when assigned as an initial treatment. Febuxostat was also more effective than allopurinol in reducing sUA levels <5 mg/dl (300 μ mol/l). Febuxostat is put to treatment for the 'treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history; or presence of, tophus and/or gouty arthritis)'. The recommended dose of Febuxostat is 80 mg, increasing to 120 mg after 2–4 weeks if sUA level has not reached the target of <6 mg/dl. It is recommended that prophylaxis (colchicines and/or NSAIDs) against acute attacks should also be used for at least the first 6 months.

The inadequacies of allopurinol, in terms of limited efficacy at the usual dose of 300 mg, need for dose adjustment in patients with renal impairment and undesirable side-effects, have highlighted the need for an additional treatment for patients with gout. The emergence of Febuxostat as a well-tolerated and efficacious gout therapy could prove to be an excellent solution.

Rheumatology key messages

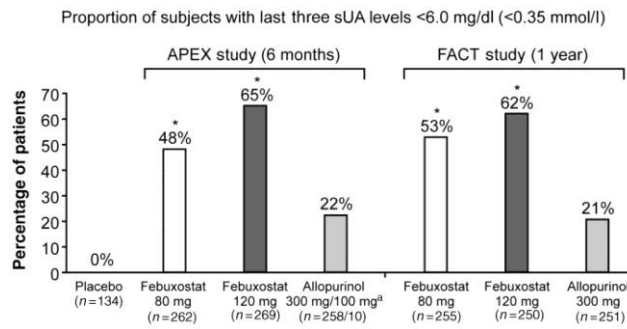
- Febuxostat is a selective XO inhibitor, requiring no dose adjustment in mild-to-moderate renal impairment.
- Significantly more patients achieved sUA <6 mg/dl with febuxostat (80 or 120 mg) than with allopurinol (300 mg).
- Prophylaxis against acute flares is required for 6 months (colchicine/NSAID); flare incidence subsequently declines with long-term treatment.



^aAverage post-baseline serum urate level at Weeks 48–52.

FIG. 3.

Proportion of patients requiring treatment for a gout flare in the last 4 weeks.



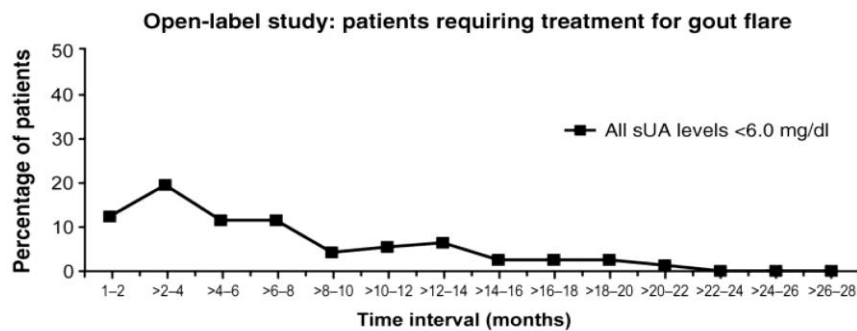
*P<0.001 vs. placebo and allopurinol.

^aWithin combined allopurinol 300/100 group, allopurinol 100 mg efficacy: 0%; allopurinol 300 mg efficacy: 23%. Intention-to-treat population: subjects with serum urate level ≥8.0 mg/dl on Day 2.

FIG. 2.

Febuxostat at both 80 and 120 mg daily was significantly more effective than allopurinol in achieving the primary endpoint, sUA 6 mg/dl (360 μmol/l) at the last three visits.

FIG. 4.



Gout flares measured in patients who remained on initial treatment (data from patients who switch therapies is not included here). Data from C02–021, long-term, open-label, extension study.

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