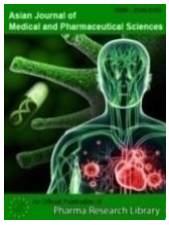

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A Review on Febuxostat as Uric Acid Lowering Agent

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A B S T R A C T

Febuxostat is a novel, potent and non-purine selective xanthine oxidase inhibitor which got approved for market in the year 2011by central drug standard control organisation (CDSCO), in India under the brand name febutaz. Febuxostat is initially developed as xanthiene oxidase inhibitor to treat hyperuricemia in gout patients, has evolved into a versatile therapeutic agent with multifecated applications. It has been shown to be effective in reducing serum uric acid levels, preventing gout attacks, and improving quality of life. Febuxostat unique mechanism of action, pharmacokinetic profile, and clinical efficacy make it a valuble to alternative to traditional uric acid lowering agent like allopurinol. Febuxostat is particularly usefull in patients with kidney disease ,where allopurinol is limited .overall this review provides a comphrensive overview of febuxostat mechanism of action ,its effectiveness in gout management ,its cardiovascular safety profile, renal and hepatic effects ,safety considerations and emerging research prospects. Its once daily dosing and lack of food interactions further enhances its clinical utility. Overall, febuxostat represents a significant advancement in the management of hyperuricemia and gout, offering a safe and effective treatment option for patients.

Keywords: Febuxostat, Uric acid lowering agent, Xanthine oxidase inhibitor, Hyperuricemia.

A R T I C L E I N F O

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C o n t e n t s

1. Introduction

Uric acid is the end product of nucleic acid metabolism. High levels of blood uric acid have long been associated with gout. Gouty arthritis (gout) is a medical Uric condition characterized by red, tender, hot, and swollen joints caused by recurrent attacks of acute inflammatory arthritis. The prevalence of gout in the United States has increased from 2.9 cases per 1,000 persons in 1990 to 5.2 cases per 1,000 persons in 1999, due to increasing age of the population. Men have a higher risk of developing gout than women due to higher baseline levels of blood uric acid. Pathologically, gout increase of blood uric acid levels, which leads to crystal deposits in joints, tendons, and other tissues and uric acid renal stones [1]. Uric acid is the final product of purine metabolism in humans. Uric acid is a chemical produced in the body when purines are broken down. The process of uric acid biosynthesis is as purine synthesis, Inosine monophosphate is created from purine salvage or denovo synthesis. Xanthine production: hypoxanthine from IMP is catalysed to xanthine by xanthine oxidase .uric acid production: xanthine oxidase catalyzes xanthine to uric

acid. The enzyme XO is found in mammals and is primarily a dehydrogenase. It's a large enzyme with an active site made up of sulfar, oxygen, and the metal molybdenum. Uric acid is mainly produced in liver, intestines, and vascular endothelium. its excreted through urine and in small amounts through blood and other bodily fluids.

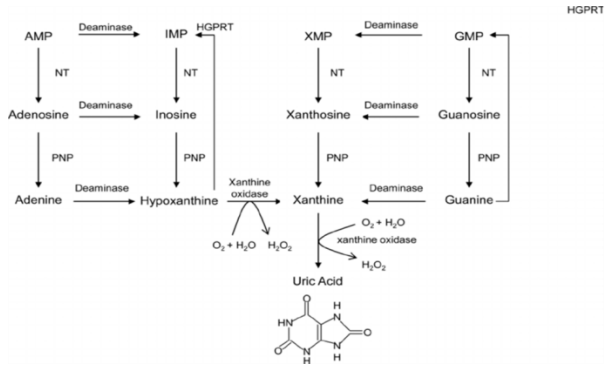


Fig.1: Biosynthesis of Uric Acid

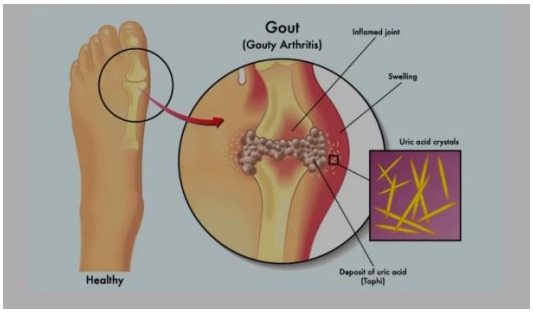


Fig:2 Uric acid deposition

Treatment Protocol:

The treatment protocol consisted of three phases: urate-lowering therapy titration (weeks 0 to 24), maintenance (weeks 25 to 48), and observation (weeks 49 to 72). During phase 1, those randomly assigned to allopurinol or febuxostat were initiated at daily doses of 100 and 40 mg, respectively, with therapies titrated until a serum urate below 6.0 mg/dl (<5.0mg/dl if tophi were present) was achieved or the maximal dose was reached. Participants taking allopurinol before the trial continued taking their pretrial allopurinol dose if randomly assigned to that arm, with dose titration delayed for those receiving 200 mg (to week 6) or 300 mg (to week 9) or, if randomly assigned to febuxostat, started at 40mg per day[6].

Febuxostat is indicated for the long term management of hyperuricemia in patients with gout. It is not recommended for use in the treatment of asymptomatic hyperuricemia. xanthine oxidase and does not inhibit other enzymes involved in purine and pyrimidine metabolism. In healthy volunteers the proportional reductions in mean serum uric acid concentrations with febuxostat doses of 10 to 120 mg. were 25% to 70%. Serum uric acid concentrations were reduced 40% with a 40 mg daily dose and 55% with an 80 mg daily dose. Febuxostat is a nonpurine selective inhibitor of xanthine oxidase. It works by noncompetitively blocking the channel leading to the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, Febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid. Most common dis- ease of high uric acid level is gout. It is a kind of arthritis that Occurs when uric acid built up in the joint.[7]

Food also helpful in case of lowering high uric acid levels in the body .To control this problem there is a special Uric Acid Diet Menu which when rigorously followed will show quick results. Besides dietary changes, you can also find ways on how to control uric acid through a combination of diet and exercises. Therefore, regular exercise is another factor which can help the digestive process but the most important thing is the kind of food you consume. For controlling this, you need to keep a check on your purine intake which is nearly 600- 1000 milligrams during the day. A Uric Acid Diet Menu will help you limit it to 100-150 milligrams a day. Now that you know the Uric Acid Meaning and how does it actually happens, we are going to highlight the Uric Acid Diet Menu and later on how to control uric acid through exercises.[4]

2. Uric Acid Diet Menu

This menu indicates what should and should not be consumed to control an excessive production of uric acid. Therefore, below are the foods to eat and avoid as to how to control uric acid through a personalized uric acid diet menu. Apple Cider Vinegar: People suffering from uric should take three tablespoons of apple cider vinegar with a glass of water to improve the situation.

Fig:3 Apple Cider Vinegar

French Bean Juice: As much as you cringe at the thought of having it but it is the most effective home remedy which should be taken twice a day which prevents the production of high uric acid.

Cherries: It is not the cherry on the cake that you should take but taken in a good potion since they have anti-inflammatory substance referred to as anthocyanin which prevents uric acid from crystallizing and getting deposited in the joints thereby curing pain.

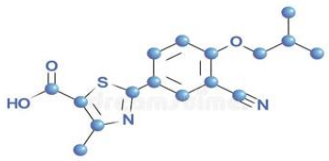
Fig: 4 Cherries

Berries:
After cherries, berries like strawberries, blueberries which are enriched with anti-inflammatory properties are super essential in curing the high uric acid content in your body.

Low Fat Dairy Products:
Dairy products are believed to increases uric acid content in the body. You can always replace milk with soy or almond milk which is rich in protein, Q paneer with soya chunks and many more. We are not suggesting you to consume any less, just telling you to alter your diet a little.

Olive Oil: Cooking food with cold-pressed olive oil will help improve your case of gout since it has antioxidants and anti- inflammatory properties.

Pinto beans: Pinto beans contain folic acid which is an important substance to reduce uric acid levels. You can even include sunflower seeds and lentils in your diet to help your case.



Febuxostat

Pharmakokinetics &Pharmacodynamics of Febuxostat
Febuxostat's pharmacokinetics and dynamics demonstrate its effectiveness in reducing serum uric acid levels understanding its pharmacokinetics and dynamics is essential for optimal dosing and therapeutic efficacy.

Absorption:
Febuxostat is rapidly absorbed after oral administration, with plasma concentrations reached within 1-2 hours, extensively distributed to tissues, with a volume of distribution of approximately 50L and metabolised primarly by CYP1A2 andCYP2C9, with minor contributions from CYP2C8 andCYP3A4finally after absorption, distribution, metabolism the drug is eliminated primarly through renal excretion (69%), with fecal excretion accounting for 21%.

Key pharmacodynamic properties:
- Mechanism of action: inhibition xanthine oxidase decreases uric acid synthesis
- Receptor binding: binds active site of xanthine oxidase, preventing conversion of hypoxanthine to xanthine and xanthine to uric acid
- Dose response relationship: febuxostat efficacy increases with dose, with 40-80mg|day effective in reducing serum uric acid levels. The bioavailability of febuxostat is approximately 50%and half-life 5-7hr steady state concentration are reached within 7-10 days.[11]

Efficacy and Clinical Trails:
Febuxostat has been extensively studied with more than 4000 patients investigated in one phase II clinical trial and three phase III randomized controlled trials, some of them followed for over 5 years. The first phase II randomized double-blind dose-response study was performed in 153 patients with chronic gout in which febuxostat 40, 80 and 120 mg/day were compared with placebo over a period of 28 days, using colchicine as prophylaxis in all groups. The phase III randomized allopurinol comparison clinical trials were FACT (Febuxostat versus Allopurinol Controlled Trial) a 52-week double blind study of 760 patients, APEX (Allopurinol Placebo-Controlled Efficacy Study of Febuxostat) a 28-week, double-blind, placebo-controlled study of 1072 patients, and CONFIRMS a phase III double-blind randomized controlled trial that further examined the comparative urate-lowering efficacy and safety of febuxostat and allopurinol in a larger number of patients (2269) followed for 6 months.

3. Safety Profile
Overall febuxostat showed the well tolerated and safety. Overall safety in all clinical trials showed that febuxostat was well tolerated. The most common treatment-related adverse effects were headaches, arthralgia, abdominal pain, nausea, mild elevation of liver function tests, and dizziness. In the first trials, cardiovascular events were a concern related to febuxostat treatment, especially concerning thromboembolic events, myocardial infarcts, and strokes However, in the CONFIRMS trial no significant differences were noted among the distinct treatment groups. It appears that cardiovascular events are more related to the known clinical associations of gout and hyperuricemia with hypertension, metabolic syndrome, diabetes, and dyslipidemia than to the initiation of therapy.

Comparision of efficacy with allopurinol:
Febuxostat and allopurinol are both medications used to treat hyperuricemia in conditions like gout, but they have some differences in efficacy and safety profiles. Febuxostat is generally more effective at lowering uric acid levels compared to allopurinol, especially patient with renal impairement. Can achieve target uric acid levels in a higher percentage of patients. Effective in those who have not responded adequetly to allopurinol. Allopurinol established first line treatment for gout for many years effective in lowering uric acid, but require dose adjustments based on renal function and response. Some patients may not reach target levels, especially if they have chronic kidney disease. In some studies state that the febuxostat have less side effects than allopurinol, while febuxostat may be more effective for some patients ,especially those who have not responded to allopurinol.[12]

Drug interactions: Febuxostat, used primarily to treat gout, can interact with several medications.

Combination of febuxostat with NSAIDS:
Non-steroidal anti-inflammatory drugs are frequently used to treat acute attacks of gout. The incidence of side effects was investigated during simultaneous therapy with febuxostat together with Indomehhacin or Naproxen.

Side effects during therapy with febuxostat and NSAID:
Number of patients who were administered the: patients with at least one side effect during therapy with febuxostat with combination of non-steroidal anti-inflammatory drugs.

Combination of febuxostat with hydrochlorothiazide: In the therapy of febuxostat together with hydrochlorothiazide, 43% of the patients developed at least one side effect. This share was 41% when the only treatment given was febuxostat. Severe side effects did not occur. The combined

therapy of febuxostat and hydrochlorothiazide was well tolerated. No dose adjustment is required for the simultaneous administration of febuxostat and hydrochlorothiazide

Combination of Febuxostat with Uricosuric Drugs:

Lesinurad (approved in Europe) and Arhalofenat (not yet approved in Europe) are drugs that increase the excretion of uric acid in the urine and are used to treat hyperuricemia and gout. In 21 patients treated with febuxostat (40 or 80 mg/day) together with Lesinurad (400 to 600 mg/day), a total of 27 side effects and no severe side effects occurred .During the combined use of febuxostat (40 and 80 mg/day) and Arhalofenat (600 or 80 mg/day) in 32 patients, 23 patients (72%) experienced at least one side effect and no severe side effects.

Combination of Febuxostat with Theophylline:

The co administration of febuxostat together with theophylline does not affect the pharmacokinetics of theophylline. Theophylline was well tolerated when administered together with febuxostat (80 mg/day) without dose adjustment of febuxostat.

Combination of Febuxostat with Azathioprine:

Two cases of a pancytopenia or eosinophilia have been published to date in response to a possible interaction between febuxostat and azathioprine. Both authors consider an interaction of these two medications as the probable source of the symptoms .Patients experienced, among other adverse reactions, nausea and vomiting, watery diarrhea with weight loss, as well as pancytopenia, other manifestations included fever and a case of eosinophilia

4. Conclusion

Febuxostat, a selective xanthine oxidase inhibitor, has demonstrated exceptional efficacy and safety in reducing serum uric acid levels and preventing gout flares. Compared to allopurinol and colchicine, febuxostat shows: Greater serum urate reduction, Improved gout flare prevention, Better tolerability and safety profile, Simplified dosing regime Long-term treatment efficacy. Clinical Implications: First-line treatment option for gout. Suitable for patients with contraindications to allopurinol, Effective in patients with renal impairment. Febuxostat is a superior uric acid lowering agent, offering improved efficacy, safety, and convenience compared to traditional treatments. Its benefits make it an ideal choice for patients with gout and hyperuricemia.

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