

## MANAGEMENT OF CHRONIC GOUT: AN UPDATE

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### Summary

*Patients who develop chronic gout usually are those whose hyperuricemia is not controlled. It is a persistent disorder of purine metabolism, characterized by abnormally high levels of serum uric acid and attacks of arthritis, with deposits of urates in the joints for chronic gout. Some dietary restriction & pharmacological agents like allopurinol, probenacid, colchicine can be tried with variable success. Febuxostat, a novel nonpurine selective inhibitor of both the oxidized and reduced forms of xanthine oxidase recently marketed in our country, was approved in February 2009 by the US Food and Drug Administration for the management of hyperuricemia in adults with gout. The purpose of this review was to summarize available information about the dietary restriction and therapeutic strategies for management of recurrent and chronic gout with an emphasis on comparison between Febuxostat and Allopurinol with respect to efficacy, and safety.*

### Key words

Chronic Gout; allopurinol; febuxostat

### Introduction

Gout is the most common inflammatory arthritis in men over 40 and has an increasing prevalence among postmenopausal women<sup>1</sup>. It results from the deposition of monosodium urate (MSU) crystals in and around the joints and soft tissues. It has been recognized that the formation of such crystals requires the presence of hyperuricemia defined as serum urate concentration above its solubility limit (6.8 mg/dl) supersaturating the body fluids<sup>2</sup>. Gout also known as podagra when it involves the big toe<sup>3</sup> is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis a red, tender, hot, swollen joint. The metatarsal-phalangeal joint at the base of the big toe is the most commonly affected (~50% of cases).

Gout is a disorder of purine metabolism,<sup>4</sup> and occurs when its final metabolite, uric acid, crystallizes in the form of monosodium urate, precipitating in joints, on tendons, and in the surrounding tissues<sup>5</sup>. These crystals then trigger a local immune-mediated inflammatory reaction<sup>5</sup> with one of the key proteins in the inflammatory cascade being interleukin 1 $\beta$ <sup>4</sup>.

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An evolutionary loss of uricase, which breaks down uric acid, in humans and higher primates is what has made this condition so common<sup>4</sup>.

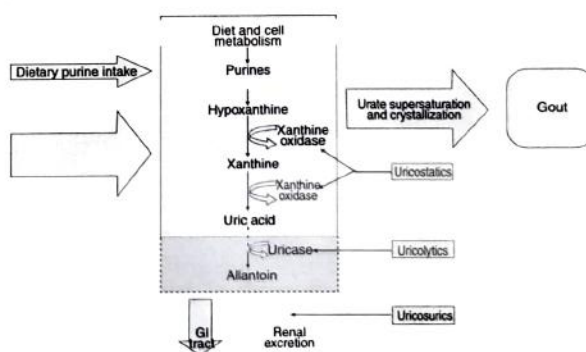
Hyperuricemia is the underlying cause of gout. This can occur for a number of reasons, including diet, genetic predisposition, or under excretion of urate, the salts of uric acid.<sup>2</sup> Renal under excretion of uric acid is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10%<sup>4</sup>. About 10% of people with hyperuricemia develop gout at some point in their lifetimes<sup>6</sup>. The risk, however, varies depending on the degree of hyperuricemia. When levels are between 415 and 530  $\mu\text{mol/L}$  (7 and 8.9 mg/dL), the risk is 0.5% per year, while in those with a level greater than 535  $\mu\text{mol/L}$  (9 mg/dL), the risk is 4.5% per year<sup>3</sup>.

### Dietary role

Dietary causes account for about 12% of gout<sup>7</sup> and include a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood<sup>5</sup>. Other triggers include physical trauma and surgery<sup>4</sup>. Recent studies have found that only animal proteins are associated with gout but not purine-rich vegetables and total protein<sup>8,9</sup>. The consumption of coffee, vitamin C and dairy products as well as physical fitness appear to decrease the risk<sup>10,11,12</sup>.

### Pathway of uric acid production

From purine bases hypoxanthine is produced. Xanthine oxidase catalyses the end conversion of hypoxanthine to xanthine and then xanthine to uric acid.



**Fig 1 :** The pathophysiology of gout and sites of action of drugs used to lower uric acid in the treatment of gout.: The three categories of urate-lowering drugs act at different steps of the urate formation and degradation pathway. Uricosuric agents increase renal excretion of urate, uricostatic agents (Allopurinol, Oxypurinol, Febuxostat) decrease urate formation, and uricolytic agents promote urate degradation.



### Uricosstatic agents

The most commonly used urate-lowering agents are uricosstatic drugs including allopurinol, probenecid, and febuxostat, which act as inhibitors to xanthine oxidase, ultimately blocking the conversion of hypoxanthine and xanthine to insoluble uric acid and thus preventing the basis of the problem encountered in gout. Xanthine oxidase inhibitors are effective agents both in overproducers and underexcretors of uric acid<sup>13</sup>. They are not usually commenced until one to two weeks after an acute attack has resolved, due to theoretical concerns of worsening the attack,<sup>7</sup> and are often used in combination with either an NSAID or colchicine for the first 3–6 months.<sup>4</sup> They are not recommended until a person has suffered two attacks of gout,<sup>7</sup> unless destructive joint changes, tophi, or urate nephropathy exist,<sup>14</sup> as it is not until this point that medications have been found to be cost effective.<sup>7</sup> Urate-lowering measures should be increased until serum uric acid levels are below 300-360  $\mu\text{mol/L}$  (5.0-6.0 mg/dL) and are continued indefinitely.<sup>4,7</sup> If these medications are being used chronically at the time of an attack, it is recommended they be continued<sup>15</sup>.

### Allopurinol

Allopurinol blocks uric acid production, and is the most commonly used hypouricemic agent before introduction of febuxostat. It is safe and well tolerated in prolonged use, and can be used in people with mild to moderate renal impairment with dose adjustment. The limitations of its use lies its dose adjustment in advanced renal failure and fatal hypersensitivity reaction in small number of individuals. Probenecid is effective for treating hyperuricemia, but has been found to be less effective than allopurinol.

### Febuxostat

Febuxostat is new xanthine oxidase inhibitor for treating chronic hyperuricemia and gout. Febuxostat, a nonpurine inhibitor of xanthine oxidase, is now available as an alternative and more potent to allopurinol. Febuxostat is the first new treatment option in 40 years for patients who have hyperuricemia and gout, according to Takeda Pharmaceuticals North America, In, Febuxostat received marketing approval by the European Medicines Agency<sup>16</sup> on April 21, 2008 and was approved<sup>17</sup> by the U.S. Food and Drug Administration on February 16, 2009. The structure of febuxostat differs from allopurinol as it is a nonpurine analogue, lacking the purine-like backbone seen in allopurinol. Febuxostat is mainly metabolized by the liver, requiring minimal renal clearance, and therefore requires no dose adjustment in patients with mild-to-moderate renal or hepatic dysfunction<sup>18,19</sup>.

The active ingredient in febuxostat is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ .

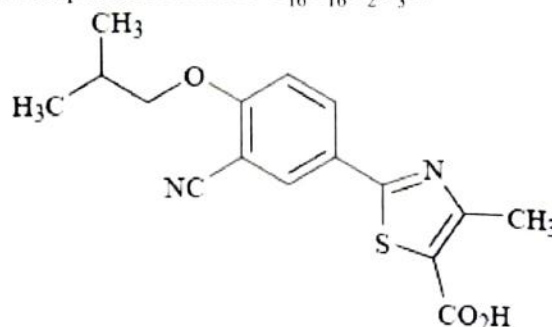


Fig 2 : Chemical structure of Febuxostat

### Mechanism of action

Febuxostat is a non-purine selective inhibitor of xanthine oxidase.

It works by non-competitively blocking the molybdenum pterin center which is 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. Febuxostat inhibits both, oxidized as well as reduced form of xanthine oxidase because of which febuxostat cannot be easily displaced from the molybdenum pterin site.

### Dose and route of administration:

For treatment of hyperuricemia in patients with gout, febuxostat is recommended at 40 mg or 80 mg once daily. No dose adjustment is necessary when administering febuxostat in patients with mild to moderate renal and hepatic impairment<sup>20</sup>.

### Materials and methods

Available studies and abstracts were identified through PubMed and Medline data bases (last 10 years), and Cochrane data bases. Key search terms were Chronic gout, gout diet, Febuxostat and Gout flares. All Available studies and abstracts describing the chronic gout, gout diet, febuxostat and gout flares were included. The reference list of review articles were also searched. The following number of references were found: Chronic gout—1426, Gout diet—593, Febuxostat—162 & Gout flares—142.

### Discussion

#### Diet

Gout is caused by an excess of uric acid in the body. Uric acid results from the breakdown of purines. Purines are part of all human tissue and found in many foods. The excess can be caused by either an over-production of uric acid by the body or the under-elimination of uric acid by the kidneys. Also, the ingestion of foods high in purines can raise uric acid levels in the blood and precipitate gout attacks in some people. Dietary causes account for about 12% of gout<sup>7</sup>, and include a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood<sup>5</sup>.



According to the American Medical Association, purine-containing foods include: Beer, other alcoholic beverages. Anchovies, sardines in oil, fish roes, herring, Yeast. Organ meat (liver, kidneys, sweetbreads) Legumes (dried beans, peas), Meat extracts, consomme, gravies. Mushrooms, spinach, asparagus, cauliflower.

On the contrary there are some foods are beneficial in the management of gout. These are: dark berries may contain chemicals that lower uric acid and reduce inflammation. Tofu which is made from soybeans may be a better choice than meats. Certain fatty acids found in certain fish such as salmon, flax or olive oil, or nuts may possess some anti-inflammatory benefits. In one review article<sup>21</sup> studies have observed an increased risk of gout among those who consumed the highest quintile of meat, seafood and alcohol. Although limited by confounding variables, low-fat dairy products, ascorbic acid and wine consumption appeared to be protective for the development of gout.

The study<sup>22</sup> named as 'Shanghai Men's Health Study' evaluated relationship between Purine-rich foods, protein intake, and the prevalence of hyperuricemia. The aim of this study was to investigate associations between high purine-content foods and protein intake with the prevalence of hyperuricemia by using data from a cross-sectional study of 3978 men aged 40-74 yrs living in Shanghai, China. Dietary information was collected by using a food frequency questionnaire. They collected information on anthropometric measurements and lifestyle factors and other potential confounding factors and disease history via interviews. Total protein consumption was not associated with hyperuricemia. They found a positive association between protein from animal sources and prevalence of hyperuricemia and an inverse association between protein from plant sources and hyperuricemia. However, these associations failed to reach significance in mutually adjusted analysis. Seafood intake was associated with higher prevalence of hyperuricemia. The ORs for quintiles of seafood intake (including fish and shellfish) were 1.00, 1.49, 1.35, 1.34, and 1.56 (p for trend: 0.01). An inverse association approaching significance between soy food consumption and hyperuricemia was observed (ORs: 1.00, 0.92, 0.86, 0.85, and 0.80 for quintiles of intake; p for trend: 0.07). No associations between consumption of purine-rich vegetables or meat and prevalence of hyperuricemia were observed. Their conclusion from this study was there was a direct association between seafood consumption and hyperuricemia and an inverse association between consumption of soy food and hyperuricemia among middle-aged, Chinese men.

Another article<sup>23</sup> showed that There has been an explosive increase in the prevalence of hyperuricemia and gout in Japan, suggesting the recent lifestyle change may be a key factor leading to this pathophysiological condition. In addition, people with hyperuricemia are often associated with various morbid conditions constituting the metabolic syndrome, such as abdominal obesity, hypertension, dyslipidemia and impaired glucose tolerance. Therefore, healthy lifestyle interventions would be a basic therapeutic approach not only to hyperuricemia but to metabolic syndrome, though it is not easy to promote behaviour changes. In one prospective study<sup>24</sup> data suggest that long-term coffee consumption is associated with a lower risk of incident gout in women.

In a review article<sup>25</sup> named Febuxostat : a selective xanthine-oxidase/xanthine- dehydrogenase inhibitor for the management of hyperuricemia in adults with gout, after reviewing a total of 88 published articles( including 14 human studies) the authors stated that 40 mg/d of Febuxostat was noninferior to conventionally dosed allopurinol(300mg/d) in the percentage of subjects achieving the primary end point of serum urate <6mg/dl(45% for febuxostat vs 42% for allopurinol), whereas 80 mg/d of febuxostat was reported to be superior (67% vs 42%; p < .001). Febuxostat 40 and 80 mg/d appeared to be well tolerated in the populations studied, with adverse events mostly limited to the liver enzyme elevations (6.6% and 4.6%, respectively), nausea (1.1% and 1.3%), arthralgias (1.1% and 0.7%), rash (0.5% and 1.6%). Febuxostat does not require dosage adjustment in patients with mild to moderate renal impairment (creatinine clearance, 30-89ml/min). In a clinical study<sup>26</sup> known as CONFIRMS trial (Confirmation of Febuxostat in Reducing and Maintaining Serum Urate), comparison was done regarding urate lowering efficacy and safety of daily febuxostat and allopurinol in subjects with gout and serum urate  $\geq$  8 mg/dl in a six month trial. Subjects (n=2,269) were randomized to febuxostat 40 mg or 80 mg, or allopurinol 300mg(200mg in moderate renal impairment). End points included the proportion of all subjects with serum uric acid level <6 mg/dl and the proportion of subjects with mild/moderate renal impairment and serum uric acid <6mg/dl. Safety assessments included blinded adjudication of each cardiovascular adverse events and death. In results they showed comorbidities included : renal impairment (65%); obesity (64%); hyperlipidemia (42%); and hypertension (53%).



In febuxostat 40 mg, febuxostat 80 mg and allopurinol groups, primary endpoint was achieved in 45%, 67%, and 42%, respectively. Febuxostat 40mg was statically non-inferior to allopurinol, but febuxostat 80 mg was superior to both ( $p < 0.001$ ). Achievement of target serum uric acid in subjects with renal impairment was also superior with febuxostat 80mg (72%;  $p < 0.001$ ) compared with febuxostat 40 mg (50%) or allopurinol (42%), but febuxostat 40 mg showed greater efficacy than allopurinol ( $p = 0.021$ ). Rates of adverse events did not differ across treatments groups. Adjudicated cardiovascular event rates were 0% for febuxostat 40 mg and .4% for both febuxostat 80 mg and allopurinol. One death occurred in each febuxostat group and three in the allopurinol group. They concluded by saying that urate lowering efficacy of febuxostat 80 mg exceeded that of febuxostat 40 mg and allopurinol (300/200mg), which were comparable. In subjects with mild/moderate renal impairment both febuxostat doses were more efficacious than allopurinol and equally safe.

In a study<sup>27</sup> known as APEX trial comparison was done between the urate lowering efficacy and safety of febuxostat, allopurinol, and placebo in a large group of subjects with hyperuricemia and gout, including persons with impaired renal function. 1,072 subjects with hyperuricemia (serum urate level  $\geq 8$  mg/dl) and gout with normal or impaired (serum creatinine level  $> 1.5$  to  $< \text{or} = 2$  mg/dl) renal function were randomized to receive once daily febuxostat (80mg, 120mg, or 240mg), allopurinol (300 or 100mg, based on renal function), or placebo for 28 weeks. Results showed that significantly ( $p < \text{or} = .05$ ) higher percentage of subjects treated with febuxostat 80mg (48%, 120mg (65%), and 240mg (69%) Attained the primary end point of at least 3 monthly serum urate levels  $< 6$  mg/dl compared with allopurinol (22%) and placebo (0%). A significantly ( $p < .05$ ) higher percentage of subjects with impaired renal function treated with febuxostat 80 mg (4 [44%] of 9), 120mg (5 [45%] of 11), and 240mg (3 [60%] of 5) achieved the primary end point compared with those treated with 100mg of allopurinol (0 [0%]). Proportion of subjects experiencing any adverse event or serious adverse event were similar across groups, although diarrhea and dizziness were more frequent in the febuxostat 240mg group. At all doses studied, febuxostat more effectively lowered and maintained serum urate levels  $< 6$  mg/dl than did allopurinol (300 or 100mg) or placebo in subjects with hyperuricemia and gout, including those with mild to moderate impaired renal function. In another study<sup>28</sup> [Febuxostat compared with allopurinol in patients with hyperuricemia and gout], known as FACT trial they randomly assigned 762 patients with gout with serum urate concentrations of at least 8 mg/dl (480 micromol/l) to receive either febuxostat (80mg or 120mg) or allopurinol (300mg) once daily for 52 weeks; 760 received the study drug.

Prophylaxis against gout flares with naproxen or clchicine was provided during weeks 1 through 8. The primary end point was a serum urate concentration of less than 6 mg/dl (360 micromol/lit) at the last 3 monthly measurements. The secondary end points included reduction in the incidence of gout flares and in tophus area. Results showed the primary end point was reached in 53% of patients receiving 80 mg of febuxostat, 62% of those receiving 120 mg of febuxostat, and 21% of those receiving allopurinol ( $p < 0.001$  for the comparison of each febuxostat group with the allopurinol group). Although the incidence of gout flares diminished with continued treatment, the overall incidence during weeks 9 through 52 was similar in all groups: 64% of patients receiving 80 mg of febuxostat, 70% of those receiving 120 mg of febuxostat, and 64% of those receiving allopurinol ( $p = .99$  for 80 mg of febuxostat vs allopurinol;  $p = .23$  for 120 mg of febuxostat vs allopurinol). The median reduction in tophus area was 83% in patients receiving 80 mg of febuxostat and 66% in those receiving 120 mg of febuxostat as compared with 50% in those receiving allopurinol ( $p = .08$  for 80 mg of febuxostat vs allopurinol;  $p = 0.16$  for 120 mg of febuxostat vs allopurinol). In conclusion they said that, febuxostat at a daily dose of 80 mg or 120 mg was more effective than allopurinol at the commonly used fixed dose of 300 mg in lowering serum urate flares. Similar reductions in gout flares and tophus area occurred in all treatment groups.

### Conclusion

Diet has got important influence in the management of gout. It was our common belief that high protein diet which contains more purine was associated with hyperuricemia. But this review showed that it is not only total amount of protein rather amount of animal protein responsible for hyperuricemia. Vegetable proteins has got inverse relationship in this context. It was also found that long term coffee consumption is associated with lower incidence of gout in woman. Since 47 years passed when Allopurinol approved in 1964 a new remedy . Febuxostat steps into scenario.. Different trials' result showed that urate-lowering efficacy of febuxostat 80 mg exceeded that of febuxostat 40 mg or allopurinol (300 mg/200 mg). It can be used in mild to moderate renal failure without dose adjustment. Unlike allopurinol it is not associated with any fatal hypersensitivity reaction. It is generally safe, well tolerated at all doses, potent and effective in lowering serum urate levels. Febuxostata is a promising alternative to allopurinol for safe and effective management of the gout and hyperuricemia.



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