

Summary

- ✓ **Febuxostat is a selective inhibitor of xanthine oxidase. Its use in the management of hyperuricemia and gout is being studied.**
- ✓ **In a 52-week, phase III randomized clinical trial, febuxostat was superior to allopurinol for lowering uric acid levels. Its efficacy in preventing gout attacks was similar to that of allopurinol. Despite a similar rate of adverse effects, individuals on febuxostat were more likely to stop treatment than those on allopurinol.**
- ✓ **The most commonly observed adverse effects with febuxostat include liver function test abnormalities, diarrhea, headache, nausea, vomiting, abdominal pain, and dizziness.**
- ✓ **Given that renal dysfunction is a risk factor for hyperuricemia and gout, the safety and efficacy of febuxostat in this population should be considered, but only limited data are available.**
- ✓ **The diffusion of febuxostat may be limited by its price relative to that of allopurinol, regardless of whether febuxostat proves to have advantages in specific populations.**

The Technology

Febuxostat (TEI-6720; TMX-67) is an oral medication for hyperuricemia (elevated serum uric acid) and gout. By selectively inhibiting the enzyme xanthine oxidase, febuxostat reduces serum uric acid levels, and this can prevent acute attacks of gout.¹

Regulatory Status

Febuxostat has not yet been approved for use in Canada, the US, or the UK.² Teijin Pharma Limited, the developer, has licensed the development and marketing of febuxostat to TAP Pharmaceutical Products Inc in North America, and to Ipsen in Europe.^{2,3} A new drug application for febuxostat was submitted to the US Food and Drug Administration in December 2004.² A European filing is expected in 2006.²

Patient Group

Gout is an inflammatory arthritis characterized by the deposition of uric acid crystals into ≥ 1 joints.⁴ The affected joint becomes red, tender, and swollen, with a decreased range of motion.^{5,6} The great toe, instep, heel, knee, wrist, fingers, and elbows are often affected.^{5,6} Tophi (firm swellings) may also be present, and can be associated with joint destruction and deformation.^{5,6} Gout attacks tend to be intermittent initially, but progression to chronic gouty arthritis or chronic tophaceous gout generally occurs.^{4,5} The definitive diagnosis involves joint aspiration, but this may be impractical. As a result, gout is often diagnosed based on symptoms.⁵

Approximately 3% of Canadians have gout, with the prevalence in males approximately four times higher than that in females.⁷ Hyperuricemia is the most important risk factor. Other risk factors include obesity, alcohol use, diet, hyperinsulinemia, dehydration, renal dysfunction, and use of medications, such as diuretics and acetylsalicylic acid, that reduce uric acid excretion.^{5,8}

Current Practice

Medications for the prophylaxis of acute gout attacks may be indicated for individuals with ≥ 2 attacks per year, tophi, or documented uric acid over-production.^{5,8-10} One goal of therapy is to reduce serum uric acid (SUA) to <0.36 mmol/L,^{5,8} because crystals may form when SUA concentrations are >0.40 mmol/L.⁵ Drugs that lower uric acid levels include uricosuric medications that promote the excretion of uric acid (probenecid and sulfinpyrazone), and uricostatic medications that interfere with the synthesis of uric acid (allopurinol).⁵ Both classes of medication are considered to be first-line therapies.^{5,10} No new medications for the prophylaxis of acute gout attacks have become available in the past 40 years (allopurinol was the last to be introduced).^{1,2,11}

Allopurinol, which is the only xanthine oxidase inhibitor on the Canadian market, is the most frequently prescribed prophylactic medication for gout.⁵ In a survey of Ontario rheumatologists, it was found that 99% prescribed allopurinol as the first choice for uric acid lowering.⁵

Compared to uricosuric agents, allopurinol has the advantage of convenient once-daily dosing.⁹ Allopurinol lowers uric acid levels regardless of whether hyperuricemia is due to over-production or under-excretion of uric acid.⁹ Allopurinol requires monitoring of SUA levels to facilitate appropriate dose titration.

The Evidence

The efficacy of febuxostat for gout has been evaluated in five phase II and III clinical trials.¹²⁻¹⁶ Febuxostat significantly reduced uric acid levels in all studies, but the duration of follow-up in most of these reports^{12,14-16} was inadequate for assessing clinical outcomes such as the incidence of gout flares, or the change in size or number of tophi.¹⁷

The longest published randomized trial of febuxostat for gout was 52 weeks in duration (Table 1). Febuxostat 80 mg and 120 mg were compared to allopurinol 300 mg in 760 participants with gout, and SUA ≥ 0.48 mmol/L.¹³ All groups were also given colchicine or naproxen during the first eight weeks of the study, to prevent the acute flares of gout that often occur when starting uric acid lowering therapies.¹³ The allopurinol dose was not titrated according to uric acid levels. The primary endpoint of this study was SUA < 0.40 mmol/L at the last three monthly visits. Secondary study endpoints, including clinical outcomes (gout flares, percent reduction in tophus area, and change in number of tophi), were also assessed.¹³ Additional subgroup analyses were reported, but not specified a priori.¹³

A significantly higher percentage of individuals who were randomized to receive febuxostat 80 mg or 120 mg per day achieved the primary study endpoint compared to individuals who were randomized to receive

allopurinol 300 mg.¹³ Febuxostat-treated individuals were also significantly more likely to achieve secondary endpoints related to SUA levels than individuals treated with allopurinol. This suggests that once-daily doses of febuxostat 80 mg and 120 mg are more effective than allopurinol 300 mg at lowering SUA. Clinical outcomes, however, were not significantly different for febuxostat and allopurinol. Among patients, 64% to 70% needed treatment for gout flares between weeks nine and 52, with no significant difference between groups.

Longer open-label trials of febuxostat for gout are underway.^{18,19} Results from a small two-year trial showed that 74% to 81% of participants achieved SUA levels < 0.40 mmol/L, and 45% to 48% reductions in SUA levels from baseline at each visit.²⁰ Approximately 59% of participants had completed 24 months of follow-up at the time of reporting.²⁰ Results have not yet been reported from an open-label trial¹⁹ that enrolled 1,500 participants from two randomized controlled trials of febuxostat.^{13,14}

Adverse Effects

Across five trials, the most frequently reported adverse effects with febuxostat included liver function test abnormalities, diarrhea, headache, nausea, vomiting, abdominal pain, dizziness,¹²⁻¹⁴ and gout flare.^{15,16} One case of Guillain-Barré syndrome was reported.¹² In the 52-week study, the probability of experiencing any adverse event was similar with febuxostat 80 mg and allopurinol 300 mg, but was lower for febuxostat 120 mg.¹³ There was no significant difference in the incidence of serious adverse events between febuxostat 80 mg, febuxostat 120 mg, and allopurinol 300 mg.¹³ The rates of discontinuation of treatment, however, were significantly higher with both the febuxostat doses.²¹

Table 1: Randomized phase III trial comparing febuxostat to allopurinol¹³

Outcome	Febuxostat 80 mg [†]	Febuxostat 120 mg [†]	Allopurinol 300 mg
<i>Primary outcome</i>			
SUA < 0.40 mmol/L at last three visits	53%, p < 0.001	62%, p < 0.001	21%
<i>Secondary outcomes</i>			
SUA < 0.40 mmol/L at final visit	74%, p < 0.001	80%, p < 0.001	36%
Change in SUA at final visit	-45%, p < 0.001	-52%, p < 0.001	-33%
Proportion of patients treated for gout flares during weeks 9 to 52	64%, p=NS	70%, p=NS	64%
Median change in tophus area at week 52	-83%, p=NS	-66%, p=NS	-50%
Median change in number of tophi at week 52	0%, p=NS	-1%, p=NS	0%

SUA=serum uric acid, NS=non-significant; [†]p-value compared to allopurinol

Administration and Cost

In the 52-week trial, the dose of febuxostat was 80 mg to 120 mg once daily, administered orally. No dosing information is available from the manufacturer. As well, no cost information for febuxostat is available. Allopurinol costs approximately \$0.04 per day for a 300 mg dose.²² SUA monitoring is an additional cost associated with allopurinol, but there is no indication that febuxostat would not require similar monitoring.¹⁰ Given that febuxostat may be more effective and more costly than allopurinol, cost effectiveness is an important consideration, however it cannot be evaluated now.

Concurrent Development

Several medications are being developed for the management of gout. A few xanthine oxidase inhibitors are in pre-clinical and phase I trials,^{2,6,23} and a uricosuric agent is in phase II trials.⁸ Pegylated uricases are in phase I and II trials for gout, but their use is potentially limited by parenteral administration, antigenicity, and short half-lives.^{2,3,5}

Rate of Technology Diffusion

Small seven-day studies suggest that febuxostat 80 mg is well tolerated in renal and hepatic impairment, and does not require dosage adjustment,^{24,25} but longer term research is needed. There is evidence to show that febuxostat is a more potent inhibitor of xanthine oxidase than allopurinol, so it may be beneficial for those who are difficult to treat.^{11,26} About 5% of individuals cannot tolerate allopurinol.² Febuxostat may be an alternative for the prevention of gout attacks in these populations.² The diffusion of febuxostat, however, could be limited by its price relative to allopurinol, regardless of whether febuxostat has advantages in specific populations.

Implementation Issues

Febuxostat has not yet been approved for use in North America.² Studies to date have been short duration. Two open-label studies of the long-term safety and efficacy of febuxostat should be completed in December 2007.^{18,19}

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