Febuxostat for gout

An alternative for allopurinol-intolerant patients

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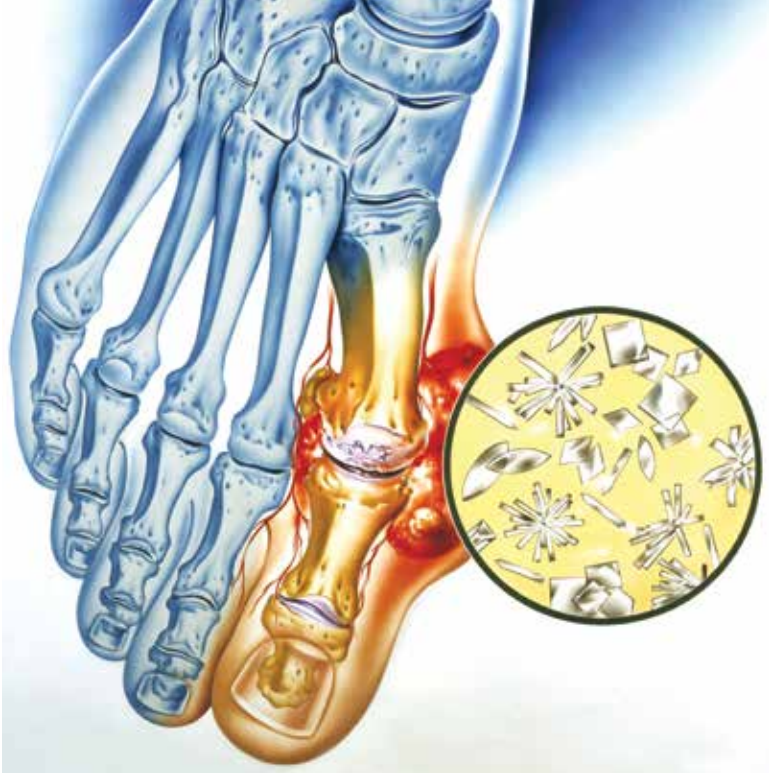

Febuxostat is a urate-lowering therapy that is now TGA-approved and PBS-listed for long-term treatment of certain patients with chronic gout. It can be prescribed by GPs and has become the usual first alternative for allopurinol-intolerant patients, replacing uricosuric therapies.

Febuxostat, like allopurinol, is a xanthine oxidase inhibitor that can lower urate levels in patients with gout and thus prevent acute attacks. It has become the usual first alternative for allopurinol-intolerant patients with gout. Febuxostat is funded by the PBS for patients with chronic gouty arthritis or chronic tophaceous gout (not just hyperuricaemia) who have a documented history of allopurinol hypersensitivity syndrome, intolerance to allopurinol necessitating permanent discontinuation or a medical contraindication to allopurinol.

Key strategies in management of gout

Treatment of an acute attack of gout depends on the patient's comorbidities. Medications can include oral NSAIDs, colchicine and corticosteroids, as described in a previous article in the August 2016 issue of *Medicine Today*.[1] Although correction of excessive alcohol intake and obesity is appropriate for many reasons, dietary change has not been shown in any long-term study to improve outcomes in gout.[1]

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Long-term control to prevent flares and joint damage in patients with gout involves the following three steps:

1. Confirming the diagnosis, usually by identifying monosodium urate monohydrate (urate) crystals with polarised microscopy of a joint or tophus aspirate
2. Reaching agreement between the clinician and patient about the need for lifelong urate-lowering drug therapy
3. Achieving the target serum urate level and maintaining this long term.

The target serum urate level depends on the urate burden, and is:

- less than 0.36 mmol/L for patients with a low urate burden and no tophi
- less than 0.30 mmol/L for those with a large urate burden as indicated by tophi, gouty erosions or chronic gouty joint damage (Figure 1 and Figures 2a and b).

The first-line urate-lowering therapy is allopurinol, which is cheap, generally safe and well tolerated. However, up to 10% of patients cannot tolerate allopurinol, although a minority of these show signs of allergy. Treatment for this group was limited in the past to uricosuric therapies such as probenecid, fenofibrate and losartan, which can increase the formation of urinary uric acid calculi and lack efficacy in patients with a low glomerular filtration rate. Febuxostat is now the next best option after allopurinol for these patients.

Pharmacology of febuxostat

Febuxostat, like allopurinol, retards the oxidation of purines to uric acid, specifically hypoxanthine to xanthine and xanthine to uric acid, by inhibiting the enzyme xanthine oxidase. However, unlike allopurinol, febuxostat is not a purine analogue. Rather, it is a 2-arylthiazole derivative that is a potent selective inhibitor of xanthine oxidase. At therapeutic concentrations, febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism.

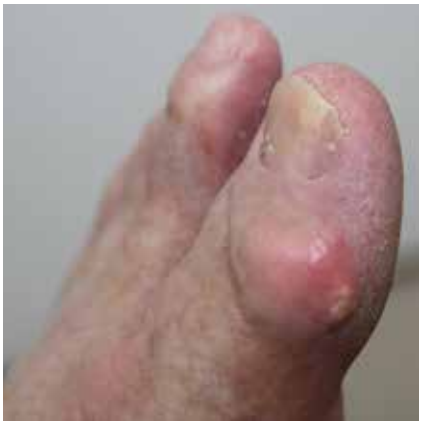
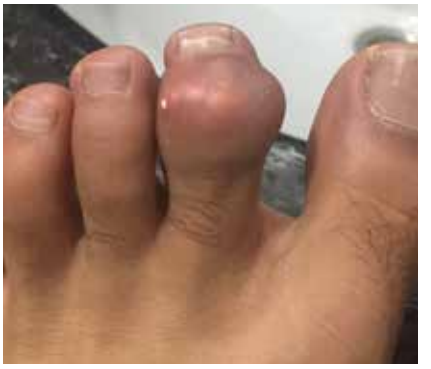
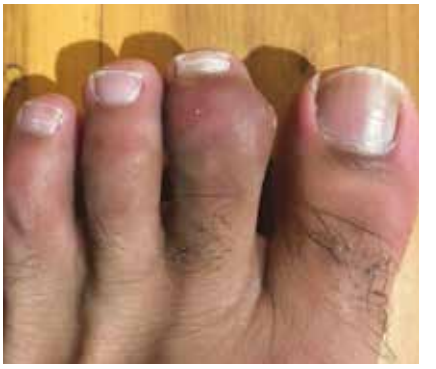


Figure 1. Tophaceous gout.





Figures 2a and b. A gouty tophus before (a, left) and after (b, right) five months of urate-lowering therapy with a target serum urate level of less than 0.30 mmol/L. The reduction in size of the tophus highlights the benefit of this target urate level.

Febuxostat is rapidly and well absorbed (at least 84%) after oral administration, is about 99% bound to plasma proteins, has an apparent mean terminal half-life of five to eight hours, and is primarily metabolised in the liver (by conjugation via the uridine diphosphate glucuronosyltransferase system and oxidation via the cytochrome P450 system). Febuxostat can be taken with or without food with similar efficacy. No dose adjustment is necessary in patients with moderate renal (creatinine clearance greater than 30 mL/min) or hepatic (Child–Pugh grade A or B) impairment or in those who are elderly.

Efficacy of febuxostat

The efficacy of febuxostat was demonstrated by a 28-day, phase II, dose-response trial in patients with gout.[2] The trial had multiple exclusions, including a serum creatinine level greater than 133 μmol/L. The target serum urate level (<0.36 mmol/L) was achieved at day 28 by none of those taking placebo, 56% taking febuxostat 40 mg daily, 76% taking febuxostat 80 mg daily and 94% taking febuxostat 120 mg daily.

Three key trials compared the efficacy of febuxostat and allopurinol (Box).[3-5] They confirmed that:

- febuxostat is effective in achieving the target urate level in patients with normal or moderately impaired renal function (estimated creatinine clearance greater than 30 mL/min)
- febuxostat 80 mg is more effective than febuxostat 40 mg
- febuxostat 80 mg daily is more effective than allopurinol 300 mg daily.

A deficiency in the published data is the lack of comparison between febuxostat and optimal dosing of allopurinol (uptitration to a dose of 600 mg daily). A recent editorial pointed out that the trials did not allow uptitration of allopurinol and expressed the view that 'labelling this arm of the study design "standard" because prescribing physicians (especially primary care physicians) often recommend allopurinol at a dosage of 300 mg/day or less does not justify its use as a fixed dose in a clinical trial. Treatment that is common should not be confused with care that is good. … The outcome of such a trial is biased to favour a new drug if the comparator group is undertreated.'[6]

It should be appreciated that there is currently no published evidence that febuxostat is more effective than an uptitrated dose of allopurinol despite evidence that this uptitration is safe.[7,8]

Indications for febuxostat

Febuxostat is TGA approved for the treatment of adult patients with chronic symptomatic hyperuricaemia with urate deposition (gouty arthritis or tophus formation). It is PBS-listed for patients who have a hypersensitivity, intolerance or medical contraindication to allopurinol. The use of febuxostat in patients with an inadequate response to allopurinol is not PBS funded.

The PBS criteria for febuxostat include a medical contraindication to allopurinol but do not specify these contraindications. However, they could reasonably be interpreted as including an increased risk of allopurinol allergy associated with the human leucocyte antigen variant allele *HLA-B58:01*, which is common among people of Han Chinese, Thai, Korean or African American descent. The cost effectiveness of screening for this allele appears borderline for these ethnic groups and not cost-effective for the general population with gout.[9] Even in these high-risk ethnic groups, the positive predictive value of the allele is only about 1.5%.[10] Testing for the *HLA-B58:01* allele is not funded by Medicare.

How is febuxostat used?

For the above groups of patients, GP prescription of febuxostat is appropriate. If allopurinol has not been sufficiently effective (i.e. the target serum urate level has not been achieved) then referral to a rheumatologist is indicated.

When prescribing febuxostat, clinicians should commence with a dose of 40 mg once daily. If the target serum urate level is not reached after one month then the dose should be increased to the maximum of 80 mg once daily. Higher doses, although used in some trials, are not approved by the TGA.

KEY TRIALS COMPARING EFFICACY OF FEBUXOSTAT AND ALLOPURINOL

Febuxostat versus Allopurinol Controlled Trial (FACT)[3]

- n = 760, exclusions included serum creatinine level (Cr) >133 µmol/L
- 52 weeks' treatment with allopurinol 300 mg daily or febuxostat 80 mg or 120 mg daily
- Target urate level <0.36 mmol/L
- Target achieved in 21% of those taking allopurinol 300 mg; 53%, febuxostat 80 mg; and 62%, febuxostat 120 mg

Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat (APEX)[4]

- n = 1072, exclusions included serum Cr >177 µmol/L
- 28 weeks' treatment with allopurinol 300 mg (serum Cr <133 µmol/L, n = 258) or 100 mg (serum Cr 133 to 177 µmol/L, n = 10) daily or febuxostat 80 mg or 120 mg daily
- Target urate level <0.36 mmol/L
- Target achieved in 0 of those taking placebo; 22%, allopurinol; 48%, febuxostat 80 mg; and 65%, febuxostat 120 mg

CONFIRMS trial[5]

- n = 2269, exclusions included estimated creatinine clearance (eCLcr) <30 mL/min
- 6 months' treatment with allopurinol 300 mg (eCLcr >60 mL/min, n = 610) or 200 mg (eCLcr 30 to 59 mL min, n = 145) daily or febuxostat 40 mg or 80 mg daily
- Target urate level <0.36 mmol/L
- Target achieved in 42% of those taking allopurinol; 45%, febuxostat 40 mg; and 67%, febuxostat 80 mg

As febuxostat 40 mg daily is a potent urate-lowering therapy, with around the same effectiveness as allopurinol 300 mg daily, prescribers should be mindful of the high risk of a gout flare when patients start this agent. It is therefore important to prescribe flare prophylaxis. If renal function is normal then colchicine 0.5 mg twice or once daily is often given, usually for three to six months. In patients with impaired renal function, a lower dose of colchicine or prednisone 5.0 to 7.5 mg daily can be used.

Although the primary PBS indication for febuxostat is allopurinol allergy or intolerance, the risk of febuxostat allergy in this group is about 20%. For example, in a study of 24 patients with prior allopurinol-related skin reactions, five developed skin reactions to febuxostat; none of these five had skin reactions to benzbromarone.[11] Patients with a history of allopurinol allergy should be warned of the risk of febuxostat allergy and monitored carefully (see below).

As with allopurinol, if the target serum urate level is not achieved with optimal dosing of febuxostat then combining febuxostat with a uricosuric drug such as probenecid can improve the chance of achieving the target.[12]

Safety and precautions

A systematic review of the safety of urate-lowering therapies found the incidence of adverse events was similar for allopurinol and febuxostat.[13] Apart from gout flares, abnormal liver function test results were the most common safety signal (with an alanine aminotransferase level more than three times the upper limit of normal in 3%).

There remains uncertainty about the cardiovascular safety of febuxostat. A five-year, randomised trial comparing allopurinol and febuxostat in 7500 patients with gout and coexisting cardiovascular disease is under way and should clarify the situation.[14] Although gout experts express a more liberal view, the Product Information states that use of febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.[15,16]

Published data on the safety of febuxostat in patients with severe renal impairment (creatinine clearance less than 30 mL/min) are limited. However, febuxostat appeared efficacious and well tolerated in the small number of these patients reported in case series.[17,18]

Patients with a contraindication to xanthine oxidase inhibitor therapy, such as most patients receiving azathioprine or mercaptopurine, should not take febuxostat or allopurinol.

Monitoring of patients taking febuxostat

A reasonable approach to monitoring in patients prescribed febuxostat is to measure serum urate and creatinine levels, from which estimated glomerular filtration rate can be calculated, and assess liver function before therapy and again after two to four weeks.

If the target serum urate level has not been achieved then the dose can be increased to 80 mg daily and the same tests repeated after another four weeks. If the target serum urate level has still not been reached then advice from a rheumatologist may be warranted for consideration of combination urate-lowering therapy.[19]

At each visit, the patient should also be checked for skin reactions that could signify febuxostat allergy.

Conclusion

Febuxostat is a potent, well-tolerated xanthine oxidase inhibitor that is now the best alternative urate-lowering therapy for most patients with chronic gout who have shown an allergy, intolerance or a medical contraindication to allopurinol. Approximately 20% of patients who are allergic to allopurinol will also be allergic to febuxostat. Febuxostat is not PBS funded for patients with an inadequate response to allopurinol and has not been shown to be more effective than optimal-dose (uptitrated) allopurinol. Uncertainties remain as to its safety in patients with ischaemic heart disease, chronic heart failure and severe renal impairment. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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