Research Review™
PRODUCT REVIEW

Febuxostat (Adenuric®) in the Treatment of Gout

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This review is a summary of evidence in support of febuxostat (Adenuric®) in the treatment of hyperuricaemia in patients with gout. Febuxostat is an orally-administered xanthine oxidase inhibitor that blocks the production of uric acid. **In Australia, febuxostat is indicated for the treatment of chronic symptomatic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation) in adults with gout.**

PBS listing

Note Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Authority required
Chronic gout

Clinical criteria: The condition must be either chronic gouty arthritis or chronic tophaceous gout, **AND**

Patient must have a medical contraindication to allopurinol; OR

Patient must have a documented history of allopurinol hypersensitivity syndrome; OR

Patient must have an intolerance to allopurinol necessitating permanent treatment discontinuation.

Independent expert commentary provided by Clinical Associate Professor Neil McGill MBBS (Hons1,Sydney), BSc (Med), FRACP

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Disclosures:

Speaker/Educational Advisor

AstraZeneca

Menarini

Introduction

Gout is a common form of inflammatory arthritis that is induced by the accumulation of monosodium urate monohydrate ('urate') crystals in the joints and characterised by recurrent episodes of acute severe joint pain, with or without soft tissue inflammation.[1,2] Patients with chronic uncontrolled hyperuricaemia can develop aggregates of urate crystals in soft tissues that can lead to disabling and deforming arthropathy (chronic tophaceous gout). In addition, some patients with persistent hyperuricaemia develop urate-associated renal disease and renal calculi.[1,2] Increasingly, gout is being accepted as a disease of uric acid overload with arthritis being a consequence of this pathological accumulation.[1]

Burden of disease

The prevalence of gout in Australia is high and getting higher,[3] which is consistent with other affluent nations.[1,3] Between 1968 and 1995/96, the population prevalence of gout in Australia increased from 0.5% to 1.7%.[3]

Gout can have a substantial impact on the lives of patients and their families if not controlled with appropriate treatment. The intense pain of an acute gout episode and/or chronic tophaceous gout can be debilitating, leading to reduced social and recreational participation and impaired occupational functioning.[1,4,5] Furthermore, important comorbidities, including cardiovascular disease, renal disease, obesity, and type 2 diabetes, are present in many patients with gout and add to the significant morbidity and functional impairment.[2] Indeed, recent pharmacoeconomic and health-related quality of life (QOL) evidence confirms the substantial and growing burden of gout, in terms of both healthcare costs and QOL outcomes.[1,4,5]

The increasing economic and humanistic burden of gout emphasises the need for effective urate-lowering treatments.

Treatment of gout

There are two fundamental tenets in the treatment of gout: symptomatic relief during an acute episode and urate-lowering therapy (ULT) for long-term prevention of additional flares.[1] Management guidelines emphasize the importance of treating to a target serum uric acid (sUA) level of <0.36 mmol/L for effective gout management.[6,7] There is also strong support for concurrent anti-inflammatory prophylaxis for gout flares during ULT.[6]

According to the recently published Australian and New Zealand recommendations for management of gout:[8]

1. Non-steroidal anti-inflammatory drugs (NSAIDs), low-dose colchicine, and glucocorticoids are all effective in the treatment of acute gout.
2. Allopurinol is the first-line ULT, with probenecid, benzbromarone, or febuxostat specified as second-line ULT and should be selected according to the clinical context.
3. Anti-inflammatory prophylaxis should be used routinely when ULT is initiated due to the known risk of ULT in precipitating flares and subsequent treatment non-adherence. NSAIDs, low-dose colchicine, and low-dose glucocorticoids can be used, alone or in combination.
4. Tophi are a definite indication for intensive ULT.

Febuxostat is one of the newer drugs to become available for ULT, widening the therapeutic options for the treatment of chronic gout.

Febuxostat: Pharmacology

The following is an overview of important pharmacological properties of febuxostat. The Product Information sheet should be viewed for full details of the pharmacology, precautions, and recommended dosage and administration of febuxostat.

Mechanism of action

Uric acid is the end product of purine metabolism and its production is dependent on catalysis by xanthine oxidase.[9] As a non-purine selective inhibitor of xanthine oxidase, febuxostat reduces sUA levels by inhibiting the transformation of hypoxanthine to xanthine and of xanthine to uric acid. Febuxostat, at therapeutic concentrations, does not inhibit other enzymes involved in purine or pyrimidine metabolism.[9]

Pharmacokinetics

Maximum plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of febuxostat (i.e. exposure to febuxostat) increased in a dose proportional manner following single and multiple doses of 40 or 80mg in healthy subjects.[9] Febuxostat is rapidly (time to C_{max} 1.0-1.5 hours) and extensively absorbed (at least 84%). After single or multiple oral 40mg and 80mg once daily doses, C_{max} is approximately 1.5-1.6 µg/mL and 2.5-2.6 µg/mL, respectively.[9]

Following multiple 80mg once daily doses with a high fat meal, no clinically significant change in the reduction in sUA level was observed (58% fed vs 51% fasting); therefore, febuxostat may be taken without regard to food.[9]

Febuxostat is metabolized by conjugation via the uridine diphosphate glucuronosyltransferase enzyme system and, to a lesser extent, by oxidation via the cytochrome P450 (CYP) system.[9] It is eliminated by both hepatic and renal pathways. Febuxostat has an apparent mean terminal elimination half-life of approximately 5-8 hours.[9]

Drug interactions

Febuxostat can be co-administered (without the need for dose adjustment) with colchicine, naproxen, indomethacin, hydrochlorothiazide, theophylline, warfarin, rosiglitazone (or other CYP2C8 substrates), or desipramine (or other CYP2D6 substrates).[9]

On the basis of its mechanism of action, febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine.[9] Inhibition of xanthine oxidase by febuxostat may substantially increase plasma concentrations of these drugs leading to severe toxicity.[9]

Because potent inducers of glucuronosyltransferase enzymes, such as phenytoin, could potentially lead to increased metabolism and reduced efficacy of febuxostat, monitoring of sUA levels is recommended 1-2 weeks after starting treatment with a potent inducer of glucuronidation.[9]

Dosage and administration

The recommended oral dose of febuxostat is 40mg or 80mg once daily with or without food. The recommended starting dose of febuxostat is 40mg once daily, which should be increased to 80mg once daily if the sUA level is >0.36 mmol/L after 2-4 weeks.[9] Treatment with febuxostat should not be commenced until a gout flare has completely subsided.[9]

An increase in gout flares often occurs after starting febuxostat and is due to changing sUA levels resulting in mobilisation of urate from tissue deposits.[9] To prevent gout flares when starting febuxostat, concurrent prophylaxis for up to 6 months with an NSAID or colchicine is recommended.[9]

If a gout flare occurs during febuxostat therapy, the flare should be managed concurrently without discontinuing febuxostat.[9] Continuous treatment with febuxostat is associated with a reduced frequency and intensity of gout flares.[9]

Special patient groups

Exposure to febuxostat has been shown to be higher in subjects with renal impairment; however, dose adjustment of febuxostat is not required in patients with mild or moderate renal impairment (creatinine clearance: 30-89 mL/min; Stages 2-3 chronic kidney disease).[9] Because of a lack of pharmacokinetic data, febuxostat should be used with caution in patients with severe renal impairment (creatinine clearance 10-29 mL/min; Stage 4 chronic kidney disease).[9]

In subjects with mild or moderate hepatic impairment, exposure to febuxostat was not affected to a clinically significant extent.[9] The pharmacokinetics of febuxostat have not been studied in subjects with severe hepatic impairment (Child-Pugh Class C) so it should be used with caution in those patients.[9]

Febuxostat exposure was similar in elderly (age ≥65 years) and younger subjects (18-40 years). Therefore, no dose adjustment is required in elderly patients.[9]

Precautions

A higher incidence of investigator-reported cardiovascular (CV) APTC [defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC)] events was observed in the febuxostat (total) group compared with the allopurinol group in phase III clinical trials.[9] Hence, treatment with febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure.[9]

Mild liver function abnormalities were also observed in patients treated with febuxostat during phase III clinical trials.[9] Liver function testing is therefore recommended prior to starting febuxostat and periodically thereafter based on clinical judgement. Liver function tests should be performed promptly in patients with symptoms that may indicate liver injury. Febuxostat treatment should be interrupted in those with abnormal liver function tests (ALT >3-times upper limit of reference range) and not restarted without another explanation for the test abnormalities.[9]

Febuxostat: Efficacy and safety

Three pivotal phase III, randomised, double-blind studies of 6-12 months' duration (FACT, APEX, and CONFIRMS) have demonstrated that febuxostat at dosages of 40 and 80 mg/day was significantly more effective in lowering sUA to target levels (<0.36 mmol/L) than allopurinol 100-300 mg/day in patients with hyperuricaemia and gout.[10-12] In addition, febuxostat showed greater urate-lowering efficacy than allopurinol in patients with mild or moderately severe renal impairment in the APEX and CONFIRMS studies.[10,12] In two open-label extension studies (EXCEL and FOCUS), 3-5 years' treatment with febuxostat maintained target sUA levels in the majority of patients and was associated with almost complete elimination of gout flares and improved tophus status.[13,14] Supporting these clinical trial data, a real-world comparative study demonstrated that significantly more febuxostat- than allopurinol-treated patients achieved target sUA levels within 6 months of commencing urate-lowing therapy in clinical practice.[15]

Treatment with febuxostat was generally well tolerated in clinical trials, with the majority of adverse events being mild or moderate in severity.[10-14] Liver function abnormalities, nausea, diarrhoea, and rash were among the most commonly reported adverse events in clinical trials and post-marketing experience.[9] Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson syndrome, have occurred in the post-marketing experience.[9] A non-significant higher incidence of investigator-reported CV events with febuxostat than with allopurinol was revealed by pooling data from the APEX, FACT, FOCUS, and EXCEL trials.[9] However, this finding was not substantiated by the larger CONFIRMS study,[10] and a causal relationship with febuxostat has not been established.[9] The long-term comparative CV safety of febuxostat and allopurinol in patients with gout is currently being evaluated in two large ongoing studies (FAST and CARES).[16,17]

Febuxostat: Key clinical trials

The following are individual summaries of five key clinical trials of febuxostat in the treatment of hyperuricaemia in patients with gout: the phase III FACT, APEX, and CONFIRMS trials and the open-label extension EXCEL and FOCUS trials.[10-14] These studies assessed a range of febuxostat dosages but only Australian-approved dosages (40 and 80 mg/day) are reported in the summaries.

All of these trials enrolled patients with gout and hyperuricaemia defined as a baseline sUA level ≥0.48 mmol/L and employed the primary endpoint of last three monthly sUA levels <0.36 mmol/L or final-visit sUA level <0.36 mmol/L. Patients received naproxen 250mg twice daily or colchicine 0.6mg once or twice daily for gout flare prophylaxis for a duration of 1-6 months in these trials.

Expert commentary describing the clinical practice relevance or implications these studies is provided by Neil McGill.

FACT study

Febuxostat compared with allopurinol in patients with hyperuricemia and gout[11]

Authors: Becker MA et al.

Background: The Febuxostat versus Allopurinol Controlled Trial (FACT) was a randomised, double-blind, 52-week, multicentre trial that compared the safety and efficacy of febuxostat with that of allopurinol in adults with gout and hyperuricaemia.

Results: Of the 762 patients randomised to treatment, 256 received febuxostat 80 mg/day and 253 received allopurinol 300 mg/day (another febuxostat dosage was evaluated but only Australian-approved dosages are reported here). The primary end point (last three monthly sUA levels <0.36 mmol/L) was reached in 53% of patients receiving febuxostat 80mg versus 21% of those receiving allopurinol (p<0.001). The incidence of gout flares diminished with continued treatment and the overall incidence during weeks 9-52 was similar in both groups: at the final visit interval the incidence was 8% in the febuxostat 80mg group and 11% in the allopurinol group (**Figure 1**-see page 3). The median reduction in tophus area was 83% in the febuxostat 80mg group versus 50% in the allopurinol group. The overall incidences of treatment-related adverse events were similar in the febuxostat 80mg (25%) and allopurinol groups (23%) as were the rates of treatment discontinuation (34% vs 26%).

Expert commentary: The study clearly demonstrated that febuxostat 80mg daily is a more potent urate-lowering therapy than allopurinol 300mg daily. Adverse effects of the two medications were very similar and generally mild. For clinical relevance, see Concluding Remarks below.

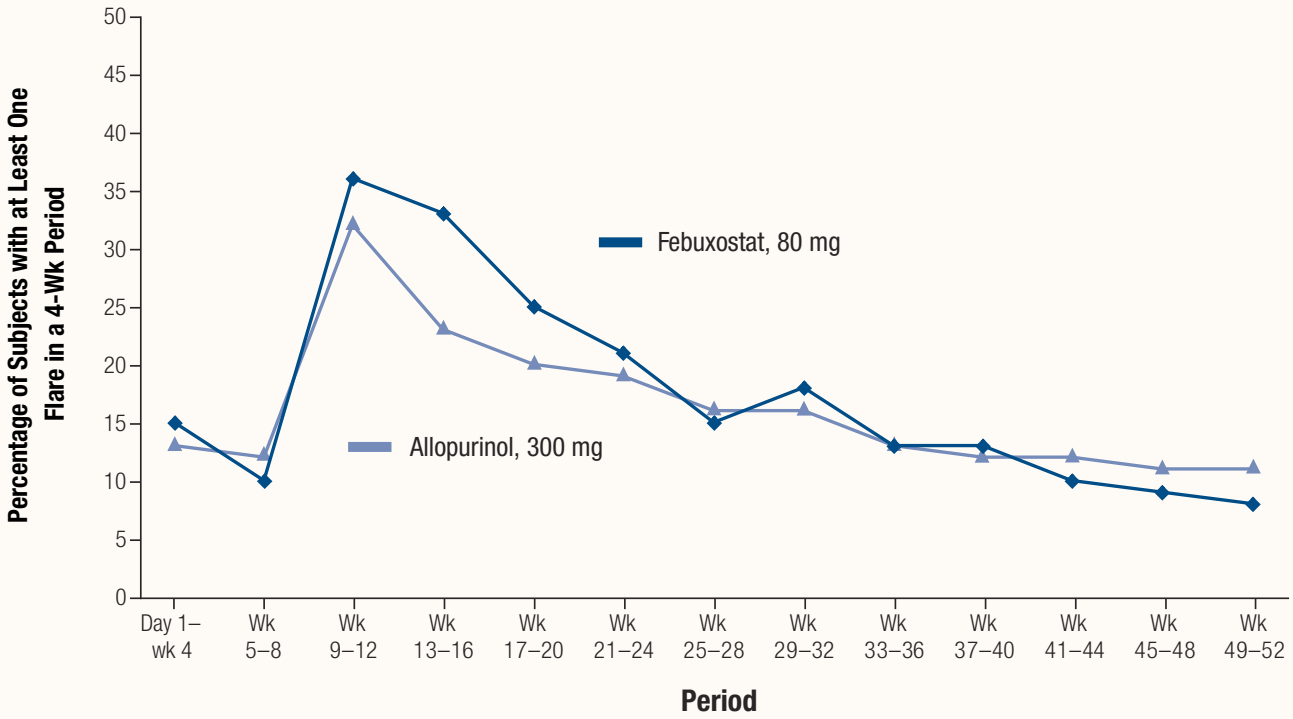

Figure 1. Patients requiring treatment for gout flares during 1 year of treatment with febuxostat 80mg or allopurinol 300mg in the FACT trial.[11] Anti-inflammatory prophylaxis was provided from day 1 to week 8.

APEX study

Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial[12]

Authors: Schumacher HA et al.

Background: The objective of the Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat (APEX) trial was to compare the safety and efficacy of febuxostat with placebo and allopurinol in patients with hyperuricaemia and gout. It also sought to confirm and expand the FACT trial findings by assessing the effects of treatment in patients with impaired renal function (serum creatinine level >130 to ≤180 µmol/L).

Results: Of 1072 patients randomised to treatment, 267 received febuxostat 80 mg/day, 258 received allopurinol 300 mg/day (10 patients with impaired renal function received 100 mg/day), and 134 received placebo (another febuxostat dosage was evaluated but only Australian-approved dosages are reported here). Significantly ($p<0.05$) higher percentages of subjects treated with febuxostat 80mg (48%) reached the primary end point (last three monthly sUA levels <0.36 mmol/L) compared with allopurinol 100mg/300mg (22%) and placebo (0%). Furthermore, a significantly ($p<0.05$) higher percentage of subjects with impaired renal function treated with febuxostat 80mg (4/9; 44%) reached the primary end point versus those treated with allopurinol 100mg (0/10; 0%). Proportions of subjects experiencing any adverse event (68% vs 75% vs 72%) or serious adverse event (4% vs 3% vs 1%) were similar in the febuxostat 80mg versus allopurinol 100mg/300mg versus placebo groups. Similarly, the frequency of withdrawals due to adverse events were comparable across treatment groups (8% vs 7% vs 5%).

Expert commentary: This study confirmed the fact that febuxostat 80mg daily is a more potent urate-lowering therapy than the sub-maximal comparative doses of allopurinol tested, and that febuxostat retains efficacy in the face of moderate renal impairment (serum creatinine ≤180 µmol/L).

Confirms study

The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial[10]

Authors: Becker MA et al.

Background: The CONFIRMS trial was a randomised, double-blind, six-month trial that further evaluated the comparative urate-lowering efficacy and safety (including CV safety) of febuxostat and allopurinol in a greater number of patients with gout and hyperuricaemia than the total that participated in the FACT and APEX trials.

Results: Of the 2269 patients randomised to treatment, 757 received febuxostat 40 mg/day, 756 received febuxostat 80 mg/day, and 145/610 received allopurinol 200/300 mg/day (dose adjusted to 200mg in patients with moderate renal impairment). The percentages of patients reaching the primary endpoint (final-visit sUA level <0.36 mmol/L) were 45%, 67%, and 42% in the febuxostat 40mg, febuxostat 80mg, and allopurinol 200/300mg groups, respectively. Urate lowering with febuxostat 40mg was statistically non-inferior to that with allopurinol but febuxostat 80mg was superior to both ($p<0.001$). Among patients with mild or moderate renal impairment, the urate-lowering response rate in the febuxostat 80mg group (72%; 360/503) was significantly higher than in both the febuxostat 40mg (50%; 238/479) and allopurinol (42%; 212/501) groups ($p\leq0.001$). In addition, the urate-lowering response rate in the febuxostat 40mg group was significantly higher than that in the allopurinol 200/300mg group ($p=0.021$). Gout flare requiring treatment occurred in 10-15% of subjects in all treatment groups during each of the first two months of treatment but declined slowly over the rest of the trial. Adverse events rates and withdrawal rates due to adverse events did not differ across treatment groups. There was no significant difference in CV events rates between groups (0.0% for febuxostat 40mg vs 0.4% for both febuxostat 80mg and allopurinol).

Expert commentary: In a larger trial, this study again confirmed that febuxostat 80mg daily is a more potent urate-lowering therapy than the sub-maximal comparative doses of allopurinol tested, and that febuxostat retains efficacy in the face of moderate renal impairment (down to an estimated glomerular filtration rate of 30 mL/min, calculated by the Cockcroft-Gault formula corrected for ideal body weight).

EXCEL trial

Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout[13]

Authors: Becker MA et al.

Background: Patients who completed the APEX and FACT studies were eligible to enrol in the fEbuXostat/allopurinol Comparative Extension Long-term (EXCEL) trial, which was an open-label extension study that evaluated the efficacy and safety of febuxostat and allopurinol in patients with gout and hyperuricaemia for up to 3 years. A total of 1086 patients were enrolled, of which 606 received febuxostat 80 mg/day and 92 received allopurinol 300 mg/day (another febuxostat dosage was evaluated but only Australian-approved dosages are reported here). ULT reassignment was permitted during months 1-6 to achieve sUA levels of between 0.18 and <0.36 mmol/L.

Results: After one month of initial treatment, 81% of subjects receiving febuxostat 80mg achieved the primary endpoint (sUA level <0.36 mmol/L) compared with 46% of subjects receiving allopurinol. After ULT reassignment, >80% of remaining patients maintained the primary efficacy endpoint for the duration of the study. More patients initially randomised to allopurinol required ULT reassignment to achieve sUA <0.36 mmol/L compared with patients randomised to febuxostat 80mg. Maintenance of sUA levels 0.36 mmol/L resulted in <4% of patients requiring gout flare treatment. Baseline tophus resolution was achieved by 46% versus 29% of patients maintained on febuxostat 80mg versus allopurinol (**Figure 2**). Rates of adverse events and serious adverse events, adjusted for 10-fold greater exposure to febuxostat than to allopurinol, did not differ significantly between treatment groups.

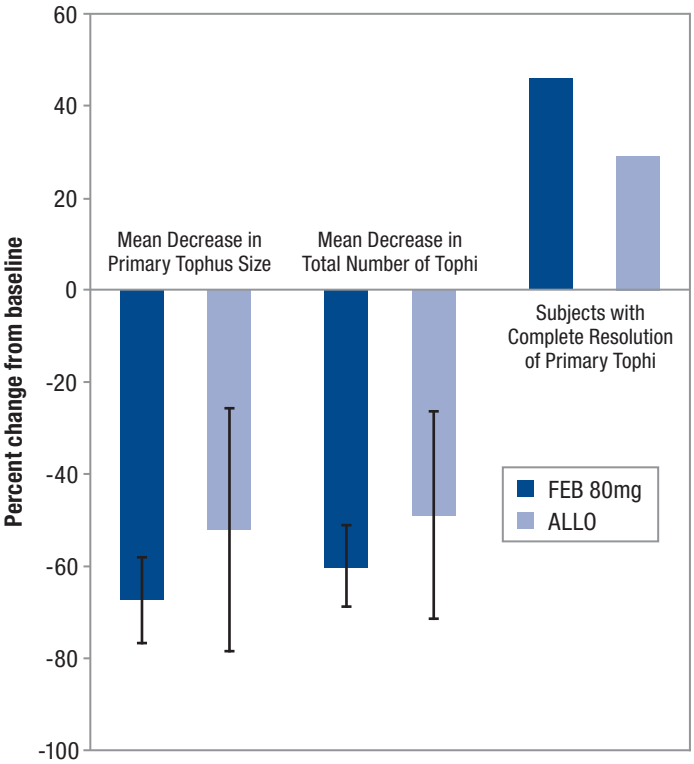

Figure 2. Tophus status at final visit compared with baseline in patients treated with febuxostat (FEB) 80mg and allopurinol (ALLO) 300mg in the EXCEL trial.[13] Error bars = 2 times standard error.

Expert commentary: For the patients who continued therapy, febuxostat 80mg daily was more effective at maintaining the serum urate below target than was allopurinol 300mg daily. Reflecting the lower serum urate concentrations, tophus regression was faster in the febuxostat group. Thirty-two percent of the febuxostat patients who were on stable therapy after six months prematurely discontinued therapy.

FOCUS trial

Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study[14]

Authors: Schumacher HR et al.

Background: The objectives of Febuxostat Open-label Clinical trial of Urate-lowering efficacy and Safety (FOCUS), which was a 5-year open-label extension of the original 28-day phase II FOCUS trial,[18] were to evaluate the durability of febuxostat urate-lowering and the efficacy, safety, and tolerability of febuxostat-induced sUA reduction and maintenance at sub-saturating levels.

Results: Of 116 patients enrolled, dose adjustments were made for 44 (38%) patients. As a result, 8 patients received febuxostat 40 mg/day and 79 received febuxostat 80 mg/day as maintenance treatment (another febuxostat dosage was evaluated but only Australian-approved dosages are reported here). Of the remaining patients at 5 years, 6/6 (100%) treated with febuxostat 40mg and 38/41 treated with febuxostat 80mg achieved the primary endpoint (maintenance of sUA levels <0.36 mmol/L). The percentage of patients that received treatment for gout flares throughout the study was 75% (6/8) with febuxostat 40mg and 47% (37/79) with febuxostat 80mg; however, the percentage of patients that required treatment for gout flares declined over time reaching zero during the fifth year of treatment. In 26 patients with a tophus at baseline (all three doses of febuxostat), resolution was achieved in 69% (18/26) by last visit on study drug at any point during the study (final visit). Adjusting for an imbalance of treatment exposure, the adverse events rates were 273.5 and 384.7 per 100 patient-years in patients who received febuxostat 40mg and 80mg, respectively. CV events were the most common serious adverse events.

Expert commentary: This study confirmed the efficacy of febuxostat over time.

Expert's concluding remarks

The clinical manifestations of gout are due to the interaction between the inflammatory system and crystals of monosodium urate monohydrate (urate), which have formed slowly over months to years. Treatment of the acute flare of gout requires suppression of the inflammatory response but does not affect the load of urate crystals and it is that load which will determine the frequency of future attacks and the risk of permanent joint and bone damage. The effective long-term management of gout requires dissolution of the urate crystals which in turn depends on maintenance of the serum (and thus synovial fluid) urate level well below saturation. The rate of crystal dissolution is dependent on the serum urate level; the lower the level, the faster the rate of dissolution. Thus international guidelines have suggested a serum urate target of ≤0.36 mmol/L for most gout patients and ≤0.30 mmol/L for those with tophi (reflecting a large load of urate crystals).

Studies from Australia,[19] US,[20] and UK,[21] all published in 2015, have confirmed earlier studies that achieving and maintaining serum urate levels below target occurs in only a minority of patients and that the overwhelmingly most important reason is failure to take medication. Allopurinol is the most frequently used urate-lowering therapy but, even when compliance appears good, 300mg daily achieves target in only a minority of patients (24% <0.30 mmol/L;[22] 21% <0.36 mmol/L[11]). The percentage achieving target can be improved markedly by escalating the dose (92%;[23] 89%[24]) to 600mg daily and occasionally higher, and this can be achieved with safety, even in patients with renal impairment.[24,25]

The studies described above have demonstrated the efficacy of febuxostat and that at a dose of 80mg daily it is more potent than allopurinol 300mg daily. Unfortunately, a comparative study of febuxostat and optimal dose allopurinol has not been published. For patients who are intolerant of allopurinol, febuxostat is a very useful alternative. Whether it will have an important role as a first-line urate-lowering drug may depend on whether the one tablet per day (as compared to two or more daily tablets of allopurinol) is shown to improve long-term compliance or a comparative study showing greater efficacy than optimal-dose allopurinol to offset the higher cost. There remains some doubt as to the safety of febuxostat in patients with cardiovascular disease, hence the precaution in the Product Information that treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.

Take-home messages

- Gout is associated with substantial morbidity and functional impairment leading to considerable healthcare costs and loss of quality of life.
- Febuxostat is an orally-active xanthine oxidase inhibitor that is used for the treatment of hyperuricaemia in patients with gout.
- Febuxostat 40 or 80 mg/day is more effective in lowering sUA levels than allopurinol 100-300 mg/day and is generally well tolerated.
- Long-term febuxostat therapy produces durable maintenance of target sUA levels in most patients, improvement in tophus status, and almost complete elimination of gout flares.
- Avoidance in patients with ischaemic heart disease or congestive heart failure and the need for liver function monitoring should be noted.
- Dosage adjustment is not required in elderly patients or patients with mild or moderate renal impairment.

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