Febuxostat treatment for gout: what the clinician needs to know

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Abstract: Febuxostat is a new non-purine based inhibitor of xanthine oxidase that will be a useful addition to the drugs available to treat gout. This short review covers general principles of the management of gout and then focuses on practical aspects and use of febuxostat.

Keywords: febuxostat, allopurinol, colchicine, probenecid, gout

Introduction

Although gout is estimated to affect up to 6.1 million people in the USA [Lawrence *et al.* 2008] and to be increasing in prevalence [Mikuls *et al.* 2005] there are still major concerns about the adequacy of care received by many sufferers of the disease. Quality-of-life (QOL) of individuals with gout is less than ideal and is affected by dramatically painful acute flares that typically last for 3–10 days, the evolution of some gout to a chronic tophaceous arthropathy and frequent comorbidities [Singh and Strand, 2008; Dalbeth *et al.* 2007; Vázquez-Mellado *et al.* 2004]. Despite excellent understanding of the pathogenesis of gout and availability of important lifestyle contributions and effective medications, evidence is accumulating that gout is not managed as recommended by published guidelines and quality-of-care proposals [Zhang *et al.* 2006; Mikuls *et al.* 2004]. This is especially true for the long-term care of intercritical and chronic gout [Roddy *et al.* 2007; Sarawate *et al.* 2006; Neogi *et al.* 2006]. Contributions to this less than ideal management begin with concerns about the accuracy of clinical diagnoses [Malik *et al.* 2009] and continue with evidence of poor understanding of optimal care by both physicians and patients. Education about gout has been neglected, at least in part, because no new drugs have been available for gout for more than 40 years. This is beginning to be remedied by the introduction of the new xanthine oxidase inhibitor, febuxostat, and research on a number of other new agents including a pegylated uricase [Sundy *et al.* 2008].

Management of gout

Management of gout is divided into the anti-inflammatory treatment of acute attacks and the

long-term urate-lowering therapy required by most patients including those with repeated acute flares, chronic arthritis, tophi or especially high serum-urate levels. Diet and lifestyle changes can have some benefit but urate-lowering drugs such as the uricosuric, probenecid, and the xanthine oxidase inhibitor, allopurinol, are needed for most patients. Note that these drugs are not generally initiated until after resolution of flares. Anti-inflammatory prophylaxis should be given on initiation of urate-lowering agents to minimize the flares that often occur during abrupt lowering [Chen and Schumacher, 2008; Borstad *et al.* 2004]. A target serum uric acid (SUA) of less than 6.0 mg/dl (0.36 mmol/dl) has received wide acceptance as it is below the level of 6.8 mg/dl (0.41 mmol/dl) at which urate deposits should dissolve as based on *in vitro* studies [Loeb, 1972]. Successful maintenance of target levels can, over time, deplete crystals from joints, decrease flares and resolve tophi [Chen and Schumacher, 2008].

What about febuxostat?

Febuxostat is a newly available xanthine oxidase inhibitor that has potentially important differences from allopurinol [Becker *et al.* 2005]. It is a nonpurine with a totally different structure than allopurinol. Thus, cross reactions in patients with allopurinol hypersensitivity are not anticipated although, to date, no patients with known severe hypersensitivity reactions to allopurinol have been treated with febuxostat. Febuxostat is less dependent on renal excretion than allopurinol and has been used effectively and safely in patients with mild-to-moderate renal disease [Schumacher *et al.* 2009; Becker *et al.* 2005]. This is a potential advantage over allopurinol

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since many physicians have been uncomfortable, or unwilling, to use allopurinol in patients with impaired renal function in large part because of a report of Hande and colleagues [Hande *et al.* 1984]. This report showed increased oxypurinol (the active metabolite of allopurinol) levels in patients with renal disease and suggested a schedule limiting the doses of allopurinol. Recent reports have shown that dosing by this schedule severely decreases the likelihood of achieving the generally accepted target SUA level of 6.0 mg/dl (0.36 mmol/dl) [Dalbeth *et al.* 2006] and that doses may be cautiously escalated to increase its effects [Vázquez-Mellado *et al.* 2001].

Efficacy

Studies with febuxostat have included doses up to 240 mg/day. All doses have achieved urate lowering more effectively than placebo or equal or better than 300 mg/day allopurinol. For example, febuxostat 80 mg once daily achieved the target of <6.0 mg/dl at 28 weeks in 76% *versus* 41% with allopurinol. Febuxostat 240 mg once daily reached the target in 94% [Schumacher *et al.* 2008].

In the USA, febuxostat is being marketed at 40 and 80 mg once daily dosages. In the recently completed studies [US FDA Center for Drug Evaluation and Research, 2009], febuxostat 40 mg once daily was comparable to allopurinol 300 mg once daily. The 80 mg dosage was again clearly more effective than allopurinol 300 mg. Febuxostat is approved in Europe for up to 120 mg once daily, and the allopurinol package insert (based on limited data) allows daily dosing up to 800 mg, but there are very limited randomized dose titration studies with either agent. A recent study showed increased success with allopurinol 600 mg/day in refractory patients [Reinders *et al.* 2009].

Practical considerations

Precautions that should be taken during the use of febuxostat and all urate-lowering therapies include using low-dose colchicine or nonsteroidal anti-inflammatory drug (NSAID) prophylaxis on initiation and probably for 6 months or until tophi are gone to decrease the risk of flares. Liver enzymes should be tested as recommended at 2 and 4 months since there can be occasional enzyme elevations, as with allopurinol, that are not dose related. Febuxostat has been used with mild-to-moderate, but not severe liver disease. The package insert for febuxostat states that in

randomized controlled studies there was a trend to a higher rate (0.74 per 200 patients years) of cardiovascular thrombotic events in patients treated with febuxostat (95% confidence interval [CI] 0.36–1.37) than with allopurinol (0.60 per 100 patient years, 95% CI 0.16–1.53). No causal relationship for drug was found in this group of patients in whom a high index of suspicion for cardiovascular comorbidity should be maintained with or without gout treatment.

Febuxostat can be given once daily and generally should be started at 40 mg. It can be used safely with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin and desipramine. No data are available about use with cytotoxic therapies or in pregnancy or by nursing mothers. The cost of treatment is likely to be substantially higher than for allopurinol.

Achieving target serum urate levels

Serum urate levels should be checked every 2–4 weeks after initiation and the dose increased if serum urate is not below 6.0 mg/dl (0.36 mmol/dl). Not all patients will meet that target with the approved doses. If the target serum urate of 6.0 mg/dl (0.36 mmol/dl) is achieved and maintained, the patients should be monitored to assure that flares do decrease or stop, and any tophi resolve. Alternatives in patients not achieving targets at least close to 6.0 mg/dl (0.36 mmol/dl) have not been studied in detail but may include further attention to lifestyle, combination with uricosurics, cautious titration above approved or well-studied doses of xanthine oxidase inhibitors, or delay until new approaches such as uricase therapy are available.

Conclusion

Gout is an underappreciated challenge in diagnosis and management which can be improved by education into the understanding of potentially confusing aspects. Febuxostat offers an attractive alternative to uricosurics and allopurinol for urate lowering. It is a needed resource for patients allergic to allopurinol and many physicians will be more comfortable using it in patients with mild-to-moderate renal disease.

Conflict of interest statement

Dr Schumacher has been a consultant to Takeda.

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