

Class Update: Analgesics for Gout

Month/Year of Review: January 2014

PDL Classes: Analgesics for Gout

Date of Last Review: February 2012

Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: ALLOPURINOL, COLCHICINE/PROBENECID
- Non-Preferred Agents: COLCHICINE (COLCRYRS®), FEBUXOSTAT (ULORIC®), PROBENECID, PEGLOTICASE (KRYSTEXXA)

Research Questions:

- Is there any new evidence about the comparative effectiveness of analgesics for the treatment of gout in reduction of gout flares or progression of disease?
- Is there any new evidence on the comparative harms of analgesics for the treatment of gout?

Previous Conclusions and Recommendation:

- There is moderate quality evidence of no difference in efficacy/effectiveness or safety between agents.
- Colchicine is the only agent for gout and Familial Mediterranean Fever
- Febuxostat reduces serum urate below 6mg/dl in a significantly greater proportion of patients with gout and hyperuricemic compared to patients receiving allopurinol but there was no difference in gout flares
- Recommend inclusion of each chemical entity
- Block pharmacy claims for pegloticase

Conclusions and Recommendations:

- Therapy with xanthine oxidase inhibitors remains first-line therapy for chronic gout/hyperuricemia.¹
- There is insufficient evidence of any significant difference between allopurinol and febuxostat in clinical outcomes such as gout flares.² The American College of Rheumatology guidelines give no preference to either agent and both are recommended as first line treatment.¹
- There is insufficient evidence for the treatment of intra-articular corticosteroids for the treatment of acute gout.³

Recommendations:

No further review or research needed. Evaluate comparative costs in executive session.

Background:

Gout is a disease caused by high uric acid levels (>6.8 mg/dl) in the blood leading to crystal formation in the joints. People with gout can have flares of red and swollen joints, usually occurring in the big toe, ankle, or knee.³ Over the past few years, the prevalence of gout has increased both in the U.S. as well as other countries.⁴ There are many possible factors for this rise, including dietary habits, increased prevalence of obesity and an increase in comorbidities that promote hyperuricemia (hypertension, chronic kidney disease, diabetes). Although there is no cure for gout, treatment can prevent recurrent attacks and improve its chronic form. Acute attacks can be caused by trauma, certain medications, hospitalization, alcohol use, and surgery. Due to declining mortality, frequent comorbidities that promote hyperuricemia, and widespread use of diuretics, elderly individuals with gout can be difficult to manage.

Treatment approaches to gout include treating acute attacks, preventing risk factors for hyperuricemia, and treating the underlying hyperuricemia. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line treatment for acute attacks. Other options include colchicine, intra-articular steroids, corticosteroids, narcotic analgesics, and interleukin-1 receptor antagonists. The goals of urate lowering therapy are to prevent future attacks, prevent joint destruction, and reduce the risk of kidney disease, hypertension, and cardiovascular events. However, clinical trials often use the surrogate outcome of uric acid levels to evaluate for efficacy. Reducing gout flares is a more relevant clinical outcome. Xanthine oxidase inhibitors (allopurinol/febuxostat) are used to treat hyperuricemia, and ultimately prevent recurrent attacks. Allopurinol has been used for more than 40 years, and febuxostat was approved in 2009 as an alternative for first-line treatment of hyperuricemia. In 2010, pegloticase was FDA approved for gout in adults who have failed therapy with maximum doses of xanthine oxidase inhibitors. Pegloticase is a uric acid-specific enzyme that leads to a decrease in uric acid concentrations. However, pegloticase has only been evaluated in clinical trials with surrogate outcomes and there are no data to indicate whether gout flares were reduced. The goals of treatment are to prevent acute gout flares

Methods:

A Medline OVID search was conducted with the following search terms: allopurinol, colchicine, probenecid, febuxostat, gout suppressants, uricosuric agents, xanthine oxidase inhibitor, gout, gouty arthritis, uric acid, urate oxidase, hyperuricemia, renal calculi, and Familial Mediterranean fever. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to September week three 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

Ye et al conducted a systematic review to examine the efficacy of febuxostat compared with placebo or allopurinol to lower uric acid levels in hyperuricemic adults.⁵ Ten trials were included; study duration varied from four to 28 weeks. Febuxostat doses varied from 20 to 240 mg per day. Allopurinol doses varied from 100 to 300 mg per day. The primary outcome was achieving a serum uric acid (sUA) level of ≤ 6.0 mg/dL. Four trials (n= 1225) were included in the analyses comparing placebo and febuxostat. Febuxostat subjects were much more likely to have a sUA of ≤ 6.0 mg/dL after the final visit than their placebo counterparts (76.5% vs. 0.8%; OR 253.73; 95% CI 75.39 to 737.08). For comparison of allopurinol, seven studies were included (n=5690) in the analysis. Febuxostat subjects more frequently achieved a sUA of ≤ 6 mg/dL than the allopurinol patients (68.8% vs. 43.3%; OR 3.14; 95% CI 1.82 to 5.44) at their final study visit. A subanalysis of four trials compared subjects on 40 mg febuxostat with subjects on 100 to 300 mg of allopurinol. Again, the febuxostat patients

more often achieved a sUA of ≤ 6 mg/dL than the allopurinol cohort (50.9% vs. 45.6%; OR 1.25; 95% CI 1.05 to 1.49). Individual study quality was assessed for randomization, blinding, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. Trials were then stratified to the following levels: A (plausible bias was unlikely to obviously alter the results); B (plausible bias raised some doubt about the results); or C (plausible bias seriously weakened confidence in the results). Of the included studies, eight were classified as level A, and two as level B.⁵

Tayar et al also examined the efficacy of febuxostat compared with placebo or allopurinol in a systematic review from the Cochrane Collaboration.² Six trials were included with 3978 participants: four randomized control trials and two open label trials. Subjects were at least 18 years old and met the preliminary criteria of the American College of Rheumatologists (ACR) for acute gout arthritis and had serum uric acid levels (sUA) of 8.0 mg/dL. Febuxostat doses ranged from 40 to 240 mg and allopurinol from 100 to 300 mg, both per day. Individual study duration lasted from two to 28 weeks. All trials reported the amount of participants with sUA levels of < 6.0 mg/dL as a primary endpoint. Compared with patients receiving placebo, subjects on febuxostat were significantly more likely to achieve a goal sUA level by the final study visit. This was true for all febuxostat doses studied: 40 mg (RR 40.1; 95% CI 2.5 to 639.1), 80 mg (RR 68.9; 95% CI 13.8 to 343.9), 120 mg (RR 80.7; 95% CI 16.0 to 405.5), and 240 mg (RR 93.4; 95% CI 13.2 to 654.5). Incidence of gout flares was measured as an additional primary outcome for this review. Subjects taking febuxostat 120 mg and 240 mg experienced more flares than placebo patients at 4 to 28 weeks (RR 1.7; 95% CI 1.3 to 2.3, and RR 2.6; 95% CI 1.8 to 3.7 respectively). No significant differences were seen with the 40 mg and 80 mg doses. Compared with allopurinol subjects, patients receiving febuxostat 80 mg or greater were significantly more likely to achieve a sUA < 6 mg/dL by the final study measurement: 80 mg (RR 1.8; 95% CI 1.6 to 2.1), 120 mg (RR 2.2; 95% CI 1.9 to 2.45), and 240 mg (RR 2.3; 95% CI 1.7 to 3.0). Comparing febuxostat 40 mg and allopurinol, there was no statistical difference in subjects achieving the sUA goal. For incidence of gout flares, only the 240 mg febuxostat dose had a significantly higher number of flares when compared with allopurinol (RR 2.3; 95% CI 1.7 to 3.0). In safety and tolerance outcomes, total adverse events were lower for 80 mg (RR 0.93; 95% CI 0.87 to 0.99) and 120 mg febuxostat (RR 0.90; 95% CI 0.84 to 0.96) than the allopurinol groups. Withdrawals for any reason were significantly higher for all of the febuxostat dose groups except the 40 mg cohort: 80 mg (RR 1.3; 95% CI 1.1 to 1.5), 120 mg (RR 1.4; 95% CI 1.1 to 1.7), and 240 mg (RR 1.7; 95% CI 1.2 to 2.2). Individual trial quality was assessed for bias by looking closely at the methodology used for randomization, allocation concealment, and blinding, and for the completeness of outcome reporting. The quality of evidence put forth by the trials was judged by the authors to range from low to high. Selective or incomplete outcome reporting, allocation concealment, and blinding procedures were all singled out for contributing to quality issues.²

Another Cochrane Collaboration Systematic Review evaluated the safety and efficacy of intra-articular glucocorticoids in the treatment of acute gout.³ After a full MEDLINE search, no trials were identified that evaluated the efficacy and safety of intra-articular glucocorticoids for acute gout. Although evidence suggests that intra-articular glucocorticoids may be a safe and effective treatment in osteoarthritis and rheumatoid arthritis, there is no evidence from RCTs to support their use in the treatment of acute gout. The results from studies in these other patient populations may be generalizable to people with acute gout, particularly in people who cannot use non-steroidal anti-inflammatory drugs or colchicine.

Guidelines:

The American College of Rheumatology updated their guidelines for treatment of hyperuricemia in adults in 2012.¹ Guideline recommendations were graded according to the quality of evidence supporting each recommendation. The following recommendations were made on drug therapy:

- Patients with a diagnosis of gouty arthritis and evidence of tophus or tophi are indicated for uric acid lowering treatment. Grade A recommendation
- Patients with a diagnosis of gouty arthritis and frequent gout flares are indicated for uric acid lowering treatment. Grade A recommendation

- Patients with a diagnosis of gouty arthritis and evidence of chronic kidney disease stage 2 or greater are indicated for uric acid lowering treatment. Grade C recommendation
- Patients with a diagnosis of gouty arthritis and evidence of past urolithiasis are indicated for uric acid lowering treatment. Grade C recommendation
- Allopurinol or febuxostat are both recommended as first line agents for uric acid lowering. Grade A recommendation
- Starting allopurinol dosage should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD. Grade B recommendation
- Gradually titrate allopurinol maintenance doses upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen SUA target. Grade C recommendation
- Dose can be raised above 300 mg allopurinol daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity. Grade B recommendation
- Prior to allopurinol initiation, consider HLA-B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function). Grade A recommendation
- Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of either. Grade C recommendation
- Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to a xanthine oxidase inhibitor. Grade B recommendation
- Probenecid is recommended as an alternative if at least one xanthine oxidase inhibitor is contraindicated. Grade B recommendation
- Probenecid is the first choice among uricosuric agents for uric acid lowering monotherapy. Grade B recommendation
- In gout patients with a creatinine clearance ≤ 50 ml/minute, probenecid is not recommended as first-line monotherapy. Grade C recommendation
- Use of agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive uric acid lowering strategy. Grade B recommendation
- History of urolithiasis contraindicates probenecid monotherapy. Grade C recommendation
- Treatment can be started during an acute flare as long as anti-inflammatory management had begun. Grade C recommendation
- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed uric acid lowering treatment. Grade A recommendation
- The use of low-dose NSAIDs or low-dose colchicine can be used to prevent against acute flares during initiation of chronic therapy. Level A recommendation

New drugs:

None

New Formulations/Indications:

None

New FDA safety alerts:

None

New Trials (Appendix 1):

A total of 22 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

A secondary analysis of the CONFIRMS trial by Wells et al examined the efficacy of febuxostat within the subpopulation of African Americans. Subjects (n=228) were randomized to receive 40 mg febuxostat, 80 mg febuxostat or 200-300 mg allopurinol for six months. The primary endpoint was the proportion of subjects in each group with a serum uric acid (sUA) level of < 6.0 mg/dL at the final visit. Subjects in the febuxostat 80 mg group (66.7%) were significantly more likely to meet the endpoint than those in both the febuxostat 40 mg group (34.9%; $p < 0.001$) and the allopurinol group (41.8%; $p = 0.004$). No statistical difference was seen between febuxostat 40 mg and allopurinol. Significantly more subjects with mild or moderate renal impairment achieved a sUA < 6.0 mg/dL in the febuxostat 80 group than in either the febuxostat 40 mg or allopurinol group ($p < 0.05$).⁶

Jackson et al also performed a secondary Ad-Hoc analysis of the CONFIRMS trial. Their evaluation examined the results for a subset of the trial population over 65 years old. Patients (n=374) were randomized to receive 40 mg febuxostat, 80 mg febuxostat or 200-300 mg allopurinol for six months. The primary endpoint was the proportion of subjects in each group with a serum uric acid (sUA) level of < 6.0 mg/dL at the final visit. Both doses of febuxostat were more likely to produce a sUA level at goal by the last study visit than was allopurinol (for febuxostat 80 mg: $p < 0.001$, 40 mg: $p = 0.029$); 82% of patients in the febuxostat 80 mg group, 61.7% of the febuxostat 40 mg group, and 47.3% of the allopurinol group achieved a sUA of 6 mg/dL. Febuxostat 80 mg was also significantly more effective at achieving sUA goal than the 40 mg dose ($p < 0.001$). This trend continued for patients with mild-to-moderate renal disease; more patients on febuxostat 40 mg (61.6%; $p = 0.028$) and febuxostat 80 mg (82.5%; $p < 0.001$) achieved an sUA of < 6 mg/dL compared to those on allopurinol 200 or 300 mg (46.9%).⁷

References:

1. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care & Research*. 2012;64(10):1431–1446. doi:10.1002/acr.21772.
2. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. In: The Cochrane Collaboration, Lopez-Olivo MA, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: <http://doi.wiley.com/10.1002/14651858.CD008653.pub2>. Accessed October 1, 2013.
3. Wechalekar MD, Vinik O, Schlesinger N, Buchbinder R. Intra-articular glucocorticoids for acute gout. *Cochrane Database Syst Rev*. 2013;4:CD009920. doi:10.1002/14651858.CD009920.pub2.
4. Terkeltaub R. Update on gout: new therapeutic strategies and options. *Nat Rev Rheumatol*. 2010;6(1):30–38. doi:10.1038/nrrheum.2009.236.
5. Ye P, Yang S, Zhang W, et al. Efficacy and Tolerability of Febuxostat in Hyperuricemic Patients With or Without Gout: A Systematic Review and Meta-Analysis. *Clinical Therapeutics*. 2013;35(2):180–189. doi:10.1016/j.clinthera.2012.12.011.
6. Wells AF, MacDonald PA, Chefo S, Jackson RL. African American patients with gout: efficacy and safety of febuxostat vs allopurinol. *BMC Musculoskeletal Disorders*. 2012;13(1):15. doi:10.1186/1471-2474-13-15.
7. Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients ≥ 65 years of age. *BMC Geriatrics*. 2012;12(1):11. doi:10.1186/1471-2318-12-11.

Appendix 1: Abstracts of Randomized Control Trials

Wells AF, MacDonald PA, Chefo S, Jackson RL. African American patients with gout: efficacy and safety of febuxostat vs allopurinol. *BMC Musculoskeletal Disorders*. 2012;13(1):15. doi:10.1186/1471-2474-13-15.

Background: African Americans are twice as likely as Caucasians to develop gout, but they are less likely to be treated with urate-lowering therapy (ULT). Furthermore, African Americans typically present with more comorbidities associated with gout, such as hypertension, obesity, and renal impairment. We determined the efficacy and safety of ULT with febuxostat or allopurinol in African American subjects with gout and associated comorbidities and in comparison to Caucasian gout subjects.

Methods: This is a secondary analysis of the 6-month Phase 3 CONFIRMS trial. Eligible gouty subjects with baseline serum urate (sUA) \geq 8.0 mg/dL were randomized 1:1:1 to receive febuxostat 40 mg, febuxostat 80 mg, or allopurinol (300 mg or 200 mg depending on renal function) daily. All subjects received gout flare prophylaxis. Primary efficacy endpoint was the proportion of subjects in each treatment group with sUA $<$ 6.0 mg/dL at the final visit. Additional endpoints included the proportion of subjects with mild or with moderate renal impairment who achieved a target sUA $<$ 6.0 mg/dL at final visit. Adverse events (AEs) were recorded throughout the study.

Results: Of the 2,269 subjects enrolled, 10.0% were African American and 82.1% were Caucasian. African American subjects were mostly male (89.5%), obese (BMI \geq 30 kg/m²; 67.1%), with mean baseline sUA of 9.8 mg/dL and mean duration of gout of 10.4 years. The proportions of African American subjects with a baseline history of diabetes, renal impairment, or cardiovascular disease were significantly higher compared to Caucasians ($p <$ 0.001). ULT with febuxostat 80 mg was superior to both febuxostat 40 mg ($p <$ 0.001) and allopurinol ($p =$ 0.004). Febuxostat 40 mg was comparable in efficacy to allopurinol. Significantly more African American subjects with mild or moderate renal impairment achieved sUA $<$ 6.0 mg/dL in the febuxostat 80 mg group than in either the febuxostat 40 mg or allopurinol group ($p <$ 0.05). Efficacy rates in all treatment groups regardless of renal function were comparable between African American and Caucasian subjects, as were AE rates.

Conclusions: In African American subjects with significant comorbidities, febuxostat 80 mg is significantly more efficacious than either febuxostat 40 mg or allopurinol 200/300 mg. Febuxostat was well tolerated in this African American population.

Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients \geq 65 years of age. *BMC Geriatrics*. 2012;12(1):11. doi:10.1186/1471-2318-12-11.

Background: The incidence of gout rises with increasing age. Management of elderly (\geq 65 years) gout patients can be challenging due to high rates of comorbidities, such as renal impairment and cardiovascular disease, and concomitant medication use. However, there is little data specifically addressing the efficacy and safety of available urate-lowering therapies (ULT) in the elderly. The objective of this post hoc analysis was to examine the efficacy and safety of ULT with febuxostat or allopurinol in a subset of elderly subjects enrolled in the CONFIRMS trial.

Methods: Hyperuricemic (serum urate [sUA] levels \geq 8.0 mg/dL) gout subjects were enrolled in the 6-month, double-blind, randomized, comparative CONFIRMS trial and randomized, 1:1:1, to receive febuxostat, 40 mg or 80 mg, or allopurinol (200 mg or 300 mg based on renal function) once daily. Flare prophylaxis was provided throughout the study duration. Study endpoints were the percent of elderly subjects with sUA $<$ 6.0 mg/dL at the final visit, overall and by renal function status, percent change in sUA from baseline to final visit, flare rates, and rates of adverse events (AEs).

Results: Of 2,269 subjects enrolled, 374 were elderly. Febuxostat 80 mg was significantly more efficacious (82.0%) than febuxostat 40 mg (61.7%; $p <$ 0.001) or allopurinol (47.3%; $p <$ 0.001) for achieving the primary efficacy endpoint. Febuxostat 40 mg was also superior to allopurinol in this population ($p =$ 0.029). In subjects with mild to moderate renal impairment, significantly greater ULT efficacy was observed with febuxostat 40 mg (61.6%; $p =$ 0.028) and febuxostat 80 mg (82.5%; $p <$ 0.001) compared to allopurinol 200/300 mg (46.9%). Compared to allopurinol 200/300 mg, the mean percent change in sUA from baseline was significantly greater for both febuxostat 80 mg ($p <$ 0.001) and febuxostat 40 mg ($p =$ 0.011) groups. Flare rates declined steadily in all treatment groups. Rates of AEs were low and comparable across treatments.

Conclusions: These data suggest that either dose of febuxostat is superior to commonly prescribed fixed doses of allopurinol (200/300 mg) in subjects \geq 65 years of age with high rates of renal dysfunction. In addition, in this high risk population, ULT with either drug was well tolerated.