Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Pharmacotherapeutic Review of Gout***

-May 2016-

Background:
Gout is one of the most common types of inflammatory arthritis, affecting about 4% of the US population. Incidence is more common in men, but does increase in postmenopausal women.[1,2,3] At the May 2016 meeting, the NPTC discussed current guidelines and literature reviewing pharmacologic agents for the treatment of acute and chronic gout. The National Core Formulary (NCF) currently includes several agents used in treating gout including NSAIDs, prednisone and allopurinol. As a result of this therapeutic review, **no changes were made to the NCF.**

Discussion:
A recent review of guidelines for treatment of gout from 2002 to 2013 shows that there are more similarities than differences in recommendations for diagnosing and treating gout. All emphasize the importance of educating patients about gout. The more recent guidelines recommend NSAIDs, glucocorticoids, or colchicine as 1st line for acute gout attacks and NSAIDs or colchicine as prophylaxis against acute attacks when starting urate lowering treatment. NSAIDs with FDA approvals for treatment of acute gout include indomethacin, naproxen, and sulindac. For treatment of chronic gout, all guidelines recommend allopurinol as a 1st line agent to decrease uric acid (UA) levels to a goal of < 6mg/dl. The American College of Rheumatology (ACR) also considers febuxostat as a 1st line urate lowering agent.[4]

Acute Gout
A 2014 Cochrane review evaluated NSAIDs vs. placebo, COX-2 inhibitors and glucocorticoids. None of the studies reviewed were deemed high quality. NSAIDs vs. placebo showed significant decrease in pain at 24 hours with NSAID use. No differences were seen between traditional NSAIDs and COX-2 Inhibitors or NSAIDs and glucocorticoids.[5]

In 2008, a Cochrane review of systemic corticosteroids for acute gout was published. Three low to moderate quality head-to-head trials were included, comparing IM triamcinolone or oral prednisolone to indomethacin or ACTH. Cochrane noted that the evidence for efficacy in gout was inconclusive.[6]

Colchicine is a 3rd line agent with indications for treatment and prophylaxis of acute gout flares. A 2014 Cochrane review looked at 2 randomized controlled trials (RCT) evaluating high-dose colchicine vs. placebo. The high-dose colchicine group had a statistically significant better response at 24 and 32-36 hours (NNTB = 4) and also a statistically significant greater risk of GI side effects (NNTH = 2). Low-dose colchicine vs. placebo in one study showed a statistically significant reduction in pain at 24 and 32 hours (NNTB=5) and no significant difference in harms. In another trial comparing high- and low-dose colchicine, no statistically significant differences in pain reduction were observed at 24 and 32 hours.[7]

A 2014 systematic review of acute gout treatment included 30 RCTs. The review provided evidence for monotherapy only in treating acute gout with NSAIDs, colchicine, glucocorticoids and IL-1β antagonists. None of the head-to-head studies showed superiority of NSAIDs, glucocorticoids nor colchicine over the others. All agents were shown to be effective in controlling/abating acute attacks.[8]

Chronic Gout
Allopurinol is a 1st line agent in the treatment of chronic gout in all current guidelines. Allopurinol does require dosage adjustments in mild to moderate renal impairment. The ACR also lists febuxostat (another xanthine oxidase inhibitor [XOI]) as a potential 1st line agent. Uricosuric agents such as probenecid, losartan or fenofibrate (off-label use) are recommended in addition to a XOI if the goal UA level is not met. Pegloticase is a recombinant urate-oxidase enzyme that converts uric acid to allantoin. It is an injectable agent that is recommended if other alternatives do not reach the UA goal. Lesinurad is an UA transporter 1 and organic anion transporter 4 inhibitor that was FDA-approved in December 2015 for use in combination with XOIs not meeting goals. It is not yet available for purchase. Both the FDA and European Union are requiring post-marketing studies evaluating renal and CV effects. Lesinurad does have a black box warning of acute renal failure and discontinuing use in CrCl<45ml/min.

A Cochrane review from 2014 studied allopurinol vs. placebo and febuxostat. Reviewers concluded that allopurinol is probably more effective than placebo and may be less effective than 80mg febuxostat at achieving UA goal, but similar effects in tophus regression.[9] In 2012, a Cochrane review of febuxostat showed all doses resulted in an increase in gout flares vs. allopurinol or placebo however this was only statistically significant at 120mg dose vs. placebo. Uric acid lowering was beneficial in all doses vs. placebo and at 80mg and 120mg doses vs. allopurinol. Higher rates of withdrawal were seen at 80mg and 120mg doses vs. allopurinol. Adverse events (vs. allopurinol) were statistically significantly lower in the febuxostat 80mg and 120mg dose groups.[10]

A 2015 systematic review and meta-analysis of allopurinol vs. placebo and febuxostat concluded that there were no differences in risks of any type of adverse events. When compared with probenecid and benzbromarone, allopurinol had higher incidence of rash, but lower incidence of GI symptoms. The reviewers concluded that allopurinol is a safe option, but higher doses and longer monitoring need to be evaluated. Most studies on allopurinol do not maximize the dose (800mg), but use a 300mg/day dose.[11]

The CONFIRMS trial was a 6 month trial comparing safety and efficacy of febuxostat vs. allopurinol in gout patients with serum UA >8mg/dl. The primary endpoint was UA < 6mg/dl. Febuxostat 40mg/day was comparable to allopurinol in achieving this goal. Safety analyses showed that reported adverse events and withdrawals were similar between treatment groups as were reports of rash and rates of liver function abnormalities. No difference was noted in cardiovascular adverse events.[12] Several post hoc analyses were performed using results of CONFIRMS. For patients >65 years old, those using febuxostat 40 or 80mg/day reached goal UA significantly more than those taking allopurinol 200-300mg/day and it was well tolerated.[13] The safety and efficacy of febuxostat and allopurinol were compared in another study in diabetic and non-diabetic gout patients; the urate-lowering efficacy of febuxostat 80mg was superior to both febuxostat 40mg and allopurinol in these patients. All treatments showed similar safety profiles between patients regardless of diabetes status.[14] Another analysis that included CONFIRMS with 2 other trials reviewed febuxostat and allopurinol in women with gout. The febuxostat 80mg showed significantly greater UA lowering than allopurinol. Adverse event rates were similar to overall reports.[15]

Findings:
Given the comparative findings from the review, the NPTC felt no changes to the NCF were necessary for the treatment of gout at this time. These findings do not limit local Pharmacy & Therapeutics committees from adding other agents to their formularies. Patient education on gout treatment is paramount as few patients understand the chronicity of gout and how it progresses.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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