BRIEF OBSERVATION

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Initiation of Allopurinol at First Medical Contact for Acute Attacks of Gout: A Randomized Clinical Trial

Thomas H. Taylor, MD,[a,b,c] John N. Mecchella, DO,[b,c] Robin J. Larson, MD,[a,b] Kevin D. Kerin, MD,[a,b] Todd A. MacKenzie, PhD[b]

[a]White River Junction VA Regional Medical Center, White River Junction, Vt; [b]Dartmouth Medical School, Lebanon, NH; [c]Dartmouth Hitchcock Medical Center, Lebanon, NH.

ABSTRACT

OBJECTIVE: Streamlining the initiation of allopurinol could result in a cost benefit for a common medical problem and obviate the perception that no treatment is required once acute attacks have resolved. Our objective was to test the hypothesis that there is no difference in patient daily pain or subsequent attacks with early versus delayed initiation of allopurinol for an acute gout attack.

METHODS: A total of 57 men with crystal-proven gout were randomized to allopurinol 300 mg daily or matching placebo for 10 days. All subjects received indomethacin 50 mg 3 times per day for 10 days, a prophylactic dose of colchicine 0.6 mg 2 times per day for 90 days, and open-label allopurinol starting at day 11. Primary outcome measures were pain on visual analogue scale (VAS) for the primary joint on days 1 to 10 and self-reported flares in any joint through day 30.

RESULTS: On the basis of 51 evaluable subjects (allopurinol in 26, placebo in 25), mean daily VAS pain scores did not differ significantly between study groups at any point between days 1 and 10. Initial VAS pain scores for allopurinol and placebo arms were 6.72 versus 6.28 ($P = .37$), declining to 0.18 versus 0.27 ($P = .54$) at day 10, with neither group consistently having more daily pain. Subsequent flares occurred in 2 subjects taking allopurinol and 3 subjects taking placebo ($P = .60$). Although urate levels decreased rapidly in the allopurinol group (from 7.8 mg/dL at baseline to 5.9 mg/dL at day 3), sedimentation rates and C-reactive protein levels did not differ between groups at any point.

CONCLUSIONS: Allopurinol initiation during an acute gout attack caused no significant difference in daily pain, recurrent flares, or inflammatory markers.

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KEYWORDS: Allopurinol; Gout; Gout outcomes

Medical teaching suggests that allopurinol should not be initiated in the setting of an acute gout attack, because rapid lowering of serum urate may exacerbate the attack. Delayed initiation may come at a price, as many patients never start definitive urate-lowering therapy and are skeptical of chronic therapy after acute symptoms resolve. Since the introduction of allopurinol in 1964, reviews have attributed acute attacks of gout or worsening of ongoing attacks to the initiation of allopurinol.[1] Inference may be implied, because gout attacks continue to occur during the first few months after allopurinol is started[2] and are proportional to the rate of uric acid lowering.[3,4] Theories to explain allopurinol-induced exacerbation of gout are controversial and lack evidence, but they generally implicate urate concentration flux and remodeling of microscopic tophi.[3,5]

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Requests for reprints should be addressed to Thomas H. Taylor, MD, White River Jct VA Regional Medical Center, Department of Medicine, Dartmouth Medical School, 215 N. Main St, White River Junction, VT 05009.

E-mail address: Tom.Taylor@va.gov.

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Recommendations have come to include complex guidelines for delayed and incremental initiation of definitive treatment, commencing after the acute attack has subsided, for both allopurinol and uricosurics.[6,7] Despite these well-intentioned guidelines, recent studies have implicated poor compliance, deficits in patient and physician knowledge, and complexity of present regimens requiring patients to return for graded increases of allopurinol as factors impeding better outcomes.[8-13] If initiation of allopurinol could be simplified and administered in an adequate dose of 300 mg at the first medical encounter during an acute attack, then opportunity for education, improved outcomes, and cost containment might be realized.

CLINICAL SIGNIFICANCE

- Guidelines recommend delayed and graded initiation of allopurinol. Poor outcomes for gout treatment might be improved if allopurinol could be initiated at the initial presentation of acute attacks.
- No difference in pain by daily visual analogue scale was seen when allopurinol was administered during the acute attack.
- The percentage of recurrent attacks was similar to that in studies in which febuxostat, allopurinol, or placebo was initiated after the attack.

Evidence in support of delayed and stepped increase of allopurinol treatment is poor and supported by 2 studies describing case series.[14,15] No study has evaluated the initiation of allopurinol during attacks in patients with primary gout as they present in primary care settings, concomitantly treated with both indomethacin and colchicine. Prophylactic colchicine has been shown to reduce the frequency of gout flares in patients with interval gout[16] and in patients beginning treatment with uricosurics[17] and allopurinol.[18] Should allopurinol predispose to exacerbation, it is equally conceivable that the best time to initiate allopurinol would be during the acute attack, when patients also receive treatment doses of indomethacin and prophylactic doses of colchicine. We challenge current teaching by testing the hypothesis that there is no difference in patient-reported pain or subsequent attacks with early initiation of allopurinol given during the acute attack, concomitant with indomethacin treatment and a prophylactic dose of colchicine.

MATERIALS AND METHODS

We designed a randomized, double-blind, placebo-controlled, parallel-arm, single-center, noninferiority study of the early initiation of full-dose allopurinol (300 mg) versus placebo in adults with acute gout, both arms receiving indomethacin treatment and a prophylactic dose of colchicine. The Research and Development Committee at the White River Junction Veteran's Affairs Medical Center and the Committee for the Protection of Human Subjects at Dartmouth College approved the original protocol and reviewed the trial annually. All subjects provided written informed consent. There was no pharmaceutical industry participation or support.

The trial was conducted between 1998 and 2009 at the Veteran's Affairs Medical Center in White River Junction, Vermont. Patients presenting within 7 days of onset of an acute gout attack were evaluated, and American College of Rheumatology criteria for acute arthritis of gout were met,[19] including the presence of monosodium urate crystals on arthrocentesis of the primary joint on the day of study entry. Exclusion criteria included secondary gout (because it is dependent on the treatment of the underlying disease); the presence of tophaceous gout (because of concern that tophi could make evaluation of resolution and exacerbations difficult); a history of congestive heart failure; anticoagulant use; a recent serum creatinine greater than 1.3 mg/dL (because these patients should not receive indomethacin); or the use of steroids, colchicine, allopurinol, uricosuric drugs, chemotherapy, or immunosuppressive therapy in the past 6 months. Although all subjects brought to the attention of the principal investigator were screened consecutively, primary providers also made decisions regarding eligibility and subjects were highly selected by study criteria; thus, information regarding the number and characteristics of those excluded could not be reliably tracked.

Randomization and Interventions

Fifty-seven eligible subjects were randomized, in a 1:1 ratio without stratification, to receive allopurinol 300 mg daily for 10 days (allopurinol group) or placebo for 10 days (placebo group). Subjects and evaluators had no access to the randomization sequence. The randomization sequence was determined by the study pharmacist using a random number generator and kept in the pharmacy vault. Study drugs were given directly to study patients through the pharmacy, and neither patients nor evaluators were aware of which medication was given. In addition to the 10-day course of allopurinol or placebo, all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days.

Outcomes and Follow-up

Two primary outcomes included pain scores at each of days 1 to 10, as measured by a visual analogue scale (VAS) standardized to 10 cm for the primary affected joint, and self-reported subsequent gout flares in any joint during days 1 to 30. For VAS scoring, subjects were given a diary in