58577	6
Phar	
Bestelidatum	20.09.2010 17:16:00
Termin	27.9. ~~18.10~~.2010 **18:00:00**
International Beteiligungs GmbH	
14 Arb. ~~Fr.~~ Schaupp	

520 AT geändert
Email

12 (neue Intern)

an Fr. Dr. Himly
nach telef. Wunsch 23.9.2010

6) Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA.
Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis.
J Rheumatol. 2004 Dec;31(12):2429-32.

Colchicine for Prophylaxis of Acute Flares When Initiating Allopurinol for Chronic Gouty Arthritis

GREGORY C. BORSTAD, LESLIE R. BRYANT, MICHAEL P. ABEL, DAREN A. SCROGGIE, MARK D. HARRIS, and JEFF A. ALLOWAY

ABSTRACT. ***Objective.*** The use of colchicine to prevent acute gout flares during initiation of allopurinol therapy is widely practiced despite lack of proven benefit. We investigated if colchicine administration during initiation of allopurinol for chronic gouty arthritis reduces the frequency and/or severity of acute gout flares.

Methods. Patients starting allopurinol for crystal-proven chronic gouty arthritis were randomized to receive colchicine 0.6 mg po bid or placebo in a randomized, prospective, double blind, placebo controlled trial. Subjects were followed for evidence of acute gout flares and remained on study drug for 3 months beyond attaining a serum urate concentration < 6.5 mg/dl. Treatment arms were analyzed regarding frequency of flares, likelihood of any flare or multiple flares, severity of flares on the visual analog scale (VAS), and length of flares in days.

Results. Forty-three subjects were studied. Subjects treated with colchicine experienced fewer total flares (0.52 vs 2.91, p = 0.008), fewer flares from 0 to 3 months (0.57 vs 1.91, p = 0.022), fewer flares 3–6 months (0 vs 1.05, p = 0.033), less severe flares as reported on VAS (3.64 vs 5.08, p = 0.018), and fewer recurrent gout flares (p = 0.001). Colchicine was well tolerated.

Conclusion. Colchicine prophylaxis during initiation of allopurinol for chronic gouty arthritis reduces the frequency and severity of acute flares, and reduces the likelihood of recurrent flares. Treating patients with colchicine during initiation of allopurinol therapy for 6 months is supported by our data. (J Rheumatol 2004;31:2429–32)

Key Indexing Terms:
COLCHICINE ALLOPURINOL GOUT

Chronic gouty arthritis is a common condition associated with significant disability and potential for joint deformity and destruction. Allopurinol is often used to treat tophaceous gout and recurrent attacks of gout. Allopurinol therapy reduces serum urate concentrations within 7 days[1,2]. The goal of therapy is to reduce serum urate concentrations to at least < 6.5 mg/dl[2-4].

Serum urate lowering may be associated with an increased frequency of acute gout flares[1,5]. Decreases in serum urate are thought to cause transient localized precipitation of monosodium urate crystals in cartilage and soft tissues, leading to acute gout flares. The frequency of these flares is disputed; earlier studies[1,5,6] are often quoted in the literature[7,8] to reflect a low frequency (25% or less) of this phenomenon. However, the studies were not standardized regarding frequency of flares and often included patients taking colchicine or nonsteroidal antiinflammatory drugs (NSAID). In 2 more recent studies, with data available on patients not taking a form of prophylaxis, the frequency of acute flares was 38%[9] and 75%[10]. Many clinicians recommend prophylactic colchicine during allopurinol initiation[1,4,11]. Prophylactic colchicine has been effective in reducing the frequency of acute gout flares in patients with intercritical gout[12,13] and in patients beginning therapy with uricosurics[3,10]; however, it has yet to be studied in the setting of allopurinol initiation.

Regarding current clinical practice, many review articles[4,14-16] and most rheumatology textbooks[17-19] note that colchicine may reduce the occurrence of acute gouty attacks when initiating allopurinol. Most rheumatologists use prophylactic colchicine when initiating allopurinol[20-22].

Colchicine side effects at prophylactic dosing include diarrhea, abdominal cramps, nausea, and vomiting, and very rarely bone marrow suppression, myopathy, and neuropathy[13,23,24]. All these are more common in patients with impaired renal function.

Due to the lack of definitive clinical trials and the potential for colchicine toxicity, the practice of colchicine prophylaxis in the setting of allopurinol initiation is not universally accepted[7,25]. There is a need for this to be addressed with a prospective trial. Thus, our aim was to determine if

From the Department of Rheumatology, Wilford Hall US Air Force Medical Center, Lackland AFB, San Antonio, Texas, USA.

The work reported herein was performed under United States Air Force Surgeon General-approved Clinical Investigation No. FWH19970125H; WHMC Human Research.

G.C. Borstad, MD, Assistant Professor of Medicine; L.R. Bryant, MD, Assistant Professor of Medicine; D.A. Scroggie, MD, Assistant Professor of Medicine, Uniformed Services University of the Health Sciences, F. Edward Hebert School of Medicine, Bethesda, Maryland; M.P. Abel, MD; M.D. Harris, MD; J.A. Alloway, MD, Department of Rheumatology, Wilford Hall USAF Medical Center.

Address reprint requests to Dr. G.C. Borstad, MAJ, USAF, MC, 60MDOS/SGOMJ, 101 Bodin Circle, Travis AFB, CA 94535, USA.

Submitted March 25, 2004; revision accepted July 20, 2004.

colchicine administration during initiation of allopurinol therapy for chronic gouty arthritis reduces acute gout flares. As a secondary endpoint, we sought to determine the time period required to achieve a benefit.

MATERIALS AND METHODS

Subjects with crystal-proven gouty arthritis were chosen based on accepted criteria for allopurinol administration: presence of tophi, uric acid overproduction, frequent attacks of gout (≥ 3 attacks/year), elevated serum urate in the setting of chronic renal insufficiency (CRI), and nephrolithiasis. Subjects were excluded if they were under 19 years of age, had been given chronic colchicine within the past 3 months, had a history of allergic reaction to allopurinol or colchicine, had severe renal insufficiency (creatinine clearance < 20 ml/min), were female with childbearing potential, or had evidence of active hepatitis. Voluntary, informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and AFI 40-402, Protection of Human Subjects in Biomedical and Behavioral Research.

Patients starting allopurinol for crystal-proven chronic gouty arthritis were randomized to receive either colchicine or placebo in prospective, double blind, placebo controlled fashion. The subjects were managed by the authors in the Rheumatology Department at Wilford Hall Medical Center throughout the study, after being recruited from the departments of internal medicine and rheumatology at Wilford Hall USAF Medical Center.

Demographic data were collected at the time of enrollment for age, sex, race, presence or absence of tophi, medical history, use of alcohol, or use of other medications known to affect serum urate concentrations.

Baseline levels of the following laboratory studies were obtained on all subjects: 24-h urine for creatinine clearance and uric acid excretion (with no dietary restriction, one time only), complete blood count (CBC), blood urea nitrogen (BUN), creatinine (Cr), thyroid stimulating hormone (TSH), aspartate and alanine aminotransferases (AST/ALT), and creatine phosphokinase. All acute gout flares in the 12 months prior to enrollment were recorded. Subjects with myelodysplastic disorder or other bone marrow disorders were not included in the exclusion criteria; however, no subject had significant hypoproliferative findings on initial CBC.

Allopurinol was initiated at 100 mg po QD. Serum urate levels were obtained at baseline, and at 2–3 week intervals. The dose of allopurinol was increased in 100 mg increments until a serum urate level of < 6.5 mg/dl was attained. In the setting of chronic renal insufficiency (defined as a creatinine clearance of 20–50 ml/min), the dose was escalated in 50 mg increments.

Subjects were randomized to receive either colchicine 0.6 mg PO BID or placebo BID in double blinded fashion. Randomization was conducted by the outpatient pharmacy. The placebo was not identical in form. Methods of treatment compliance were not obtained. Once-daily dosing was utilized for subjects with chronic renal insufficiency. Subjects who experienced any gastrointestinal side effects while on twice-daily dosing had their dose decreased to once daily. Providers were required to maintain a subject on the study drug for 3 months beyond attaining a serum urate level of < 6.5 mg/dl. Chronic NSAID were not permitted, but short term NSAID use for acute gout flares was allowed. Acute gout flares were managed in a manner deemed appropriate by individual physicians who enrolled and were following individual subjects. Oral colchicine dosing to manage acute gout flares was not allowed.

Subjects were evaluated at 3 and 6-month timepoints for evidence of acute gout flares, and for any clinical evidence of medication toxicity. Patient information sheets were used to record length of flares, medications used, and overall assessment of the severity of flares on a visual analog scale (VAS). Serum urate levels were measured while titration of allopurinol was taking place, as well as at the 3 and 6-month timepoints. At the 6-month timepoint, routine CBC, BUN, creatinine, AST, and ALT were measured to monitor for evidence of drug toxicity.

All subjects who received a study drug were included in the statistical analysis. T-test for equality of means was used to compare the average age of subjects in the treatment groups (colchicine vs placebo). Chi-square analyses were used to compare the 2 treatment groups with regard to sex, race, presence or absence of tophi, medical conditions associated with gout (chronic renal insufficiency, hypertension, hypothyroidism, coronary artery disease), use of alcohol, side effects, withdrawals, and use of drugs known to affect serum urate levels (diuretics, aspirin, cyclosporin A, niacin, ethambutol). Chi-square analyses were also used to compare the 2 groups regarding the number of acute gout flares that occurred in the 12 months prior to enrollment, study drug dosing (QD vs BID), and dose of allopurinol required to achieve a therapeutic serum urate level.

Average serum urate levels were compared between the 2 treatment groups at baseline, 3 months, and 6 months. A repeated measures analysis of variance statistic was used to compare the change of serum urate levels between the 0 and 3-month timepoints. This method was repeated for only those patients who experienced acute flares of gout. The treatment groups were analyzed at the 3 and 6-month timepoints regarding mean number of flares (T-test for equality of means), number of patients with > 0 flares (Pearson chi-square test), and number of patients with > 1 flare (Pearson chi-square test). Mann-Whitney analysis for nonparametric data was used to analyze mean VAS scores per flare and average length of flare in days between both groups, because the data were not normally distributed.

Statistical analyses were performed with the use of SPSS, v.11.5 software (SPSS, Chicago, IL, USA).

RESULTS

Fifty-one patients were enrolled. Eight patients did not participate beyond an initial enrollment visit and did not receive study drug. A remaining 43 patients were analyzed in the study (mean age 63 years, 37 men, 6 women). Twenty-one subjects were treated with colchicine, while 22 were treated with placebo. All 43 subjects who received a study drug were included in the analysis.

The treatment groups did not vary significantly with regard to baseline demographics (age, sex, race) or medical conditions associated with gout (chronic renal insufficiency, hypertension, hypothyroidism, coronary artery disease). The 2 groups had similar rates of tophaceous involvement (62% in colchicine arm, 64% in placebo arm). The groups did not vary significantly regarding use of drugs known to affect serum urate levels (aspirin, cyclosporin A, niacin, ethambutol), with the notable exception of a higher rate of baseline diuretic use in the colchicine group. The 2 groups had similar numbers of gout flares in the year before entering the study. These findings are summarized in Table 1.

Table 2 summarizes pertinent treatment effects, side effects, and withdrawals. The 2 groups took similar doses of allopurinol to obtain therapeutic serum urate concentrations. The groups had similar withdrawal rates. The colchicine group did have a significantly higher rate of diarrhea by self-report, but this was never a reason for withdrawal and responded to decreased study drug dosage in all cases. There was a trend toward a higher rate of QD dosing compared to BID dosing in the colchicine group. There were no serious adverse events in either treatment group.

Considering the 43 patients analyzed, there were 7 withdrawals, 3 in the colchicine group and 4 in the placebo group. The colchicine group had one subject with a stroke at 3 months, one subject who discontinued the drug due to subjective muscle weakness at 2.5 months, and one subject who

Table 1. Baseline demographics and clinical characteristics (n = 43: colchicine = 21, placebo = 22).

Demographic/Characteristic	Colchicine	Placebo	p
Mean age, yrs	63.5	62.5	0.798
Male, %	81	91	0.412
Caucasian race, %	67	73	0.665
Chronic renal insufficiency, %	14	9	0.664
Hypertension, %	90	77	0.412
Hypothyroidism, %	0.05	0.05	1.000
Coronary artery disease, %	29	27	1.000
Tophi, %	62	64	0.907
Alcohol use, %	33	18	0.255
Drugs affecting serum urate levels, %	38	55	0.364
Diuretic use at baseline, %	57	27	0.047
Flares during prior year (mean number)	2.48	2.09	0.343

Table 2. Treatment effects and side effects/withdrawals (n = 43: colchicine = 21, placebo = 22).

Treatment/Side Effects	Colchicine	Placebo	p
Allopurinol dose (mean QD dose, mg)	265	245	0.453
Study drug QD instead of BID, %	62	36	0.094
Withdrawals, %	14.3	18.2	0.729
Any side effect, %	43	36	0.760
Diarrhea as side effect, %	38	4.5	0.009

was lost to followup after being treated 3 months. The stroke occurred in the setting of significant medical comorbidities and was not deemed related to the study medication. The subject who experienced subjective muscle weakness had no objective evidence of weakness, and no laboratory evidence of muscle damage. The symptoms resolved upon discontinuation of the study drug. The placebo group had 2 withdrawals due to high frequency of flares (at 2 and 3 months), one withdrawal due to inadvertent medication discontinuation after 3 months, and one subject whose frequent traveling prevented adequate followup after 4 months.

Lowering of serum urate concentrations to < 6.5 mg/dl was achieved in each subject. The average baseline serum urate level in the colchicine group was 9.49 mg/dl versus 9.15 mg/dl in the placebo group. At 3 months, the average level was 6.35 mg/dl in the colchicine group versus 6.21 mg/dl in the placebo group. At 6 months, the average level was 6.03 mg/dl in the colchicine group versus 5.97 mg/dl in the placebo group. Regarding only those subjects who experienced an acute gout flare, the baseline serum urate level was 9.15 mg/dl in the colchicine group versus 9.15 in the placebo group, with 3-month levels of 6.07 mg/dl in the colchicine group versus 6.13 in the placebo group. There was no significant difference in the change of serum urate level from baseline to 3 months for all subjects (p = 0.552) or for only those subjects who had an acute gout flare (p = 0.648) during the study.

There were a total of 77 acute gout flares: 12 in the colchicine group and 65 in the placebo group. Subjects in the colchicine group were treated with study drug for an average of 5.21 months, those in the placebo group for an average of 5.18 months. Figure 1 summarizes that subjects treated with colchicine had fewer acute gout flares overall, fewer flares from 0 to 3 months, and fewer flares from 3 to 6 months. Acute gout flares occurred in 33% of the colchicine subjects and 77% of the placebo subjects (p = 0.008). Multiple gout flares occurred in 14% of the colchicine subjects and 63% of the placebo subjects (p = 0.004). Severity of acute gout flares measured subjectively by VAS averaged 3.64 in the colchicine group versus 5.08 in the placebo group (p = 0.018). The average length of acute gout flares did not vary significantly between the groups (6.0 days for colchicine and 5.56 days for placebo; p = 0.566).

DISCUSSION

Colchicine therapy for acute gout prophylaxis during initiation of allopurinol is routinely used by rheumatologists, but not without risk. Rare cases of myopathy, neuropathy, and bone marrow suppression have been reported[7,13,25], although these are extremely rare at the low doses used in this setting. In addition, low dose colchicine can be associated with diarrhea, abdominal cramps, nausea, and vomiting.

This prospective trial is the first study assessing the efficacy and safety of prophylactic oral colchicine during allopurinol initiation. Of subjects taking placebo, 77% experienced an acute gout flare in the first 6 months of allopurinol therapy. This is similar to the more recent studies describing a relatively high frequency of flares[9,10]. The results indicate that colchicine decreases the average number of acute gout flares, decreases the likelihood of having one or multiple acute flares, and decreases the severity of flares. The benefit was observed overall, from 0 to 3 months, and from 3 to 6 months. In this study, subjects were merely required to continue colchicine for at least 3 months beyond attaining a therapeutic serum urate concentration. However, a significant difference persisted for those subjects who continued taking colchicine for 6 months in total. Therefore, our

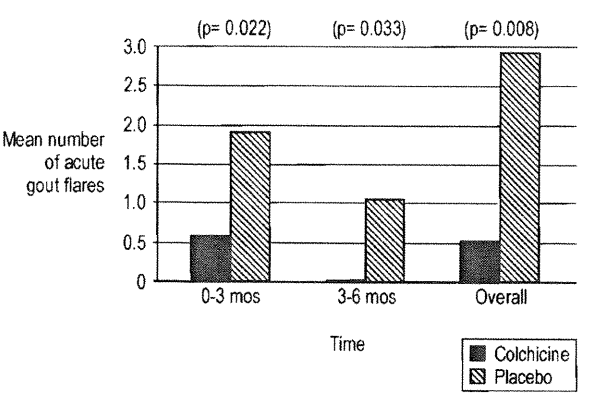

Figure 1. Mean number of acute gout flares at the 0–3 and 3–6 month time periods, and overall (n = 43: colchicine = 21, placebo = 22).

recommendation is for patients to be treated for 6 months after allopurinol is started. Recommendations beyond the 6-month time period cannot be made on the basis of this study. It is reasonable to consider continuation for a period of time if flares persist or if large tophi are present. Chronic, continuous use of colchicine prophylaxis should probably be avoided due to the potential for side effects. The use of colchicine in any setting needs to include a thorough patient discussion about its risks and benefits.

The colchicine was well tolerated. One subject had a mild, self-limited, subjective muscle weakness that resolved with discontinuation of colchicine. A significant number of subjects developed diarrhea that resolved with a lowering of the dose (to once daily) in all cases. This likely led to the trend toward QD dosing compared to BID dosing in the colchicine group. The time at which subjects changed from BID to QD dosing was not recorded, and the relative efficacy of QD versus BID dosing was not studied. If explored in such fashion, this could have given support to consideration of QD versus BID colchicine therapy to potentially minimize side effects.

The data may be limited in that the acute gout flares were recorded retrospectively and subjects were not examined at the time of each flare. Also, the relatively high percentage of subjects with tophaceous gout may make the results less applicable to those with no tophaceous involvement. The relatively high proportion of subjects with tophaceous involvement in our sample (62%–64%) is possibly due to referral bias to our rheumatology practice for complex/polyarticular gout cases or cases associated with advanced age and chronic renal insufficiency. Another possibility is that many patients were screened with radiographs to look for tophaceous changes. The higher rate of baseline diuretic use in the colchicine group, if anything, strengthens the conclusions, as diuretics are known to elevate serum urate concentrations and make patients prone to acute gout flares.

Chronic gouty arthritis is a common and markedly debilitating illness and allopurinol therapy is commonly used for longterm therapy. Prophylactic use of colchicine upon initiation of allopurinol will decrease the frequency, severity, and incidence of multiple acute gout attacks. It should be given for 6 months after initiation of allopurinol, and could be considered for longer periods of time in certain clinical scenarios. Prophylactic colchicine was well tolerated in our sample. Our study is the first to provide objective clinical data supporting the common clinical practice of using prophylactic colchicine therapy during initiation of allopurinol.

ACKNOWLEDGMENT

We thank Anneke C. Bush, ScD, MHS, Epidemiologist/Biostatistical Support, 59th Medical Wing, Clinical Research Squadron, for assistance with statistical analysis.

REFERENCES

1. Rundles RW, Metz EN, Siberman HR. Allopurinol in the treatment of gout. Ann Intern Med 1966;64:229-58.
2. Fam AG. Strategies and controversies in the treatment of gout and hyperuricemia. Baillieres Clin Rheumatol 1990;4:177-92.
3. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheum 1974;17:609-14.
4. Emmerson BT. The management of gout. N Engl J Med 1996;334:445-51.
5. Thompson FR, Duff IF, Robinson WD, Mikkelsen WM, Galindez H. Long term uricosuric therapy in gout. Arthritis Rheum 1962;5:384-96.
6. Klinenberg JR, Goldfinger SE, Seegmiller JE. The effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout. Ann Intern Med 1965;62:639-47.
7. Fam AG. Should patients with interval gout be treated with urate lowering drugs? [editorial]. J Rheumatol 1995;22:1621-3.
8. Schlesinger N, Schumacher HR. Gout: can management be improved? Curr Opin Rheumatol 2001;13:240-4.
9. Yamanaka H, Togashi R, Hakoda M, et al. Optimal range of serum urate concentrations to minimize risk of gouty attacks during anti-hyperuricemic treatment. Adv Exp Med Biol 1998;431:13-8.
10. Hollingworth P, Reardon JA, Scott JT. Acute gout during hypouricemic therapy: prophylaxis with colchicine. Ann Rheum Dis 1980;39:529-30.
11. Emmerson BT. Therapeutics of hyperuricemia and gout. Med J Aust 1984;141:31-6.
12. Yu TF, Gutman AB. Efficacy of colchicine prophylaxis. Prevention of recurrent gouty arthritis over a mean period of 5 years in 208 gouty subjects. Ann Intern Med 1961;55:179-91.
13. Yu T. The efficacy of colchicine prophylaxis in articular gout. A reappraisal after 20 years. Semin Arthritis Rheum 1982;12:256-64.
14. Harris MD, Siegel LB, Alloway JA. Gout and hyperuricemia. Am Fam Phys 1999;59:925-34.
15. Kot TV, Day RO, Brooks PM. Preventing acute gout when starting allopurinol therapy. Colchicine or NSAIDs? Med J Aust 1993;159:182-4.
16. Doornum S, Ryan PF. Clinical manifestations of gout and their management. Med J Aust 2000;172:493-7.
17. Terkeltaub R. Pathogenesis and treatment of crystal-induced inflammation. In: Koopman WJ, editor. Arthritis and allied conditions. 14th ed. Philadelphia: Lippincott Williams and Wilkins; 2001:2339-40.
18. Wortmann RL, Kelley WN. Gout and hyperuricemia. In: Ruddy S, Harris ED, Sledge CB, editors. Kelley's textbook of rheumatology. 6th ed. Phildadelphia: W.B. Saunders; 2001:1367-8.
19. Cohen MG, Emmerson BT. Gout. In: Klippel JH, Dieppe PA, editors. Rheumatology. London: Mosby–Year Book Europe Limited; 1994:7.12.1-16.
20. Stuart RA, Gow PJ, Bellamy N, Campbell J, Grigor R. A survey of current prescribing practices of anti-inflammatory and urate-lowering drugs in gouty arthritis. NZ Med J 1991;104:115-17.
21. Bellamy N, Gilbert JR, Brooks PM, Emmerson BT, Campbell J. A survey of current prescribing practices of anti-inflammatory and urate lowering drugs in gouty arthritis in the Province of Ontario. J Rheumatol 1988;15:1841-7.
22. Bellamy N, Brooks PM, Emmerson BT, Gilbert JR, Campbell J, McCredie M. A survey of current prescribing practices of anti-inflammatory and urate-lowering drugs in gouty arthritis in New South Wales and Queensland. Med J Aust 1989;151:531-2, 535-7.
23. Wallace SL, Singer JZ, Duncan GJ, Wigley FM, Kuncl RW. Renal function predicts colchicine toxicity: Guidelines for the prophylactic use of colchicine in gout. J Rheumatol 1991;18:264-9.
24. Kuncl RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M. Colchicine myopathy and neuropathy. N Engl J Med 1987;316:1562-8.
25. Ferraz MB. An evidence based appraisal of the management of nontophaceous interval gout. J Rheumatol 1995;22:1618-20.