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High Versus Low Dosing of Oral Colchicine for Early Acute Gout Flare

Twenty-Four–Hour Outcome of the First Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Comparison Colchicine Study

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Objective. **Despite widespread use of colchicine, the evidence basis for oral colchicine therapy and dosing in acute gout remains limited. The aim of this trial was to compare low-dose colchicine (abbreviated at 1 hour) and high-dose colchicine (prolonged over 6 hours) with placebo in gout flare, using regimens producing comparable maximum plasma concentrations in healthy volunteers.**

Methods. **This multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared self-administered low-dose colchicine (1.8 mg total over 1 hour) and high-dose colchicine (4.8 mg total over 6 hours) with placebo. The primary end point was ≥50% pain reduction at 24 hours without rescue medication.**

Results. **There were 184 patients in the intent-to-treat analysis. Responders included 28 of 74 patients (37.8%) in the low-dose group, 17 of 52 patients (32.7%) in the high-dose group, and 9 of 58 patients (15.5%) in the placebo group ($P = 0.005$ and $P = 0.034$, respectively, versus placebo). Rescue medication was taken within the first 24 hours by 23 patients (31.1%) in the low-dose group ($P = 0.027$ versus placebo), 18 patients (34.6%) in the high-dose group ($P = 0.103$ versus placebo), and 29 patients (50.0%) in the placebo group. The low-dose group had an adverse event (AE) profile similar to that of the placebo group, with an odds ratio (OR) of 1.5 (95% confidence interval [95% CI] 0.7–3.2). High-dose colchicine was associated with significantly more diarrhea, vomiting, and other AEs compared with low-dose colchicine or placebo. With high-dose colchicine, 40 patients (76.9%) had diarrhea (OR 21.3 [95% CI 7.9–56.9]), 10 (19.2%) had severe diarrhea, and 9 (17.3%) had vomiting. With low-dose colchicine, 23.0% of the patients had diarrhea (OR 1.9 [95% CI 0.8–4.8]), none had severe diarrhea, and none had vomiting.**

Conclusion. **Low-dose colchicine yielded both maximum plasma concentration and early gout flare efficacy comparable with that of high-dose colchicine,**

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with a safety profile indistinguishable from that of placebo.

Colchicine is mainly used in the treatment and prophylaxis of gout flare, although the evidence basis for its use in treating acute gout flare remains remarkably limited. Only 1 randomized, placebo-controlled trial (n = 43) exploring colchicine in gout flare has previously been reported (1). The regimen in that study was two 0.5-mg tablets followed by one tablet every 2 hours until relief or marked toxicity (such as diarrhea, nausea, or vomiting) occurred (1). Patients received a mean dose of 6.7 mg colchicine (1). Colchicine demonstrated statistical superiority over placebo in pain reduction in 48 hours, but diarrhea developed in 100% of colchicine recipients by the time of clinical response (1).

High-dose (or prolonged) colchicine regimens, such as the one described by Ahern et al (1), are commonly prescribed for acute gout (2) despite a high risk-to-benefit ratio (3–6). Lower-dose (or abbreviated) regimens of colchicine have been suggested (5,7,8) but never rigorously studied.

The AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study compared low- and high-dose colchicine using a randomized, placebo-controlled design. A list of clinical investigators in the AGREE trial is provided in Appendix A. Pharmacokinetic profiles of the high- and low-dose regimens were previously obtained in healthy volunteers and demonstrated comparable maximum blood concentrations (C_{max}). The self-administered high-dose prolonged colchicine regimen (4.8 mg total over 6 hours) was selected to mimic common practice (1,2) and was compared with a placebo and a novel low-dose abbreviated regimen (1.8 mg total over 1 hour). The results at the primary 24-hour end point demonstrate superior safety of low-dose colchicine, without loss of efficacy, relative to high-dose colchicine for early acute gout flare (self-administered within 12 hours of flare onset).

PATIENTS AND METHODS

Characterization of colchicine pharmacokinetics. Prior to the AGREE trial, the pharmacokinetics of low-dose colchicine (1.2 mg followed by 0.6 mg in 1 hour [1.8 mg total]), "high-dose" colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours [4.8 mg total]), and single-dose (0.6 mg) colchicine were evaluated in healthy volunteers who had fasted. None of these healthy volunteers participated in the AGREE trial. Colchicine, United States Pharmacopeia (USP) 0.6-mg tablets (Colcrys), was provided by URL Pharma (Philadelphia, PA). Pharmacokinetic sampling occurred over 96 hours. Analytic data from the samples were used to calculate C_{max}, area under the curve $(AUC)_{0-\infty}$, and terminal half-life. Statistical analyses were performed using WinNonlin software, version 5.0.1 (Pharsight, St. Louis, MO).

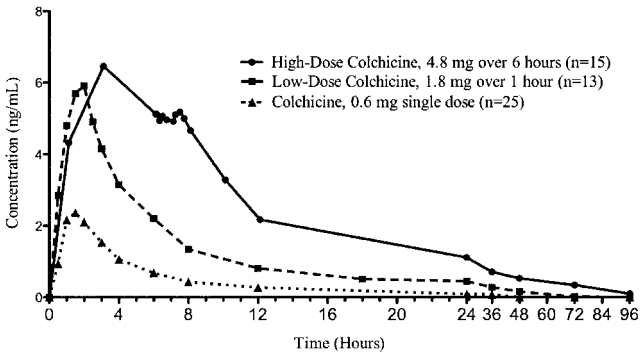

Figure 1. Pharmacokinetic properties of low-dose, high-dose, and single-dose colchicine in healthy normal volunteers. Peak blood concentrations were similar in the low- and high-dose colchicine groups, while total colchicine exposure (area under the curve from zero to infinity) was proportional to the total colchicine dose received. Values are the mean.

Peak blood levels (C_{max}) for single-dose, low-dose, and high-dose colchicine were 2.5, 6.19, and 6.84 ng/ml, respectively, in healthy volunteers, and exposure to colchicine ($AUC_{0-\infty}$) was 14.1, 52.1, and 118.2 nanograms $\times$ hours/ml, respectively. The terminal half-lives for single-dose, low-dose, and high-dose colchicine were 6.36, 23.6, and 31.4 hours, respectively (Figure 1).

AGREE study population. Male and postmenopausal female patients $\geq$18 years of age with a confirmed past diagnosis of gout (according to the American College of Rheumatology [ACR] classification criteria [9]) and having had $\geq$2 gout flares within the prior 12 months were eligible for randomization. A stable regimen of urate-lowering therapy was permitted. A total of 575 patients were randomized to 1 of 3 treatment groups: 1) "low-dose" colchicine (1.2 mg followed by 0.6 mg in 1 hour followed by placebo doses every hour for 5 hours [1.8 mg total]), 2) "high-dose" colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours [4.8 mg total]), or 3) placebo (2 placebo capsules initially, followed by 1 placebo capsule every hour for 6 hours).

AGREE study design. This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study conducted between April 2007 and October 2008. A total of 54 centers in the US randomized and reported at least 1 patient with a gout flare. Overencapsulated (to preserve double-blindedness) colchicine (USP 0.6-mg tablets [Colcrys]) and matching overencapsulated (to preserve double-blindedness) placebo were provided by URL Pharma.

A key aspect of the study design was that patients were enrolled and were dispensed a double-blinded blister card of study medication, at screening, prior to the onset of a gout flare. Patients were required to call the Gout Flare Call Center before taking study medication. This center was staffed 24 hours a day by medically trained personnel (e.g., nurses). Upon clearance from the Gout Flare Call Center, patients were

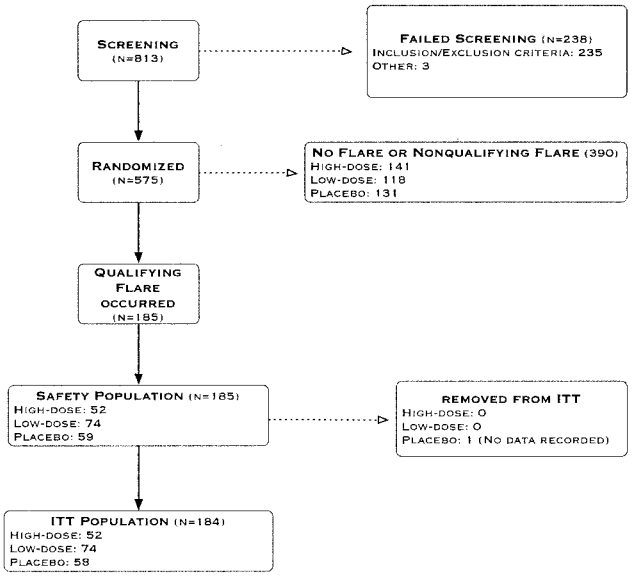

Figure 2. AGREE (Acute Gout Flare Receiving Colchicine Evaluation) patient flow diagram. ITT = intent-to-treat.

instructed to take all of the study medication, regardless of pain status. A standard script was used to confirm that flare onset was within the prior 12 hours (study drug must have been started within 12 hours of flare onset), that 4 cardinal signs of inflammation were present, that joint pain was assessed at ≥4 on a 0–10 numeric rating scale, and that there had been no use of prohibited medication or change in medical history since randomization. The patient was specifically asked about the presence of nausea, vomiting, diarrhea, and abdominal pain every time the patient rated pain, along with an open-ended question about other adverse events (AEs).

The patient was also supplied with a standardized diary to track pain, symptoms, AEs, and rescue medication use. Patients rated intensity of joint pain on an 11-point Likert scale that ranged from 0 (no pain) to 10 (worst possible pain). Ratings were to be made at baseline, then hourly for the first 8 hours and every 8 hours thereafter (while awake) until 72 hours following the initial dose or symptom resolution. The 24-hour time point was mandatory. Patients were permitted to stop study medication due to AEs. Rescue medication (individualized to each patient by his or her study physician, e.g., nonsteroidal antiinflammatory drugs [NSAIDs]) was permitted if intolerable pain continued after taking at least 1 dose of study drug. Uric acid–lowering therapy was not to be discontinued at the onset of flare.

Patients were to return to the study clinic as soon as possible following the onset of the flare, with the target for the first postflare visit being within 48 hours. After flare onset, there were up to 3 more planned visits, the last being 7 days after flare onset. Safety was assessed by monitoring AEs and vital signs as well as by physical examinations and laboratory tests at scheduled visits. At the first postflare visit, blister cards were examined, and the number of remaining pills, if any, was recorded. The study physician also reviewed the patient's diary and recorded pertinent information on standardized case report forms.

The intensity of AEs was graded as mild, moderate, or severe based on the study physicians' clinical judgment. Established US Food and Drug Administration (FDA) criteria were used to define serious AEs (10). No data-monitoring safety board or any other unblinded oversight committee was used in this study.

Ethics. All patients provided written informed consent and signed the Health Insurance Portability and Accountability Act of 1996 Authorization Form. The study was performed in accordance with good clinical practice standards and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996. The study was reviewed, and approval was provided by the central ethics review board (Sterling Institutional Review Board). The study complied with the requirements set forth in International Conference on Harmonisation guidelines and in FDA regulations outlined in 21 CFR Part 56.

AGREE statistical analysis and end points. The primary end point was the proportion of patients who responded to treatment. Responders were defined as having a pretreatment pain score within 12 hours of flare onset and a ≥50% reduction in pain within 24 hours of the first dose of study medication without the use of rescue medication during that time frame.

The primary analysis compared the proportion of responders in the high-dose colchicine and placebo groups (using an unstratified Pearson chi-square test due to sites not having patients in all treatment groups). Comparison of low-dose colchicine with placebo was declared a priori a secondary outcome measure. Additional alternate definitions of response including 1) treatment response based on the target joint pain score 32 hours after the first dose, 2) treatment response based on at least a 2-unit reduction in the target joint pain score 24 hours after the first dose, and 3) treatment response based on at least a 2-unit reduction in the target joint pain score 32 hours after the first dose were declared a priori secondary outcome measures.

Proportions of responders (using the primary efficacy end point definition) were compared using the unstratified chi-square test by generating the 95% confidence interval (95% CI) around the mean values for the effect of age (<45, 45–65, or >65 years), serum urate (≤7 versus >7 mg/dl), allopurinol use, diuretic use, time since first diagnosis of gout (less than the median duration versus greater than or equal to the median duration), number of flares within the last 12 months (≤3 versus >3), admitted alcohol use, and creatinine clearance. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the AGREE study subjects. A total of 813 patients were screened, and 575 patients were randomized into the trial. Of those, 185 patients had an eligible gout flare and took study medication (safety population); 52 patients received high-dose colchicine, 74 patients received low-dose colchicine, and 59

Table 1. Baseline characteristics of the patients (safety population, n = 185)*

	High-dose colchicine (n = 52)	Low-dose colchicine (n = 74)	Placebo (n = 59)	Overall (n = 185)
Demographics				
Age, mean ± SD years	51.9 ± 10.02	51.4 ± 11.79	51.2 ± 11.36	51.5 ± 11.12
Men	49 (94.2)	72 (97.3)	55 (93.2)	176 (95.1)
Race				
American Indian/Alaska Native	0 (0)	1 (1.4)	0 (0)	1 (0.5)
Asian	0 (0)	1 (1.4)	1 (1.7)	2 (1.1)
Black/African American	10 (19.2)	4 (5.4)	11 (18.6)	25 (13.5)
White/Caucasian	40 (76.9)	66 (89.2)	47 (79.7)	153 (82.7)
Other	2 (3.8)	2 (2.7)	0 (0)	4 (2.2)
History of gout				
Age at onset, mean ± SD years	40.7 ± 11.83	40.7 ± 12.38	41.6 ± 13.20	41.0 ± 12.44
Attacks in the year prior to screening, mean ± SD	4.7 ± 3.28	4.4 ± 2.24	3.8 ± 2.02	4.3 ± 2.52
Time since most recent flare, mean ± SD months	1.4 ± 1.44	1.6 ± 1.36	1.7 ± 1.84	1.6 ± 1.55
Urate concentration, mean ± SD mg/dl	9.2 ± 1.7	8.5 ± 1.8	8.9 ± 1.9	8.8 ± 1.8
Concurrent allopurinol use	10 (19.2)	29 (39.2)	15 (25.4)	54 (29.2)
Presence of ≥1 tophi	7 (14)	5 (7)	5 (9)	17 (9)
Previously met ACR preliminary criteria for acute gout	52 (100)	74 (100)	59 (100)	185 (100)
Body weight, mean ± SD lb	228 ± 38.10	228 ± 42.44	228 ± 41.69	228 ± 40.80
BMI, mean ± SD kg/m^2	32.9 ± 4.63	33.2 ± 6.27	32.8 ± 5.82	33.0 ± 5.68

* Except where indicated otherwise, values are the number (%) of patients. ACR = American College of Rheumatology; BMI = body mass index.

patients received placebo. All but 1 patient (n = 184) had a flare confirmed by the Gout Flare Call Center (intent-to-treat population) (Figure 2). Demographic and gout characteristics were similar among the 3 treatment groups. The majority of patients were overweight white men ~50 years of age with an elevated serum urate concentration and a 10-year history of gout. Less than one-third of patients were receiving concurrent urate-lowering therapy at the start of the study. No patient started or altered urate-lowering therapy during the study. Tophi were present in ~9% of patients (Table 1). According to investigator assessment, 94.6% of patients were compliant with taking their study medication.

Findings of the AGREE efficacy evaluation. Both colchicine regimens were significantly more effective than placebo, with 17 responders (32.7%) in the high-dose group, 28 responders (37.8%) in the low-dose group, and 9 responders (15.5%) in the placebo group ($P = 0.034$ and $P = 0.005$, respectively, versus placebo). Alternate definitions of response were declared a priori secondary outcome measures (Table 2). The percent of responding patients was proportionally greater in the low-dose group compared with that in the high-dose and placebo groups across the entire pain improvement range (Figure 3).

Most rescue medications used in this trial were NSAIDs, with indomethacin predominating. Rescue medication was taken within the first 24 hours by 23 patients (31.1%) in the low-dose colchicine group, 18 patients (34.6%) in the high-dose colchicine group, and 29 patients (50.0%) in the placebo group. These patients were considered nonresponders. Compared with patients receiving placebo, significantly fewer patients in the low-dose colchicine group (odds ratio [OR] 0.45 [95% CI 0.22–0.92], $P = 0.027$) took rescue medication prior to hour 24. Fewer patients in the high-dose colchicine group than in the placebo group (OR 0.53 [95% CI 0.25–1.14]) took rescue medication prior to hour 24, although the difference did not reach statistical significance ($P = 0.103$).

The computation of the OR (95% CI) for confounding bias did not detect differences in any of the prespecified parameters that included demographics (age, sex, or race) or other baseline characteristics (concomitant use of allopurinol or diuretics, time since first diagnosis of gout, number of flares within the past 12 months, or alcohol use) associated with the proportion of patients who met response criteria at 24 hours. Although serum urate levels chosen a priori (≤7 versus >7 mg/dl) showed no confounding bias, post hoc exploratory analysis showed that patients with a serum urate level >10.0 mg/dl at screening were less likely to be responders compared with patients with a serum urate level ≤10 mg/dl (OR 0.29 [95% CI 0.12–0.74]).

Findings of the AGREE safety evaluation. There were no deaths, serious AEs, or patient withdrawals due to AEs in this study. All AEs in the low-dose group were mild to moderate in intensity, while 19.2% of the

Table 2. Efficacy analysis (intent-to-treat population, n = 184)*

	Colchicine dose			High-dose colchicine vs. placebo		Low-dose colchicine vs. placebo	
	High (n = 52)	Low (n = 74)	Placebo (n = 58)	OR (95% CI)	*P*	OR (95% CI)	*P*
Primary end point							
Treatment response based on target joint pain score 24 hours after the first dose	17 (32.7)	28 (37.8)	9 (15.5)	2.64 (1.06–6.62)	0.034	3.31 (1.41–7.77)	0.005
Alternate definition of response							
Treatment response based on target joint pain score 32 hours after the first dose	19 (36.5)	31 (41.9)	10 (17.2)	2.76 (1.14–6.69)	0.022	3.46 (1.52–7.88)	0.002
Treatment response based on at least a 2-unit reduction in target joint pain score 24 hours after the first dose	18 (34.6)	32 (43.2)	10 (17.2)	2.54 (1.04–6.18)	0.037	3.66 (1.61–8.32)	0.002
Treatment response based on at least a 2-unit reduction in target joint pain score 32 hours after the first dose	20 (38.5)	34 (45.9)	10 (17.2)	3.00 (1.24–7.24)	0.012	4.08 (1.80–9.27)	0.001

* Values are the number (%) of responding patients. The primary end point was the proportion of patients who responded to treatment. Responders were defined as having a pretreatment pain score within 12 hours of flare onset and a ≥50% reduction in pain within 24 hours of the first dose of study medication without the use of rescue medication during that time frame. Both low-dose and high-dose colchicine regimens were significantly more effective than placebo in terms of proportions of responders. Using a priori alternate definitions of response did not alter the findings. OR = odds ratio; 95% CI = 95% confidence interval.

high-dose group had AEs of severe intensity, all of which were diarrhea.

The overall AE rates for the high-dose, low-dose, and placebo groups were 76.9%, 36.5%, and 27.1%, respectively. AEs occurred in a much greater proportion of patients taking high-dose colchicine compared with low-dose colchicine or placebo. Incidences of side effects in the low-dose colchicine and placebo groups were similar.

The most common AE was diarrhea, occurring in

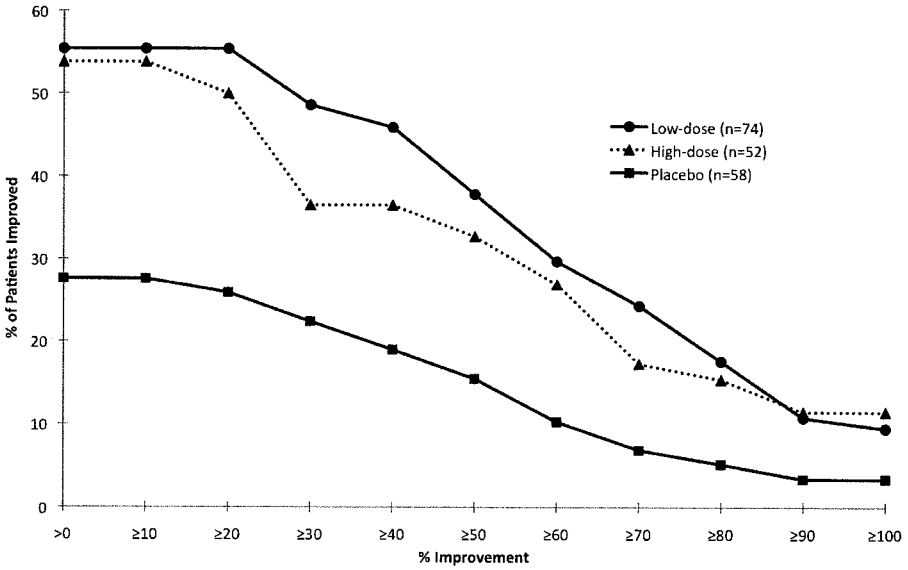

Figure 3. Distribution of percent improvement (intent-to-treat [ITT] population, n = 184). Shown is the percent of patients who improved in each category of percent improvement for the pain score 24 hours after the initial dose of study medication (ITT population).

Table 3. Incidence of most frequent adverse events (safety population, n = 185)*

	Colchicine dose			OR (95% CI)		
	High (n = 52)	Low (n = 74)	Placebo (n = 59)	High-dose colchicine vs. placebo	Low-dose colchicine vs. placebo	High-dose colchicine vs. low-dose colchicine
Adverse events	40 (76.9)	27 (36.5)	16 (27.1)	9.0 (3.8–21.2)†	1.5 (0.7–3.2)‡	5.8 (2.6–12.9)†
Gastrointestinal adverse events	40 (76.9)	19 (25.7)	12 (20.3)	13.1 (5.3–32.3)†	1.4 (0.6–3.1)‡	9.6 (4.2–22.1)†
Diarrhea (all occurrences)	40 (76.9)	17 (23.0)	8 (13.6)	21.3 (7.9–56.9)†	1.9 (0.8–4.8)‡	11.2 (4.8–25.9)†
Nausea (all occurrences)	9 (17.3)	3 (4.1)	3 (5.1)	3.9 (1.0–15.3)‡	0.8 (0.2–4.1)‡	5.0 (1.3–19.3)†
Vomiting (all occurrences)	9 (17.3)	0 (0)	0 (0)	–§	–§	–§
Severe intensity adverse events¶	10 (19.2)	0 (0)	1 (1.7)	13.8 (1.7–112)†	–§	–§
Diarrhea (only severe intensity)	10 (19.2)	0 (0)	0 (0)	–§	–§	–§
Melena (only severe intensity)	1 (1.92)	0 (0)	0 (0)	–§	–§	–§
Nausea (only severe intensity)	1 (1.92)	0 (0)	0 (0)	–§	–§	–§
Gout (only severe intensity)	0 (0)	0 (0)	1 (1.7)	–§	–§	–§
Serious adverse events#	0 (0)	0 (0)	0 (0)	–§	–§	–§

* Values are the number (%) of patients.
† Statistically significant difference (1 is not encompassed by 95% confidence interval [95% CI] of the odds ratio [OR]).
‡ No statistically significant difference (1 is encompassed by 95% CI of the OR).
§ OR could not be calculated since zero events occurred in at least 1 treatment group.
¶ Severity of adverse events (mild, moderate, and severe) was determined by a blinded study physician.
# As defined by Title 21, Code of Federal Regulations, Volume 5, Section 312, Part 32; Revised April 1, 2002.

76.9% of the high-dose group, 23.0% of the low-dose group, and 13.6% of the placebo group. Nausea occurred in 17.3%, 4.1%, and 5.1% of the high-dose, low-dose, and placebo groups, respectively. Vomiting was reported in 17.3% of patients in the high-dose group but did not occur in the low-dose or placebo group. In the high-dose group, 40 patients (76.9%) reported diarrhea, and 10 patients (19.2%) experienced severe diarrhea, whereas no patient in the low-dose or placebo group reported severe diarrhea (Table 3). The risk of experiencing gastrointestinal events was similar when demographic characteristics, concomitant allopurinol use, or estimated creatinine clearance was compared.

DISCUSSION

This is the first report of the pharmacokinetic profile of low- and high-dose colchicine regimens for the treatment of gout flare. The high-dose regimen had a >2-fold colchicine exposure compared with the low-dose regimen; significantly, however, in view of the clinical results, both treatment regimens achieved similar peak blood levels in healthy volunteers. Based on the results of the pharmacokinetic and AGREE studies, it appears that achieving a peak blood colchicine level of ~6 ng/ml provides significant reduction in pain associated with early gout flare. Increasing total colchicine exposure by using doses >1.8 mg over 1 hour ($AUC_{0-\infty}$ of 43.8 nanograms × hours/ml) may lead to increased side effects without additional clinical benefit. Further studies correlating colchicine blood levels, colchicine cellular concentrations (e.g., in neutrophils and endothelial cells), and clinical outcome are warranted.

The AGREE trial is the first placebo-controlled comparison of low-dose and high-dose colchicine in the treatment of acute gout flares. Results showed that self-administered low-dose colchicine is just as effective as high-dose colchicine in reducing pain associated with early acute gout flare, defined as occurring within 12 hours of onset. The side-effect profile of low-dose colchicine was comparable with that of placebo.

The benefit of treating acute gout flares with low-dose colchicine extends beyond a dramatic reduction in gastrointestinal side effects. This regimen should reduce potential drug–drug interactions known to be strongly correlated with reported colchicine toxicity. P-glycoprotein and cytochrome P450 (CYP) 3A4 mediate the metabolism and elimination of colchicine (11). Severe AEs and deaths have been reported when colchicine is combined with strong inhibitors of both P-glycoprotein and CYP 3A4 (e.g., clarithromycin [12,13] and erythromycin [14]) or with strong P-glycoprotein inhibitors (e.g., cyclosporine [13,15–18]). Drug interaction studies show that colchicine blood levels triple when combined with strong inhibitors of CYP 3A4 or with P-glycoprotein inhibitors (13,19). Importantly, the low-dose regimen used in this study exposes patients to two-thirds less colchicine than do the traditional higher-dose regimens (1). Therefore, low-

dose colchicine in a patient population likely to use multiple concomitant drugs adds a safety margin without compromising efficacy. Further studies are warranted to optimize colchicine dosing with selected concomitant medications.

The AGREE trial was designed to evaluate the efficacy and safety of colchicine as typically administered in community practice. As such, colchicine was self-administered within 12 hours of symptom onset, and this study shows that therapy may be optimized by employing the low-dose regimen described herein. Additional studies are needed to determine whether treatment start time, concomitant urate-lowering therapy, extent of tophaceous crystal deposits, sites of arthritis, renal function, or other doses affect efficacy or safety.

In the AGREE trial, the primary end point was ≥50% pain reduction in 24 hours. A 50% reduction of baseline pain, which is considered clinically significant (20–22), was used in the original colchicine efficacy trial (1) and continues to be a standard for measuring efficacy in current acute gout studies (23). Patients who took rescue medication within the first 24 hours after taking the study drug, regardless of their intent, were not classified as responders. In acute gout trials with NSAIDs (24–26) or prednisone (26), the primary end point has been therapy for ≥48 hours. Confounding concomitant use of colchicine was allowed in some of these trials (24,25), with some investigators not specifying its use. Regardless, the typical pain response of acute gout to NSAIDs does not reach complete resolution within the first 72 hours; in general, pain is reduced from excruciating to bearable. For example, in a recent trial comparing etoricoxib with indomethacin, the mean pain reduction from maximum was only ~30% at 24 hours, and 50% pain reduction was achieved only at 48–72 hours (25).

Comparisons between the AGREE trial results and those from previous gout trials with NSAIDs, corticosteroids, or high-dose colchicine (1,24–28) are limited by several factors. Specifically, direct comparisons are precluded by dissimilar patient cohorts, allowing confounding concomitant medication, treatment randomized and given in a research center rather than prerandomization to self-treatment regimens, different end points, and longer durations of the active gout flare prior to treatment than the 12-hour time point assessed in the AGREE trial. Nevertheless, low-dose colchicine treatment may have advantages over NSAIDs or steroids in certain populations, such as gout patients with renal, gastrointestinal, or endocrine comorbidities that disfavor or prevent the use of these medications. A randomized, placebo-controlled trial comparing colchicine, corticosteroids, and NSAIDs would be valuable. The possibility that low-dose colchicine therapy may be enhanced with concomitant use of corticosteroids, NSAIDs, or other agents also needs to be explored.

All patients in this trial previously met the ACR preliminary criteria for the classification of the acute arthritis of primary gout (9). Our study focused on the first 24 hours of a single gout flare. A critical feature of our design was the attempt to overcome the ethical issues of using a placebo control by limiting the time (1 day) that a patient in the placebo group would be untreated. A 7-day active comparator, non–placebo-controlled trial against NSAIDs and corticosteroids would allow comparisons with other studied treatment regimens (24–26). This proposed active comparator, non–placebo-controlled design would also give adequate time to evaluate changes from baseline in quality of life, joint function, physician global assessments, and effectiveness at days 2–7. Additional colchicine studies are needed to determine whether concomitant urate-lowering therapy, extent of tophaceous crystal deposits, location of gout flare, renal function, or other dose regimens affect efficacy or safety.

In conclusion, the results of the AGREE trial provide the first evidence basis, after centuries of colchicine use, for low-dose colchicine therapy in the treatment of early acute gout flare. The low-dose colchicine regimen maintained efficacy equivalent to that of high-dose colchicine. It had a side effect profile significantly better than that of high-dose colchicine and comparable with that of placebo. The results are consistent with recent, expert opinion–based European League Against Rheumatism recommendations (8) and support an immediate change in clinical practice from a high-dose colchicine regimen to a low-dose colchicine regimen for treatment of early gout flare.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terkeltaub had full access to all

of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

URL Pharma funded the study and choose United BioSource Corporation to be the Contract Research Organization to run the study. Dr. Davis is the Chief Medical Officer for URL Pharma and had key roles in the study design, data collection, data analysis, and writing of the manuscript. Prior to the start of the study, URL Pharma agreed that the authors had full rights to submit the manuscript for publication, URL Pharma approval of the content of the submitted manuscript was not required, and publication of the manuscript was not contingent upon the approval of URL Pharma. The authors had full access to all data, and Dr. Terkeltaub made the final editorial decisions.

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