A Randomized Trial of Colchicine for Acute Pericarditis

Massimo Imazio, M.D., Antonio Brucato, M.D., Roberto Cemin, M.D.,
Stefania Ferrua, M.D., Stefano Maggiolini, M.D., Federico Beqaraj, M.D.,
Daniela Demarie, M.D., Davide Forno, M.D., Silvia Ferro, M.D.,
Silvia Maestroni, M.D., Riccardo Belli, M.D., Rita Trinchero, M.D.,
David H. Spodick, M.D., and Yehuda Adler, M.D., for the ICAP Investigators*

ABSTRACT

From the Cardiology Department, Maria Vittoria Hospital, Turin (M.I., F.B., D.D., D.F., S.F., R.B., R.T.), the Internal Medicine Department, Ospedale Papa Giovanni XXIII, Bergamo (A.B., S. Maestroni), the Cardiology Department, San Maurizio Regional Hospital, Bolzano (R.C.), the Cardiology Department, Ospedale degli Infermi, Rivoli (S.F.), and the Cardiovascular Department, S. Leopoldo Mandic Hospital, Merate (S. Maggiolini) — all in Italy; the Internal Medicine Department, St. Vincent Hospital, Worcester, MA (D.H.S.); and Chaim Sheba Medical Center, Tel Hashomer and Sacker Faculty of Medicine, Tel Aviv, Israel (Y.A.). Address reprint requests to Dr. Imazio at the Cardiology Department, Maria Vittoria Hospital, Via Luigi Cibrario 72, 10141 Turin, Italy, or at massimo_imazio@yahoo.it.

*A full list of trial investigators and committees in the Investigation on Colchicine for Acute Pericarditis (ICAP) study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 1, 2013, at NEJM.org.

BACKGROUND

Colchicine is effective for the treatment of recurrent pericarditis. However, conclusive data are lacking regarding the use of colchicine during a first attack of acute pericarditis and in the prevention of recurrent symptoms.

METHODS

In a multicenter, double-blind trial, eligible adults with acute pericarditis were randomly assigned to receive either colchicine (at a dose of 0.5 mg twice daily for 3 months for patients weighing >70 kg or 0.5 mg once daily for patients weighing ≤70 kg) or placebo in addition to conventional antiinflammatory therapy with aspirin or ibuprofen. The primary study outcome was incessant or recurrent pericarditis.

RESULTS

A total of 240 patients were enrolled, and 120 were randomly assigned to each of the two study groups. The primary outcome occurred in 20 patients (16.7%) in the colchicine group and 45 patients (37.5%) in the placebo group (relative risk reduction in the colchicine group, 0.56; 95% confidence interval, 0.30 to 0.72; number needed to treat, 4; P<0.001). Colchicine reduced the rate of symptom persistence at 72 hours (19.2% vs. 40.0%, P=0.001), the number of recurrences per patient (0.21 vs. 0.52, P=0.001), and the hospitalization rate (5.0% vs. 14.2%, P=0.02). Colchicine also improved the remission rate at 1 week (85.0% vs. 58.3%, P<0.001). Overall adverse effects and rates of study-drug discontinuation were similar in the two study groups. No serious adverse events were observed.

CONCLUSIONS

In patients with acute pericarditis, colchicine, when added to conventional antiinflammatory therapy, significantly reduced the rate of incessant or recurrent pericarditis. (Funded by former Azienda Sanitaria Locale 3 of Turin [now Azienda Sanitaria Locale 2] and Acarpia; ICAP ClinicalTrials.gov number, NCT00128453.)

COLCHICINE HAS BEEN USED FOR CENTUries to treat and prevent gouty attacks[1] and more recently has been recommended to treat and prevent serositis in patients with familial Mediterranean fever and recurrent pericarditis.[2,3] Preliminary data from nonrandomized trials have also supported the use of colchicine for the treatment and prevention of acute pericarditis.[4] In a single-center, open-label, randomized trial, called the Colchicine for Acute Pericarditis (COPE) study, the addition of colchicine to conventional therapy with either aspirin or glucocorticoids halved the recurrence rate after an initial attack of acute pericarditis.[5] Our study, called the Investigation on Colchicine for Acute Pericarditis (ICAP), was a randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the efficacy and safety of colchicine to treat a first attack of acute pericarditis and to prevent recurrences.[6]

METHODS

STUDY DESIGN

The rationale, design, and methods of the study have been reported previously.[6] The trial was designed by the first author, and the design was approved by the steering committee and the ethics committee at each participating center. The data were gathered by all authors and were received, checked, and analyzed at the cardiology department of Maria Vittoria Hospital, Turin, Italy, after blinded adjudication of events. The first draft of the manuscript was written by the first author and revised by all authors. All the authors vouch for the accuracy and completeness of the data and the analyses and for the fidelity of this report to the trial protocol, available with the full text of this article at NEJM.org.

The study was supported by former Azienda Sanitaria Locale 3 of Turin (now Azienda Sanitaria Locale 2). Acarpia (Madeira, Portugal) provided colchicine and placebo as an unrestricted grant and had no role in the planning of the study, analysis of the data, or writing of this manuscript.

ELIGIBILITY CRITERIA

The study was conducted at five general hospitals in Northern Italy. Consecutive patients who were 18 years of age or older with a first episode of acute pericarditis (idiopathic, viral, after cardiac injury, or associated with connective-tissue disease) were eligible for enrollment. Acute pericarditis was diagnosed with at least two of the following criteria: typical chest pain (sharp and pleuritic, improved by sitting up and leaning forward), a pericardial friction rub, suggestive changes on electrocardiography (widespread ST-segment elevation or PR depression), and new or worsening pericardial effusion.[7-13]
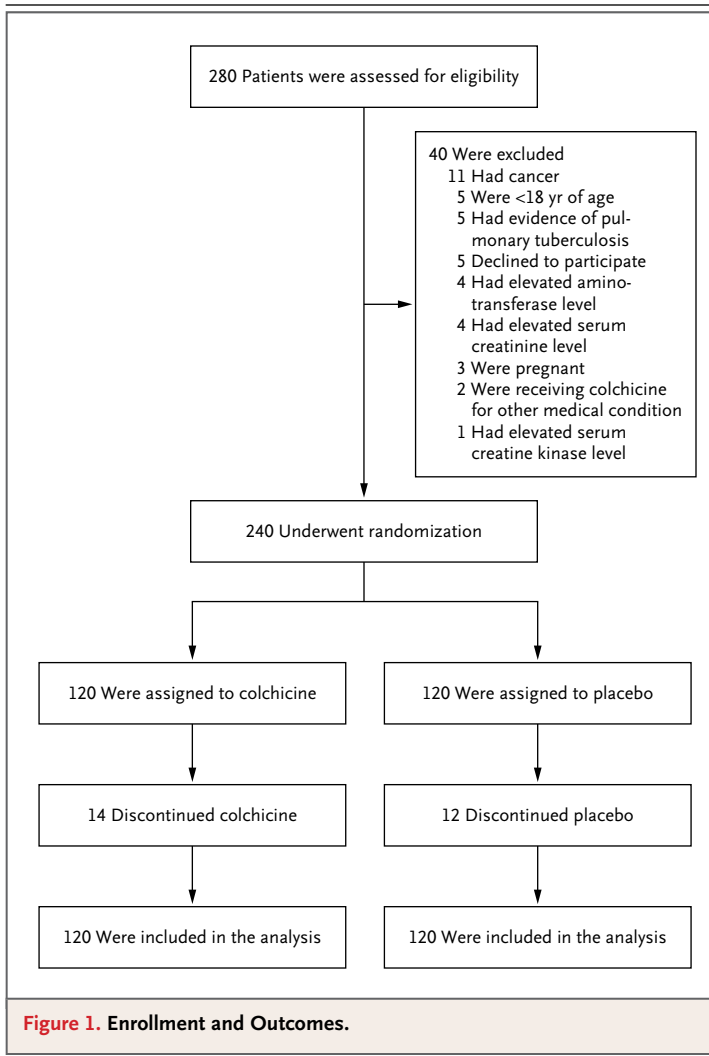
EXCLUSION CRITERIA

Patients with any of the following criteria were not eligible to participate in the trial: tuberculous, neoplastic, or purulent pericarditis; severe liver disease or current aminotransferase levels of more than 1.5 times the upper limit of the normal range; a serum creatinine level of more than 2.5 mg per deciliter (221 μmol per liter); skeletal myopathy or a serum creatine kinase level above the upper limit of the normal range; blood dyscrasia; inflammatory bowel disease; hypersensitivity to colchicine or other contraindication to its use; current treatment with colchicine; and life expectancy of 18 months or less. Pregnant or lactating women or women of childbearing potential who were not protected by a contraception method were also ineligible, as were patients with evidence of myopericarditis, as indicated by an elevation in the serum troponin level.[13] All patients provided written informed consent.

RANDOMIZATION AND STUDY-DRUG ADMINISTRATION

Patients were randomly assigned to receive colchicine or placebo in a 1:1 ratio with the use of a central computer-based automated sequence. Randomization was based on permuted blocks, with a block size of four. The random-assignment sequence was implemented with the use of sequentially numbered study-drug containers. All patients and investigators were unaware of study-group assignments.

Colchicine was administered at a dose of 0.5 to 1.0 mg daily for 3 months. The duration of colchicine therapy was based on previous studies (a small, nonrandomized study and an open-label, single-center trial).[4,5] The lower dose (0.5 mg daily) was given to patients weighing 70 kg or less and to those who had side effects at the higher dose (0.5 mg twice daily). Colchicine tablets contained

Figure 1. Enrollment and Outcomes.

1 mg of the active drug. All tablets (colchicine and placebo) were identical in color, shape, and taste and were premarked to allow splitting into two equal parts. Adherence to study-drug therapy was assessed on the basis of counts of pills in dispensed boxes, with a target of at least 80% adherence.

All patients also received conventional treatment for acute pericarditis. For most patients, this consisted of either 800 mg of aspirin or 600 mg of ibuprofen given orally every 8 hours for 7 to 10 days, followed by tapering during a period of 3 to 4 weeks. Glucocorticoid therapy (0.2 to 0.5 mg of prednisone per kilogram of body weight per day for 2 weeks with gradual tapering)[14] was administered to patients with contraindications to aspirin and ibuprofen (i.e., allergy, history of peptic

ulcer or gastrointestinal bleeding, or use of oral anticoagulant therapy when the bleeding risk was considered high or unacceptable) or a history of side effects. All patients received a proton-pump inhibitor for gastroduodenal prophylaxis.[10-12]

FOLLOW-UP AND OUTCOMES

We followed all patients for at least 18 months after enrollment. Regular visits were planned at 1 week, 1 month, 3 months, 6 months, 12 months, and every 6 months thereafter until the end of the study. Testing at each visit included blood chemical analyses (C-reactive protein, aminotransferases, creatinine, and creatine kinase), a complete blood count, an electrocardiogram, and an echocardiogram.

The primary study end point was incessant or recurrent pericarditis. Secondary end points were symptom persistence at 72 hours, remission within 1 week, number of recurrences, the time to the first recurrence, disease-related hospitalization, cardiac tamponade, and constrictive pericarditis. A clinical-end-point committee whose members were unaware of study-group assignments adjudicated all events.

Criteria for the diagnosis of recurrent pericarditis included a documented first attack of acute pericarditis, according to previously stated diagnostic criteria; a symptom-free interval of 6 weeks or longer; and evidence of subsequent recurrence of pericarditis. Patients with persistent pericarditis or those with a symptom-free interval of less than 6 weeks were given the diagnosis of incessant pericarditis.[15] Recurrence was documented by recurrent pain and one or more of the following signs: a pericardial friction rub, changes on electrocardiography, echocardiographic evidence of pericardial effusion, and an elevation in the white-cell count, erythrocyte sedimentation rate, or C-reactive protein level.[16] These criteria for recurrent pericarditis are based on previous studies, reviews, and expert opinion.[5,12,13,16] Patients were considered to have a remission when they were symptom-free with disappearance of clinical, electrocardiographic, and echocardiographic signs of disease.[11,12,16]

DATA MANAGEMENT

Investigators who were unaware of study-group assignments collected data using case-report and clinical-events forms, with adjudication by the clinical-end-point committee. During follow-up,

all adverse events were monitored and recorded. Unblinded data were made available to an independent data and safety monitoring board.

STATISTICAL ANALYSIS

We assumed a rate of incessant or recurrent pericarditis of 30% in the placebo group at 18 months[5,16] and estimated that colchicine could reduce the proportion of patients with incessant or recurrent pericarditis by half. With a two-sided alpha level of 0.05, a total enrollment of 240 patients was needed to attain a power of 80% to detect an absolute reduction of 15 percentage points in the proportion of patients with incessant or recurrent pericarditis in the colchicine group.

All analyses were performed on the basis of the intention-to-treat principle. Data were expressed as means and standard deviations. We used the Mann–Whitney test for continuous variables and the chi-square test for categorical variables. A two-sided P value of less than 0.05 was considered to indicate statistical significance. We used the Kaplan–Meier method to estimate time-to-event distributions, which were compared with the use of the log-rank test. Analyses were performed with SPSS software, version 13.0.

RESULTS

PATIENTS

Enrollment started in August 2005 and ended in December 2010. Follow-up continued through June 2012, with a predetermined stopping point providing a minimum of 18 months of follow-up for the primary outcome.

Study enrollment, randomization, and retention are shown in Figure 1. Of the 280 patients who were screened, 240 (85.7%) were enrolled; 120 patients were randomly assigned to each of the two study groups. The baseline demographic and clinical characteristics of the patients were similar in the two groups (Table 1). The mean age of the patients was 52.1±16.9 years, and 60% were male. Clinical signs and symptoms were consistent with previous findings from published unselected series of patients with acute pericarditis.[7-9]

There was more than 95% adherence to the study-drug regimen before the primary outcome was reached or the study was completed, and adherence rates did not differ significantly between the two study groups. All patients who tolerated treatment with colchicine or placebo discontinued therapy at 3 months, as planned. No open-label colchicine was administered after the end of the study period. No patient was lost to follow-up, and all patients were analyzed for outcomes according to the original study-group assignments. Patients were followed for an average of 22 months.

OUTCOMES

The main outcome results are reported in Table 2. The primary outcome of incessant or recurrent pericarditis occurred in 20 patients (16.7%) in the colchicine group and in 45 patients (37.5%) in the placebo group (relative risk reduction in the colchicine group, 0.56; 95% confidence interval

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=120)	Colchicine (N=120)
Age — yr	50.7±17.5	53.5±16.2
Male sex — no. (%)	74 (61.7)	71 (59.2)
Cause of pericarditis — no. (%)		
Idiopathic	93 (77.5)	92 (76.7)
Post–cardiac injury syndrome	23 (19.2)	25 (20.8)
Connective-tissue disease†	4 (3.3)	3 (2.5)
Clinical findings — no. (%)		
Pericarditic chest pain	119 (99.2)	120 (100.0)
Pericardial rub	38 (31.7)	44 (36.7)
ST-segment elevation	26 (21.7)	35 (29.2)
Pericardial effusion‡	82 (68.3)	76 (63.3)
Mild (<10 mm)	76 (63.3)	64 (53.3)
Moderate (10–20 mm)	2 (1.7)	9 (7.5)
Large (>20 mm)	4 (3.3)	3 (2.5)
Cardiac tamponade	2 (1.7)	2 (1.7)
Elevated C-reactive protein level	89 (74.2)	85 (70.8)
Medications — no. (%)		
Aspirin	96 (80.0)	86 (71.7)
Ibuprofen	18 (15.0)	24 (20.0)
Prednisone	6 (5.0)	10 (8.3)

* Plus–minus values are means ±SD. There were no significant differences between the two groups.
† Included in the category of connective-tissue disease are systemic lupus erythematosus in 4 patients, Sjögren's syndrome in 2 patients, and rheumatoid arthritis in 1 patient.
‡ Pericardial effusion was mild in 105 of 185 patients (56.8%) with an idiopathic cause of pericarditis and in 35 of 55 patients (64%) with other causes. Moderate or large effusions occurred in 14 of 185 patients (7.6%) with an idiopathic cause and in 4 of 55 patients (7%) with other causes.

[CI], 0.30 to 0.72; P<0.001). The number of patients who would need to have been treated to prevent one case of incessant or recurrent pericarditis was 4. The recurrence rate was 9.2% in the colchicine group and 20.8% in the placebo group (relative risk reduction, 0.56; 95% CI, 0.13 to 0.99; P=0.02; number needed to treat, 9). Kaplan–Meier survival curves for freedom from incessant or recurrent pericarditis are shown in Figure 2. Results were similar regardless of whether the concomitant antiinflammatory therapy was aspirin or ibuprofen (Table 2).

Colchicine also reduced the frequency of symptom persistence at 72 hours (19.2% vs. 40.0%, P=0.001), the number of recurrences per patient (0.21 vs. 0.52, P=0.001), and the rate of hospitalization related to pericarditis (5.0% vs. 14.2%, P=0.02). Colchicine also improved the rate of remission within 1 week (85.0% vs. 58.3%, P<0.001) and prolonged the time to first recurrence (24.7 weeks vs. 17.7 weeks, P<0.001). In multivariable analysis, independent risk factors for recurrences were the use of glucocorticoids (odds ratio, 4.17; 95% CI, 1.28 to 13.53; P=0.02) and C-reactive protein elevation at presentation (odds ratio, 3.15; 95% CI, 1.05 to 9.49; P=0.04).

ADVERSE EVENTS

The incidence and type of adverse events are reported in Table 3. The overall rates of adverse events were similar in the two study groups (11.7% in the colchicine group and 10.0% in the placebo group, P=0.84). Rates of study-drug discontinuation were also similar in the two groups (11.7% and 8.3%, respectively; P=0.52). A medical decision was the main cause of study-drug discontinuation in 21 of 24 patients (87.5%).

No serious adverse events were observed. Gastrointestinal disturbance was the main side effect and was reported with similar frequency in the two groups (9.2% in the colchicine group and 8.3% in the placebo group, P=0.67).

DISCUSSION

In this multicenter, double-blind, randomized trial, the use of colchicine in addition to conventional antiinflammatory therapy significantly reduced the rate of incessant or recurrent pericarditis, reduced the number of recurrences of pericarditis, and prolonged the time to recurrence, as compared with placebo. Most of the study patients were treated with aspirin and a smaller number with ibuprofen, and the results were consistent regardless of the concomitant background antiinflammatory therapy. Diarrhea was the major limiting side effect associated with colchicine and was reported in less than 10% of patients, and no serious adverse events were recorded.

The exact mechanism of benefit of colchicine

Table 2. Trial Outcomes.*			
Outcome	Placebo (N=120)	Colchicine (N=120)	P Value
Incessant or recurrent pericarditis: primary end point — no. (%)‡	45 (37.5)	20 (16.7)	<0.001†
Symptom persistence at 72 hr — no. (%)	48 (40.0)	23 (19.2)	0.001
Remission at 1 wk — no. (%)	70 (58.3)	102 (85.0)	<0.001
Incessant course — no. (%)	20 (16.7)	9 (7.5)	0.046
Recurrent course — no. (%)	25 (20.8)	11 (9.2)	0.02
No. of recurrences per patient	0.52±0.81	0.21±0.52	0.001
Time to first recurrence — wk	17.7±9.0	24.7±11.0	<0.001
Cardiac tamponade — no. (%)	3 (2.5)	0	0.25
Constrictive pericarditis — no. (%)	1 (0.8)	0	1.00
Pericarditis-related hospitalization — no. (%)	17 (14.2)	6 (5.0)	0.02
Mean follow-up — mo	22.3±8.7	22.9±8.7	0.61

* Plus–minus values are means ±SD.
† The P value was calculated by means of the log-rank test.
‡ The type of background antiinflammatory therapy had no significant effect on the proportions of patients with incessant or recurrent pericarditis.

in patients with pericarditis is not fully understood. The therapeutic effect seems to be related to its ability to disrupt microtubules and to concentrate in leukocytes, especially granulocytes, where its peak concentration may be more than 16 times the peak concentration in plasma, even at low oral doses, such as those used in this trial.[2,17]

Colchicine was recommended as a first-line treatment for recurrent pericarditis (class I indication) in the 2004 guidelines of the European Society of Cardiology regarding the management of pericardial diseases[18] on the basis of small, nonrandomized studies and on expert consensus. In 2005, an open-label, randomized trial, the Colchicine for Recurrent Pericarditis (CORE) study, showed a benefit of colchicine in the treatment of recurrent pericarditis.[19] This was followed by the report of the multicenter, double-blind Colchicine for Recurrent Pericarditis (CORP) trial[16] and a subsequent meta-analysis[3] supporting the use of colchicine in such patients.

These trials, however, did not address the use of colchicine for the initial attack of acute pericarditis. Among such patients, the cause of the disease is different from recurrent pericarditis. There is evidence that cases of recurrent pericarditis are immune-mediated, and colchicine may help to disrupt the inflammatory cycle involved in its pathogenesis.[20,21] In contrast, acute pericarditis often has an infectious cause that is presumed to be viral in most patients in developed countries.[10-12,22] In such cases, the interference of colchicine with white-cell function may theoretically be deleterious for the clearance of the infectious agent. Given these differences in pathogenesis, the efficacy and safety of colchicine in acute pericarditis require separate confirmation.

The 2004 European guidelines gave the use of colchicine in acute pericarditis a class IIa indication.[18] The subsequent COPE trial was a single-center, open-label, randomized trial that suggested a benefit of colchicine in acute pericarditis.[5] Our study now confirms these preliminary findings with the stronger evidence provided by a multicenter, double-blind trial and a larger number of cases.

Current guidelines recommend colchicine doses of 2 mg per day for 1 to 2 days, followed by a maintenance dose of 1 mg per day.[18] However, lower doses may improve patient compliance and be equally efficacious. The COPE, CORE, and CORP trials used a maintenance dose of 0.5 mg twice daily, which was reduced to 0.5 mg daily in
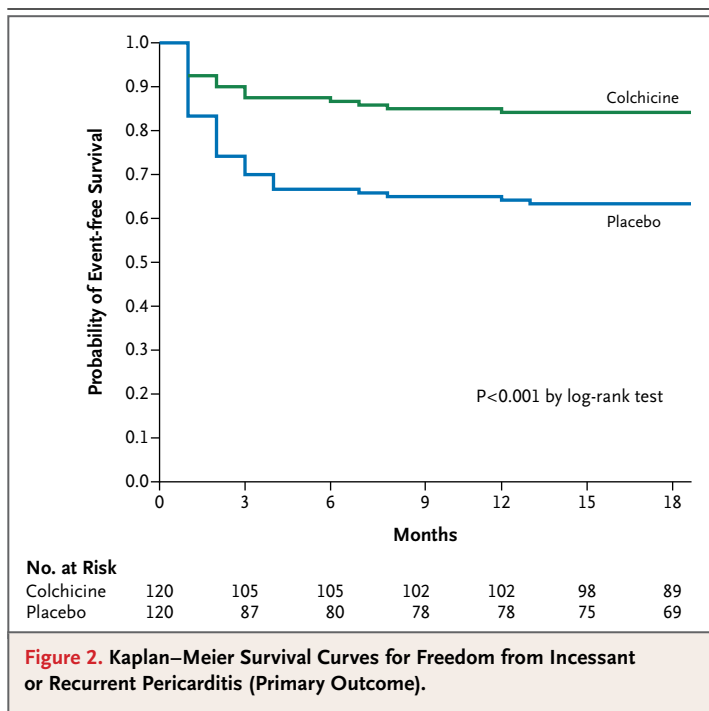

Figure 2. Kaplan–Meier Survival Curves for Freedom from Incessant or Recurrent Pericarditis (Primary Outcome).

No. at Risk
Colchicine	120	105	105	102	102	98	89
Placebo	120	87	80	78	78	75	69

Table 3. Adverse Events.

Adverse Event	Placebo (N=120)	Colchicine (N=120)	P Value
	no. (%)		
Overall	12 (10.0)	14 (11.7)	0.84
Gastrointestinal disorder*	10 (8.3)	11 (9.2)	0.67
Hepatotoxicity†	1 (0.8)	2 (1.7)	
Myotoxicity	0	0	
Alopecia	1 (0.8)	1 (0.8)	
Other	0	0	
Serious adverse event‡	0	0	
Drug discontinuation	10 (8.3)	14 (11.7)	0.52
Physician decision	9 (7.5)	12 (10.0)	
Patient decision	1 (0.8)	2 (1.7)	

* Gastrointestinal disorders included diarrhea, nausea, cramping, abdominal pain, and vomiting.
† Hepatotoxicity was defined as an elevation in aminotransferase levels above the normal reference range.
‡ Adverse events were considered to be serious if they were fatal or life-threatening, required hospitalization, or resulted in substantial or permanent disability or a medically significant event (i.e., one that could have jeopardized the patient or required medical or surgical intervention to prevent an adverse outcome).

patients weighing less than 70 kg. In our study, a loading dose was not given, and patients had similar side effects in the colchicine and placebo groups, a finding that supports the use of a

weight-adjusted maintenance dose without any loading dose.

A number of limitations of our study should be considered. Our findings might not be generalizable to other clinical conditions or other patient populations; in this regard, we excluded patients with elevated levels of aminotransferases, creatinine, or troponin and those with liver disease, myopathy, blood dyscrasias, or inflammatory bowel disease. Our results should not be applied to women who are pregnant or lactating or to children. We also excluded patients with bacterial or neoplastic pericarditis. Of note, colchicine is not approved for the prevention of recurrent pericarditis in North America or Europe, and its use as such is off-label. Our limited sample size might have precluded the identification of rare adverse effects. Further research is needed to identify the best duration of colchicine treatment, since we selected the arbitrary treatment length of 3 months on the basis of previous studies,[3-5] and we speculate that a longer duration might further decrease the 9 to 10% recurrence rate.

In conclusion, we conducted a randomized trial of colchicine versus placebo, in addition to conventional antiinflammatory therapy, in patients with a first episode of acute pericarditis. Colchicine reduced the rate of incessant or recurrent pericarditis in these patients, as compared with placebo.

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