

Colchicine as First-Choice Therapy for Recurrent Pericarditis

Results of the CORE (COLchicine for REcurrent pericarditis) Trial

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Background: Colchicine seems to be a good drug for treating recurrences of pericarditis after conventional treatment failure, but no clinical trial has tested the effects of colchicine as first-line drug for the treatment of the first recurrence of pericarditis.

Methods: A prospective, randomized, open-label design was used to investigate the safety and efficacy of colchicine therapy as adjunct to conventional therapy for the first episode of recurrent pericarditis. Eighty-four consecutive patients with a first episode of recurrent pericarditis were randomly assigned to receive conventional treatment with aspirin alone or conventional treatment plus colchicine (1.0-2.0 mg the first day and then 0.5-1.0 mg/d for 6 months). When aspirin was contraindicated, prednisone (1.0-1.5 mg/kg daily) was given for 1 month and then was gradually tapered. The primary end point was the recurrence rate. Intention-to-treat analyses were performed by treatment group.

Results: During 1682 patient-months (mean follow-up, 20 months), treatment with colchicine significantly decreased the recurrence rate (actuarial rates at 18 months were 24.0% vs 50.6%; $P = .02$; number needed to treat = 4.0; 95% confidence interval 2.5-7.1) and symptom persistence at 72 hours (10% vs 31%; $P = .03$). In multivariate analysis, previous corticosteroid use was an independent risk factor for further recurrences (odds ratio, 2.89; 95% confidence interval, 1.10-8.26; $P = .04$). No serious adverse effects were observed.

Conclusion: Colchicine therapy led to a clinically important and statistically significant benefit over conventional treatment, decreasing the recurrence rate in patients with a first episode of recurrent pericarditis.

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RECURRENT PERICARDITIS IS the most troublesome complication of acute pericarditis, occurring in 15% to 50% of patients.¹⁻⁴ It is generally accepted that relapse is an autoimmune process.¹⁻⁶ However, the optimal treatment for preventing recurrences has not been established,^{1,2,4} and no therapy has been proven to prevent sequelae (such as cardiac tamponade and constriction). Therapeutic modalities are nonspecific and include nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and pericardiectomy.^{1,4-7} Although most patients respond to nonsteroidal anti-inflammatory drugs, others have a prolonged course and respond only to corticosteroids.^{1,2,5} In this setting, prolonged or frequent administration of corticosteroids may be necessary, possibly leading to corticosteroid dependence and adverse drug effects.^{1,2,4}

Several small studies^{4,8-11} have successfully used colchicine to prevent acute pericarditis recurrences after failure of conven-

tional treatment. On the basis of cumulative anecdotal evidence, observational studies, and opinion of experts, colchicine is recommended in the treatment of recurrent pericarditis.¹² However, randomized trials are lacking to guide the evaluation and management of pericarditis, and strategies to prevent recurrences require further study.¹³

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To our knowledge, no clinical trial has tested the effects of colchicine as the first-choice drug for the treatment of the first recurrence of pericarditis. The aims of this work are to verify the safety and efficacy of colchicine therapy as an adjunct to conventional therapy for the first episode of recurrence and to verify whether the natural history of the disease may change because of the early use of colchicine. No characteristics of the first episode have been reported to predict the likelihood of recurrences^{1,2,4,6,10};

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thus, the secondary aim is to search for possible risk factors for further recurrences.

METHODS

STUDY DESIGN

A prospective, randomized, open-label, parallel-group study was conducted. The validation of clinical events was ensured by an ad hoc committee of expert cardiologists blinded to patient treatment assignment. The study was conceived and managed by the Cardiology Department, Maria Vittoria Hospital, Torino. Data analyses were performed by an external data analysis committee masked to treatment assignment. We obtained approval for the study protocol from the institutional review board, and all the participants gave informed consent.

PARTICIPANTS

Between January 1, 2001, and August 31, 2004, all consecutive patients with a first episode of recurrence were enrolled in this study. Eligible patients had no contraindication to colchicine, provided informed consent, and had no unfavorable short-term outlook. Inclusion criteria were a diagnosis of recurrent pericarditis (first episode); previous idiopathic, viral, and autoimmune etiologies (including postpericardiotomy syndromes and connective tissue diseases) of the first episode of acute pericarditis; 18 years or older; and informed consent. Exclusion criteria were tuberculous, neoplastic, or purulent etiologies of the first episode; known severe liver disease or current transaminase levels greater than 1.5 times the upper limit of normal; a current serum creatinine level greater than 2.5 mg/dL ($>221 \mu\text{mol/L}$); known myopathy or a current serum creatine kinase level greater than the upper limit of normal; known blood dyscrasias or gastrointestinal disease; pregnant and lactating women or women of childbearing potential not protected by a contraception method; known hypersensitivity to colchicine; and current treatment with colchicine for any indication. The primary end point was the recurrence rate. The secondary end point was symptom persistence 72 hours after treatment onset. We also evaluated risk factors for recurrences.

DEFINITION OF RECURRENCE

Acute pericarditis was diagnosed when at least 2 of the following criteria were present: pericarditic chest pain, pericardial friction rub, and widespread ST-segment elevation on the electrocardiogram.¹⁴⁻¹⁷ Criteria for the diagnosis of recurrent pericarditis^{1,6,18} were (1) a documented first attack of acute pericarditis according to definite diagnostic criteria and (2) evidence of either recurrence or continued activity of pericarditis. Recurrence was documented by recurrent pain and 1 or more of the following signs: fever, pericardial friction rub, electrocardiographic changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count or erythrocyte sedimentation rate or C-reactive protein.^{1,2,6,18}

RANDOMIZATION AND TREATMENT REGIMEN

Patients were randomized to receive conventional treatment with aspirin, 800 mg orally every 6 or 8 hours for 7 to 10 days, with gradual tapering for 3 to 4 weeks (group 1), or treatment with aspirin at the same dose combined with colchicine, 1.0 to 2.0 mg the first day and then a maintenance dose of 0.5 to 1.0 mg daily for 6 months (group 2). The lower dose (an attack dose of 1.0 mg and a maintenance dose of 0.5 mg/d) was given to patients who weighed less than 70 kg or who were intolerant

of the highest dose (an attack dose of 1.0 mg twice daily and a maintenance dose of 0.5 mg twice daily). Randomization was based on permuted blocks, with a block size of 4.

As the preferred nonsteroidal anti-inflammatory drug, we used aspirin according to our published experience,^{16,17} and for the colchicine dose we considered previous experiences in the treatment of recurrent pericarditis^{4,8-10} and our previous experience^{11,19} to assign patients to the lowest effective dose, thus reducing adverse effects and improving drug tolerability. When aspirin was contraindicated (allergy, history of peptic ulcer or gastrointestinal bleeding, or oral anticoagulant therapy when the bleeding risk was considered high or unacceptable), corticosteroid therapy was prescribed, using prednisone as the agent of choice. Prednisone was given at 1.0 to 1.5 mg/kg per day for 4 weeks and then was gradually tapered. In every patient, gastroduodenal prophylaxis was adopted using omeprazole, 20 mg daily, also without initial evidence of gastrointestinal intolerance as previously published.¹⁶⁻¹⁹

All the patients had M-mode, 2-dimensional, and Doppler echocardiographic studies performed using a Sonos 2500 or 5500 (Hewlett-Packard, Palo Alto, Calif). Clinical and echocardiographic follow-up were performed at 48 to 72 hours, 7 to 10 days, 1 month, 3 months, 6 months, and 1 year, and then yearly in noncomplicated cases.

Patients were considered to have remission when they were symptom free, with the disappearance of clinical, electrocardiographic, and echocardiographic signs.^{10,18} Conversely, we considered treatment failure in patients with an unfavorable clinical reaction with persistence of fever, pericardial effusion appearance or worsening, and general illness lasting more than 7 days.^{1,2,10,18}

SAFETY ASSESSMENTS

During follow-up, monitoring and recording of all adverse events was performed. A severe adverse event was considered an untoward event that was fatal or life-threatening, or that required hospitalization, or that was significantly or permanently disabling or medically significant (may jeopardize the patient and may require medical or surgical intervention to prevent an adverse outcome). A safety monitoring committee masked to treatment assignment performed an interim analysis.

STATISTICAL ANALYSIS

During the planned 3.2 years of study, we estimated a minimum recurrence rate of 22.5% in the control group based on previous local experience.^{11,17,19} The trial sample size was calculated to test the hypothesis that the combined treatment (aspirin and colchicine) would decrease by another 50% the recurrence rate of the control group according to previous experiences.^{4,11,20,21} Analysis was done by intention to treat.

Data are expressed as mean $\pm$ SD. Comparisons between patient groups were performed using unpaired *t* tests for continuous variables and χ^2 tests for categorical variables. A *P* < .05 was considered statistically significant. Kaplan-Meier survival analyses and logistic regression multivariate analysis were performed using a software program (SPSS version 13.0; SPSS Inc, Chicago, Ill).

RESULTS

PARTICIPANT CHARACTERISTICS

Eighty-four consecutive patients were recruited. None of the participants were ineligible. Information on vital status and clinical follow-up data were available in all patients for a mean of 20 months (range, 8-44 months). Forty-two patients (age, 51.2 ± 16.3 years; 13 men) were randomly

Table 1. Baseline Demographic and Clinical Characteristics of Randomized Patients According to Treatment Assignment*

Characteristic	Group 1 (n = 42)	Group 2 (n = 42)	P Value
Age, mean $\pm$ SD, y	51.2 $\pm$ 16.3	56.4 $\pm$ 16.9	.16
Male sex	13 (31)	16 (38)	.65
Pericarditic chest pain	42 (100)	42 (100)	>.99
Pericardial rub	14 (33)	15 (36)	>.99
Electrocardiographic changes	29 (69)	31 (74)	.81
Pericardial effusion	27 (64)	26 (62)	>.99
Cardiac tamponade	0	1 (2)	.99
Previous idiopathic pericarditis	34 (81)	36 (86)	.78
Previous autoimmune etiologies†	8 (19)	6 (14)	.77
Previous corticosteroid use‡	16 (38)	14 (33)	.82
Time from first attack, mean $\pm$ SD, mo	5.1 $\pm$ 6.9	5.8 $\pm$ 7.0	.65

*Data are given as number (percentage) except where indicated otherwise. Group 1 received conventional treatment alone, and group 2 received conventional treatment plus colchicine.

†Autoimmune etiologies include connective tissue diseases and postpericardiotomy syndromes.

‡Corticosteroid administration during the index attack.

assigned to receive conventional treatment alone (group 1), and 42 (age, 56.4 $\pm$ 16.9 years; 16 men) were assigned to receive conventional treatment plus colchicine (group 2). Baseline demographic and clinical characteristics were well balanced across the groups (**Table 1**).

PRIMARY END POINT

The overall efficacy profile of the 2 treatments is summarized in **Table 2**. During 1682 patient-months of follow-up, a higher recurrence rate was recorded in group 1 compared with group 2. Actuarial recurrence rates at 18 months were 50.6% vs 24.0%, respectively ($P = .02$), with an absolute risk reduction of 26.6%. Thus, the number needed to treat was 4.0 (95% confidence interval, 2.5-7.1).

Patients in group 2 had a longer symptom-free interval than patients in group 1 (17.2 $\pm$ 12.2 months vs 10.6 $\pm$ 9.6 months; $P = .007$). The event-free survival rates in the 2 study groups are shown in **Figure 1**. The event-free survival rates according to treatment subgroups (aspirin alone, aspirin plus colchicine, prednisone alone, and prednisone plus colchicine) are shown in **Figure 2**. Patients treated with prednisone plus colchicine exhibited an event-free survival similar to that of the aspirin subgroup (actuarial recurrence rates at 18 months were 58.7% vs 65.8%; $P = .91$).

SECONDARY END POINT AND RISK FACTORS FOR RECURRENCE

Lower symptom persistence rates at 72 hours were recorded in group 2 than in group 1 (10% vs 31%; $P = .03$) (Table 2). Patients with further recurrence during follow-up had a higher rate of previous corticosteroid use than patients without further recurrence (57% vs 25%; $P = .008$; **Table 3**). After multivariate analysis, including as independent variables the reported clinical

Table 2. Follow-up Data: Overall Efficacy and Safety Profiles According to Treatment Assignment*

Characteristic	Group 1 (n = 42)	Group 2 (n = 42)	P Value
Follow-up, mean $\pm$ SD, mo	21.4 $\pm$ 12.9	18.6 $\pm$ 11.5	.30
Recurrences	19 (45)	9 (21)	.04
Actuarial recurrence rate at 18 mo, %	50.6	24.0	.02
Symptom persistence at 72 h	13 (31)	4 (10)	.03
Adverse effects	6 (14)	3 (7)	.48
Severe adverse effects	0	0	>.99
Cardiac tamponade	0	0	>.99
Constrictive pericarditis	1 (2)	0	.99
Symptom-free period, mean $\pm$ SD, mo	10.6 $\pm$ 9.6	17.2 $\pm$ 12.2†	.007
Recurrences, mean $\pm$ SD, No.	1.7 $\pm$ 0.8	1.2 $\pm$ 0.5	<.001

*Data are given as number (percentage) except where indicated otherwise. Group 1 received conventional treatment alone and group 2 received conventional treatment plus colchicine.

†Comparison of the symptom-free periods before and after colchicine treatment yielded significant differences in study group 2 (mean $\pm$ SD, 5.8 $\pm$ 7.0 vs 17.2 $\pm$ 12.2 mo; $P < .001$).

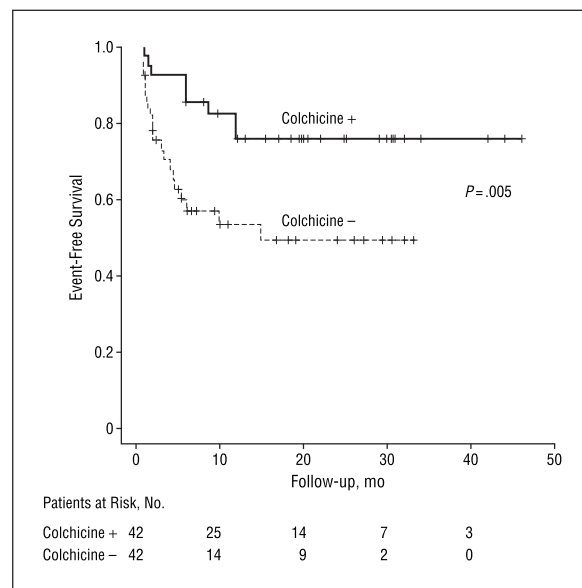


Figure 1. Kaplan-Meier event-free survival curves according to subgroup.

characteristics given in Table 3, only previous corticosteroid use was an independent risk factor for the subsequent development of recurrences (odds ratio, 2.89; 95% confidence interval, 1.10-8.26; $P = .04$), whereas colchicine use was found to be protective (odds ratio, 0.34; 95% confidence interval, 0.12-0.95; $P = .04$).

SAFETY ASSESSMENTS AND ADVERSE EFFECTS

Safety profiles of the studied treatments are summarized in Table 2. Overall drug tolerability was good for aspirin and colchicine: no serious adverse drug effects were recorded in the study groups. Diarrhea was reported as the reason for discontinuing therapy for 3

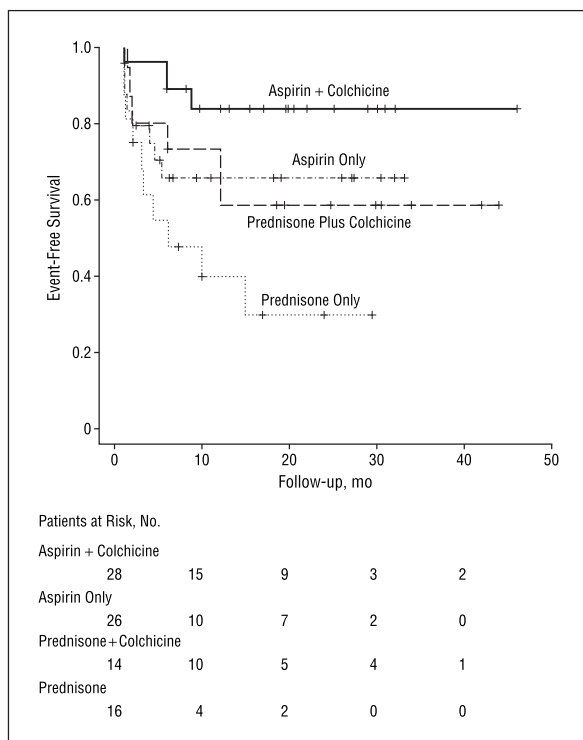


Figure 2. Kaplan-Meier event-free survival curves according to treatment subgroups ($P=.007$).

patients (7%) in the colchicine group (group 2), and it was promptly reversed after drug withdrawal. Two patients experienced relapses after colchicine discontinuation.

COMMENT

Previous studies^{1,2,4,8-11,20} have shown that colchicine is effective and safe for the treatment and prevention of recurrent pericarditis after conventional treatment failure. In the largest prospective study,²⁰ only 7 (14%) of 51 patients had new recurrences during 1004 patient-months of colchicine treatment. In a recent retrospective, multicenter analysis²² in which published and unpublished patients treated with colchicine after at least 2 relapses were aggregated, only 21 (18%) of 119 patients had new recurrences with colchicine treatment, and 30% had new recurrences after its discontinuation.

On the basis of cumulative anecdotal evidence, previous observational experiences, and expert opinion, colchicine (0.5 mg twice daily) is recommended for the treatment of recurrent pericarditis.¹² However, several researchers recommend that colchicine be administered to patients with 2 or more relapses and, thus, only after the failure of conventional treatment.^{1,2} It is unfortunate that such a broad acceptance of this drug has been based on rather weak evidence.^{2,13} Although randomized trials are lacking to guide the evaluation and management of pericarditis,¹³ evidence for colchicine use in recurrent pericarditis comes from observational studies in which colchicine was used after the failure of conventional treatment, whereas no studies reported the treatment of patients with

Table 3. Baseline Demographic and Clinical Characteristics (First Recurrence) of Patients With and Without Further Recurrences During Follow-up*

Characteristic	Patients With Further Recurrences (n = 28)	Patients Without Further Recurrences (n = 56)	P Value
Age, mean $\pm$ SD, y	52.9 $\pm$ 14.6	54.2 $\pm$ 17.8	.74
Female sex	22 (79)	33 (59)	.12
Pericardial effusion	19 (68)	34 (61)	.69
Severe pericardial effusion	3 (11)	7 (13)	.91
Cardiac tamponade	1 (4)	0	.72
Previous idiopathic etiology	20 (71)	50 (89)	.08
Previous autoimmune etiologies†	8 (29)	6 (11)	.08
Previous corticosteroid use	16 (57)	14 (25)	.008
Colchicine use‡	9 (32)	33 (59)	.04

*Data are given as number (percentage) except where indicated otherwise. Further recurrences refer to those after the first recurrence.

†Autoimmune etiologies include connective tissue diseases and postpericardiotomy syndromes.

‡For treatment of the first recurrence, as in the study protocol.

a first episode of recurrent pericarditis. The finding of drugs to treat and prevent such a complication would be useful.^{1,2} Colchicine therapy may be a way to cope with this complication. Because it is generally accepted that recurrence is an autoimmune process,^{1,2,4,5} early treatment may be more useful and beneficial than later treatment, after the failure of conventional treatment.

This study reports the first randomized trial in this area, to our knowledge. In the present study, the adjunct of colchicine to conventional treatment significantly decreased the recurrence rate in patients with a first episode of recurrent pericarditis. Moreover, patients treated with colchicine showed lower symptom persistence at 72 hours of treatment, suggesting that the drug may be useful to control symptoms faster than with simple nonsteroidal anti-inflammatory drugs or prednisone. These data are similar to what has been described in patients with gouty attack. Most patients respond to colchicine within 18 hours, and joint inflammation subsides in 75% to 80% of patients within 48 hours.²³

Our findings support the current recommendations, providing a stronger evidence base for the use of colchicine. This study also shows that colchicine might be considered as first-choice therapy for recurrent pericarditis. Moreover, similar event-free survival rates were recorded in patients treated with aspirin alone and in those treated with prednisone plus colchicine. Thus, prednisone plus colchicine seems to be a reasonable therapy for patients who cannot take aspirin (Figure 2).

The exact mechanism of colchicine action is not fully understood. Colchicine has been used for hundreds of years as an anti-inflammatory agent for acute attacks of gout. Most of the pharmacologic effects of colchicine on cells involved in inflammation seem to be related to the capacity of colchicine to disrupt microtubules. Colchicine inhibits the process of microtubule self-assembly by binding β -tubulin with the formation of tubulin-colchicine complexes. This action takes place either in the mitotic spindle or in the interphase stage; thus, col-

chicine inhibits the movement of intercellular granules and the secretion of various substances and various leukocyte functions, and this effect should be the most significant for the anti-inflammatory action.^{23,24} Moreover, colchicine shows a preferential concentration in leukocytes, and the peak concentration of colchicine may be more than 16 times the peak concentration in plasma. This effect seems to enhance its therapeutic effect.^{4,23,24}

In previous prospective studies,^{1,2} no characteristics of the first episode predicted the likelihood of recurrences. However, concern has been raised that treating pericarditis with prednisone may increase the risk of recurrence.^{1,2,13} Our study seems to support this fear because previous corticosteroid use was an independent risk factor for the subsequent development of recurrences (odds ratio, 2.89; 95% confidence interval, 1.10-8.26). This result is consistent with findings in patients with at least 2 relapses, as reported in a recent retrospective analysis.²² Animal studies^{2,13} have shown that corticosteroids may exacerbate virally induced pericardial injury. Thus, these data argue against the routine administration of corticosteroids during acute or recurrent pericarditis.^{2,13}

The good tolerability of aspirin was probably due to the efficacy of the gastroduodenal prophylaxis that was adopted, also without evidence of gastrointestinal intolerance. At doses of 1 to 2 mg/d, colchicine has been found to be safe even when given continuously for decades.^{4,24,25} Gastrointestinal adverse effects are not uncommon, although generally mild, and may resolve with dose reduction.²³⁻²⁶ Moreover, no interference of colchicine treatment was recorded in either growth rate or fertility after a cumulative 15 000 years of follow-up in patients with familial Mediterranean fever.²⁶

When colchicine was used to treat recurrent pericarditis, temporary discontinuation of the drug or a reduction of its dose was needed in approximately 10% to 14% of patients.⁴ These adverse effects may limit its therapeutic applicability. In the present study, using weight-adjusted doses, diarrhea was reported as a reason for discontinuing therapy in 7% of the patients and was promptly reversed after drug withdrawal. This drug regimen is reduced compared with other proposed prescriptions in recent articles (2.0 mg/d for 1 or 2 days, followed by 1.0 mg/d for all patients),^{1,2,12} but it seems to be effective, reducing adverse effects and thus improving patient compliance.

A possible study limitation is the open-label design. This work was designed as a preliminary study to test the hypothesis that early treatment of the first recurrence with colchicine may reduce the subsequent recurrence rate. However, the validation of clinical events was ensured by an ad hoc committee of expert cardiologists blinded to patient treatment assignment, whereas data analyses were performed by an external data analysis committee masked to treatment assignment. The strict adherence to the intention-to-treat principle ensures that the effects seen correspond closely to what is achievable in clinical practice. Despite these limitations, our findings provide stronger evidence for the use of colchicine as the first-line drug in the treatment of recurrent pericarditis.

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