Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial

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Summary

Background Colchicine is effective for the treatment of acute pericarditis and first recurrences. However, conclusive data are lacking for the efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis.

Methods We did this multicentre, double-blind trial at four general hospitals in northern Italy. Adult patients with multiple recurrences of pericarditis (≥two) were randomly assigned (1:1) to placebo or colchicine (0·5 mg twice daily for 6 months for patients weighing more than 70 kg or 0·5 mg once daily for patients weighing 70 kg or less) in addition to conventional anti-inflammatory treatment with aspirin, ibuprofen, or indometacin. Permuted block randomisation (size four) was done with a central computer-based automated sequence. Patients and all investigators were masked to treatment allocation. The primary outcome was recurrent pericarditis in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT00235079.

Findings 240 patients were enrolled and 120 were assigned to each group. The proportion of patients who had recurrent pericarditis was 26 (21·6%) of 120 in the colchicine group and 51 (42·5%) of 120 in the placebo group (relative risk 0·49; 95% CI 0·24–0·65; p=0·0009; number needed to treat 5). Adverse effects and discontinuation of study drug occurred in much the same proportions in each group. The most common adverse events were gastrointestinal intolerance (nine patients in the colchicine group vs nine in the placebo group) and hepatotoxicity (three vs one). No serious adverse events were reported.

Interpretation Colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences. Taken together with results from other randomised controlled trials, these findings suggest that colchicine should be probably regarded as a first-line treatment for either acute or recurrent pericarditis in the absence of contraindications or specific indications.

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Introduction

Clinical trials have shown that low-dose colchicine (0·5–1·0 mg daily) is efficacious and safe for treatment and prevention of acute pericarditis and first recurrences.[1–3] However, the treatment of patients with multiple recurrences—especially after the use of colchicine—remains a major clinical problem.[4,5] Although preliminary evidence from non-randomised studies suggests that colchicine might be useful in this setting, little reliable evidence is available and there is an unmet clinical need for proven treatments. Several other drugs have been proposed for treatment of multiple recurrence of pericarditis, including azathioprine,[6] high-dose intravenous human immunoglobulins,[7] interleukin-1 receptor antagonist (anakinra),[8] and other immunosuppressive treatments.[9] As a last option, pericardiectomy can also be considered for patients who are refractory to drug treatment.[10] Unfortunately, treatment guidelines provide few recommendations.[11]

Colchicine could be a cheap and safe alternative to expensive and potentially harmful treatments, and management with colchicine is relatively simple.[12] We did the Colchicine for Recurrent Pericarditis 2 (CORP-2) trial to assess the efficacy and safety of colchicine to treat patients with multiple recurrences of pericarditis.[13]

Methods

Study design and participants

The CORP-2 trial was a randomised, double-blind, placebo-controlled, multicentre study. The rationale, design, and methods have been reported previously.[13] The trial was done at four general hospitals in northern Italy. Consecutive patients aged 18 years or older with two or more recurrences of pericarditis (idiopathic, viral, post-cardiac injury, or caused by connective tissue disease) were eligible for enrolment.

Recurrent pericarditis was diagnosed by a documented first episode of acute pericarditis, 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 diagnosed with incessant pericarditis.[14] Recurrence was documented by recurrent pain and one or more of the following signs: a pericardial friction rub,

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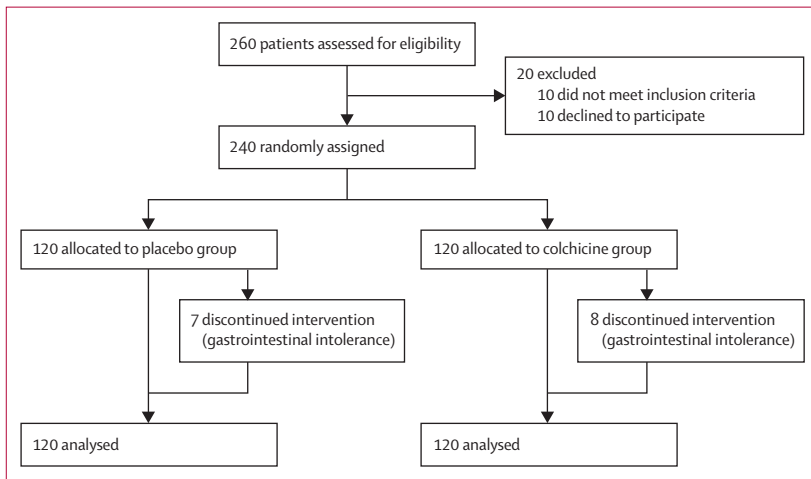**massimo_imazio@yahoo.it**

***Figure 1:* Trial profile**
All patients assigned to each treatment received that treatment.

electrocardiograph (ECG) changes, echocardiographic evidence of pericardial effusion, and an increase in white blood cell count, erythrocyte sedimentation rate, or C-reactive protein concentration.[1,3] These criteria are based on previous studies, reviews, and expert opinion.[1,3,9,15,16] Acute pericarditis was diagnosed by having 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 ECG changes (widespread ST elevation or PR depression), and new or worsening pericardial effusion.[2]

Patients with any of the following were ineligible: tuberculous, neoplastic, or purulent pericarditis; severe liver disease or current aminotransferase concentrations more than 1·5 times the upper limit of the normal; serum creatinine concentration more than 221·00 μmol/L; skeletal myopathy or serum creatine kinase concentration more than the upper limit of the normal; blood dyscrasia; inflammatory bowel disease; hypersensitivity to colchicine or other contraindication to colchicine; current treatment with colchicine; and life expectancy of 18 months or less. Pregnant or lactating women or women of childbearing potential not using contraception were also ineligible, as were patients with evidence of myopericarditis as indicated by any increase of serum troponin concentration.[17,18]

All participants provided written informed consent. The trial was approved by the steering committee, and the ethics committee at each participating centre. The appendix shows the protocol.

See **Online** for appendix

Randomisation and masking

Participants were randomly assigned to receive colchicine or placebo (1:1) with a central computer-based automated sequence. Randomisation was done in permuted blocks, with a block size of four. The random allocation sequence was implemented with sequentially numbered study drug containers. All patients and investigators were

masked to treatment allocation. Unmasked data were made available to an independent data and safety and monitoring board. Colchicine and placebo tablets were identical in colour, shape, and taste and premarked to enable splitting into two equal parts.

Procedures

Colchicine was given at a dose of 0·5 or 1·0 mg daily for 6 months without a loading dose to reduce potential gastrointestinal side-effects and improve patient compliance. The duration of colchicine treatment was based on previous studies.[1,3] The lower dose (0·5 mg daily) was given to patients weighing 70 kg or less and to those intolerant of the higher dose (0·5 mg twice daily) at scheduled follow-up visits. Colchicine tablets contained 1 mg of active drug. Assessment of adherence to study drug was based on counts of pills in dispensed boxes, with a target of at least 80%.

All patients also received conventional treatment for recurrent pericarditis based on three possible non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, and indometacin) according to the treating physician and assuming an equal efficacy. For most patients, this consisted of either aspirin 800 mg, ibuprofen 600 mg, or indometacin 50 mg orally every 8 h for 7–10 days with tapering over 3–4 weeks. Corticosteroid treatment (prednisone 0·2–0·5 mg/kg per day for 4 weeks, then tapered)[19] was given to patients already taking corticosteroids or who had contraindications to aspirin, ibuprofen, and indometacin (allergy, history of peptic ulcer, or gastrointestinal bleeding, or use of oral anticoagulant treatment when the bleeding risk was deemed high or unacceptable), or a history of intolerance. All patients received a proton pump inhibitor as gastroduodenal prophylaxis. Placebo was used as the comparator because anti-inflammatory treatment alone was standard treatment when the trial was planned.

All patients were followed up for at least 18 months after enrolment. Visits were planned for 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 chemistry (C-reactive protein, aminotransferase, creatinine, and creatine kinase concentrations), a complete blood count, an ECG, and an echocardiogram. Data were collected with case report and clinical events forms by investigators. A clinical endpoint committee (DHS and YA) adjudicated all events including primary and secondary outcomes. During follow-up, all adverse events were monitored and recorded.

Outcomes

The primary endpoint was recurrent pericarditis during follow-up. Secondary endpoints were persistence of symptoms at 72 h after onset of symptoms, remission within 1 week, number of recurrences, time to first subsequent recurrence, disease-related admission to hospital, cardiac tamponade, and constrictive pericarditis.

Statistical analysis

We assumed that 30% of patients would have recurrent pericarditis in the placebo group at 18 months[13] and estimated that colchicine could reduce the proportion of patients with recurrent pericarditis by half. With a two-sided α level of 0·05, a total enrolment of 240 patients was needed to attain power of 0·80 to detect a 15% absolute reduction in the proportion of participants who had recurrent pericarditis in the colchicine group.

We did all analyses by intention to treat. We compared treatment groups by t test or the Mann-Whitney test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. A two-sided p<0·05 indicated statistical significance. We used the Kaplan-Meier method to estimate time-to-event (recurrent pericarditis) distributions and compared groups with the log-rank test. We did a multivariable analysis to assess possible risk factors for recurrences including sex, cause of pericarditis, previous use of colchicine and corticosteroids, current treatment with corticosteroids, and pericardial effusion at presentation. All analyses were done with SPSS (version 13.0) and MedCalc (version 12.7.2).

This trial is registered with ClinicalTrials.gov, number NCT00235079.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to data and were responsible for the decision to submit the report.

Results

Enrolment started in November, 2005, and ended in January, 2012. The long enrolment time is a result of the need for patients to have multiple recurrences (second or subsequent). Follow-up continued up to July 31, 2013, a predetermined stopping point, providing a minimum of 18 months of follow-up for the primary outcome.

Of the 260 patients who were screened, 240 (92·3%) were enrolled. 120 patients were randomly assigned to each group (figure 1). No patients were lost to follow-up and all were analysed for outcomes. The baseline demographic and clinical characteristics of each group were similar (table 1). The mean age of the trial participants was 48·7 (SD 14·6 years; median 49 years, range 18–83 years) and 50% were men.

Adherence was more than 95% and did not differ significantly between treatments (data not shown). All patients who tolerated treatment with colchicine or placebo discontinued treatment at 6 months, as planned. No patients took open-label colchicine after the end of the experimental treatment. Mean follow-up was 20 months.

Table 2 shows the main outcomes results. Pericarditis reoccurred in 26 of 120 patients (21·6%) in the colchicine group and 51 of 120 patients (42·5%) in the placebo group (relative risk 0·49, 95% CI 0·24–0·65; p=0·0009;

number needed to treat [NNT] 5). Figure 2 shows Kaplan-Meier survival curves for subsequent recurrences. Results were much the same irrespective of whether concomitant anti-inflammatory treatment was aspirin, ibuprofen, or indometacin (table 2).

In post-hoc analyses, recurrence at 18 months in patients treated previously with corticosteroids occurred in 15 (62·5%) of 24 patients in the placebo group versus

	Placebo group (n=120)	Colchicine group (n=120)
Age (years)	48·9 (15·5)	48·6 (13·6)
Men	54 (45·0%)	66 (55·0%)
Previous cardiac surgery	5 (4·2%)	5 (4·2%)
Previous myocardial infarction	6 (5·0%)	11 (9·1%)
Time from first episode of pericarditis (months)*	17·1 (3–180)	14·2 (3–156)
Cause		
Idiopathic	102 (85·0%)	96 (80·0%)
Post-cardiac injury syndrome	8 (6·7%)	13 (10·8%)
Connective tissue diseases	8 (6·7%)	8 (6·7%)
Clinical findings		
Fever	43 (35·8%)	30 (25·0%)
Pericarditic chest pain	119 (99·2%)	120 (100·0%)
Pericardial rub	38 (31·7%)	44 (36·7%)
Pericardial effusion	68 (56·7%)	70 (58·3%)
High hs-CRP at presentation (>3 mg/L)	89 (74·2%)	85 (70·8%)
Ejection fraction (%)	58% (4·4)	58% (4·8)
Drug treatments		
Previous use of corticosteroids	24 (20·0%)	16 (13·3%)
Previous use of colchicine	79 (65·8%)	78 (65·0%)
Aspirin	96 (80·0%)	86 (71·7%)
Ibuprofen	18 (15·0%)	24 (20·0%)
Indometacin	10 (8·3%)	12 (10·0%)
Prednisone	6 (5·0%)	10 (7·5%)

Data are or mean (SD) or n (%) unless stated otherwise. hs-CRP=high-sensitivity C-reactive protein. *Mean (range).

Table 1: **Baseline characteristics**

	Placebo group (n=120)	Colchicine group (n=120)	p value
Recurrent pericarditis	51 (42·5%)	26 (21·6%)	0·0009*
Symptom persistence at 72 h	53 (44·2%)	23 (19·2%)	0·0001
Remission at 1 week	71 (59·2%)	100 (83·3%)	0·0001
Incessant course	32 (26·7%)	10 (8·3%)	0·0004
Number of recurrences per patient	0·63 (0·87)	0·28 (0·58)	0·0004
Time to subsequent recurrence (months)	5·3 (4·2)	8·1 (11·1)	0·220
Cardiac tamponade	2 (1·7%)	0 (0·0%)	0·478
Constrictive pericarditis	4 (3·3%)	0 (0·0%)	0·097
Pericarditis-related admission to hospital	12 (10·0%)	2 (1·7%)	0·013
Follow-up (months)	20·0 (4·4)	19·3 (3·1)	0·149

Data are n (%) or mean (SD). Similar proportions of recurrent pericarditis were recorded irrespective of the background anti-inflammatory treatment (49 of 182 [26·9%] patients taking aspirin, 12 of 42 [28·6%] patients taking ibuprofen, six of 22 [27·3%] patients taking indomethacin). *From log-rank test.

Table 2: **Outcomes**

five (31·3%) of 16 in the colchicine group (p=0·10). For patients treated with prednisone during follow-up, recurrence at 18 months occurred in 12 (52·2%) of 23 patients versus seven (36·8%) of 19 (p=0·50). Colchicine had a significant effect in patients with idiopathic pericarditis (43 [42·2%] of 102 vs 18 [18·8%] of 96; p=0·0006) but not those with non-idiopathic pericarditis (eight [44·4%] of 18 versus eight [33·3%] of 24; p=0·68). Nevertheless, these analyses were not prespecified and the subgroups include too few patients to draw definitive conclusions (table 2).

Colchicine also reduced the frequency of symptom persistence at 72 h (19·2% vs 44·2%; p=0·0001), the number of recurrences per patient (0·28 vs 0·63; p=0·0004), and the proportion of patients admitted to hospital for reasons related to pericarditis (1·7% vs 10·0%; p=0·013; table 2). Colchicine also improved the proportion of patients who had remission within 1 week

Figure 2: Kaplan-Meier survival curves for recurrent pericarditis

Hazard ratio for colchicine vs placebo 0·46 (95% CI 0·30–0·72); log-rank p=0·0006

Number at risk
	0	3	6	9	12	15	18
Colchicine	120	109	105	101	97	94	94
Placebo	120	96	87	83	80	77	77

	Placebo group (n=120)	Colchicine group (n=120)	p value
Overall	10 (8·3%)	14 (11·7%)	0·519
Gastrointestinal intolerance*	9 (7·5%)	9 (7·5%)	..
Hepatotoxicity†	1 (0·8%)	3 (2·5%)	..
Myotoxicity‡	0 (0·0%)	1 (0·8%)	..
Alopecia	0 (0·0%)	1 (0·8%)	..
Other	0 (0·0%)	0 (0·0%)	..
Serious adverse events§	0 (0·0%)	0 (0·0%)	..
Drug discontinuation	7 (5·8%)	8 (6·7%)	..

*Diarrhoea, nausea, cramping, abdominal pain, or vomiting. †Any increase of aminotransferase concentration above normal reference range. ‡Any increase of creatine kinase concentration above normal reference range. §Fatal or life-threatening, requiring admission to hospital, or significantly or permanently disabling or medically significant (could have jeopardised the patient or required medical or surgical intervention to prevent an adverse outcome).

Table 3: Adverse events

(83·3% vs 59·2%; p=0·0001). Pericardial effusion at presentation was the only independent risk factor for additional recurrences in multivariable analyses (odds ratio 3·1, 95% CI 1·69–5·84; p=0·0001).

Adverse events (table 3) occurred in similar proportions in each group (14 [11·7%] in the colchicine group vs ten [8·3%] in the placebo group; p=0·519), suggesting that they were largely related to the underlying non-steroidal anti-inflammatory treatment. The proportion of patients who discontinued study were also much the same in each group (6·7% vs 5·8%). No serious adverse events occurred. Gastrointestinal intolerance was the main side effect, but was reported with equal proportions in each group (table 3).

Discussion

Colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences. It also reduced the number of recurrences during follow-up, and disease-related admissions to hospital, compared with placebo. Colchicine also had a beneficial effect compared with placebo for several other measures of multiple recurrence pericarditis. The results were consistent irrespective of the concomitant background anti-inflammatory treatment. Gastro-intestinal intolerance was the major limiting side effect but no serious adverse events were recorded.

The exact pathogenesis of recurrences is not well understood but evidence suggests an immune-mediated mechanism in most cases.[9,14,20,21] The benefit of colchicine for patients with pericarditis seems to be related to its ability to disrupt microtubules and to concentrate in leucocytes—especially granulocytes—where its peak concentration can be more than 16 times the peak concentration in plasma, even at low oral doses such as those used in our trial.[1,2,12]

Colchicine is recommended as a first-line treatment for recurrent pericarditis (class 1 indication) in the 2004 guidelines of the European Society of Cardiology for the management of pericardial diseases,[11] based on small non-randomised studies and expert consensus. The guidelines also support the use of attack doses for 1 or 2 days (1·0–2·0 mg daily) followed by fixed maintenance doses of 1·0 mg daily. In 2005, an open-label, randomised trial—the Colchicine for Recurrent Pericarditis (CORE) trial—showed a benefit of colchicine for treatment of the first recurrence of pericarditis.[3] This study was followed by the multicentre, double-blind Colchicine for Recurrent Pericarditis (CORP) trial,[1] and a subsequent meta-analysis[22] supporting the use of colchicine in this setting.

However, these trials did not address the use of colchicine for multiple recurrences of pericarditis, one of the most challenging difficulties in the management of pericardial diseases. In this setting, clinicians often have to cope with trying to control present symptoms while
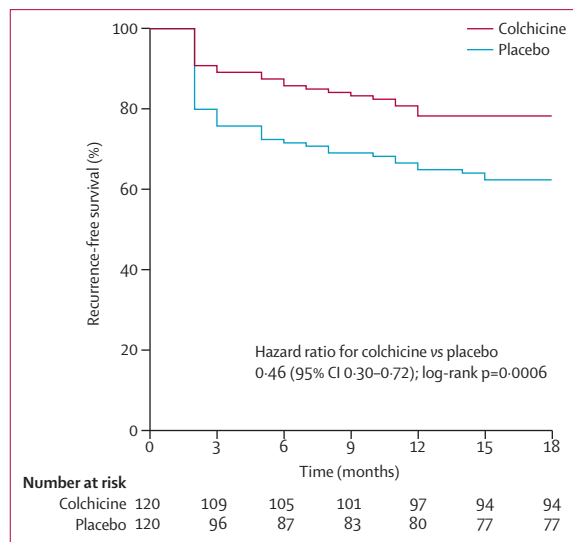
Panel: **Research in context**

Systematic review

We searched PubMed on Sept 5, 2013, with search terms "pericarditis" and "colchicine" for reports published in English (with no date restriction) to identify any additional clinical trials that have examined colchicine for treatment of recurrent pericarditis. We did not identify any randomised studies of colchicine for treatment of patients with multiple recurrences of pericarditis. Colchicine is efficacious and safe for treatment of the first recurrence of pericarditis[1] and for acute pericarditis.[2]

Interpretation

An unmet clinical need exists for effective treatment of multiple recurrences of pericarditis. The CORP-2 trial is the first multicentre randomised trial to test the efficacy and safety of colchicine for this indication. Our results show that colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences. In addition, colchicine reduced the number of recurrences during follow-up and disease-related admission to hospital compared with placebo. All these results were consistent irrespective of the concomitant background anti-inflammatory treatment (aspirin, ibuprofen, indometacin, or prednisone) and without any increase of side-effects compared with placebo. Taken together, our findings suggest that colchicine should probably be regarded as a first-line treatment for either acute or recurrent pericarditis in the absence of contraindications or specific indications. Thus, colchicine maintains its effects across the whole range of pericarditis (acute, first recurrence, and multiple recurrences) in the studied patient populations.[1,2]

preventing subsequent relapses. A recurrence is often perceived by either the physician or the patient as a failure of previous treatments with the need for new therapeutic strategies. Such treatments—generally including different immunosuppressive options—are often empirical and expensive, with potentially more complications and side-effects and fewer robust evidence-based indications than non-steroidal anti-inflammatory drugs, corticosteroids, and colchicine. Clinicians may want to know whether these first-line treatments—especially colchicine—have any additional role for patients with multiple recurrences. Non-steroidal anti-inflammatory drugs, corticosteroids, and colchicine could be combined, providing a cheap treatment with less severe side-effects and easier management.[9,23,24] Nevertheless, no previous clinical trials have investigated whether colchicine is efficacious and safe for treatment of multiple recurrences of pericarditis (panel).

The CORP-2 study shows that low bodyweight-adjusted doses of colchicine without a loading dose might provide a safe and efficacious treatment for patients with multiple recurrences of pericarditis. Colchicine seems to halve subsequent recurrences, even in patients with multiple recurrences, with a significant reduction of

disease-related admissions to hospital. We suggest that colchicine should be considered as a first line-treatment for either acute or recurrent pericarditis in the absence of contraindications or specific indications. Thus, colchicine maintains its effects across the whole range of pericarditis (acute, first recurrence, and multiple recurrences).[1,2]

Our study has several limitations. We excluded children, pregnant or lactating women, and patients with potential contraindications or at high risk of complications after the administration of colchicine. We also excluded patients with bacterial or neoplastic pericarditis. Thus, our results should only be applied to populations that were eligible for the study.

At present, colchicine is not approved for treatment of recurrent pericarditis in North America or Europe, and its use as such is off-label. Moreover, our sample size and length of follow-up might have precluded identification of rare adverse effects or long-term effects of the drug. Further research is needed to identify the best duration of colchicine treatment for recurrences; treatment for 6 months was arbitrarily selected on the basis of previous studies.[1,3,9,12,15] A longer treatment duration (6–12 months) might further decrease recurrences.

Contributors

MI designed they study, did the statistical analyses, and wrote the first draft of the report. DHS and YA assessed the outcomes. All authors collected and interpreted data and revised the report.

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