Recurrent Pericarditis

Relief With Colchicine

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Recurrent is one of the major complications of pericarditis. Treatment of recurrence is often difficult, and immunosuppressive drugs or surgery may be necessary. We conducted an open-label prospective study of nine patients (seven men and two women; age, 18–64 years; mean age, 41.7±13.7 years). Patients were treated with colchicine (1 mg/day) to prevent recurrences. All patients had suffered at least three relapses despite treatment with acetylsalicylic acid, indomethacin, prednisone, or a combination. Pericarditis was classified as idiopathic in five patients, postpericardiotomy in two, post–myocardial infarction in one, and associated with disseminated lupus erythematosus in one. For statistical analysis, we conducted a paired comparison design (Student’s t test). All patients treated with colchicine responded favorably to therapy. Prednisone was discontinued in all patients after 2–6 weeks (mean, 26.3±10.9 days), and colchicine alone was continued. After a mean follow-up of 24.3 months (minimum, 10 months; maximum, 54 months), no recurrences were observed in any patient; there was a significant difference between the symptom-free periods before and after treatment with colchicine (p<0.002). Our study suggests that colchicine may be useful in avoiding recurrence of pericarditis, although these results need to be confirmed in a larger, double-blind study. (Circulation 1990;82:1117–1120)

One of the main difficulties in the management of acute pericarditis is recurrence.1–4 In Spain, the recurrence rate after the first episode of acute pericarditis is 20%.3 It is not known why the disease is self-limiting in some patients and recurrent in others, but an immunological phenomenon is probably involved. Recurrences may occur over a period of many years, frequently after cessation or reduction of doses of anti-inflammatory drugs.

The optimal therapy to avoid recurrences once secondary causes (e.g., neoplasm, systemic diseases, or renal insufficiency) have been eliminated has not been established. Nonsteroidal anti-inflammatory drugs are usually considered first-choice drugs, and corticosteroids are frequently used to treat repeated or severe recurrences. When pericarditis recurs despite prednisone treatment, excessively high and prolonged doses are needed; when side effects appear, some recommend pericardiectomy,5,6 and others recommend immunosuppressive agents, particularly azathioprine.7

Colchicine has been used for several centuries as an effective anti-inflammatory agent for acute gouty arthritis8 and more recently for recurrent polyserositis in familial Mediterranean fever.9–11 We report the results of a prospective open-label study in nine patients with recurrent pericarditis who did not respond to corticoid therapy and who were treated with colchicine to prevent recurrences.

Methods

The study included nine patients (seven men and two women; age, 18–64 years; mean age, 41.7±13.7 years) who experienced recurrent pericarditis despite treatment with acetylsalicylic acid, indomethacin, prednisone, or a combination. These patients were treated with colchicine (1 mg/day). Clinical characteristics are given in Table 1. Before treatment with colchicine, all patients had experienced a minimum of three recurrences (maximum, seven; mean, 4.3±1.4); the mean interval between each recurrence was 3.3±4.3 months (minimum, 0.5 month; maximum, 24 months).

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Recurrent pericarditis was classified as idiopathic in five patients (1, 2, 5, 7, and 9), postpericardiotomy in two (aortic valve replacement and aortocoronary bypass; patients 6 and 8, respectively), post-myocardial infarction (Dressler syndrome) in patient 4, and associated with disseminated lupus erythematosus in patient 3.

Before inclusion in the protocol, eight of nine patients had been treated for an initial episode with acetylsalicylic acid (3–4 g/day). In two patients (7 and 9), treatment with indomethacin (25 mg/8 hr) was attempted with an unsatisfactory outcome before prednisone was given. All patients had received prednisone (10–60 mg/day), but only one had been treated with prednisone from the onset (patient 4). Another patient (1) had received chloroquine sulphate as well as acetylsalicylic acid and prednisone due to panulitis. Because recurrence of pericarditis appeared whenever reduction of the doses of prednisone was attempted, we decided to administer colchicine (initial dosages of 0.5 mg/12 hr) with prednisone. Once the acute crisis was under control, the dose of prednisone was progressively reduced until the patient received colchicine alone. During the follow-up, patients were routinely evaluated every 3 months.

**Statistics**

We conducted a paired comparison design (Student’s t test) comparing the difference between the average symptom-free periods before and after colchicine treatment.

**Results**

All nine patients treated with colchicine responded favorably to therapy. Steroid treatment was discontinued in all patients after 2–6 weeks (mean, 26.33±10.9 days). The mean current follow-up is 24.3±16.1 months (maximum, 54 months; minimum, 10 months). No recurrence has been observed in any of the patients during treatment. The differences between the symptom-free periods before colchicine administration (mean interval between pericarditis crises, 3.33±4.3 months) and after treatment with colchicine (mean interval, 24.3±16.1 months) are statistically significant (p<0.002) (Table 1). Moreover, the symptom-free period after treatment with colchicine is more than twice the maximum period before treatment in seven patients; for patients 1 and 9, the maximum intervals between crises were 24 and 7 months, respectively, and the symptom-free periods after colchicine were 32 and 10 months, respectively.

In patients 1–3, colchicine treatment was stopped after symptom-free periods of 26, 24, and 18 months, respectively, patient 1 experienced a recurrence 6 months after colchicine treatment was withdrawn. Treatment was restarted (0.5 mg/12 hr) with prednisone (30 mg/day in decreasing doses until withdrawal at week 4). Twenty-two months later, the patient remained asymptomatic. Patients 2 and 3 remained

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Etiology</th>
<th>Crises before colchicine (n)</th>
<th>Months between crises</th>
<th>Previous treatment</th>
<th>Date colchicine started</th>
<th>Total follow-up (months)</th>
<th>Withdrawal date</th>
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<tr>
<td>1</td>
<td>43</td>
<td>M</td>
<td>Idiopathic</td>
<td>4</td>
<td>24, 6, 8</td>
<td>Prednisone, acetylsalicylic acid</td>
<td>03-18-85</td>
<td>54</td>
<td>05-05-87(*)</td>
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<td>6</td>
<td>4, 1, 2, 2, 3</td>
<td>Prednisone, acetylsalicylic acid</td>
<td>03-14-86</td>
<td>42</td>
<td>03-10-88</td>
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<tr>
<td>3</td>
<td>28</td>
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<td>1, 2</td>
<td>Prednisone, acetylsalicylic acid</td>
<td>06-05-86</td>
<td>39</td>
<td>01-15-88</td>
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<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>Post-acute myocardial infarction</td>
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<tr>
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<td>3</td>
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<td>05-04-88</td>
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<td>56</td>
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<td>4</td>
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<td>11-10-88</td>
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</tbody>
</table>

Mean±SD 3.33±4.3 p<0.002 24.33±16.1

*Recurrence appears 6 months after colchicine was stopped.

**TABLE 1. Clinical Characteristics and Follow-Up**

*Recurrence appears 6 months after colchicine was stopped.*
asymptomatic 18 and 20 months, respectively, after treatment with colchicine was stopped.

Inclusion of patient 3 requires explanation: the acute pericarditis was associated with disseminated lupus erythematosus characterized by photosensitivity, arthritis, oral ulcers, and positive antinuclear antibodies. The patient was initially treated with acetylsalicylic acid (4 g/day) and presented with a recurrence 1 month later. Prednisone treatment was begun (initial dosage, 60 mg/day; gradually reduced to 5 mg/wk). After 2 months, prednisone was reduced to 15 mg, and the patient presented with another recurrence. Prednisone was increased to 30 mg/day, and colchicine (1 mg/day) was started. Prednisone was again progressively reduced until suppression of symptoms; colchicine was continued for 18 months. No additional recurrences were observed. In this patient, although the initial acute pericarditis was associated with disseminated lupus erythematosus, subsequent recurrences were not accompanied by other manifestations of disseminated lupus erythematosus. Furthermore, although these recurrences were secondary to disseminated lupus erythematosus, colchicine proved efficacious in their prevention.

During follow-up, no side effects requiring modification of the therapeutic regimen were observed.

**Discussion**

Acute idiopathic pericarditis is a relatively benign condition. One of the main complications is recurrence, which occurs in 15–25% of patients after the cessation of anti-inflammatory drug therapy, either immediately or after a symptom-free interval of weeks or months. Levy and Patterson reported recurrences in three of 27 patients, one appearing 8 years and one appearing 10 years after the initial attack. In Spain, the incidence rate of recurrence after the first episode is 20% (44 of 221). Of these 44 cases, 22 experienced two recurrences, 19 experienced from three to five relapses, and five experienced more than five recurrences. Although recurrences are often self-limiting, the duration of the active or recurrent process was 5 years or more in 19 of 31 patients as reported by Fowler and Harbin. In seven patients, the duration was 8 years or more. Colchicine has been used for several centuries as an anti-inflammatory agent for the treatment of acute gouty arthritis. Colchicine is also used in the treatment of acute crises of chondrocalcinosis and other arthritic crises (e.g., sarcoidosis). Colchicine is the adjuvant prophylactic drug needed when starting hypouricemic treatment with uricosuric or uricolytic drugs to prevent acute gouty crisis due to sudden mobilization of uric acid.

Colchicine binds to tubulin, blocks mitosis, and inhibits a variety of functions of polymorphonuclear leukocytes, both in vivo and in vitro. Colchicine interferes with the transcellular movement of collagen. The proximity of lymphoid components and fibroblasts at inflammatory sites and the production of lymphokines, which influences fibroblast chemotaxis, proliferation, and protein synthesis, are now well-recognized phenomena. Because of these effects, colchicine has been advocated for use in the treatment of many diseases. The peak concentration of colchicine in white blood cells may be at least 16-fold greater than the peak concentration in plasma. This preferential concentration of colchicine in lymphocytes is related to its observed therapeutic effects.

The side effects of colchicine are usually reversible and consist mainly of nausea, diarrhea, and abdominal pain. Other reported complications are rare and include alopecia, agranulocytosis, aplastic anemia, myopathy, angioneurotic edema, epistaxis, chromosomal dysfunction, and azoospermia.

In a recent report, we described the characteristics of the first three patients with recurrent pericarditis who were treated with colchicine (patients 1–3 in Table 1). Based on these promising results, we began an open-label prospective study in which we included patients with recurrent pericarditis (minimum, three crises) who had not responded to standard treatment. The results show good tolerance to treatment with no side effects or recurrences. Only one patient (patient 1, in whom colchicine was withdrawn after a symptom-free period of 26 months) presented with a recurrent episode of pericarditis that appeared after treatment with colchicine had been stopped (6 months later). Once the acute crisis was controlled with prednisone and colchicine, prednisone was progressively decreased until total withdrawal at 1 month. The patient is presently asymptomatic 22 months later and is on only colchicine.

Recurrent pericarditis is usually self-limiting. Therefore, it is possible that the absence of symptoms in some of our patients was a manifestation of spontaneous resolution. However, we consider this unlikely because of the frequency of recurrences in our patients (seven in one patient) before treatment with colchicine. In the patient we described above, who had been asymptomatic for more than 2 years, a recurrence appeared 6 months after colchicine had been stopped. This observation supports the suppressive effect of this drug. Furthermore, this patient remains asymptomatic after treatment with colchicine was restarted, lending additional support to this possibility.

The beneficial effects of colchicine may be explained in two ways. First, colchicine may act independently from prednisone and be effective alone in preventing recurrences. Second, it is possible that colchicine is effective in preventing recurrences only once the flare-up has been controlled by a corticosteroid, allowing withdrawal of the latter after a short period of treatment. We are inclined to support this second possibility because all of our patients had received prednisone either alone or associated with nonsteroid anti-inflammatory drugs (Table 1). Furthermore, in one patient in whom the recurrent crisis was treated with colchicine alone...
during the acute phase (a 47-year-old patient with a previous myocardial infarction and five previous recurrences of pericarditis), treatment was unsuccessful.31 We do not consider colchicine to be a failure in the prevention of recurrences in this case as it was used to treat only the acute phase of pericarditis. In summary, although colchicine may not be efficient in the acute phase of pericarditis (with severe inflammation), it may help avoid the triggering mechanism of the recurrence (probably immunological).

We have not found any data in the literature regarding the usefulness of colchicine in the treatment of recurrent pericarditis. Our results, although encouraging, should be interpreted as preliminary due to the small number of patients studied. A large, placebo-controlled clinical trial is warranted to demonstrate whether colchicine is successful in preventing new recurrences of acute pericarditis.

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