

## Colchicine for the Prevention of Recurrent Pericarditis

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### Abstract

The most troublesome complication of acute pericarditis is recurrent episodes of pericardial inflammation, which occur in 15–32% of cases. It was recently found that viral infection has a major role, but in many cases the cause is unknown. The optimal method for prevention has not been fully established; accepted modalities include non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and pericardiectomy. Based on the proven efficacy of colchicine in familial Mediterranean fever, several small and large-scale international clinical trials have shown the beneficial effect of colchicine therapy in preventing recurrent pericarditis. Indeed, colchicine-treated patients consistently display significantly fewer recurrences, longer symptom-free periods, and even when attacks occur they are weaker and shorter in nature. It was also found that pretreatment with corticosteroids substantially attenuates the efficacy of colchicine, as evidenced by significantly more recurrence episodes and longer therapy periods. Colchicine is a safe and effective modality for the treatment and prevention of recurrent pericarditis, especially as an adjunct to other modalities, since it provides a sustained benefit superior to all current modalities. The safety profile seems superior to other drugs such as corticosteroids and immunosuppressive drugs.

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Pericardial inflammation, which is characterized by a combination of clinical signs, symptoms and diagnostic tests such as electrocardiography and chemical blood analysis, is not a rare disorder. Practically, the etiology remains obscure in most cases although many causes have been identified. Usually, pericarditis manifests acutely but can further evolve to chronic or recurrent forms in up to a third of the cases. The management of pericarditis generally includes treatment of the acute phase and prevention of further episodes. Much attention has been given in the last few decades to identification of new and effective preventive measures for recurrent episodes of pericarditis. Here we review the potential use of the drug colchicine, which has been proven efficacious in familial Mediterranean fever, in the prevention of recurrent pericarditis, and provide the current European guidelines accordingly.

### Acute pericarditis

Acute pericarditis is an inflammatory disease of the epicardium, diagnosed in one in every 1000 hospital admissions in the United States [1]. Diagnosis of AP is based on the presence of at least

two of the following clinical and/or laboratory findings: excruciating pleuritic chest pain, pericardial friction rub, widespread saddle-shaped or concave upward ST segment elevation or PR depression on the electrocardiogram, and new or worsening pericardial effusion. Elevation of inflammatory markers, such as C-reactive protein, is essential to confirm the diagnosis. Several etiologies may account for AP, including viral, bacterial, autoimmune, post-pericardiotomy, post-myocardial infarction, cardiac trauma, and neoplasm. In the majority of cases (about 85%) the etiology remains unknown also after exclusion of the main specific causes (tuberculous, other bacterial, neoplastic, related to connective tissue diseases), and they are labeled “idiopathic.” Treatment usually consists of aspirin or a non-steroidal anti-inflammatory agent, corticosteroids, and treatment of the underlying cause, when possible [1]. Corticosteroid therapy has few specific indications in autoimmune and autoreactive forms, and when aspirin or NSAID is contraindicated.

### Recurrent pericarditis

Recurrent pericarditis is generally manifested by recurrence of AP symptoms after resolution and elimination of the inciting agent [2-4]. RP develops in 15–32% of AP patients not treated with colchicine [3,5-6], usually within 18 to 20 months after the initial AP episode, but may occur after longer periods [6,7]. The disease usually has a relapsing-remitting pattern [2-4], but may be more chronic in some cases [8]. RP was defined in the CORE study as the combination of a documented initial AP attack with evidence of either recurrence or, less often, of persistent pericarditis [9]. The definition of recurrence includes pleuritic chest pain (most common symptom) and one or more of the following signs: fever, pericardial friction rub, ECG changes, echocardiographic evidence of pericardial effusion, and an elevation in the white blood cell count, erythrocyte sedimentation rate or C-reactive protein [9]. Elevated markers of inflammation confirm the diagnostic suspicion. There is a considerable variability in the number of recurrences and in the length of remission intervals among patients. Up to 50% have only one to two recurrences [7,9], usually over several months to a few years or, in some cases, as

AP = acute pericarditis

NSAID = non-steroidal anti-inflammatory drugs

RP = recurrent pericarditis

long as 15 years [3]. Tamponade and constrictive pericarditis are rare complications even in patients who had tamponade during the initial episode [10], which seldom leads to cardiomyopathy [3,10]. Idiopathic forms of recurrence have a very good prognosis without risk of constriction, even if there were several recurrences [11].

Most clinicians and investigators regard RP as an autoimmune phenomenon, based on serological findings and frequent responsiveness to immunosuppressive therapy. However, European investigators have recently demonstrated a higher prevalence of infectious etiology (infection or re-infection) by employing pericardioscopy, epicardial biopsy and polymerase chain reaction [8,12]. Autoreactive pericarditis can be determined only if other etiologies (infectious, neoplastic, systemic or metabolic) have been excluded and pericardial fluid analysis reveals several immunological features, including increased number of mononuclear cells, anti-sarcolemmal antibodies and inflammatory cytokines (interleukins-6 and 8 and interferon-gamma) [8,12]. Clinical features have a limited yield in predicting the development of RP, but lack of response to NSAID treatment increases the risk for RP and pericardial constriction [5]. Similarly, inappropriate corticosteroid therapy in AP promotes development of RP, possibly due to enhanced viral replication [6,9,13,14].

## Treatment

Treatment of RP may be prolonged, which requires compliance and effective communication with the patient. Therapeutic modalities include NSAIDs, colchicine, corticosteroids, intrapericardial therapy and pericardiectomy. The 2004 European Society of Cardiology guidelines issued a class I recommendation for the use of NSAIDs to treat AP [15] [see box]. High dose short-term corticosteroid therapy usually induces remission, but requires prolonged or frequent administration, potentially leading to serious complications and even to an increased rate of recurrence [6,9,14,16]. Therefore, it is recommended that the use of steroids for RP be limited. Moreover, the experience from treating serositis in other autoimmune forms suggests that lower doses, such as 25–50 mg of prednisone/day, may be equally effective to treat the disease and has less severe side effects [17]. In this review we will focus on the role of colchicine in the prevention and treatment of RP.

## Colchicine

Colchicine is an alkaloid drug that is effectively used in several inflammatory diseases, such as familial Mediterranean fever, chronic gout and Behçet's syndrome. Colchicine inhibits tubulin polymerization, thereby inhibiting migration of polymorphonuclear cells into inflamed sites and decreasing metabolic activity and phagocytosis to efficiently break the inflammation cycle.

The beneficial effect of colchicine in RP was demonstrated in a 1990 study of nine patients who had at least three recurrences either on NSAID or corticosteroid treatment [18]. While the symptom-free period before initiation of colchicine treatment was 3.3 months, none of the patients exhibited a recurrence after treatment during a mean follow-up of 24.3 months ( $P < 0.002$ )

[18]. Similar results were observed in another study of eight RP patients who were treated either with a combination of NSAIDs and corticosteroids (6/8 patients) or with corticosteroids followed by pericardiocentesis (2/8 patients). The mean symptom-free period before initiation of colchicine treatment was 6 months, and 26 months during follow-up on colchicine [19].

A multicenter international review of the efficacy of 1 mg/day colchicine in 51 patients with 187 recurrences and a mean symptom-free period of 3 months, despite conventional treatment with NSAIDs and corticosteroids, has demonstrated remarkable results [20]. Indeed, only seven patients exhibited a total of 10 minor clinical relapse events on colchicine treatment over 36 months of follow-up; half of these events occurred after corticosteroids were stopped. Colchicine was discontinued in 39 patients, of whom 14 (36%) relapsed with a total of 10 events within 1 month or with a total of 17 events within 1 year of cessation of colchicine. It is noteworthy that all recurrences were clinically minor. The beneficial effect of colchicine was evident by the increasing symptom-free period both during treatment (3.1 months vs. 17.8 months,  $P < 0.001$ ) and after treatment (3.1 months vs. 30.3 months,  $P < 0.001$ ); the symptom-free period globally was 3.1 to 43 months ( $P < 0.001$ ). Furthermore, it was found that the use of colchicine with or without NSAIDs reduces or eliminates the need for corticosteroids in patients with RP, since the number of recurrences decreased from 4.5 to 2.5 ( $P < 0.001$ ) and the period of colchicine treatment itself was considerably shortened from 28.3 months to 8.4 months [20].

The most recent data come from the randomized CORE study, in which 84 consecutive patients with a first episode of RP were randomly assigned to 1 month aspirin either alone or in combination with colchicine for 6 months [9]. Colchicine therapy was safe, did not exhibit any significant toxicity, and resulted in an impressive clinical outcome. Colchicine-treated patients displayed a marked and significant reduction in the primary endpoint of the actuarial rate of recurrence at 18 months (24% vs. 51%) and a significant reduction in the secondary endpoint of symptom persistence at 72 hours (10% vs. 31%), when compared to aspirin alone [9]. Similar benefits were noted with colchicine in the COPE trial of patients with a first episode of acute, usually idiopathic pericarditis [6]. In addition, a potential benefit for colchicine has been shown in the prevention of post-pericardiotomy syndrome in patients after cardiac surgery (10.6% vs. 21.9% placebo,  $P < 0.135$ ) [21]. Further evaluations in larger clinical trials are warranted. The use of colchicine in addition to an NSAID or as monotherapy for RP was given a class I recommendation by the 2004 European Society of Cardiology guidelines [15]. Importantly, previous therapy with corticosteroids in the CORE study was an independent predictor of further recurrences after colchicine therapy [9].

Another study showed that pretreatment with corticosteroids attenuates the beneficial effect of colchicine treatment [16]. This international multicenter study included 119 patients under full colchicine treatment for up to 185 months of follow-up (71 were treated with corticosteroids prior to the study, 48 patients were not). A substantially higher percentage of patients relapsed

among the 71 patients both during colchicine treatment (20% vs. 10%) and after colchicine was discontinued (40% vs. 10%). The striking differences between the two groups were further evident in the length of the required treatment with colchicine (24.5 months vs. 9.7 months,  $P = 0.001$ ) and in relapses per patient (0.65 vs. 0.18,  $P = 0.006$ ) [16]. Importantly, there were two relapses per patient in the steroid group as compared to the no-steroid group (5.1 vs. 2.81,  $P = 0.001$ ). No correlation between the number of relapses/patient and any continuous parameter could be identified. Multivariate logistic regression analysis for prediction of having relapses after colchicine treatment was statistically significant for male gender (odds ratio = 4.2,  $P = 0.03$ ) and previous corticosteroid treatment (odds ratio = 6.7,  $P = 0.01$ ) [15].

#### Colchicine regimen: recommendations of the European Society of Cardiology

- 2 mg/day for one or two days, followed by a maintenance dose of 1 mg/day. Use of loading dose is controversial (may increase the risk of side effects), while lower maintenance doses such as 0.5 mg/day may be equally effective with fewer side effects (above all in patients < 70 kg). RP patients should be treated with aspirin or other NSAID plus colchicine (1–2 mg on the first day, followed by 0.5 once or twice daily for 6 months). The lower colchicine dose (1 mg initial dose followed by 0.5 mg once daily) is given to patients who weigh less than 70 kg or who do not tolerate the higher dose. A practical approach is to use low starting doses (0.5 mg/day), then increasing up to 0.5 mg twice a day in patients > 70 kg, if tolerated.
- Maintenance/prophylactic dose should be reduced by 50% in individuals > age 70, and in patients with glomerular filtration rates below 50 ml/min.
- All patients should undergo a careful monitoring of possible side effects, including blood analyses (transaminases, serum creatinine, creatine kinase, and blood cell count) before initiation of therapy, and at least after 1 month of treatment.

#### Precautions and future research

Although colchicine at low doses (0.5–1.2 mg per day) has been found to be safe even when given continuously over decades, there are other less common (< 1%) possible side effects to be considered (bone marrow suppression, hepatotoxicity, myotoxicity) beyond the well-known gastrointestinal side effects encountered in 5–10% of cases. Chronic renal insufficiency leading to increased colchicine levels appears to be the major risk factor for side effects and other possible negative interactions. Colchicine is also a substrate of P-glycoprotein, a transporter involved in the elimination of several drugs. Macrolides are inhibitors of P-glycoprotein and cytochrome P450-dependent enzymes and may decrease colchicine excretion. Co-administration of colchicine and macrolides may impair colchicine elimination, resulting in possible drug excess, particularly in the elderly and those with renal insufficiency.

At present, it seems reasonable to avoid the co-administra-

tion of colchicine and macrolides. It is also prudent to reduce the maintenance/prophylactic dose by 50% in individuals over the age of 70 and in patients with impaired renal function and glomerular filtration rates below 50 ml/min. Every patient should undergo a careful monitoring of possible side effects, including blood analyses (transaminases, serum creatinine, creatine kinase, and blood cell count) before starting the drug, and later after at least 1 month of treatment. Further studies are required to validate the use of colchicine in AP, while stronger evidence supports its use in RP.

#### Conclusions

Colchicine is a safe and effective modality for the treatment and prevention of recurrent pericarditis, especially as an adjunct to other modalities since it provides a sustained benefit superior to all current modalities. Moreover, the safety profile seems superior to other drugs such as corticosteroids and immunosuppressive drugs.

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