Reviews

Prevention of Recurrent Pericarditis With Colchicine in 2012

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ABSTRACT

The most troublesome complication of acute pericarditis is recurrent pericardial inflammation, which occurs in 15%–32% of cases. The optimal method for prevention has not been fully established; accepted modalities include nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, and pericardiectomy. Over the last years, objective clinical evidence has matured and clearly indicates the important role and beneficial clinical effect of colchicine therapy in preventing recurrent pericarditis caused by various etiologies. Colchicine-treated patients consistently display significantly fewer recurrences and longer symptom-free periods, and even when attacks occur, they are weaker and shorter in nature. Notably, pretreatment with corticosteroids substantially attenuates the efficacy of colchicine, causing significantly more recurrences and longer therapy periods. The safety profile seems superior to other drugs, such as corticosteroids and immunosuppressive drugs. Colchicine is a safe and effective modality for the treatment and prevention of recurrent pericarditis, especially as an adjunct to other modalities, because it provides a sustained benefit, superior to all current modalities.

Introduction

Pericardial inflammation is not a rare disorder. It is characterized by a combination of clinical signs, symptoms, and diagnostic tests such as electrocardiography (ECG) and chemical blood analyses. Practically, the etiology remains obscure in most cases, although many causes have been identified. Usually, pericarditis manifests acutely but can further evolve in up to third of the cases to chronic or recurrent forms. The management of pericarditis generally includes treatment of the acute phase and prevention of further episodes. Much attention has been given in the last several decades to identification of new and efficient 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 and in the prevention of recurrent pericarditis, and comment on the current European guidelines accordingly.

Acute Pericarditis

Acute pericarditis (AP) is an inflammatory disease of the epicardium, diagnosed in 1 in every 1000 hospital admissions in the United States.[1] Diagnosis of AP is based on the presence of ≥2 of the following clinical and/or laboratory findings: pleuritic chest pain, pericardial friction rub, widespread saddle-shaped or concave upward ST-segment elevation or PR-segment depression on the ECG, and new or worsening pericardial effusion. Elevation of inflammatory markers, such as C-reactive protein, is useful to confirm the clinical suspicion. Several etiologies may account for AP, including viral, bacterial, and autoimmune etiologies as well as postpericardiotomy, 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. A recent prospective study on 500 AP patients showed that development of constrictive pericarditis is a rare complication of viral or idiopathic forms, whereas it is relatively frequent for specific etiologies, such as tuberculous pericarditis (20%–25%; 31.65 cases per 1000 person-years) and purulent pericarditis (30%–33%; 52.7 cases per 1000 person-years).[2] Treatment usually consists of aspirin or a nonsteroidal anti-inflammatory drug (NSAID), 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 (RP) is generally manifested by recurrence of AP symptoms after resolution and elimination

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Received: September 1, 2012
Accepted with revision: January 2, 2013

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22098

of the inciting agent.[3–5] Recurrent pericarditis develops in 15%–32% of AP patients not treated with colchicine,[3,6,7] usually within 18–20 months after the initial AP episode, but it also may occur after longer periods.[6,8] The disease usually has a relapsing-remitting pattern[3–5] but may be more chronic in some cases.[9] Recurrent pericarditis was defined in the Colchicine for Recurrent Pericarditis (CORE) study as the combination of a documented initial AP attack with evidence of either recurrence or, less often, persistent pericarditis.[10] The definition of recurrence includes pleuritic chest pain (most common symptom) and ≥1 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.[10] 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 1–2 recurrences,[8,10] usually over several months to a few years, or, in some cases, as long as 15 years.[3] Tamponade and constrictive pericarditis are rare complications, even in patients who had tamponade during the initial episode,[11] and seldom lead to cardiomyopathy.[3,11] Idiopathic forms of recurrence have a very good prognosis without risk of constriction, even if there were several recurrences.[12]

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 reinfection) by employing pericardioscopy, epicardial biopsy, and polymerase chain reaction.[9,13] 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, antisarcolemmal antibodies, and inflammatory cytokines (interleukin-6, interleukin-8, and interferon-γ).[9,13] 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.[7] Similarly, inappropriate corticosteroid therapy in AP promotes development of RP, possibly due to enhanced viral replication.[6,10,14,15]

Treatment

Treatment of RP may be prolonged and 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 (see Appendix).[16] 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.[6,10,15,17] Therefore, it is recommended that the use of steroids for RP should 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 with less-severe side effects.[18] 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 Beh¸et 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 9 patients who had ≥3 recurrences either on NSAID or corticosteroid treatment.[19] Although 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 ($P < 0.002$).[19] Similar results were observed in another study of 8 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.[20]

A multicenter international review of the efficacy of 1 mg/day colchicine in 51 patients with 187 recurrences, despite conventional treatment with NSAIDs and corticosteroids, and a mean symptom-free period of 3 months, has demonstrated remarkable results.[21] Indeed, only 7 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 mo vs 17.8 mo, $P < 0.001$) and after treatment (3.1 mo vs 30.3 mo, $P < 0.001$); the symptom-free period globally was 3.1–43 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, as 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.[21]

The first significant data came 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.[10] 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 with aspirin alone.[10] Similar benefits were noted with colchicine

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22098

in the Colchicine for Acute Pericarditis (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 postpericardiotomy syndrome in patients after cardiac surgery (10.6% vs 21.9% placebo, $P < 0.135$).[22] 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.[16] Importantly, previous therapy with corticosteroids in the CORE study was an independent predictor of further recurrences after colchicine therapy.[10] Recently, the Colchicine for Recurrent Pericarditis (CORP) trial, a prospective, randomized, double-blind, placebo-controlled multicenter trial, evaluated the efficacy and safety of colchicine for the secondary prevention of recurrent pericarditis in 120 RP patients.[23] Patients were randomly assigned to receive either placebo or colchicine, in addition to conventional therapy. Remarkably, the recurrence rate was 24% in the colchicine group and 55% in the placebo group at 18 months (absolute risk reduction, 0.31 [95% confidence interval {CI}: 0.13-0.46]; relative risk reduction, 0.56 [95% CI: 0.27-0.73]; number needed to treat, 3 [95% CI: 2-7]). Colchicine also reduced the persistence of symptoms at 72 hours (absolute risk reduction, 0.30 [95% CI: 0.13-0.45]; relative risk reduction, 0.56 [95% CI: 0.27-0.74]) and mean number of recurrences, increased the remission rate at 1 week, and prolonged the time to subsequent recurrence. There were no differences in rates of side effects and drug withdrawal.[23]

Another study shows that pretreatment with corticosteroids attenuates the beneficial effect of colchicine treatment.[17] 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 and 48 patients were not). A substantially higher percentage of patients treated with corticosteroids 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 2 groups, steroids vs no steroids, were further evident in the length of the required treatment with colchicine (24.5 mo vs 9.7 mo, respectively, $P = 0.001$) and in relapses per patient (0.65 vs 0.18, respectively, $P = 0.006$).[17] Importantly, there were 2 relapses per patient in the steroid group as compared with the no-steroid group (5.1 vs 2.81, respectively, $P = 0.001$). 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 sex (odds ratio: 4.2, $P = 0.03$) and previous corticosteroid treatment (odds ratio: 6.7, $P = 0.01$).[16]

Recently, further positive lines of evidence for the role of colchicine in prevention of perdicardial disease were obtained. The Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) study,[24] a multicenter, double-blind, randomized trial, tested 360 patients who were randomized to receive on third day postpericardiectomy for placebo or colchicine. Remarkably, colchicine significantly reduced the incidence of the postpericardiotomy syndrome at 12 months compared with placebo (respectively, 8.9 vs 21.1%, $P = 0.002$; number needed to treat, 8). Colchicine also reduced the secondary endpoint, which included the combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses, as compared with placebo (respectively, 0.6 vs 5.0%, $P = 0.024$).

Moreover, an additional beneficial preventive effect of colchicine in the postoperative setting is also its possible capability to prevent postoperative atrial fibrillation. Colchicine administration significantly reduced the incidence of postoperative atrial fibrillation (12.0% vs 22.0%, respectively, $P = 0.021$; relative risk reduction, 45%; number needed to treat, 11), with a shorter in-hospital stay (9.4 $\pm$ 3.7 d vs 10.3 $\pm$ 4.3 d, $P = 0.040$) and rehabilitation stay (12.1 $\pm$ 6.1 d vs 13.9 $\pm$ 6.5 d, $P = 0.009$).[25] There were no significant differences in the rate of side effects in the colchicine and placebo groups (respectively, 8.9 vs 5.0%, $P = 0.212$).[24,25] The beneficial role of colchicine in prevention of postpericardiotomy pericarditis was concomitantly suggested by a meta-analysis conducted on available data.[26]

Precautions and Future Research

Although colchicine at low doses (0.5–1.2 mg/d) 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. Coadministration 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 coadministration of colchicine and macrolides. It is also prudent to reduce the maintenance/prophylactic dose by 50% in individuals age >70 years and in patients with impaired renal function and glomerular filtration rates <50 mL/minute. 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 probably when caused by certain etiologies, whereas stronger evidence supports its use in RP.[27–30]

Conclusion

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

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DOI:10.1002/clc.22098

Appendix

Colchicine regimen: recommendations of the European Society of Cardiology:

- Dose of 2 mg/day for 1 or 2 days, followed by a maintenance dose of 1 mg/day. Use of loading dose is controversial (may increase the risk of side effects), whereas lower maintenance doses such as 0.5 mg/day may be equally effective with fewer side effects (above all in patients <70 kg). Recurrent pericarditis patients should be treated with aspirin or another nonsteroidal anti-inflammatory drug 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 <70 kg or who do not tolerate the higher dose. A practical approach is to use low starting doses (0.5 mg/d), then increasing up to 0.5 mg twice a day in patients >70 kg, if tolerated. Avoiding the loading dose may improve the compliance.
- Maintenance/prophylactic dose should be reduced by 50% in individuals age >70 years and in patients with glomerular filtration rates <50 mL/minute.
- 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 after at least 1 month of treatment.

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DOI:10.1002/clc.22098