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SCIENTIFIC EDITORIAL

Colchicine in acute pericarditis: A new standard?

La colchicine fait-elle partie du traitement systématique des péricardites aiguës ?

Philippe Meurin*, Jean-Yves Tabet

Les Grands-Prés, 27, rue Sainte-Christine, 77174 Villeneuve-Saint-Denis, France

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Background

Acute pericarditis is a common disease; despite the lack of precise epidemiological data, approximately 1% of hospitalized patients and 5% of patients admitted to emergency departments for non-acute myocardial infarction chest pain exhibit acute pericarditis [1]. With acute pericarditis, some simple questions must be raised.

Is it idiopathic or viral pericarditis, or is there a need for an extensive aetiological search?

In developed countries, idiopathic or viral pericarditis (IVP) is the most common final diagnosis in the immunocompetent patient and a more precise diagnosis is often not needed [2]. However, in about 15—20% of cases, a specific cause must be ruled out: systemic disease (usually autoimmune); tuberculosis; neoplasic pericarditis; or postcardiac injury syndrome. A few clinical factors can suggest secondary pericarditis and therefore indicate a need for a full aetiological search [1]: fever greater than 38 °C; subacute onset (symptoms developing over several days or weeks); large pericardial effusion or tamponade; lack of response to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) after at least 1 week; and female sex.

Abbreviations: CI, confidence interval; HR, hazard ratio; IVP, idiopathic or viral pericarditis; NSAID, non-steroidal anti-inflammatory drug; PPS, postpericardiotomy syndrome; RP, recurrent pericarditis.

* Corresponding author.
E-mail address: philippemeurin@hotmail.com (P. Meurin).

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Finally, diagnostic tests for suspected pericarditis should routinely include electrocardiography, echocardiography, chest X-rays and simple biological tests (to search for inflammation and myocardial lesions); in the absence of the factors detailed above, an extensive aetiological search is not necessary [2,3].

What is the evolution?

Results from analysis of a large registry published in 2007 [1] are revealing: 453 patients (IVP 83%; mean age 52 ± 18 years; men 55%) with acute pericarditis were followed up for 31 months on average. Complications were detected in 95 patients: tamponade (3.1%); constrictive pericarditis (1.5%); and, mostly, recurrences (18.3%). On multivariable analysis, risk factors for complications were only female sex (hazard ratio [HR]: 1.65; 95% confidence interval [CI]: 1.08—2.52), large pericardial effusion (HR: 2.51; 95% CI: 1.37—4.61) and failure of aspirin or NSAID treatment (HR: 5.50; 95% CI: 3.65—8.51). These results confirm previous results published by the same team [4]: among 300 consecutive patients with acute pericarditis, 254 (85%) were at low risk and therefore not admitted to hospital. The protocol was safe because no case of cardiac tamponade was observed.

The most troublesome complication is recurrence (15—50%), which has a strong negative impact on the quality of life of patients. The aetiology and pathogenesis of idiopathic acute recurrent pericarditis (RP) are controversial and seem to involve a mixture of infectious, autoimmune and autoinflammatory pathways [5]. Relapses may occur with reduced drug doses (incessant pericarditis) or at varying intervals after discontinuation of the treatment (RP). In survey results [6] published in 2005 for 55 patients with recurrences, the mean recurrence number was 1.45/patient (range: 1—5). The only factor independently associated with risk of recurrence was previous use of corticosteroids (odds ratio: 10.35; 95% CI: 4.46—23.99; $P < 0.001$). In a subsequent study, elevated C-reactive protein after 1 week also seemed to be a risk factor for recurrence [7].

What treatment should we use?

Because of the relative lack of randomized trials, the management of pericardial diseases is largely empirical. However, European guidelines [3] were published in 2004, and a few teams — mostly Italian — are expanding our knowledge on this subject.

Corticosteroid administration must be avoided in most cases; indeed, as explained above, such administration is a risk factor for recurrence, and because the treatment is often prolonged, side effects are frequent [2,8]. However, in systemic autoimmune diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus, polymyositis), treatment for the underlying disease, which can include corticosteroids, must be intensified [3].

Aspirin or NSAIDs remain the (historical) mainstay of treatment (level of evidence B, class I in the European guidelines). The treatment is efficient if the drug is used at an appropriate anti-inflammatory dosage (e.g. aspirin 2—4 g per day, ibuprofen 1600—3200 mg per day) for 1—2 weeks. Afterwards, the optimal length of treatment is debatable (4—8 weeks) and the need for gradual tapering is increasingly proposed [2]. C-reactive protein concentration could be used as a marker of disease activity to guide treatment length [7].

What is the role for colchicine in this setting?

Meadow saffron bulbs have been used for about 3000 years as therapeutic agents for gout and constipation, and for their emetic effects. Colchicine was isolated in 1820 and Alfred Houdé was the first pharmacist to sell colchicine pills in 1884 in Paris. The compound can be extracted from two plants of the Lily family: *Colchicium autumnale* (meadow saffron) and *Gloriosa superba* (glory lily).

The official indication for colchicine is the treatment and prevention of gouty attacks but it is also widely used (off label) for treating familial Mediterranean fever and primary biliary cirrhosis. The exact mechanism of action of the drug is not fully understood. It shows preferential concentration in white blood cells (more than 16 times the peak concentration in plasma), where it reduces the inflammatory response. Most of the pharmacological effects seem to be related to the capacity of the drug to inhibit the process of microtubule self-assembly by binding beta-tubulin with the formation of tubulin-colchicine complexes, thus interfering with several cellular functions (e.g. chemotoxis, degranulation, phagocytosis) [9]. In this way, colchicine decreases leucocyte motility and phagocytosis.

Because of the proven efficacy of colchicine in preventing relapses of systemic inflammatory processes in familial Mediterranean fever (recurrent polyserositis), in 1987, Rodriguez de la Serna et al. tested colchicine to prevent recurrences of acute pericarditis in three patients with RP (two idiopathic and one with systemic lupus erythematosus) [10]. Thereafter, several retrospective studies [9] involving 9 to 51 patients seemed to confirm the efficiency of the drug in RP.

In 2005, 1 year after the publication of the European guidelines on management of pericardial diseases [3], the results of two important (but open-label) studies were made available. In the CORE (COlchicine for REcurrent pericarditis) trial [11], 84 patients with a first episode of RP were randomly assigned to receive conventional treatment with aspirin alone (or corticosteroids when aspirin was contraindicated) or aspirin plus colchicine. Anti-inflammatory drugs were given for about 3—5 weeks (progressively tapered) and colchicine (0.5—1 mg per day) for 6 months. The results were impressive: recurrence rates at 18 months were 50.6% in the conventional treatment group vs 24.0% in the conventional treatment plus colchicine group ($P = 0.022$).

The results of the COPE (COlchicine for PEricarditis) study [12] even suggested prescribing colchicine not only for RP but also at the first pericarditis attack. Indeed, in this trial, 120 patients with a first episode of acute pericarditis were randomly assigned to conventional treatment with aspirin or conventional treatment plus colchicine for 3 months. After a mean follow-up of 18 months, the mean

recurrence rate was reduced from 32.3% (conventional group) to 10.7% (plus colchicine group) ($P = 0.004$). These results confirm those of a preliminary French study of 19 patients published in 1991 [13].

Further studies are required to validate the use of colchicine for pericarditis. We must be grateful to Imazio et al. for conducting the CORP, CORP-2 and ICAP studies [14], which are double-blind, randomized, prospective trials testing colchicine (as adjunct to conventional therapy) in first-attack pericarditis and RP. Results should be available soon.

In the meantime, the results of the COPPS (COlchicine for the Prevention of the Post-pericardiotomy Syndrome) study have been recently published [15]: in this double-blind, placebo-controlled study, colchicine, administered for 1 month from the third postoperative day as a preventive treatment for postpericardiotomy syndrome (PPS) after heart surgery seemed to be efficient. However, the PPS definition was imprecise, the number of 'events' was therefore artificially increased and most were not clinically significant. For instance, only one cardiac tamponade occurred during the study.

Therefore, whether colchicine could help to reduce the volume of postoperative pericardial effusions or prevent the occurrence of tamponades is impossible to predict. The answer to this question will be given by the results of the POPE2 (PostOperative Pericardial Effusion 2) study (promoted by the French society of cardiology) in 2013—2014. For the record, the POPE1 study [16] demonstrated the absence of efficacy of NSAIDs in this particular situation.

In conclusion, growing evidence suggests that colchicine may be useful for acute pericarditis, especially when combined with aspirin or an NSAID and particularly to prevent recurrences, which are the most frequent complication of this disease. Results of four ongoing double-blind trials will help define the indications in first-attack pericarditis and RP, as well as perhaps postoperative pericardial effusions.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Imazio M, Cecchi E, Demichelis B, et al. Indicators of poor prognosis of acute pericarditis. Circulation 2007;115:2739—44.
[2] Imazio M, Spodick DH, Brucato A, et al. Controversial issues in the management of pericardial diseases. Circulation 2010;121:916—28.
[3] Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; the task force on the diagnosis and management of pericardial diseases of the European society of cardiology. Eur Heart J 2004;25:587—610.
[4] Imazio M, Demichelis B, Parrini I, et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. J Am Coll Cardiol 2004;43:1042—6.
[5] Brucato A, Maestroni S, Cumetti D, et al. Recurrent pericarditis: infectious or autoimmune? Autoimmun Rev 2008;8:44—7.
[6] Imazio M, Demichelis B, Parrini I, et al. Management, risk factors, and outcomes in recurrent pericarditis. Am J Cardiol 2005;96:736—9.
[7] Imazio M, Brucato A, Maestroni S, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis: implications for the diagnosis, therapy, and prognosis of pericarditis. Circulation 2011;123:1092—7.
[8] Imazio M, Brucato A, Cumetti D, et al. Corticosteroids for recurrent pericarditis: high versus low doses: a non-randomized observation. Circulation 2008;118:667—71.
[9] Imazio M, Brucato A, Trinchero R, et al. Colchicine for pericarditis: hype or hope? Eur Heart J 2009;30:532—9.
[10] Rodriguez de la Serna A, Guindo Soldevila J, Marti Claramunt V, et al. Colchicine for recurrent pericarditis. Lancet 1987;2:1517.
[11] Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med 2005;165:1987—91.
[12] Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation 2005;112:2012—6.
[13] Millaire A, de Groote P, Decoulx E, et al. Treatment of recurrent pericarditis with colchicine. Eur Heart J 1994;15:120—4.
[14] Imazio M, Cecchi E, Ierna S, et al. CORP (COlchicine for Recurrent Pericarditis) and CORP-2 trials — two randomized placebo — controlled trials evaluating the clinical benefits of colchicine as adjunct to conventional therapy in the treatment and prevention of recurrent pericarditis: study design and rationale. J Cardiovasc Med (Hagerstown) 2007;8:830—4.
[15] Imazio M, Trinchero R, Brucato A, et al. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. Eur Heart J 2010;31:2749—54.
[16] Meurin P, Tabet JY, Thabut G, et al. Nonsteroidal anti-inflammatory drug treatment for postoperative pericardial effusion: a multicenter randomized, double-blind trial. Ann Intern Med 2010;152:137—43.