Therapy for recurrent acute pericarditis: A rheumatological solution?

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Abstract

Objective

To assess the efficacy of a multidrug protocol in recurrent acute pericarditis. We tried also to assess the specific role of colchicine.

Methods

We studied 58 patients (34 males) in the largest monocentric observational study. All patients received prolonged courses of non-steroidal anti-inflammatory drugs; generally we do not start a corticosteroid in recurrent acute pericarditis, but if a steroid had already been started, we planned a very slow tapering; if necessary azathioprine, hydroxychloroquine, and other immunosuppressive drugs were used; 44 patients (27 males, 61.4%) were treated also with colchicine and 14 patients (7 males, 50%) were not given this drug.

Results

After starting our protocol recurrences dropped from 0.48 to 0.03 attacks/patient/month ($p < 0.00001$) within 12 months and remained at the same level till the end of the follow-up (mean 8.1 years) in the whole cohort. In the 44 patients treated with colchicine recurrences dropped from 0.54 to 0.03 attacks/patient/month ($p < 0.00001$) within 12 months, and in 14 patients not given colchicine recurrences decreased from 0.31 to 0.06 attacks/patient/month ($p = 0.002$). In patients treated with colchicine the decrease was significantly higher (0.51) than in patients not taking this drug (0.25) ($p = 0.006$). Colchicine was discontinued by 16.3% of patients because of side effects.

Conclusion

A multidrug protocol including non-steroidal anti-inflammatory drugs at high dosage, slow tapering of corticosteroid, colchicine, reassurance and close clinical monitoring is very effective in recurrent pericarditis; this improvement is more dramatic in colchicine treated patients, but also patients who do not tolerate it can achieve good control of the disease.

Key words

Pericarditis, pericardial diseases, colchicine, anti-inflammatory agents, non-steroidal, prednisone.

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Introduction

Recurrent acute pericarditis is generally idiopathic or post-cardiac injury (PCIS: Post Cardiac Injury Syndrome), and is often a frustrating disease, for both the patient and the physician. Several therapies, particularly colchicine (1-9), can be effective, but these findings have not always been confirmed (10). The role, type and dosages of non-steroidal anti-inflammatory drugs (NSAIDs) are not well established. Steroids have been associated with an higher risk of recurrences (11), and a decreased effectiveness of colchicines (6). It is now a current practice in Rheumatology to treat several diseases with a combination of different drugs, with the aim of minimizing side effects while increasing effectiveness. No study has assessed the role of a similar multidrug therapy in recurrent acute pericarditis.

The primary aim of this study was to assess whether an integrated protocol including non-steroidal anti-inflammatory drugs at high dosage, slow tapering of corticosteroid, colchicine, reassurance and close clinical monitoring might be useful to obtain a good control of the disease; secondary aim was to evaluate the relative efficacy of colchicine by comparing patients treated and not treated with the drug.

Patients and methods

Protocol

We enrolled all patients with recurrent acute pericarditis seen by the senior author AB at Niguarda Hospital, Milan, since 1987. For each patient we selected the time of our first evaluation as the moment that arbitrarily divided his or her clinical course into two phases: the first ran from the onset of the disease to our first assessment, and the second phase from our first assessment, when we implemented our protocol, to the end of follow-up (October 2004). At the first assessment (T0) we started a protocol including (7, 12):

a) NSAIDs used for a long time, till complete normalization of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), at appropriate dosages (preferably indomethacin 75-150 mg/day; if not tolerated ibuprofen 1200-1800 mg/day or aspirin 1500-2400 mg/day or nimesulide 200 mg/day);
b) Generally we do not start a corticosteroid in recurrent acute pericarditis, according to accepted guidelines (3, 4, 13-15) but most of our patients were already taking them when we first saw them, with a long history of recurrences at each withdrawal; we always planned a very slow tapering (using mainly prednisone), over months, having as a target its complete discontinuation if possible;
c) From 1994 colchicine was introduced, if tolerated; to minimize gastrointestinal side effects we started with the dosage of 0.5 mg daily for 7 days, then 1 mg daily; therapy with colchicine was planned for 1-2 years, and was not intended to cure the current attack, but to reduce the rate of subsequent recurrences; colchicine was always added to the previous therapy (NSAIDs and often steroids), and was never used alone;
d) Close clinical monitoring in the acute phase, with monthly clinical evaluations and monthly tests of CRP, ESR, ECG, and frequent echocardiographic controls, but avoiding hospital admission whenever possible;
e) Reassurance concerning possible late sequelae;
f) Introduction of other drugs if needed to reduce the steroid dosage such as hydroxychloroquine, azathioprine, cyclosporine or methotrexate.

The daily cost of a therapy with prednisone 10 mg, colchicine 1 mg and indomethacine 100 mg daily will be about 0.55 euro in Italy, or 1.5 USD in USA.

Patients and inclusion criteria

We studied 61 consecutive patients with recurrent acute pericarditis; 2 were lost to follow-up. One patient with a post-myocardial infarction recurrent pericarditis died 4 months after the first attack for a new myocardial infarction. Thus 58 patients were enrolled in this observational study: fifty-two (89.7%) had been referred to us from other centers after failing to respond to previous therapy. Thirty-four (58.6%) males and

24 (41.4%) females (present mean age 48 yrs, range 19-76) were followed for an average of 8.1 years (median 6, range 1.4 - 43.2 yrs). Their ages at the onset of the disease (first attack) ranged from 9 to 67 years (mean 38.8 years). Patients were included if they presented with an original attack of acute pericarditis defined by the presence of all the following features (12): typical chest pain (with or without a pericardial friction rub); electrocardiographic (ECG) changes suggestive of acute pericarditis; echocardiographic evidence of pericardial effusion; increased C-reactive protein (CRP) or increased erythrocyte sedimentation rate (ESR). Recurrences were defined as the combination of: 1) typical chest pain; 2) increased CRP or ESR; 3) ECG and/or echocardiographic alterations. Since acute pericarditis is an intense inflammatory disease we specified that CRP or ESR had to be elevated in all cases during an acute attack.

At the beginning of the follow-up there was no evidence of definable chronic systemic illness, for example connective tissue disease, neoplasm or chronic infection. In all patients we performed a detailed clinical and immunological evaluation (12). In 8 patients (13.8%) recurrences occurred after pericardiotomy due to cardiac surgery; 2 patients developed recurrent pericarditis immediately after hemopericardium, 1 after curative transcatheter ablation to prevent arrhythmia, and the other after a trial perforation during implantation of a pacemaker; 3 patients (5.2%) developed recurrent pericarditis after acute myocardial infarction. Interestingly we observed 6 patients (10.3%) in which one relative had a confirmed diagnosis of acute idiopathic pericarditis (16). Data were analysed retrospectively. All patients gave written informed consent.

Statistical methods

The proportions were compared with the chi-square test with continuity correction, and the means with the two-tailed *t* test for paired or unpaired samples, as appropriate.

Results

During the period of active disease we observed 358 episodes, with a mean of 2.1 episodes per patient per year (range 0.1-8). The interval among recurrences ranged from 1 month to 39 yrs (median 3 months). These patients had a total of 145 hospital admission for acute recurrent pericarditis, with a mean of 2.6 per patient. Almost all these (135) were before our first evaluation, and in other hospitals, because it is our policy to limit admissions for acute recurrent pericarditis. Cardiologists are generally concerned by a possible evolution in constrictive pericarditis, and a detailed analysis of the good long-term outcome of these patients is object of a separate paper (32).

The majority of the patients (52, 89.7%) were already on a corticosteroid (prednisone in 47 patients, at a dosage ranging from 50 to 20 mg daily, and prednisolone in 5) when we saw them for the first time, and we attempted to taper these very gradually; 9 (15.5%) are still taking them.

Notably no patient was treated with a combination of NSAIDs plus steroids plus colchicine before our first assessment, and only 11 (18.9%) patients were treated with both steroids and NSAIDs; one patient (1.7%) was on NSAIDs plus colchicine. The large majority of the patients arrived to our first evaluation on monotherapy: 31 (53.4%) on steroid only, 14 (24.1%) on NSAIDs only and 1 (1.7%) on colchicine only.

In all the 58 patients we immediately started the multidrug protocol described, with a striking benefit. We defined "attack rate" as the number of recurrences each patient had on average each month: attacks/patient/month; we assessed it at T0 (time of our first assessment), T1 (12 months after), and T2 (end of follow-up, October 2004) (see Fig. 1). The basal attack rate, at our first assessment (T0), was 0.48 attacks/ patient/month; the attack rate dropped to 0.03 attacks/patient/month in the first 12 months after implementing the protocol ($p<0.00001$) (T1), and remained at the same level till the end of the follow-up (T2) (8.1 years on average from the first attack). After implementing the protocol there was no further recurrence in 38/58 patients (65.5%).

In some patients the tapering of steroids required the introduction of other drugs: hydroxychloroquine in 2 patients, azathioprine in 2 patients, cyclosporine in 1 patient, and methotrexate in 1 patient. In the absence of solid data, the choice of the drug derived from a discussion with the patient and the referring physicians (17).

We made also a sub-analysis in which

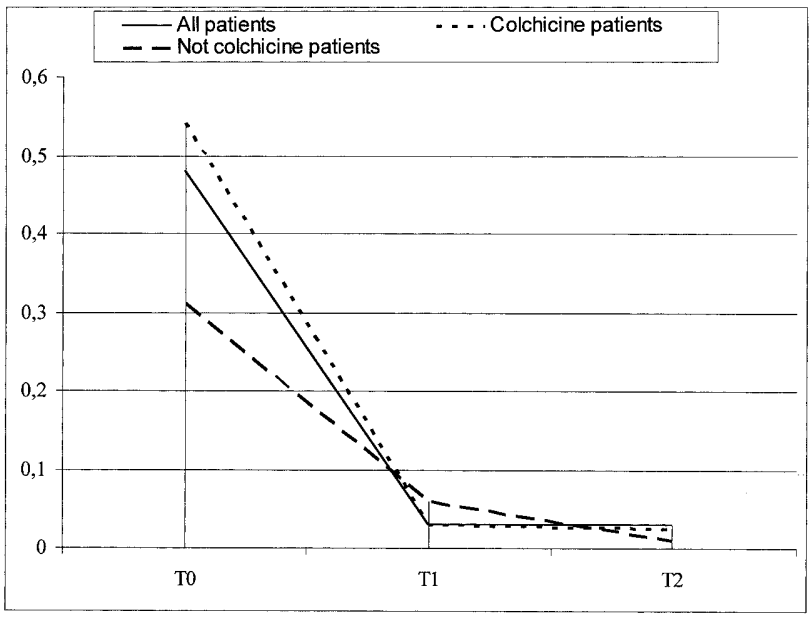

Fig. 1. Attack rates in all the patients and in the subgroups of patients treated (Colchicine patients) and not treated with colchicine (Not colchicine patients) at T0 (basal), T1 (in the first 12 months after implementation of the protocol) and at T2 (at the end of follow up).

we retrospectively compared patients treated or not treated with colchicine. Three patients were treated before 1994, before we started using colchicine. To the other 55 patients we proposed colchicine; 6 refused and 49 took the drug. Five of these 49 patients stopped colchicine within 4 weeks (10%), because of gastrointestinal intolerance (mainly diarrhea): these 5 patients were considered not treated with colchicine. Two other patients stopped colchicine after 3 months, one because of gastrointestinal intolerance and one for a skin rash, and another one stopped colchicine after 6 months because of failure. These 3 patients were included in the group of patients treated with colchicine, because we assumed that 3 or 6 months of therapy might have affected the natural course of the disease. Two other patients complained mild gastrointestinal side effects, but did not stop taking the drug. On the whole 10/49 patients suffered side effects (20.4%), and 8/49 stopped colchicine because of them (16.3%). For this analysis we consider as "colchicine patients" the 44 who took the drug for at least three months. Treatment lasted on average 17.9 months (range 3-74). On the other hand we considered "not colchicine patients" the 14 who did not receive the drug: 3 because before 1994 we did not use it, 5 because they took it for less than 4 weeks because of intolerance, and 6 because they did not want to try the drug even though we proposed it. These patients chose not to take it for fear of side effects and/or because they thought it was not useful to add another drug to their current therapy.

The colchicine and not-colchicine groups were comparable (see Table I) for sex and mean age; idiopathic cases were significantly more prevalent among the colchicine patients (p = 0.03), and PCIS cases were more prevalent in the non-colchicine group. They were not also comparable as regards the introduction of other drugs to reduce the steroids dosage, since only the colchicine patients received them. This might mean these patients were more "complicated" and resistant to therapy.

The basal attack rate, before our first assessment (at T0), was 0.54 attacks/patient/month in colchicine patients and 0.31 in not colchicine patients (p = 0.017); this too might indicate that the former initially had a more active disease. In the 44 colchicine patients the basal attack rate was 0.55 attacks/patient/month at T0, dropping to 0.03 attacks/patient/month in the first 12 months after implementing the protocol with colchicine (p < 0.00001) (T1), and remaining at a similar level till the end of the follow-up (8.1 years on average from the first attack). In the 14 non-colchicine patients the basal attack rate (0.31 attacks/patient/month) dropped to 0.06 (p = 0.002 from baseline) in the first 12 months after implementing the protocol without colchicine, and then fell further to 0.01 attacks/patient/month by the end of follow-up (8.2 years on average) (Fig. 1).

The attack rate was similar at the end of the follow-up (T2) in both the groups; this situation, 8.1 years on average after the first attack, seems therefore to correspond to the late dormant phase of the disease.

The decrease in the attack rate during the first 12 months after implementing the protocol was 0.51 (0.54-0.03) in the 44 colchicine patients, and 0.25 (0.31-0.06) in the 14 patients not treated with colchicine. We compared these decreases with a two-tailed *t* test for unpaired sample: p was 0.006.

After implementing the protocol there was no further recurrence in 29/44 colchicine patients (65.9%) and 9/14 non-colchicine patients (64.3%). Two patients experienced a new recurrence 3 and 4 months after stopping colchicine.

During our follow up, in the 46 patients originally labeled as idiopathic we made a new diagnosis of primary Sjögren's syndrome according to accepted criteria (18) in 4 patients (8.7%) and of rheumatoid arthritis (ACR criteria) in 1 patient (2.2%). Considering the whole cohort of 46 originally idiopathic patients, ANA were positive in 27 patients (59%) at a titre > 1/80, and in 7 of them (15%) at a titre > 1/160, and rheumatoid factor was positive in 7 (15%). These data are presented in detail in a separate paper (12).

Table I. Main features of colchicine and non-colchicine patients.

	Colchicine patients (n = 44)		Non-colchicine patients (n = 14)	
Mean age at onset (years)	39		39	
Gender	27 males	(61.4%)	7 males	(50%)
Idiopathic	37	(84.1%)	9	(64.3%)
PCIS*	7	(15.9%)	5	(36%)
Use of immunosuppressive drugs	6	(13.6%)	0	

*PCIS: Post-cardiac injury syndrome.

Discussion

This is the first study to assess the role of a multidrug protocol in the therapy of recurrent acute pericarditis. In the largest monocentric study reported till now we found here that a protocol including : a) very slow tapering of the corticosteroid (months) , similar to what is often done in many rheumatological conditions; b) NSAIDs used at the recommended dosages; c) colchicine if tolerated; d) close clinical monitoring in the acute phase, avoiding hospital admission; e) reassurance concerning possible late sequelae; f) introduction of other drugs if needed to reduce the dosage of the corticosteroid, may be very useful in controlling the activity of recurrent acute pericarditis. The improvement was more marked and quicker when colchicine was used.

There is a general consensus that colchicine is safe and effective for the management of recurrent pericarditis in the adult (3-5, 13, 14, 19), although this drug has not been tested in randomized trials. Many papers suggested that the drug might be useful (1, 2, 7-9, 20), but other authors did not confirm these findings (10) or observed slightly less favourable findings (21). Many possible explanations exist. It has been suggested that recurrent acute pericarditis

has a chronic course irrespective of the therapy given (10). Controlled studies are lacking, apart from ones in which each patient was his/her own control, before and after therapy. Patients with a subclinical form of familial Mediterranean fever may be differently represented in series from America and from Europe and Israel, even if we have recently demonstrated that familial Mediterranean fever mutations are absent in idiopathic recurrent acute pericarditis (12). In patients with many recurrences, already on prednisone, adding colchicine will give a good chance of controlling the disease, but stopping all the other therapies and using only colchicine will probably lead to another failure: colchicine is useful, but it is not a magic bullet that alone will cure all the most complicated cases of recurrent acute pericarditis.

In our study not all patients tolerated colchicine; 20.4% suffered side effects causing 16.3% to stop taking the drug. The sub-analysis we made regarding colchicine had limitations. Analysis was retrospective; therapy with colchicine was not randomized; different diagnoses had different prevalence in colchicine and not colchicine patients. We did not use an intention-to-treat analysis, thus 5 patients who stopped colchicine within 4 weeks were considered as "not treated" with colchicine, because we assumed that less than four weeks of therapy had no effect on the course of the disease, but we recognize that this is a problematic decision. We acknowledge these limitations, but their clinical significance seems modest; probably some controls had milder disease, since their basal attack rate was significantly lower than in colchicine patients, none of them needed other immunosuppressive drugs and the refusal of some of them to add colchicine to their current therapy might indicate that they were not as "desperate" as other cases. Secondly, this comparison, although flawed, is the first reported in literature. Finally, a large double-blind, controlled, prospective trial is difficult considering the low likelihood that physicians would want to enter their patients as controls when a simple safe therapy of unproven but apparent efficacy is available (19).

In general, glucocorticoid treatment should be restricted to patients with severely symptomatic recurrent pericarditis that is unresponsive to NSAIDs and colchicine (3, 4, 13, 14, 19). Moreover French authors have suggested that corticosteroids given in the index attack can favour the occurrence of relapses (11). Recently we and others have demonstrated that pretraetment with steroids attenuates the efficacy of colchicine in preventing recurrent pericarditis (6) in a multicenter all-case analysis which enrolled 119 total patient, 41 of which are coming from the cohort of patients object of the present study. On the other hand in the real world steroids are commonly employed; in fact e.g. they were administered to 60% of patients prior to initiation of colchicine in the largest multicenter study (6). In our experience in these patients no drug on its own is able to control the disease and prevent recurrences unless the corticosteroid is tapered extremely slowly. Furthermore, in case of recurrence during tapering, our practice coincides with what suggested by Soler-Soler (3): to not increase again or reinstitute the administration of a steroid, but to try to control the symptoms with NSAIDs. Actually the experience of the Rheumatologist may be invaluable also in the tapering of steroids in these patients.

NSAIDs are commonly employed in the treatment of acute pericarditis, but often with unsatisfactory results (8, 10). Some of these failures may be partially due to low dosages or too short courses. For instance, Guindo *et al*. (8) report only two patients treated with indomethacin, at a low dosage: 25 mg/8 hr, and Millaire *et al*. (9) describe one patient treated only with paracetamol. We used NSAIDs for long courses and at high dosages, till complete normalization of CRP and ESR. This is probably important to control the ongoing attack. Indomethacin may induce flow reduction in the coronaries, but this is probably a class effect of minor clinical relevance shared by other NSAIDs (24-26). Moreover in the rheumatological experience this drug is often effective and well tolerated. NSAIDs may be troublesome in patients with Post-Cardiac Injury Syndrome pericarditis who are on warfarin; in these case therapy must be tailored and strictly monitored. We had one of these cases, that we treated with nimesulide, with no complication.

Idiopathic recurrent acute pericarditis is a disease of suspected, yet unproven, immune-mediated pathogenesis (3, 15). This is suggested by the presence of pro-inflammatory cytokines in the pericardial fluid (27), the presence of anti-heart antibodies in the sera of these patients (28) and the absence of the common mutations linked to familial Mediterranean fever (12). Thus a rheumatological approach can be useful also in rare selected cases of "refractory" recurrent pericarditis (14, 15, 19), in which rheumatological "second line" drugs are proposed: azathioprine has been employed in 5 patients (10, 23, 29), cyclophosphamide in one (23), methotrexate in 5 (10), and cyclosporine in one (10). Recently Peterlana described 4 cases treated with intravenous immunoglobulin (30). We have suggested that immunosuppressive agents and steroid sparing agents might be used very rarely in refractory cases (17), acknowledging that we have neither evidence based data or hypothesis on how these drugs act on the pathogenetic mechanisms, preferring the less toxic and less expensive drugs (e.g. azathioprine, methotrexate), tailoring the therapy on the single patient and, importantly, with the patient informed consent. Experience in the use of these drugs is mandatory, and rheumatologists may well be of help for cardiologists in these cases.

The basal attack rates (0.48 attacks/patient/month: approximately one recurrence every 2 months) and the final attack rates (0.03: 3 recurrences every 100 months) might be considered manifestations of the clinical course of the disease irrespective of the different therapeutical protocols (10), with an initial very active phase and a late dormant phase. Anyway the highly significant decrease of the attack rate, both statistically and clinically, in the first 12 months after starting up the protocol clearly reflects a response to therapy.

Accordingly we also observed a marked drop in the number of hospital admissions; this was partly due to our policy to limit admissions as much as possible, reassuring patients while treating them; so we agree that most acute pericarditis cases can be safely treated as outpatients (31).

Our inclusion criteria selected patients with acute attacks of an inflammatory disease involving the pericardium who had to have high CRP, so our conclusions apply only to this type of patient. Cases with acute or chronic cardiac effusions or thoracic pain not fulfilling our inclusion criteria (e.g. with normal CRP) were excluded, and our therapeutic protocol does not apply to them.

In conclusion we found in the largest monocentric study that if patients with recurrent acute pericarditis are treated with a multidrug protocol which should be familial to many Rheumatologists, in which steroids are tapered very slowly (over months), NSAIDs are used at the recommended dosages, colchicine is added if tolerated, and including close clinical monitoring in the acute phase, with reassurance about late sequelae and avoiding hospital admission, the clinical course and patients' quality of life will show rapid improvement, gratifying both the patient and the physician. These results are more likely if colchicine is used, but the disease can be controlled well even in patients who do not tolerate it.

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