# Corticosteroids and immunosuppressive agents for idiopathic recurrent pericarditis

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**ABSTRACT**

Recurrent pericarditis is a frequent and troublesome complication of acute pericarditis. Aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are the mainstay of therapy but few data is available on second-line treatment. We retrospectively analyzed 13 patients, 7 females (54%), median age 40 years, with a median of 4 (IQR 1-6) recurrences per patient despite a well conducted first-line treatment and a median follow-up of 59 months (IQR 38-70). Ten patients received steroids as second-line therapy; 6 out of 10 responded to this therapy while 4 needed the addition of azathioprine. Three other patients received an immunosuppressive agent as second-line therapy (azathioprine, methotrexate, mycophenolate mofetyl). Overall, the mean frequency per month (± SD) of pericarditis recurrences was 0.69 (± 0.40) with aspirin/NSAIDs and colchicine, 0.22 (± 0.34) with corticosteroids alone and 0.01 (± 0.04) with immunosuppressive agents ($p<10^{-4}$). Immunosuppressive agents including azathioprine, methotrexate and mycophenolate mofetyl seem efficacious and well tolerated in patients with idiopathic recurrent pericarditis unresponsive to corticosteroids, corticosteroids-dependent or when corticosteroids side effects are judged unacceptable.

**KEYWORDS:** Idiopathic pericarditis, recurrent pericarditis, immunosuppressive agents

## INTRODUCTION

Recurrent pericarditis is one of the most common and troublesome complications after an episode of acute pericarditis. The recurrence rate after a first episode of acute pericarditis ranges from 20 to 30%, and may increase to 50% after a first recurrence in patients not treated with colchicine (1,2). The mainstay of therapy for acute pericarditis is aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), associated with colchicine (3). Colchicine has proved to be effective to reduce the rate of recurrences in clinical trials (2,4–6). Recurrent pericarditis is diagnosed after a symptom-free interval of at least 4–6 weeks and clinical, biological or radiological evidence of recurrence of pericarditis. Some of these patients are diagnosed with auto-immune or infectious diseases; however most of the cases of recurrent pericarditis remain idiopathic (>80%). The pathophysiology of idiopathic recurrent pericarditis, not fully understood, may be related to auto-inflammatory and/or auto-immune mechanisms. There are clues in favor of this interpretation, such as the finding of anti-heart antibodies (7), the presence of inflammatory cytokines in pericardial effusion (8), and the efficacy of immunosuppressive agents. Recurrent pericarditis should be initially managed with aspirin or NSAIDs and colchicine. There is still controversy to know if and when corticosteroids or immunosuppressive agents should be considered (9). Current guidelines favor the addition of corticosteroids at low to moderate doses (i.e. prednisone 0.2–0.5 mg/kg/day) in cases of incomplete response or recurrences on aspirin/NSAIDs and colchicine. However, studies have shown that corticosteroids could increase the rate of recurrence when used in acute pericarditis (10–12). Other therapeutic choices have been described in retrospective case series, including immunosuppressive therapies [e.g. azathioprine(13)], intravenous immunoglobulins (IVIGs) (14), interleukin-1

(IL-1) antagonists (e.g. anakinra)(15–18), or pericardiectomy (19). We report herein thirteen patients with idiopathic recurrent pericarditis refractory to aspirin/NSAIDs and colchicine and that were treated successfully with corticosteroids and immunosuppressive agents.

## PATIENTS AND METHODS

Using the French hospital coding system, we reviewed all the patients of our Department of Internal Medicine and Clinical Immunology, between 1998 and 2019, that were coded as having pericarditis. We selected all patients who received corticosteroids and/or immunosuppressive agents for idiopathic recurrent pericarditis. We excluded patients that presented only one episode of pericarditis, patients who had recurrent pericarditis controlled by aspirin/NSAIDs and/or colchicine, and patients with an established etiology of pericarditis (e.g., lupus, tuberculosis).

Recurrent pericarditis was diagnosed after a documented first attack of acute pericarditis with a symptom-free interval of 4–6 weeks or longer and evidence of subsequent recurrence of pericarditis. A recurrence of pericarditis was defined by recurrent pain compatible with pericarditis and one or more of the following signs: pericardial friction rub, changes on electrocardiography, echocardiographic evidence of new or worsening pericardial effusion, AND elevation in the white-cell count, erythrocyte sedimentation rate, or C-reactive protein level. We defined recurrent pericarditis as idiopathic if no auto-immune or infectious disease were diagnosed after a thorough clinical and biological work-up. All patients had clinical examination by a clinical immunologist or rheumatologist and a laboratory work-up including search for antinuclear and extractable nuclear antigens antibodies and viral serologic testing.

Patients with a history or clinical examination compatible with tuberculous pericarditis were systematically excluded.

Clinical records were retrospectively reviewed, and the relationship between pericarditis recurrences and treatments used were carefully collected: total number of pericarditis recurrences, number of recurrences with each treatment course and frequency of recurrences (i.e. the number of new episodes of pericarditis per month). We recorded the dosage of corticosteroids and immunosuppressive agents that were used. In most of the cases, the choice of using an immunosuppressive agent and the choice of the molecule were discussed among a multidisciplinary staff including cardiologists, rheumatologists and clinical immunologists. Descriptive statistics included absolute numbers, proportions, standard deviation (SD), interquartile range (IQR) and confidence intervals (CI) at 95% confidence level. We used R software (version 3.2.4) for statistical analysis to compare the mean frequency of pericarditis recurrences between treatments using a one-way ANOVA.

**RESULTS**

Among 145 patients coded as having pericarditis, we found 26 patients who received corticosteroids or immunosuppressive drugs to control recurrent pericarditis. We excluded 13 patients who had a specific etiology i.e. 5 with systemic lupus, 2 rheumatoid arthritis, 2 familial Mediterranean fever, 1 antiphospholipid syndrome, 1 Sjögren's syndrome, 1 Whipple's disease and 1 bacterial pericarditis. The remaining 13 patients were diagnosed with idiopathic recurrent pericarditis refractory to aspirin/NSAIDs and colchicine and included in the present analysis. Seven patients were females, and the median age was 40 years (IQR, 40-47 years) (***Table 1***).

The median duration of follow-up between the first episode of pericarditis and the last evaluation was 59 months (IQR, 38-70 months). The total number of recurrences of pericarditis was 56. The median CRP level was 78 mg/L (IQR 54-120 mg/L). The median number of recurrences per patient after the first episode of pericarditis was 3 (IQR, 1-6).

With the exception of one patient (who had a history of Quincke edema related to aspirin), all patients were treated with aspirin/NSAIDs with gradual tapering and at least 3 months of colchicine for their first episode of acute pericarditis. They received a high dose of aspirin or NSAIDs (e.g., aspirin 3 g/day, ibuprofen 1200–1800 mg/day) and colchicine 1 to 2 mg per day (according to patient's weight). The patient with a history of anaphylaxis only received colchicine as first-line therapy. Each recurrence of pericarditis, including recurrences on corticosteroids or immunosuppressive drugs, were treated as the first episode of acute pericarditis with aspirin/NSAIDs with gradual tapering and colchicine (except for one patient who only had colchicine).

Following aspirin/NSAIDs and colchicine failure, second-line therapy included corticosteroids (10 patients) or immunosuppressive agents (3 patients)(***Table 1***). For the latter, side-effects of corticosteroids were judged to be inacceptable. During second-line therapy, we noted 16 recurrences of pericarditis in seven out of thirteen patients (6 on steroids, 1 on immunosuppressant) occurring at a mean corticosteroids dose of 17 mg/day. Amongst the 10 patients on corticosteroids, 4 had to be switched to azathioprine after a mean duration of 8 months because of the persistence of pericarditis recurrences (n=3) or high-dose corticosteroids dependence (30 mg/day, n=1). Amongst the 4 patients switched to azathioprine, corticosteroids were withdrawn after gradual tapering (n=3) or decreased to less than 10 mg/day (n=1). One patient had

to be switched from azathioprine to methotrexate because of a mild episode of asymptomatic pancytopenia when receiving concomitant azathioprine/allopurinol therapy. Amongst the 3 patients who received immunosuppressive agents directly after aspirin/NSAIDs and colchicine failure, one received azathioprine and two received methotrexate. One patient on methotrexate had to be switched to mycophenolate mofetyl after 35 months because of the persistence of pericarditis recurrences.

Overall, thirteen patients were on aspirin or NSAIDs and colchicine for a total duration of 128 months. Eight patients were on corticosteroids at 1 mg/kg/d in five patients and 0.5 mg/kg/d in five patients, with slow tapering after complete resolution of the recurrence, for a total duration of 145 months. Four patients were on azathioprine at 1 mg/kg/day in two patients and 2 mg/kg/day in three, for 73 months. In one patient, we managed to stop azathioprine with no recurrence and decreased the dose to 50 mg/day in two patients and 25 mg/day in one patient. Four patients received methotrexate at doses ranging from 0.1 to 0.3 mg/kg/week, for 104 months. One patient was on mycophenolate mofetyl at 2 grams per day for 15 months.

The mean (± SD) number of pericarditis recurrences was 3.17 (± 2.8) on aspirin/NSAIDs and colchicine, 1.2 (± 1.6) on corticosteroids, and 1.33 (± 2.3) on methotrexate. The median CRP level decreased from 78 mg/L (IQR 54-120 mg/L) during recurrences episodes to 5 mg/L after treatment (IQR 2-5 mg/L). There was no pericarditis recurrence on azathioprine or mycophenolate mofetyl. Overall, the frequency of pericarditis recurrences was significantly lower with immunosuppressive agents (0.01 ± 0.04 per month) than with corticosteroids alone (0.22 ± 0.34 per month) or aspirin/NSAIDs and colchicine (0.69 ± 0.40 per month) ($p<10^{-4}$) (***Figure 1***).

After a median duration of 24 months (IQR 12-38 months) after the first episode of pericarditis, 8 out of 13 (62 %) patients were able to withdraw all treatments. Six out of these eight patients received corticosteroids for a median duration of 12 months (IQR 11-29 months) before discontinuation, one methotrexate for 8 months, and one azathioprine for 20 months. After a median follow-up of 27 months after treatment withdrawal (IQR 22-104 months), none of these eight patients presented recurrence of pericarditis. At the last follow-up, five patients still continued treatment without recurrence of pericarditis, three on azathioprine for a median duration of 17 months, one on methotrexate for 61 months, and one on mycophenolate mofetyl for 15 months.

Main side effects of corticosteroid were myopathy (n=1), osteoporosis with fracture (n=1) and hypertension plus dyslipidemia (n=1). Tolerance of immunosuppressive agents was good with one case of mild asymptomatic transitory pancytopenia in a patient taking allopurinol plus azathioprine.

**DISCUSSION**

Although major advances have been realized in the treatment of acute pericarditis, in recurrent idiopathic pericarditis refractory to aspirin/NSAIDs and colchicine treatment, the place of corticosteroids and/or immunosuppressive agents remains to be defined. In this cohort of patients' non-responder to a well-conducted first-line therapy, 6 out of 10 patients responded to steroids as second-line therapy while 4 needed the use of an immunosuppressive agent. Three other patients received an immunosuppressive agent as second-line therapy (azathioprine, methotrexate, or mycophenolate mofetyl) and none presented pericarditis recurrence.

Two recent systematic reviews described the existing evidence for immunosuppressive drugs in idiopathic refractory recurrent pericarditis (22,23). A

strength of this cohort is that every patient has been taken in charge in a single center with an adequate initial treatment including aspirin/NSAIDs and colchicine at optimal doses. We used corticosteroids according to guidelines that were applicable at the time of treatment. Azathioprine proved to be successful and well tolerated for the prevention of recurrences. In the largest reported experience of idiopathic refractory recurrent pericarditis treatment, azathioprine was administered at a dose of 1.5–2.5 mg/kg/day for 13.6 ± 5.1 months in 45 patients (13). It was associated with remission after steroid discontinuation in more than fifty percent of patients and well tolerated. In our cohort, methotrexate decreased the frequency of recurrences too. Further work would be needed to clarify the place of methotrexate in recurrent idiopathic pericarditis as few patients have been described (20). A review of thirty published cases on intravenous immunoglobulin described 73% pericarditis recurrence-free and 17% still receiving corticosteroids after a mean follow-up of 33 months (21).

Interestingly, the present cohort showed a better efficacy of steroids and immunosuppressive agents as second-line therapy compared to aspirin/NSAIDs and colchicine used at optimal doses. However, the decision to switch needs to be discussed on a case-by-case analysis. Three out of the ten patients put on corticosteroids developed side effects (12). Amongst the seven patients treated with immunosuppressive agents, none had severe side effect. Of note, 8 out of 13 patients were able to stop all treatments with no recurrence of pericarditis after a long follow-up. As some patients in our cohort were treated before the current guidelines on recurrent pericarditis, they received high-doses of colchicine (up to 2 mg daily) that are no longer recommended in 2015 guidelines (3). We also noted that some patients received 1 mg/kg/day of prednisone instead of the more recently recommended dose of 0.5

mg/kg/day. This could account for some of the steroids side effects we have observed. This cohort was too small  to look for difference in recurrences rate between low and high dose steroids (12).

Despite its limitations, our study shows that immunosuppressive agents seem efficacious and well tolerated in idiopathic recurrent pericarditis unresponsive to corticosteroids, who cannot stop taking corticosteroids or when corticosteroids side effects are judged unacceptable. Current guidelines support the use of azathioprine in such patients and consider more recently anakinra as alternative (3,15–18). Our cohort is the first to suggest that methotrexate or mycophenolate mofetyl could be also considered in patients with azathioprine contraindication or side effects. Further large size studies are needed to confirm our preliminary results.

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**Competing Interests**

None

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None

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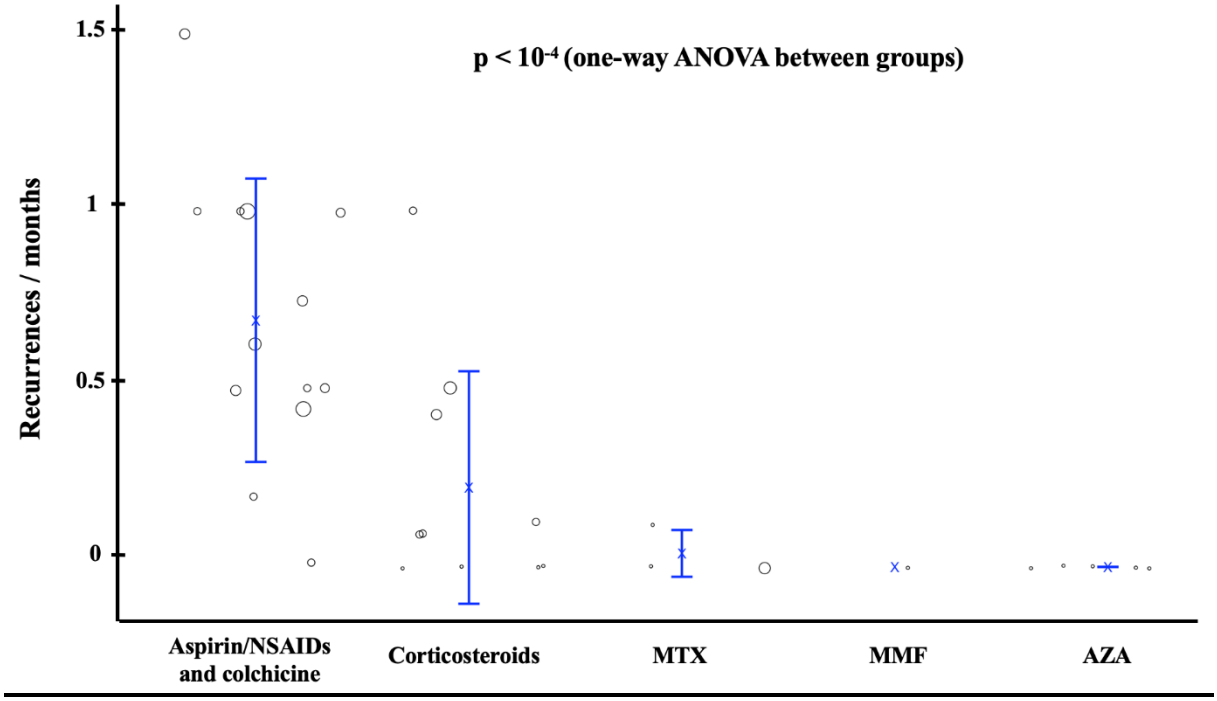
## Legends

**Figure 1:** Frequency of recurrences of pericarditis per month when patients were receiving aspirin/NSAIDs and colchicine, corticosteroids, methotrexate, mycophenolate mofetyl and azathioprine [Mean (+/- SD)].

*Each circle corresponds to a patient and shows the frequency of recurrences per month with the size of the circle adjusted to the number of recurrences. NSAID = non-steroidal anti-inflammatory drugs; AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetyl.*

**Table 1:** Main features, treatment and follow-up of patients with recurrent idiopathic pericarditis treated with corticosteroids or immunosuppressive agents.


p < 10-4 (one-way ANOVA between groups)
Recurrences / months
1.5
1
0.5
0
Aspirin/NSAIDs and colchicine
Corticosteroids
MTX
MMF
AZA

| | Gender | Weight (kg) | Age (years) | First line therapy* | | Second line therapy* | | | Third line therapy* | | Fourth line therapy* | | Follow-up after treatment withdrawal | Treatment side effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Treatment | Dose (mg/day) | Treatment | Dose (mg/day) | | Treatment | Dose (mg/day) | Treatment | Dose (mg/day) | | |
| | | | | | | | Initial | Recurrences | | | | | | |
| **1** | M | 55 | 37 | ASA<br>Colchicine<br>6 months, 3 recurrences | 3000<br>2 | Corticosteroids<br>11 months, 1 recurrence | 20 | 10 | | | | | 27 months<br>no recurrence | |
| **2** | M | 71 | 49 | Colchicine<br>4 months, 2 recurrences | 1 | Corticosteroids<br>11 months, 1 recurrence | 60 | 4 | | | | | 4 months<br>no recurrence | |
| **3** | F | 59 | 42 | ASA<br>Colchicine<br>3 months, 2 recurrences | 3000<br>2 | Corticosteroids<br>41 months, no recurrence | 30 | | | | | | 25 months<br>no recurrence | Osteoporosis with fractures |
| **4** | F | 63 | 42 | ASA<br>Colchicine<br>3 months, 1 recurrence | 3000<br>2 | Corticosteroids<br>34 months, no recurrence | 30 | | | | | | 25 months<br>no recurrence | Hypertension, dyslipidemia |
| **5** | F | 70 | 40 | ASA<br>Colchicine<br>70 months, 1 recurrence | 3000<br>1 | Corticosteroids<br>14 months, no recurrence | 70 | | | | | | 122 months<br>no recurrence | Myopathy |
| **6** | F | 65 | 40 | Indometacin<br>Colchicine<br>18 months, 8 recurrences | 150<br>2 | Corticosteroids<br>1 month, 1 recurrence | 40 | 20 | | | | | 145 months<br>no recurrence | |
| **7** | M | 69 | 58 | ASA<br>Colchicine<br>3 months, 1 recurrence | 3000<br>1 | Corticosteroids<br>8 months, no recurrence | 60 | | AZA<br>4 months, no recurrence | 150 | | | Treatment ongoing<br>no recurrence | |
| **8** | F | 64 | 26 | Diclofenac<br>Colchicine<br>3 months, 3 recurrences | 150<br>2 | Corticosteroids<br>7 months, 3 recurrences | 30 | 7 | AZA<br>17 months, no recurrence | 50 | | | Treatment ongoing<br>no recurrence | |
| **9** | M | 80 | 40 | ASA<br>Colchicine<br>3 months, 1 recurrence | 3000<br>1 | Corticosteroids<br>10 months, 5 recurrences | 80 | 28 | AZA<br>2 months, no recurrence | 100 | MTX<br>8 months, no recurrence | 30 | 87 months<br>no recurrence | Pancytopenia on AZA + allopurinol |
| **10** | M | 83 | 47 | Ketoprofen<br>Colchicine<br>8 months, 5 recurrences | 200<br>2 | AZA<br>34 months, no recurrence | 175 | | | | | | Treatment ongoing<br>no recurrence | |
| **11** | F | 104 | 70 | ASA<br>Colchicine<br>5 months, 1 recurrence | 3000<br>1 | MTX<br>61 months, no recurrence | 15 | | | | | | Treatment ongoing<br>no recurrence | |
| **12** | F | 112 | 32 | ASA<br>Colchicine<br>9 months, 9 recurrences | 2000<br>1 | MTX<br>35 months, 4 recurrences | 30 | 20 | MMF<br>15 months, no recurrence | 2000 | | | Treatment ongoing<br>no recurrence | |
| **13** | M | 74 | 40 | ASA<br>Colchicine<br>4 months, 3 recurrences | 3000<br>2 | Corticosteroids<br>8 months, 1 recurrence | 70 | 5 | AZA<br>20 months, no recurrence | 150 | | | 4 months<br>no recurrence | |

*F = female, M = male; ASA = acetylsalicylic acid; AZA= azathioprine; MTX = methotrexate; MMF = mycophenolate mofetil*

**Each recurrence, including on corticosteroids or immunosuppressive agents, was treated with aspirin/NSAIDs with gradual tapering and colchicine*

**HIGHLIGHTS**

- Idiopathic refractory recurrent pericarditis is a rare immune-mediated disease
- The place of corticosteroids and immunosuppressive agents in this disease remains to be defined
- Six patients responded to corticosteroids whereas seven patients needed an immunosuppressive drug
- Azathioprine and methotrexate seemed well tolerated and effective in this cohort