Review

Corticosteroids and immunosuppressive agents for idiopathic recurrent pericarditis

Nathan Peiffer-Smadja[a,d], Fanny Domont[a,d], David Saadoun[a,b,c,d], Patrice Cacoub[a,b,c,d,*]

[a] *Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005 Paris, France*
[b] *INSERM, UMR_S 959, F-75013 Paris, France*
[c] *CNRS, FRE3632, F-75005 Paris, France*
[d] *AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013 Paris, France*

ARTICLE INFO

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 corticosteroids 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 ($\pm$ SD) of pericarditis recurrences was 0.69 ($\pm$ 0.40) with aspirin/NSAIDs and colchicine, 0.22 ($\pm$ 0.34) with corticosteroids alone and 0.01 ($\pm$ 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.

1. 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.

2. 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 amongst 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.

3. Results

Amongst 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 < 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/day in five patients and 0.5 mg/kg/day 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 g 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) ($p < 10^{-4}$) (Fig. 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.

4. Discussion

Although major advances have been realized in the treatment of

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

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

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

[a] Each recurrence, including on corticosteroids or immunosuppressive agents, was treated with aspirin/NSAIDs with gradual tapering and colchicine.
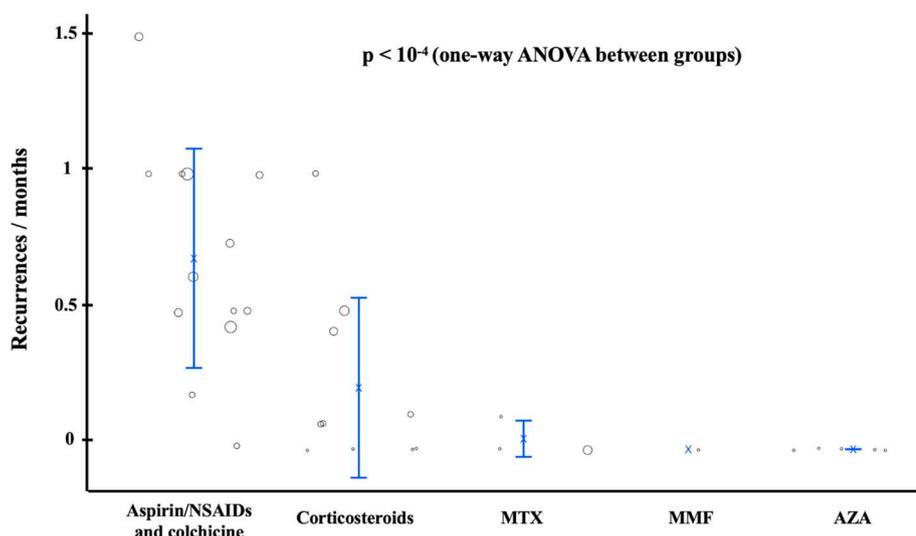
Fig. 1. Frequency of recurrences of pericarditis per month when patients were receiving aspirin/NSAIDs and colchicine, corticosteroids, methotrexate, mycophenolate mofetyl and azathioprine [Mean (+/− SD)].
Each circle corresponds to a patient and shows the frequency of recurrences per month with the size of the circle adjusted to the number of recurrences. NSAID = non-steroidal anti-inflammatory drugs; AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetyl.

acute pericarditis and 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 corticosteroids 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.

4.1. First-line therapy

First-line therapy for any acute pericarditis, including a recurrence of pericarditis, associates recommendations about physical activity and an adequate use of aspirin/NSAIDs and colchicine. Physicians should recommend patients to avoid physical activity beyond ordinary life activities until complete clinical resolution of symptoms and normalization of CRP. Medical treatment should rely on the use of aspirin / NSAIDs (e.g. aspirin 1000 mg every 8 h) for at least two weeks and until complete resolution of symptoms and colchicine 0.5 mg every 12 h for three months (or 0.5 mg daily for patients < 70 kg). Colchicine has proved to quicken the resolution of symptoms and to prevent recurrences in randomized clinical trials and has not been linked to a significant increase of adverse effects [4,5,20]. Aspirin or NSAIDs should then gradually be tapered by decreasing doses over 4 weeks. Tapering of colchicine is not mandatory according to guidelines but may be considered [21]. The first recurrence of pericarditis is managed in the same way but colchicine is administered for at least 6 months before being gradually discontinued.

4.2. The place of corticosteroids

It is widely accepted that corticosteroids should be avoided in the treatment of idiopathic acute pericarditis and used only in patients with contraindications to NSAIDs. This follows studies suggesting that corticosteroids used early in the course of the disease may increase the risk of recurrent episodes [5]. In a systematic review including 564 patients, steroids were associated with a trend toward increased risk of recurrent pericarditis (OR = 7.50 [0.62–90.65]) [22]. Moreover, the adverse effects related to the use of corticosteroids are numerous and well described. However, the place of corticosteroids in the management of recurrent pericarditis is less well defined. European guidelines recommend them at low to moderate doses as the first addition to NSAIDs/aspirin and colchicine [21] despite contradictory evidence regarding an increase in the risk of recurrence and adverse effects

[11,23]. When corticosteroids are required for the management of recurrent pericarditis, a moderate dosing (0.25 to 0.5 mg/kg/day of prednisone) should be preferred to a high dosing as it was linked to a lower risk of recurrence and adverse effects [12,22]. Steroids should be used for at least 4 weeks and tapered with slow decrements after resolution of symptoms and normalization of CRP. A particular attention for recurrences should be paid at the critical threshold of 10–15 mg/day dose of prednisone or equivalent [3]. In case of recurrences during tapering, the reintroduction of NSAIDs/aspirin with colchicine and exercise restriction should be tried before increasing the dose of corticosteroids. Colchicine should be maintained at the dose of 0.5 mg twice daily (or 0.5 mg daily for patients < 70 kg) as long as the patient requires corticosteroids and then can be gradually tapered over several months. A particular attention should be paid to the prevention and management of the adverse effects of corticosteroids. Preexisting conditions such as diabetes mellitus, hypertension and cardiovascular disease should be assessed for and treated. The patients should receive the recommended immunizations, such as pneumococcal and influenza vaccines, and prevention of steroid-induced osteoporosis: calcium and vitamin D supplementation associated with appropriate screening of bone mineral density. Intrapericardial administration of non-absorbable corticosteroids may be an alternative to systemic glucocorticoids but require further studies and present technical difficulties particularly when there is no effusion [24].

4.3. The place of immunosuppressive drugs for prevention of recurrence

Two recent systematic reviews describe the existing evidence for immunosuppressive drugs in idiopathic refractory recurrent pericarditis [25,26]. The use of immunosuppressive drugs is mainly reserved to prevent recurrences in patients who do not respond adequately to corticosteroids or who do not tolerate this treatment, e.g. due to the need of maintaining an unacceptably high dose of steroids to avoid pericarditis recurrences. Azathioprine (2 mg/kg/day to be slowly uptitrated) is the immunosuppressive drug that probably has accumulated the most evidence supporting its efficacy in long-term treatment requiring high doses of corticosteroids [27]. 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 > 50% of patients and well tolerated. Anakinra, an interleukin 1 receptor antagonist, could be an alternative to azathioprine [15–18,21] as well as intravenous immunoglobulins. In a randomized controlled trial, patients treated with anakinra had less recurrences and could stop corticosteroids more

often when compared to patients treated with placebo [16]. However, the discontinuation of anakinra is often followed by recurrences, usually managed by the reintroduction of the drug [15]. 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 [28]. Intravenous immunoglobulin therapy is usually administered for five days (400 to 500 mg/kg/day), with repeated cycles as needed according to the clinical response.

4.4. What does this cohort add to the evidence?

A strength of this cohort is that every patient has been taken in charge in a single center with an adequate first-line treatment including aspirin/NSAIDs and colchicine at optimal doses. Then, we used corticosteroids or immunosuppressive drugs as second-line therapy. In this cohort, corticosteroids were successful in 6 out of 10 patients who could stop all drugs for pericarditis after a median of 12 months. The four patients in whom corticosteroids were not effective were switched to immunosuppressive drugs. This adds to the evidence that corticosteroids should be tried in patients who do not respond to first-line therapy. However, three out of the ten patients put on corticosteroids developed side effects in this cohort whereas amongst the seven patients treated with immunosuppressive agents, none had severe side effect. We confirm that azathioprine seems successful and well tolerated for the prevention of recurrences but the optimal duration of therapy is unknown. Interestingly, methotrexate in three patients and mycophenolate mofetyl in one patient also successfully decreased the frequency of recurrences. These treatments could present interesting alternatives for patients who cannot be treated with azathioprine because of a contraindication (e.g. treatment with allopurinol) or expected side-effects (e.g. drug hypersensitivity). Methotrexate is usually well tolerated and may present a lower infectious risks than azathioprine [29,30] although the data is conflicting [31]. Mycophenolate mofetyl could be preferred to azathioprine in patients at risk of leucopenia [32]. Moreover, the cost of methotrexate or mycophenolate mofetyl therapy is much lower than biologic agents as interleukin-1 receptor antagonists [33] or intravenous immunoglobulin therapy [34]. Further works are needed to clarify the place of methotrexate and mycophenolate mofetyl in recurrent idiopathic pericarditis as few patients have been described [35]. No patient in this cohort required the use of anakinra, sometimes presented as a last-resort medical alternative for patients with refractory recurrent pericarditis, before considering pericardiectomy [36]. Another interesting observation is that 8 out of 13 (62%) patients were able to withdraw all treatments in our cohort. Few studies address the discontinuation of long-term treatment for recurrent idiopathic pericarditis. Our data adds to the evidence that gradual tapering of immunosuppressive drugs can be done successfully in selected patients. However, this decision needs to be discussed on a case-by-case analysis. As some patients in our cohort were treated before the current guidelines on recurrent pericarditis, they sometimes received high-doses of colchicine (up to 2 mg daily) that are no longer recommended in 2015 guidelines [21]. We also note that 5 patients received 1 mg/kg/day of prednisone instead of the more recently recommended dose of 0.5 mg/kg/day but this cohort was too small to compare recurrences rate between low and high dose corticosteroids [12].

5. Conclusion

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 intravenous immunoglobulin and anakinra as alternatives [15–18,21]. Our cohort suggests 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.

References

[1] Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med sept 2005;165(17):1987–91.

[2] Arancibia F, Cortes CP, Valdés A, Cerda J, Hernández A, Soto L, et al. Colchicine for recurrent pericarditis (CORP) a randomized trial. Ann Intern Med 2014(9):290–6.

[3] Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015;36(42):2921–64. 7 Nov 2015.

[4] Imazio M, Brucato A, Cemin R, Ferrua S, Maggiolini S, Beqaraj F, et al. A randomized trial of colchicine for acute pericarditis. N Engl J Med 2013;369(16):1522–8.

[5] Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005;112(13):2012–6.

[6] Imazio M, Belli R, Brucato A, Cemin R, Ferrua S, Beqaraj F, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. Lancet 2014;383(9936):2232–7.

[7] Caforio ALP, Brucato A, Doria A, Brambilla G, Angelini A, Ghirardello A, et al. Anti-heart and anti-intercalated disk autoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. Heart. 2010;96(10):779–84.

[8] Imazio M. Idiopathic recurrent pericarditis as an immune-mediated disease: current insights into pathogenesis and emerging treatment options. Expert Rev Clin Immunol 2014;10(11):1487–92.

[9] Cacoub PP. Editorial - colchicine for treatment of acute or recurrent pericarditis. Lancet 2014;6736(14):13–4.

[10] Imazio M, Demichelis B, Parrini I, Cecchi E, Demarie D, Ghisio A, et al. Management, risk factors, and outcomes in recurrent pericarditis. Am J Cardiol 2005;96(5):736–9.

[11] Artom G, Koren-Morag N, Spodick DH, Brucato A, Guindo J, Bayes-De-Luna A, et al. Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-Centre all-case analysis. Eur Heart J 2005;26(7):723–7.

[12] Imazio M, Brucato A, Cumetti D, Brambilla G, Demichelis B, Ferro S, et al. Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation. Circulation. 2008;118(6):667–71.

[13] Vianello F, Cinetto F, Cavraro M, Battisti A, Castelli M, Imbergamo S, et al. Azathioprine in isolated recurrent pericarditis: a single Centre experience. Int J Cardiol 2011;147(3):477–8.

[14] Moretti M, Buiatti A, Merlo M, Massa L, Fabris E, Pinamonti B, et al. Usefulness of high-dose intravenous human immunoglobulins treatment for refractory recurrent pericarditis. Am J Cardiol 2013;112(9):1493–8.

[15] Lazaros G, Imazio M, Brucato A, Vassilopoulos D, Vasileiou P, Gattorno M, et al. Anakinra: an emerging option for refractory idiopathic recurrent pericarditis: a systematic review of published evidence. J Cardiovasc Med Hagerstown Md avr 2016;17(4):256–62.

[16] Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, et al. Effect of Anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. JAMA 8 nov 2016;316(18):1906–12.

[17] Jain S, Thongprayoon C, Espinosa RE, Hayes SN, Klarich KW, Cooper LT, et al. Effectiveness and safety of Anakinra for Management of Refractory Pericarditis. Am J Cardiol 15 oct 2015;116(8):1277–9.

[18] Finetti M, Insalaco A, Cantarini L, Meini A, Breda L, Alessio M, et al. Long-term efficacy of interleukin-1 receptor antagonist (anakinra) in corticosteroid-dependent and colchicine-resistant recurrent pericarditis. J Pediatr juin 2014;164(6):1425–1431.e1.

[19] Khandaker MH, Schaff HV, Greason KL, Anavekar NS, Espinosa RE, Hayes SN, et al. Pericardiectomy vs medical management in patients with relapsing pericarditis. Mayo Clin Proc 2012;87(11):1062–70.

[20] Alabed S, Cabello JB, Irving GJ, Qintar M, Burls A. Colchicine for pericarditis. Cochrane Database Syst Rev 2014(8):CD010652. 28 août.

[21] Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases. Eur Heart J 2015;36(42):2921–64.

[22] Lotrionte M, Biondi-Zoccai G, Imazio M, Castagno D, Moretti C, Abbate A, et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for acute pericarditis and its recurrences. Am Heart J Oct 2010;160(4):662–70.

[23] Imazio M, Demichelis B, Parrini I, Cecchi E, Pomari F, Demarie D, et al. Recurrent pain without objective evidence of disease in patients with previous idiopathic or viral acute pericarditis. Am J Cardiol 1 oct 2004;94(7):973–5.

[24] Frasiolas JAG, Cahoon WD. Intrapericardial triamcinolone administration for autoreactive pericarditis. Ann Pharmacother oct 2010;44(10):1641–6.

[25] Imazio M, Lazaros G, Brucato A, Gaita F. Recurrent pericarditis: new and emerging therapeutic options. Nat Rev Cardiol 2015;13(Box 2):99–105.

[26] Lotan D, Wasserstrum Y, Fardman A, Kogan M, Adler Y. Usefulness of novel immunotherapeutic strategies for idiopathic recurrent pericarditis. Am J Cardiol 2016;117(5):861–6.

[27] Imazio M, Battaglia A, Gaido L, Gaita F. Recurrent pericarditis. Rev Médecine Interne 1 mai 2017;38(5):307–11.

[28] Imazio M, Lazaros G, Picardi E, Vasileiou P, Carraro M, Tousoulis D, et al. Intravenous human immunoglobulins for refractory recurrent pericarditis: a systematic review of all published cases. J Cardiovasc Med (Hagerstown) Apr 2016;17(4):263–9.

[29] Vorselaars ADM, Wuyts WA, Vorselaars VMM, Zanen P, Deneer VHM, Veltkamp M, et al. Methotrexate vs azathioprine in second-line therapy of sarcoidosis. Chest Sept 2013;144(3):805–12.

[30] Maetzel A, Wong A, Strand V, Tugwell P, Wells G, Bombardier C. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatol Oxf Engl sept 2000;39(9):975–81.

[31] Pagnoux C, Mahr A, Hamidou MA, Boffa J-J, Ruivard M, Ducroix J-P, et al. Azathioprine or methotrexate maintenance for ANCA-associated Vasculitis. N Engl J Med 25 déc 2008;359(26):2790–803.

[32] Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Mitjavila F, Castro Salomó A, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. Ann Rheum Dis Sept 2017;76(9):1575–82.

[33] Nurmohamed MT, Dijkmans BAC. Efficacy, tolerability and cost effectiveness of disease-modifying antirheumatic drugs and biologic agents in rheumatoid arthritis. Drugs. 2005;65(5):661–94.

[34] Beauté J, Levy P, Millet V, Debré M, Dudoit Y, Le Mignot L, et al. Economic evaluation of immunoglobulin replacement in patients with primary antibody deficiencies. Clin Exp Immunol mai 2010;160(2):240–5.

[35] Raatikka M, Pelkonen PM, Karjalainen J, Jokinen E. Recurrent pericarditis in children and adolescents: report of 15 cases. J Am Coll Cardiol août 2003;42(4):759–64.

[36] Brucato A, Emmi G, Cantarini L, Di Lenarda A, Gattorno M, Lopalco G, et al. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. Intern Emerg Med 1 juin 2018;13(4):475–89.