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PC planned and conducted this analysis, and wrote the first draft. CM contributed to the final analysis and the writing of the final version. PC is responsible for the overall content as guarantor.

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Abstract

Acute idiopathic or so-called “viral” pericarditis is a frequent and usually benign disease, although recurrences are frequent. Data strongly suggest the presence of underlying auto-inflammatory and/or auto-immune disorders. It has been reported an inflammatory response of the innate immune system typical of “auto-inflammatory diseases”, predominantly mediated by interleukin-1 [IL-1]. This may result from the activation of the inflammasome by a cardiotropic virus or a nonspecific agent. The inflammatory response of the adaptive immune system, typical of “auto-immune diseases” - mainly mediated by autoantibodies or autoreactive T lymphocytes - seems also involved as anti-heart or anti-intercalated disk autoantibodies were associated with a higher number of recurrences and hospitalizations. Current guidelines recommend that aspirin/non-steroid anti-inflammatory drugs (NSAIDs) for a few weeks should be associated to colchicine for 6 months in recurrent pericarditis. In refractory cases, low dose corticosteroids or immunosuppressive drugs have been proposed with limited efficacy. Growing evidences suggest a place of IL-1 receptor antagonists in the treatment of recurrent pericarditis. Many retrospective studies, one recent randomized placebo controlled study and data of a real life large international registry showed the good efficacy of anakinra with a good safety profile. Other IL-1 receptor antagonists showed promising results (canakinumab, rilonacept). However, IL-1 receptor antagonists position in the treatment algorithm of recurrent pericarditis needs further evaluation in larger prospective clinical trials to replicate initial findings as well as to assess safety, cost-effectiveness and long-term efficacy.

Key words: recurrent pericarditis; autoinflammatory; autoimmune; treatment; interleukin 1

Background

Acute pericarditis is a frequent and usually benign disease characterized by chest pain, pericardial friction rub, widespread saddle-shaped or concave upward ST segment elevation on the electrocardiogram (ECG), and pericardial effusion [1]. Diagnostic evaluation include auscultation, electrocardiogram, echocardiography, biomarkers of inflammation (C-reactive protein [CRP]) and myocardial lesion (troponin), and chest X-ray. The major causes of pericarditis are summarized in **Table 1**. In developed countries, idiopathic or so-called "viral" pericarditis is the commonest final diagnosis [2,3,4]. In a biopsy study including 259 patients with a large pericardial effusion, the underlying cause was identified by molecular and immune-histological methods mainly as autoreactive/lymphocytic (i.e. idiopathic or "viral", 35%), malignant (28%), traumatic (i.e. post-cardiac surgery, 15%), and viral (12%) [5]. The etiologic spectrum is different in developing countries, with a high prevalence of tuberculosis (70% of pericarditis in sub-Saharan Africa, and ≥ 90% when associated with HIV infection). Some features have proved to be independent predictors of a specific cause (non-viral or non-idiopathic pericarditis), i.e. fever >38°C (hazard radio [HR], 3.56), subacute course (HR, 3.97), large pericardial effusion or cardiac tamponade (HR, 2.15), and failure of non-steroid anti-inflammatory drugs (NSAIDs)(HR, 2.50) [6,7,8,9].

After the first episode of acute pericarditis, recurrences are frequent (20 to 50%). Recurrent pericarditis is defined as a recurrence of chest pain associated with at least one of the following objective evidence of disease activity: fever, pericardial rub, ECG changes, new or worsening pericardial effusion and/or elevation of biomarkers of inflammation (elevation in white blood cell count, erythrocyte sedimentation rate, or CRP) after a free interval of 4-6 weeks following the first episode (**Figure 1**). These criteria, although arbitrary, are generally accepted.

The pathogenesis of recurrent pericarditis has long been poorly understood. Recent data strongly suggest underlying auto-inflammatory and/or auto-immune disorders, with viral infections as possible triggers (**Figure 2)**. On the one hand, the inflammatory response of the innate immune system typical of "auto-inflammatory diseases" - predominantly mediated by

cytokines (mainly interleukin-1 [IL-1]) - has been reported in patients with recurrent pericarditis [10,11]. Conversely, auto-inflammatory diseases such as cryopyrin-associated periodic syndromes and familial Mediterranean fever (FMF) are characterized by spontaneous onset of intermittent inflammatory attacks with fever and serositis frequently including pericarditis [12,13,14,15]. In recurrent pericarditis, the auto-inflammatory mechanism may result from activation of the inflammasome by a cardiotropic virus or a nonspecific agent in a patient who has abnormal innate immunity. This will cause release of pro-inflammatory cytokines including interleukins - mainly IL-1 - that bring neutrophils and macrophages to the injured area [16]. Of note, colchicine is able to modulate innate immunity and to block the processing of IL-1β. Its efficacy in the treatment of FMF relapses is largely proved, as well as in the reduction of pericarditis recurrences [2,3,7]. More recently, anakinra - a short-acting IL-1 receptor antagonist - has shown good results in controlling very quickly the acute attack and decreasing relapses in idiopathic recurrent pericarditis. On the other hand, the inflammatory response of the adaptive immune system, typical of “auto-immune diseases” - mainly mediated by autoantibodies or autoreactive T lymphocytes [9] - also seems to be involved in idiopathic recurrent pericarditis. Anti-heart autoantibodies (AHA) or anti-intercalated disk autoantibodies (AIDA) have been found in adult cases and were associated with a higher number of recurrences and hospitalizations [17].

Recurrent acute attacks of pericarditis have a negative impact on morbidity and quality of life of patients. The presence of large effusion and tamponade (HR, 2.51) and NSAIDs failure (HR, 5.50) identify increased risk of complications during follow-up [6]. However, the overall long-term prognosis of idiopathic recurrent cases is very good. The most serious risk - the risk of pericardial constriction - has been estimated to be below 1% among 500 patients, after a median follow-up of 72 months [18,19,20].

Treatment

The treatment of first episode of recurrent pericarditis is quite similar to the treatment of the initial episode of acute pericarditis. In the presence of multiple recurrences, other

111 therapeutic options should be discussed (all therapeutic options are summarized in **Figure**
112 **3**). Of course, in the event of an underlying etiology identified and for which therapeutic
113 options are available (i.e. curable infectious diseases, cancers, systemic diseases…), the
114 treatment of such causal disease is of major importance. Physical activity may have a role in
115 the recurrence and exacerbation of pericarditis. A moderate restriction of physical activity up
116 to what is necessary to perform domestic tasks and undertake sedentary work is generally
117 advised [21].

118 ***Colchicine and NSAIDs***

119 For the treatment of acute pericarditis, aspirin and NSAIDs are mainstays and should
120 be used at full anti-inflammatory doses until symptoms disappear and CRP completely
121 normalizes [2,4,22]. First evidence-based to support the use of colchicine came from open
122 label trials. The COlchicine for PEricarditis (COPE) trial included 120 patients with a first
123 episode of acute pericarditis [23]. Colchicine for three months on top of aspirin or NSAIDs
124 decreased the recurrence rate and symptom persistence at 72 hours. In a multicentre,
125 double blind trial [Investigation on Colchicine for Acute Pericarditis (ICAP)], two hundred and
126 forty adults with acute pericarditis were randomly assigned to receive for three months either
127 colchicine or placebo, in addition to NSAIDs [24]. Incessant or recurrent pericarditis occurred
128 less frequently in the colchicine versus the placebo group (16.7 % vs. 37.5 %; $P<0.001$).
129 Colchicine significantly reduced the rate of symptom persistence at 72 hours, the remission
130 rate at one week, the number of recurrences per patient, and the hospitalization rate.

131 For the treatment of patients with one or two recurrences of pericarditis, preliminary
132 evidence for the use of colchicine came from non-randomized studies. The COlchicine for
133 Recurrent Pericarditis (CORE) trial included eighty-four patients with recurrent pericarditis
134 [25]. Colchicine plus aspirin or NSAIDs for six months decreased the recurrence rate of
135 pericarditis at 18 months (24.0% vs. 50.6%; $P<0.022$). A prospective, randomized, double
136 blind, placebo-controlled multicenter trial [Colchicine for Recurrent Pericarditis (CORP)] [26],
137 demonstrated the efficacy of colchicine in 120 patients with a first recurrence of pericarditis.

For patients with multiple (≥ 2) pericarditis recurrences, another multicenter, double-blind randomized trial evaluated the efficacy of colchicine for six months in addition to NSAIDs [Colchicine for Recurrent Pericarditis 2 (CORP-2)] [27]. The relative risk reduction of recurrent pericarditis in the colchicine vs. the placebo group was 0.49 (95% CI 0.24-0.65). Colchicine significantly reduced the rate of symptom persistence at 72 hours, the number of recurrences per patient, and the hospitalization rate and increased the remission rate at one week. Of note, adverse effects and rates of study-drug discontinuation were similar in the two study groups.

Corticosteroids or immunosuppressive agents

There is still controversy to know if (and when) corticosteroids or immunosuppressive agents should be considered for recurrent pericarditis [2]. Studies have shown that corticosteroids could increase the rate of recurrence [28,29]. High dose of steroids should be avoided as they proved to have less benefit and higher risk of corticosteroid-dependence than low doses [29]. A recent report showed that in patients with idiopathic pericarditis recurrences despite a well conducted treatment with aspirin or NSAIDs and colchicine, steroids or immunosuppressive agent (azathioprine, methotrexate, and mycophenolate mofetil) may help to control the disease [30]. 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 ($p<0.001$). 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. Two recent systematic reviews described the existing evidence for immunosuppressive drugs in idiopathic refractory recurrent pericarditis [7,31]. In the largest reported experience, azathioprine was administered at a dose of 1.5–2.5 mg/kg/day for 13.6 ± 5.1 months in forty-five patients [32]. It was associated with remission after steroid discontinuation in more than fifty percent of patients and well tolerated.

Intravenous immunoglobulins have been proposed in refractory cases [33,34]. High dose intravenous immunoglobulins associated to NSAIDs, steroids, or colchicine treatment

have been used for 11 months in nine patients with recurrent pericarditis (mean of 5 relapses per patient) [33]. Patients showed complete clinical remission with no further relapse after one or two intravenous immunoglobulins session (n=6), a single minor relapse responsive to short-term NSAIDs (n=2), and no response (n=1).

The era of interleukin-1 receptor antagonist

There is accumulating evidences of effectiveness of anti-IL1 agents. Three molecules are available. Anakinra is a recombinant form of the IL-1 antagonist receptor (IL-1Ra). Rilonacept, a dimeric fusion protein blocking IL-1, contains the extracellular parts of the IL-1 receptors (IL-1R1 and IL-1RAcP). Canakinumab is a humanized antibody that prevents IL-1β from binding to its receptor.

Anakinra has first shown its effectiveness in pediatric recurrent pericarditis [35,36] (**Table 2**). In a retrospective study, corticosteroid-dependent patients received anakinra 1 to 2 mg/kg/d [36]. All patients showed a complete response within a few days and were able to rapidly withdraw corticosteroids. During anakinra tapering, 6 out of 14 patients experienced a relapse, with a prompt response after anakinra reintroduction. After a mean follow-up of 39 months, authors reported a 95% reduction of pericarditis flares vs. pre-treatment period. Ten adult patients with idiopathic recurrent pericarditis treated with anakinra were analyzed [37]. All patients were resistant and/or intolerant to previous treatment with NSAIDs, colchicine and corticosteroids, while two had failed also azathioprine therapy. The mean number of recurrences was 8, the mean baseline dose of prednisolone was 14.1 mg/day and the mean baseline CRP level was 74 mg/dL. Patients were given daily subcutaneous anakinra (100 mg) for six months followed by alternate day dosing for another six months. Anakinra was highly effective in all cases leading to rapid symptom relief (within 2 days), CRP normalization (5.9 days) and tapering/discontinuation of corticosteroids (37.5 days). Five out of 7 patients relapsed shortly after anakinra discontinuation and in 4 out of 5 patients anakinra was re-started with immediate control of symptoms. Side effects included minor local reactions at the injection site and transient transaminasemia. In a retrospective study from the Mayo clinic, thirteen patients with treatment-refractory recurrent idiopathic

pericarditis for a mean duration of 3 years (1.1 to 6.0) received anakinra [38]. Response to therapy was rapid (2 to 5 days) and included complete (n=12) or partial (n=1) resolution of symptoms. At last follow up, 11 out of 13 patients discontinued NSAIDs, colchicine, and glucocorticoids, 2 stopped anakinra without flare, and 11 patients remained on anakinra. The experience of the NIH was recently reported [39]. A series of 10 patients had recurrent idiopathic pericarditis refractory to NSAIDs, colchicine and steroids (n=10), and immunosuppressant (n=6). After patients received anakinra (100 or 200 mg/day) for a mean duration of 26.5 months (11.5-66.8), they showed a complete response (n=5), a partial response (n=4), and no response (n=1). In their review, Lazaros et al [40] analyzed nine reports (34 patients, 20 men, mean age 26.8 years) of anakinra in patients with idiopathic recurrent pericarditis. The mean disease duration was 31 months and the mean number of recurrences 8.2. Anakinra was administered as a daily subcutaneous injection of 100 mg or a mean dose of 1.1 mg/kg/d in weight-adjusted regimens. The mean full-dose duration was 9.2 months. CRP normalized within 7.1 days, and steroids were withdrawn within 62 days. Dose tapering was adopted in 65% of patients, leading to recurrence in 26% of cases. After a mean of 28.3 months follow-up, eight out of 34 (23.5%) patients were disease free without treatment, after having received anakinra for 10.4 months overall. Mild local reaction were reported in 44% of patients.

Recently, a double blind, placebo-controlled, randomized trial was conducted among twenty-one patients who presented three or more previous recurrences of pericarditis, colchicine resistance, and corticosteroid dependence [Anakinra Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP)] [41]. In a first phase, anakinra was administered to all patients at 2 mg/kg per day, up to 100 mg, for two months; then patients who responded with resolution of pericarditis were randomized to continue anakinra (n = 11) or switch to placebo (n = 10) for six months or until a pericarditis recurrence. Recurrent pericarditis occurred in 9 of 10 patients (90%; incidence rate, 2.06% of patients per year) assigned to placebo and 2 of 11 patients (18.2%; incidence rate, 0.11% of patients per year) assigned to anakinra. Median flare-free survival after randomization was 72 days in the placebo group and not reached in

the anakinra group (P <0.001). During anakinra treatment, 95.2% of patients experienced transient local skin reactions, 4.8% herpes zoster, 14.3% transaminase elevation, and 4.8% ischemic optic neuropathy. No adverse events occurred during placebo treatment. Data of a large international multicenter registry of anakinra in the treatment of recurrent pericarditis were recently published [42]. A total of 224 patients (46 years old, 63% women, 75% idiopathic) with recurrent pericarditis for 17 months who were corticosteroid dependent and colchicine resistant and treated with anakinra were included. Most patients had elevated CRP (91%) and pericardial effusion (88%). After a median anakinra (100 mg per day subcutaneously) treatment of 6 months, pericarditis recurrences were reduced six-fold (2.33-0.39 per patient per year), emergency department admissions 11-fold (1.08-0.10 per patient per year), and hospitalizations seven-fold (0.99-0.13 per patient per year). Corticosteroid use was decreased from 80% to 27%. Adverse events consisted mostly of transient skin reactions (38%) at the injection site, which led to anakinra discontinuation in only 3%. A full-dose anakinra duration of over 3 months followed by a tapering period of over 3 months were the therapeutic schemes associated with a lower risk of recurrence.

Finally, in a recent multicenter phase II clinical trial, rilonacept has been used in twenty-five symptomatic or corticosteroid dependent patients with idiopathic or post-pericardiotomy recurrent pericarditis. Twenty-three patients completed 6 months of rilonacept treatment, 160 mg SC weekly after a 320 mg load dose, with a good efficacy on pain and CRP levels [43].

Of note, anti-IL1 agents must be used taking into account possible contraindications, infectious diseases or underlying immunosuppression, and the risk of infection. Anakinra is contraindicated in kidney failure. The therapeutic choice must also take into account the cost of such molecules, particularly for canakinumab.

Remaining challenges

Although major advances have been done during the last decade, there remain some issues in the care of patients with recurrent pericarditis. What is the best length of colchicine treatment for acute or recurrent pericarditis? Current guidelines suggest a duration of

treatment with colchicine of 3 months in the first acute episode and 6 months in recurrent pericarditis. In recurrent more severe cases, considering the good tolerance, a longer use of the colchicine up to 12 to 24 months, tailored to the individual patient and with gradual tapering, may be useful [4]. The dose and duration of NSAIDs treatment are still debatable as well as the need for gradual tapering. What is the efficacy and safety of colchicine in non-viral/non-idiopathic pericarditis ? The Colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS and COPPS2) trials published in 2011 and 2014 showed efficiency of colchicine on preventing post-pericardiotomy syndrome but not of postoperative atrial fibrillation or postoperative pericardial/pleural effusion. Colchicine treatment was associated with a higher rate of digestive side effects. The efficacy and safety of colchicine in systemic autoimmune diseases remains unknown [44,45]. How to manage patients with recurrent pericarditis and corticosteroid dependence? Although growing evidence suggests a place of IL-1 receptor antagonists (anakinra, canakinumab, rilonacept), their position in the treatment algorithm of recurrent pericarditis needs further evaluation in larger prospective clinical trials to replicate initial findings as well as to assess safety, cost-effectiveness and long-term efficacy.

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443 **Table 1. Major causes of pericarditis.**

444

Idiopathic
Malignancy
Post-Cardiac injury syndrome
Post-myocardial infarction
Post-pericardiotomy
Post-traumatic
Infectious diseases
Viral, including HIV
Bacterial and mycobacterial
Fungal
Radiation
Systemic disorders
Connective tissue diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Systemic sclerosis
Sjögren's syndrome
Myositis
Granulomatosous diseases
Sarcoïdosis
Vasculitis
Behçet syndrome
Small vessels : eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis
Medium-sized vessels : polyarteritis nodosa, Kawasaki disease
Auto-inflammatory diseases
Familial Mediterranean Fever (FMF)
Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)

445
446

Table 2: Series of anakinra use in recurrent pericarditis.

Reference, year	Methods	Patient number	Resistance to treatment	Anakinra dose	Complete response	Partial response	Pericarditis relapse after anakinra withdrawal
34, 2014	Retrospective cohort	14	CS	1-2 mg/kg/d	100%	0%	43%
35, 2014	Retrospective cohort	10	NSAIDs, CS, colchicine, azathioprine	100 mg/d	70%	30%	71%
36, 2015	Retrospective cohort	13	NSAIDs, CS, colchicine	100 mg/d	92%	8%	NA
38, 2016	Literature review	34	NSAIDs, CS, colchicine	100 mg/d or 1.1 mg/kg/d			
39, 2016	Prospective, double blind, placebo controlled	21	NSAIDs, CS, colchicine	2 mg/kg/d up to 100 mg/d	100% under anakinra open label phase	0%	90% placebo group vs. 18% anakinra group during double blind phase
37, 2018	Retrospective cohort	10	NSAIDs, CS, colchicine, IS	100-200 mg/d	50%	40%	NA
42, 2019	Prospective international registry	224	NSAIDs, CS, colchicine	100 mg/d	43%	29%	2.33 to 0.39 per patient/yr

NSAIDs, non-steroid anti-inflammatory drug; NA, not available

Figure 1. Recurrent pericarditis diagnosis flowchart.

Figure 2. Schematic of the pathogenesis of recurrent pericarditis and impact of main treatment used.

After pericardial damage (viral, traumatic…), two separate pathways of immunity may be activated. From innate immunity, a group of pattern recognition receptors (TLR and NLR) will assemble and oligomerize into the inflammasome, an activating structure of caspase 1. This will lead to the production of inflammatory cytokines including IL1ß, which will cause the production of cycloxygenase (COX) resulting in the production of prostaglandins. At the same time, an involvement of the adaptive immune system has been proposed via the production of anti-heart (AHA) and anti-intercalated disk antibodies (AIDA), produced by lymphocytes activated by antigen-presenting cells (having encountered pericardial antigens released after the pericardial lesion). These lymphocytes also produce inflammatory cytokines such as IL6, IL8 and IFNgamma. Corticosteroids will have an impact on both sides of the immune system, innate and adaptive. Other treatments currently used in recurrent pericarditis have an impact on innate immunity: colchicine inhibits the action of the inflammasome, anti-IL1 agents counter the inflammatory activity of IL1 and NSAIDs inhibit COX.

AHA, anti-heart antibodies; AIDA, anti-intercalated-disk autoantibodies; DAMPs, damage-associated molecular patterns; NLR, nod-like receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMPs, pathogens-associated molecular patterns; TLR: toll-like receptor

Figure 3. Recurrent pericarditis therapeutic options flowchart.