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IM - REVIEW

Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism

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Abstract
Recurrent pericarditis is one of the most frequent pericardial diseases, affecting up to 30% of the patients who have experienced acute pericarditis. While the diagnosis of acute pericarditis is sometime straight forward, its etiology and therapeutic management are still a challenge for physicians. In developed countries, the idiopathic form is the most frequent, and the search for an infectious etiology is almost invariably negative. Nevertheless, since standard treatment with nonsteroidal anti-inflammatory drugs and colchicine is not always able to neutralize pericardial inflammation in recurrent pericarditis, anakinra, an IL-1 receptor antagonist, has been proposed as a possible therapeutic alternative for refractory forms. IL-1 is a cytokine that exerts a pivotal role in innate immunity and in the pathogenesis of some autoimmune diseases, such as rheumatoid arthritis, and in autoinflammatory disorders, as familial Mediterranean fever and cryopyrin-associated periodic syndromes. The successful management of patients with acute idiopathic recurrent pericarditis (IRP) needs a teamwork approach, where cardiologists, rheumatologists, clinical immunologists and internists are involved. In this review, we will discuss the clinical and therapeutical challenges of IRP both in adults and children from a clinical practice standpoint. We will also briefly illustrate the main pathogenic mechanisms of IRP to provide internists and cardiologists with the rationale for approaching the use of anakinra in selected clinical cases.

Keywords Pericardial diseases · Recurrent pericarditis · Autoimmune diseases · Autoinflammatory diseases · Interleukin-1Ra · Anakinra

Introduction

Acute pericarditis, particularly in its recurrent form, often requires the input of other specialists, such as rheumatologists and clinical immunologists in addition to cardiologists and internists. Not only can pericarditis be a clinical feature of a generalised autoimmune disorder, such as systemic lupus erythematosus (SLE), or of an autoinflammatory disease, such as familial Mediterranean fever (FMF), but it can also be secondary to an infectious or a malignant disease [1]. In developed countries, the idiopathic forms are the more frequently encountered in Emergency and Internal Medicine

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Units, and internists, together with cardiologists, often initially deal with these conditions [2]. Despite its diagnosis sometimes being straight forward, recurrent pericarditis challenges the physicians with therapeutic management [1]. Indeed, it is not infrequent in clinical practice to observe patients with recurrences due to an inappropriate therapeutic approach. In particular, corticosteroids sometimes are also used for the first acute episode, are known to favor relapses and chronicity [3], as well as an extreme rapid tapering of appropriate treatment [1]. In selected cases, when neither NSAIDs nor colchicine are able to induce a stable remission of pericardial inflammation, the use of anakinra, an IL-1 receptor antagonist (IL-1Ra), seems to offer a valuable therapeutic option [4, 5].

In this review, we will outline the main aetiopathogenic, diagnostic and clinical aspects of idiopathic recurrent pericarditis (IRP), with particular attention to the new therapeutic options, such as anakinra, with the aim to help teamwork and interaction between the different specialists involved in the clinical management of these patients.

Search strategy and selection criteria for review

We searched PubMed mainly matching the key search terms "idiopathic recurrent pericarditis", "anakinra and pericarditis", "interleukin-1 and pericarditis", "recurrent pericarditis and treatment". Full texts, as well as abstracts of 98 published original articles were reviewed. We also include some review papers. We considered 66 articles for the final literature revision. The search was limited to papers published in English language, and was conducted without any date limits through December 2017.

Epidemiology

Pericarditis has an important socio-economic impact, since it accounts for about 0.1% of hospitalisation for all causes. Moreover, it is responsible for 0.2% of all cardiovascular admissions, and about 5% of emergency department admissions for chest pain are due to pericarditis [6, 7]. Men, especially in the very young and adult age, have a higher risk of pericarditis than women, and mortality for acute pericarditis during hospitalisation is estimated to be about 1.1%, increasing with age and co-infections [8, 9].

In developed countries, acute pericarditis is a quite frequent disease. According to available studies, its incidence varies on the basis of the studies, ranging from 27.7 to 168/100,000 people/year [10, 11]. Data from Finland show an incidence of hospitalisations for acute pericarditis of about 3.3/100,000 people/year, but these data probably underestimate the problem, since it accounts for only hospitalized patients [9]. Additionally, IRP is not a rare event, considering that up to 30% of patients within 18 months after the first episode of acute pericarditis have a relapse [12]. Moreover, patients with a previous recurrence of pericarditis, have a new relapse in up to 50% of cases [13].

Aetiopathogenesis

In developed countries, about 80% of pericarditis cases are defined as "idiopathic" [12–15]. This term probably reflects our current incapacity to reveal the intimate mechanisms of the disease both for acute as for recurrent episodes [16]. The more accepted pathogenetic scenario is represented by the interaction between infectious agents (mostly viral), and the immune system via different pathways [17, 18]. For years, a derangement of adaptive immunity has been considered the main explanation for the recurrence of pericarditis. The most important direct and indirect clues supporting this hypothesis are: (1) the occurrence of pericardial involvement in autoimmune diseases, especially SLE [19], (2) the positive response to glucocorticoids [17], immunosuppressants interfering with cell mediated immunity (azathioprine) [20] or immunomodulatory treatments (intravenous immunoglobulins, IVIg) [21], and (3) the frequent presence of antinuclear antibodies (ANA) and the demonstration of auto-antibodies directed towards specific cardiac antigens [22].

However, more recently, innate immunity has emerged as pivotal in the pathogenesis of recurrent pericarditis [23, 24]. There is much evidence, including clinical, genetic and therapeutic that allows to assignment of several cases with recurrent pericarditis to autoinflammatory disorders. Many of the idiopathic forms, especially in the pediatric age, have a phenotype characterised by abrupt episodes of fever, dramatic elevation of inflammatory markers (erythrocyte sedimentation rate, ESR and C-reactive protein, CRP) and sometimes along with pleuropulmonary involvement, polyserositis and arthralgias [21]. Similarly, episodes are often followed by interval-free symptoms with complete wellness and full normalization of ESR and CRP [24]. In addition, this clinical course of IRP surprisingly resembles the clinical features of some autoinflammatory disorders, such as familial Mediterranean fever (FMF) or periodic syndrome associated with the tumor necrosis factor receptor (TRAPS) [25].

Autoinflammatory syndromes are a heterogeneous group of monogenic and polygenic disorders characterised by inflammation due to apparently unprovoked activation of the innate immune system [24, 26]. Genetic mutations mainly involve cryopyrin, a major component of a complex intracellular platform, known as inflammasome [27]. The latter is an enzymatic complex activated by cellular sensors like pathogen associated molecular patterns (PAMPs) or damage

associated molecular patterns (DAMPs) through specific membrane (toll-like receptors, TLRs) or intracellular (NOD-like receptors, NLRs) receptors. This mechanism leads to the production of large amounts of IL-1, which in turn is able to recruit effector cells such as monocytes, macrophages and neutrophils [27]. The great production of IL-1 explains the remarkable therapeutic response to IL-1 receptor antagonist anakinra [24, 26] (Fig. 1).

FMF mutations are generally absent in IRP [28], while those associated with TRAPS have been observed in about 6–7% of patients with recurrences [29, 30]. Most of TRAPS-positive patients have a family history for pericarditis or recurrent fever syndromes, and usually are resistant to colchicine [24]. On the other hand, recurrent pericarditis can be one of the clinical manifestations of an autoinflammatory disorder, such as TRAPS [31] and FMF [32], and of note, a familial predisposition is present in up to 10% of the cases.

Diagnostic criteria and definitions

Acute, recurrent and refractory disease

Acute pericarditis

Acute pericarditis is defined as an inflammatory condition involving the *pericardium*, with a sudden onset, and characterised by at least two of the four following clinical features:

(a) typical chest pain (almost in 100% of cases in adults);

(b)pericardial rubs (33% of cases);

(c)typical electrocardiographic changes (e.g., new widespread ST-elevation or PR segment depression) in about 50–60% of cases;

(d)pericardial effusion (new or worsening) in 60% of cases, and usually mild, less than 10 mm.

Acute pericarditis can be accompanied by other systemic manifestations, depending on the underlying causes (e.g., fever, arthralgias, pleural involvement, etc), elevation of

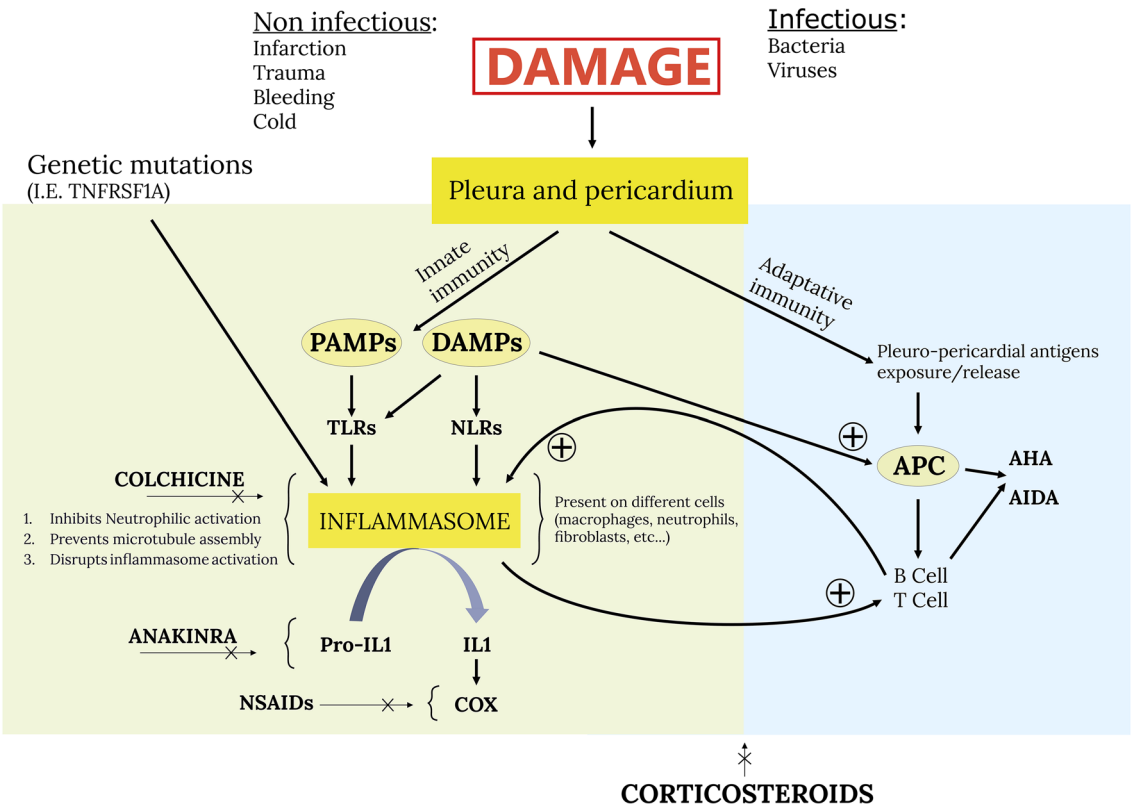

Fig. 1 General scheme of the supposed pathogenetic mechanisms of acute idiopathic recurrent pericarditis. *PAMP* pathogens associated molecular patterns, *DAMPs* damage associated molecular patterns, *TLR* toll-like receptors, *NLR* NOD-like receptors, *AHA* anti-heart antibodies, *AIDA* anti-intercalated-disk antibodies, *IL-1* interleukin-1, *NSAIDs* nonsteroidal anti-inflammatory drugs, *APC* antigen-presenting cells

ESR and CRP and leukocytosis are common (80% of cases) [1, 33]. Pleural effusions and pleuropulmonary involvement occur in approximately one-third of cases, particularly during the first and often more severe attacks, often associated with fever and elevated CRP [3].

Recurrent pericarditis

Pericarditis is defined as recurrent when a symptom-free interval of 4–6 weeks or longer occurs between a first acute episode and a relapse [1]. Clinical and ECG criteria of a recurrence are the same as in the first acute episode, the elevation of CRP being the most reliable biomarker, which is raised in approximately 80% of cases [1, 33]. As mentioned above, recurrences are relatively frequent (ranging from 15 to 50% of cases), and often occur due to inappropriate treatment of a first episode [1]. In doubtful or atypical cases, imaging can help to reach the diagnosis by the demonstration of pericardial inflammation by CT or cardiac magnetic resonance imaging (pericardial edema on T2-weighted imaging or pericardial late gadolinium enhancement) [1].

Refractory pericarditis

"Refractory pericarditis" is a pericarditis that recurs despite optimal medical therapy including colchicine and corticosteroids. In general, refractory cases (approximately 5% of the recurrent forms) are those that need to be controlled with: (a) doses of prednisone chronically higher than 10–15 mg/day, (b) alternative treatment (e.g., azathioprine, intravenous immunoglobulin) despite adequate treatment with aspirin or NSAIDs at high dosages plus colchicine [33].

Clinical course and management

When should I have to test for secondary forms of pericarditis?

In clinical practice, during the first episode of acute pericarditis, it is not mandatory to test for secondary forms [1]. Indeed, at least in industrialized countries, idiopathic (and probably viral) forms are the most common, and to find a specific viral diagnosis is often irrelevant for the management and treatment. Clinical features at presentation associated with a non-viral or non-idiopathic etiology are: (a) fever > 38 °C, (b) subacute course (symptoms developing over several days or weeks), (c) large pericardial effusion (diastolic echo-free space > 20 mm in width) or cardiac tamponade, and (d) inadequate response within 7 days to NSAIDs [34]. When one or more of these factors are present, a detailed diagnostic work-up is recommended based on the pre-test probability of a specific condition, such as neoplasms or tuberculosis or a defined rheumatic autoimmune disease (e.g., chest CT scan to assess possible neoplasms) [1].

Examples may be patients with: (1) refractory/recurrent courses despite adequate treatment, (2) familial or personal history for periodic fevers, (3) associated systemic symptoms (e.g., weight loss, arthralgias, pleural involvement, proteinuria, etc), and (4) coming from geographic area at high prevalence of tuberculosis.

Due to the risk of procedural complications (4–10% of cases) and the low diagnostic yield (the sensitivity of cytology for neoplasms is approximately 50%, as well as the sensitivity of *Mycobacterium* culture for tuberculosis), pericardiocentesis is generally indicated for symptomatic huge pericardial effusions not responsive to medical therapy or when high suspicion of infectious or neoplastic etiology is present [1].

How should I manage a patient with pericarditis? Poor prognostic factors, needs for hospital admission and biomarkers

Commonly, pericarditis has a good clinical course and prognosis in both adults and children [1, 35]. However, some risk factors (major and minor) are associated with a worse prognosis. Major risk factors, according to multivariate analysis [34], are the same described above as associated with a non-viral and non-idiopathic etiology (high-fever, subacute course, large pericardial effusion, and inadequate response to NSAIDs). Minor prognostic risk factors are less clearly defined, but the following are considered: (i) the presence of associated myocarditis, (ii) immune depression (determined from the presence of underlying inflammatory disease or due to the use of immunosuppressants), (iii) trauma, and (iv) oral anticoagulant treatment [1].

In clinical practice, every patient with a risk factor (either major or minor) should be hospitalized for a safer management, and the search carried out for secondary causes of pericarditis [1]. On the contrary, when risk factors are absent, patients can be safely managed and treated in the outpatient clinic. In this case, the use of empirical therapy with aspirin or NSAIDs plus colchicine is suggested, together with a short term follow-up (usually 1 week), to look for early complications [1] (Fig. 2).

The most reliable biomarker for monitoring pericarditis is CRP [1]. The normalisation of CRP, together with the disappearance of symptoms is used in clinical practice to follow patients, and to adjust and taper treatment. In particular, every tapering or discontinuation of the treatment

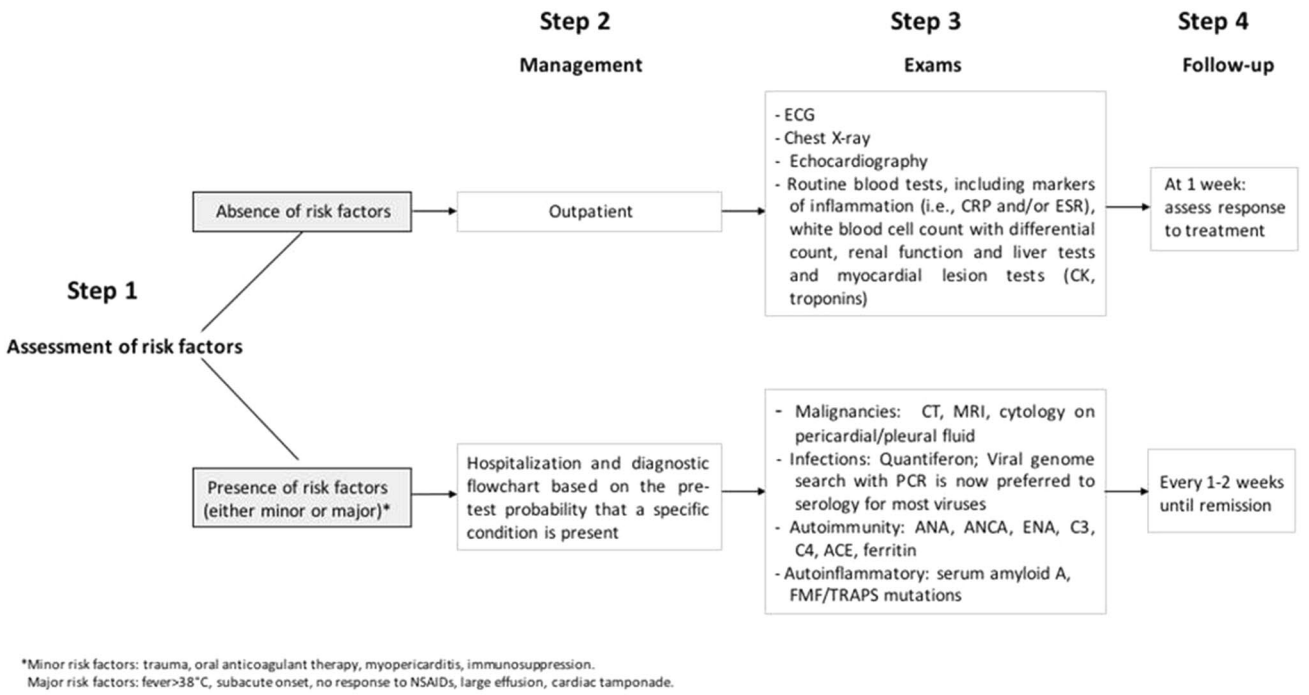

Fig. 2 Management of pericarditis in adults based on the assessment of risk factors

Table 1 Therapeutic algorithm of pericarditis in adults

	DRUGS	DOSES	DURATION	TAPERING
IST LINE TREATMENT	**Aspirin**	500-1000mg/8h	2 weeks-months	250-500 mg every 1-2 weeks
	Ibuprofen	600-800mg/8h	2 weeks-months	250-400 mg every 1-2 weeks
Follow-up based on: 1)symptoms 2)CRP/ESR elevated 3)alterations on ECG/echocardiogram	**Indomethacin**	75-150 mg/24 h	2 weeks-months	25 mg every 1–2 weeks
	Naproxen	500-1500 mg/24 h	2 weeks-months	125–250 mg every 1–2 weeks
	Colchicine	0.5-1mg/24h	3-6 months	Not mandatory
IInd LINE TREATMENT	**Corticosteroids**	0.2-0.5 mg/kg/24h	Based on follow-up	2.5 mg/24h every 2-6 weeks
REFRACTORY PERICARDITIS	**Azathioprine**	2-3 mg/kg/24h	Based on follow-up	Based on follow-up
	IVIg	400 mg/kg/day	Based on follow-up	Based on follow-up
	Anakinra	100 mg/24 h	Based on follow-up	See figure 3

(aspirin/NSAIDs, colchicine or corticosteroids), should be done according to CRP levels [1, 7, 33]. Among others, IL-8 (also known as CXCL8, a serum chemochine able to recruit neutrophils) has been related with a more frequent transition from acute pericarditis to IRP [36]. Nevertheless, its usage is currently limited to the research area.

Treatments

General overview

The first line treatment of acute and recurrent pericarditis is essentially the same, and consists of the use of aspirin or

NSAIDs in combination with colchicine [1, 37] (Table 1). In selected cases (e.g., patients intolerant or in whom first line drugs have failed), low-doses of corticosteroids are allowed, but when possible, they should always be avoided as first line treatment, since they favor recurrences [38]. The treatment should be tailored to the patients' features, co-morbidity and co-treatments, to increase the therapeutic compliance and reduce recurrences [1, 37]. As previously reported, the treatment duration, adjustment or discontinuation, need to be adequate according to clinical course and CRP levels [1] (Table 1).

Important practical tips to reaching a good control of the disease are the following: (a) use of NSAIDs at higher tolerated dosages, (b) aspirin, ibuprofen, and indomethacin should be administered every 8 h, (c) intravenous preparations are preferred in hospitalized patients, (d) add analgesics at fixed intervals (not on demand) such as codeine, tramadol, opioids for better pain control instead of increasing the dose of corticosteroids, (e) add paracetamol at fixed intervals for a better control of hyperpyrexia, (f) aspirin is preferred in patients who need antiplatelet therapy.

With regard to colchicine, avoid loading dosage or a daily dose higher than 1 mg (0.5 mg twice daily in patients with a body weight > 70 kg, and 0.5/day if under 70 kg or in patients over 70 kg who do not tolerate the standard daily dose). The dose is usually reduced in elderly patients and for renal insufficiency, considering that colchicine interacts with chlarytromicin, statins and diltiazem.

When combined with NSAIDs and colchicine, low doses of prednisone, starting with 7.5–10 mg/daily, usually allows control of pericarditis. Furthermore, the tapering of prednisone must be very slow since recurrences are typically expected when corticosteroid is reduced or discontinued. In case of relapse, NSAIDs should be increased instead of prednisone. Even though it is well known that corticosteroids should be avoided in the absence of a specific indication, they are often used in clinical practice, and also are sometimes also the first line treatment in pericarditis. Corticosteroids work very well in pericarditis, but unfortunately they have several drawbacks in this condition. Indeed, corticosteroids can (a) favor the recurrences of pericarditis, especially when used at high dose, (b) promote steroid-dependence, (c) reduce the efficacy of colchicine, and finally (d) cause severe side effects, especially in children, like growth retardation and disfiguring striae rubrae [1, 21]. However, corticosteroids can have a role in specific conditions, and in particular, to treat pericarditis secondary to autoimmune diseases (e.g., SLE) and in patients who are intolerant of aspirin or NSAIDs [1].

Therapy of refractory cases

The first therapeutic choice for refractory pericarditis is represented by the association of aspirin or NSAIDs at full dosage, intravenously in hospitalized patients combined with colchicine at the maximum dosage of 1 mg/daily plus low dose corticosteroids [33]. During drug tapering, it is not unusual for relapses to occur. Indeed, about 5% of the patients do not respond to this combined treatment. These patients, corticosteroid-dependent or colchicine-resistant, are the true refractory cases, and need a more intensive treatment, sometimes with immunosuppressive therapies [1].

In these cases, the treatments available are azathioprine (at a dosage of 2–3 mg/kg/day) [20], and IVIg [39] as on top treatment. More recently, the IL-1Ra anakinra has been successfully used [4, 40, 41] both in adults and children. Other systemic immunosuppressive treatments as cyclophosphamide [42], methotrexate and cyclosporine [43] have been anecdotally reported (Table 1). Finally, in selected patients with refractory recurrent pericarditis, pericardiectomy can be considered as an alternative to medical treatments [44].

Role of anakinra

Anakinra has emerged as a useful drug, beyond its indication in rheumatoid arthritis (RA) and cryopyrin-associated periodic syndromes (CAPS) [45]. Indeed, anakinra is currently used in several inflammatory immune-mediated conditions, most of them considered as polygenic autoinflammatory disorders [46–49].

Evidences supporting the use of anakinra for acute idiopathic recurrent pericarditis

Several previous data (mainly derived by case reports, case series and retrospective studies) and one recent randomised controlled trial, have demonstrated in the past few years, the valuable role of anakinra for the treatment of acute IRP [50].

Case reports and case series

Picco et al. described the first small series of patients treated with anakinra in 2009 [51]. Anakinra was prescribed to three pediatric subjects with corticosteroid-dependent IRP with an immediate clinical and laboratory response. This proof-of-concept observation points out three important conclusions: (1) all the patients were able to reduce/withdraw corticosteroids, (2) all the patients experienced a relapse during the follow-up after treatment was stopped, (3) for the first time the autoinflammatory nature of IRP was suggested. After a few years, Vassilopoulos and colleagues described the efficacy of anakinra in three adult patients with IRP [52],

while two following case reports also reported a good clinical response in two pediatric subjects [53, 54].

Reports of particular cases

Some additional interesting cases were published in 2014. Massardier reported the efficacy of anakinra in two female patients over 60-years-old, with pericardial constriction refractory to conventional treatments. Interestingly, both the patients were steroid free at the time of starting anakinra because of comorbidities (diabetes in one and RA in the other one). The clinical message of interest for clinicians is that anakinra can be prescribed to patients with contraindications to corticosteroids, or with other systemic conditions that respond to anti-IL1ra [55]. In recent years, some papers have reported the efficacy of anakinra in refractory, truly autoinflammatory pericarditis, related to TNF-receptor mutations [30, 56, 57].

A minority (about 1%) of patients with acute IRP can develop in a few weeks/months subacute constrictive forms [1]. In such cases, the first line treatment consists of NSAIDs and colchicine, eventually followed by corticosteroids. However, these drugs can also worsen the haemodynamic of these patients, inducing further retention of water and sodium [16, 58]. In these cases, anakinra, at least in isolated case reports, seems to represent an effective alternative to pericardiectomy [41, 58, 59].

Retrospective studies

Two retrospective studies support the efficacy of anakinra in recurrent/refractory forms of pericarditis. The first one was a retrospective multicentric national evaluation of the long-term efficacy of anakinra both in children ($n = 12$) and adults ($n = 3$) with recurrent steroid-dependent pericarditis. All patients experienced a clinical and laboratory response, and were able to withdraw treatments (including corticosteroids). During the attempt to taper the treatment with anakinra, about half of the patients experienced a flare of disease, promptly controlled by the reintroduction of anakinra. Interestingly, during the whole follow-up (median 39 months, range 6–57 months), a reduction of about 95% of relapses was observed in respect to the pre-treatment period, thus demonstrating the long-term efficacy of anakinra monotherapy [60]. In one other retrospective study, Jain and colleagues evaluate the efficacy of anakinra in 13 patients with recurrent pericarditis, refractory to conventional treatments. All the patients experienced a response (complete or partial) in a few days. At the last follow-up (about 2 years), 85% of the patients had discontinued other treatments (including corticosteroids), and two of them had also discontinued anakinra [61]. More recently, in a multicentre cohort study comprising 110 pediatric cases of recurrent pericarditis collected in dedicated centres in Italy, anakinra was prescribed in 12 patients, with a significant reduction of recurrences [21].

Prospective studies

Lazaros [62] published a prospective open label study with anakinra as rescue treatment in ten refractory adult patients with IRP non-responder or intolerant to first line treatments (aspirin and NSAIDs), colchicine, steroids and azathioprine. The anti-IL-1ra was rapidly effective in all the patients, allowing a discontinuation of corticosteroids and colchicine. Following the discontinuation of anakinra, about 70% of the patients experience a relapse, well managed by reintroducing the drug.

Randomised controlled trial

Brucato et al. published the AnakInRa-Treatment of Recurrent Idiopathic Pericarditis trial (AIR-TRIP), the first randomised controlled trial on the efficacy of anakinra in patients with IRP colchicine-resistant or corticosteroid-dependent [4]. All patients included in the study (20 adults and 1 child 15-years-old) had a history of at least three recurrences and high levels of CRP.

The study clearly shows that anakinra, compared to placebo, was able to significantly reduce the risk of recurrence for a median period of 14 months, thus allowing the discontinuation of treatment with corticosteroids. Pericarditis flares were are markedly reduced in patients receiving anakinra, occurring in only 2 out of 11 (18%) patients randomised to anakinra, compared to nine out of ten (90%) patients randomised to placebo during the double-blind period [4]. Two out of 11 patients have flares of pericarditis during anakinra treatment, giving a rate of failure or of incomplete response to the standard dose of approximately 10–20%. This is in agreement with our current real world experience in which few patients need higher dosages of anakinra, or a combined therapy with colchicine or NSAIDs or low-dose corticosteroids to maintain complete control of the disease.

For a complete list of the studies on the use of anakinra in IRP see Table 2.

Anakinra in refractory pericarditis in the clinical practice: a brief guide

When to start anakinra and in which patient

In adults, anakinra should be reserved to adult patients with refractory corticosteroid-dependent and colchicine-resistant IRP and, importantly, elevated CRP. In children, anakinra should probably be considered instead of corticosteroids as a second line treatment after the failure of truly high doses

Table 2 List of the main studies performed on the use of anakinra for idiopathic recurrent pericarditis in adults and in children

Year of publication	Type of study	Number of treated patients	Age of life of patients	Dosage	Outcome	Side effects	Ref
2009	Case series, prospective, open label	3	Pediatric	Case 1: 1 mg/kg/day for 6 weeks. (Then restarted following relapse) Case 2: 1 mg/kg/day for 2 months (then restarted following relapse) Case 3: 1.25 mg/kg/day for 14 days (then restarted following relapse)	Case 1: Fever and chest pain disappeared within 24 h; CRP normalisation after 48 h. Relapse after 2 weeks from discontinuation Case 2: Prompt resolution of the clinical symptoms with normalisation of acute phase reactant levels. Relapse after 1 week from discontinuation Case 3: Dramatic clinical improvement within 12 h. Normalisation of echocardiographic results within 5 days. Relapse after around 1.5 month from discontinuation	NA	[51]
2010	Case report	1	Adult	100 mg/day	Remarkable improvement of symptoms and decrease of laboratory parameters within a few weeks. Tapering and discontinuation of corticosteroids. Disease free during a 6-month follow-up	NA	[56]
2012	Case series	3	Adult	Case 1: 50 mg/day subcutaneously for 3 months, then at alternating days for other 3 months (after relapse, restarted at 150 mg/day for 6 months and on alternate days thereafter) Case 2: 100 mg/day subcutaneously; discontinued after 6 weeks for side effects Case 3: 100 mg/day for 6 months	Case 1: Immediate and dramatic clinical response, with concomitant prompt normalisation of acute phase reactants Recurrence (mild symptoms compatible with pericarditis along with slight CRP elevation) 1 month after tapering Case 2: Immediate symptoms resolution and normalisation of the inflammatory markers; corticosteroids tapering and discontinuation Disease free during a 15-month follow-up without any therapy Case 3: Prompt clinical and laboratory response; corticosteroids tapering and discontinuation. Recurrent symptoms 1 month after discontinuation, treated with colchicine and ibuprofen. 8 months follow-up without recurrent symptoms	Case 2: Elevation of aminotransferase levels (at week 6)	[52]
2013	Case report	1	Pediatric	2 mg/kg/day for 1 year (then restarted following relapse; taken at alternating days)	Successful steroid withdrawal Relapse after 4 weeks from discontinuation 3-years follow-up: asymptomatic	NA	[53]

Table 2 (continued)

Year of publication	Type of study	Number of treated patients	Age of life of patients	Dosage	Outcome	Side effects	Ref
2013	Case report	1	Pediatric	100 mg/day, equal to 0.7 mg/kg/day. From month 10, taken at alternate days	Rapid steroid tapering and subsequent discontinuation of steroid therapy after 3 months. Symptoms disappeared, and markers of inflammation became completely negative a few days after treatment beginning. 12-month follow-up: no recurrence, normal laboratory parameters	No side effects	[54]
2014	Case report	1	Adult	100 mg/day	Regression of symptoms and normalisation of inflammatory markers. After 8 months, no recurrence of pericarditis after withdrawal of corticosteroid therapy	NA	[30]
2014	Single center, prospective, open label	10	Adult	100 mg/day for 6 months followed by alternate day dosing for another 6 months	Rapid symptom relief (within 48 h), CRP normalisation (mean time 5.9 days) and tapering/discontinuation of corticosteroid (median time to discontinuation 37.5 days). 7 patients relapsed shortly (mean time to relapse 18 days) after initial anakinra discontinuation	Minor local reactions at the injection site ($n=6$); transient transaminasemia ($n=1$)	[62]
2014	Case series, retrospective, multicenter, open label	15	12 pediatrics and 3 adults	Mean starting dose of 1.3 mg/kg/day (range 1–2 mg/kg/day). Median duration of treatment of 12 months (range 5–17) Different tapering strategies: some progressively reduced the days of administration during the week (6 days a week for a given period of time, then 5 days a week, etc.), others directly passed to an alternate day regimen (following relapse, treatment was restarted at the same dosage in all patients)	Mean time of clinical manifestations disappearance of 2.2 days (range 12 h– 7 days). Decrease of acute phase reactants and leukocyte count with normalisation in 8.3 days (mean, range 4–15). Complete normalisation of echocardiography or ECG findings within 7 days (range 2–15 days). Rapid tapering and subsequent discontinuation of concomitant medications (colchicine, steroids, NSAIDs…) No relapse during treatment The mean time from the start of anakinra tapering to relapse was 8.5 months (range 6–13 months) After a median follow-up of 39 months (range 6–57), 5 patients in remission without any medication, and 10 patients in remission with anakinra as monotherapy at full dosage or during tapering	Skin reactions at the injection-site ($n=5$)	[60]

Table 2 (continued)

Year of publication	Type of study	Number of treated patients	Age of life of patients	Dosage	Outcome	Side effects	Ref
2014	Case report, open label	2	Adult	Case 1: Initial dosage NA; weaning between the 5th and 9th month Case 2: Initial dosage NA; weaning started at the 6th month of treatment	Case 1: Favorable clinical response at day 3 (resumption of diuresis, disappearance of precordialgia and dyspnea). Regression of biological inflammation at day 12. At 2 months of treatment asymptomatic, without inflammation and pericardial effusion Case 2: Gradual improvement of symptoms, reduction in biological inflammation at day 6 and the disappearance of echocardiographic signs of constriction	NA	[55]
2015	Case report	1	Adult	100 mg/day subcutaneously for 1 year, then tapering. Follow-up at 18 months: taken at alternate days	Prompt clinical remission and CRP normalisation. 6-month follow-up: reduction of pericardial thickness (~2 mm) and absence of late gadolinium enhancement	NA	[41]
2015	Case series, retrospective, open label	13	Adult	100 mg/day subcutaneously. Three of the patients continued therapy at 50 mg/day. In 5 subjects, weaning was unsuccessful due to recurrence of symptoms. In two patients, successful weaning after 8 and 11 months without recurrence of symptoms over 2 years of follow-up	12 subjects had complete resolution and 1 had partial resolution. 11 patients discontinued concomitant therapy with NSAIDs, glucocorticoids or colchicine	Transient injection site reaction ($n=4$)	[61]
2015	Case report	1	Adult	100 mg daily subcutaneously. After 6 months gradual tapering: − 100 mg/week every month Discontinuation after 9 months	Significant improvement in echocardiographic parameters after 15 days of treatment. Complete resolution of constriction documented at cardiac magnetic resonance imaging and at echocardiogram after 3 months	NA	[58]
2016	Case report, multicenter, retrospective	12	Pediatric	1.0 mg/kg/day subcutaneously	Number of recurrences dropped from 4.29 per year before anakinra to 0.14 per year during anakinra treatment ($P<0.05$). However, recurrences occurred after its discontinuation	NA	[21]

Table 2 (continued)

Year of publication	Type of study	Number of treated patients	Age of life of patients	Dosage	Outcome	Side effects	Ref
2016	Prospective, multicenter, randomised, double-blind, placebo-controlled	21	20 adults and 1 pediatric	Adults: 100 mg/day; children: 2 mg/kg per day up to 100 mg, subcutaneously	Pericarditis recurrence risk: − 0.718 (95% CI − 1.01; − 0.42) compared to placebo. Incidence rate of recurrence: 0.11 (0.03–0.45) for anakinra vs 2.06 (1.07–3.97) for placebo. Days to flare: 76.5 (range 33–120) for anakinra vs 28.4 (2–90) for placebo	Local reaction at the injection site ($n = 20$); herpes zoster ($n = 1$); ischemic optic neuropathy ($n = 1$); elevation of transaminases ($n = 3$)	[4]
2016	Case report	1	Adult	100 mg/day subcutaneously for 3 months	Symptoms resolution within 1 week. ECG after therapy returned to normal without ST or T wave changes; insignificant pericardial effusion, no diastolic or septal abnormalities. No relapses after 15 months from discontinuation	Herpes zoster reactivation during co-treatment with leflunomide	[59]
2017	Case report	1	Adult	100 mg/day subcutaneously	Complete resolution of symptoms; normalisation of laboratory tests. No relapses after 1 year follow-up	Mild arthralgias predominantly in wrists, which require occasional treatment with NSAIDs	[57]

of NSAIDs (i.e., full dosage every 8 h or intravenously) in combination with colchicine. This difference is due to the side effects of corticosteroids that heavily affect children more than adults. Moreover, children have a more overt autoinflammatory "phenotype" with fever, arthralgias and pleural involvement [21].

Dosage and duration of the treatment: suggestions from the studies and the clinical practice

In adults, the standard dose of anakinra is 100 mg/day subcutaneously, while in children, the suggested dose is 1–2 mg/kg/day. All studies have recorded high percentages of recurrences after anakinra discontinuation, so it should be cautiously tapered, only after a complete resolution of the symptoms and normalisation of serum inflammatory markers (especially CRP).

In Fig. 3 we propose a practical scheme based on expert-opinion, to gradually taper anakinra after a 3–6 months symptom-free-period and CRP normalisation.

Safety profile, adverse effects and management of the injection-site reactions

Among biological treatments, anakinra has demonstrated a good safety profile, particularly considering the very low risk of tuberculosis reactivation observed. However, whenever is possible, a serological screening is recommended before starting the treatment [46, 63, 64].

Severe reactions to anakinra have rarely been reported, but mild to moderate cutaneous adverse manifestations (mainly erythematous) at the injections site are frequent. In the AIR-TRIP trial they occurred in 20/21 patients (95%) during the first month of therapy, and then disappeared; three patients temporarily discontinued anakinra but resumed it after topical treatment and systemic antihistamines, and no patients discontinued the study for this adverse events.

In particular, warming the syringe to room temperature before use is advisable, along with application of a cold pack to the injection site approximately 2–3 min before and immediately after the injection. Patients should be informed in advance about the potential for such reactions to prevent unjustified drug discontinuation.

In selected cases, when anakinra has been poorly tolerated, desensitization to anakinra-related acute and delayed reactions have been proposed [65, 66].

Selection of the patients to treat with anakinra

Strict selection of patients is important: only patients with a clear inflammatory phenotype are good candidates for this therapy. Such patients usually have a history of high-fever, strikingly elevated levels of CRP, and pleural effusion,

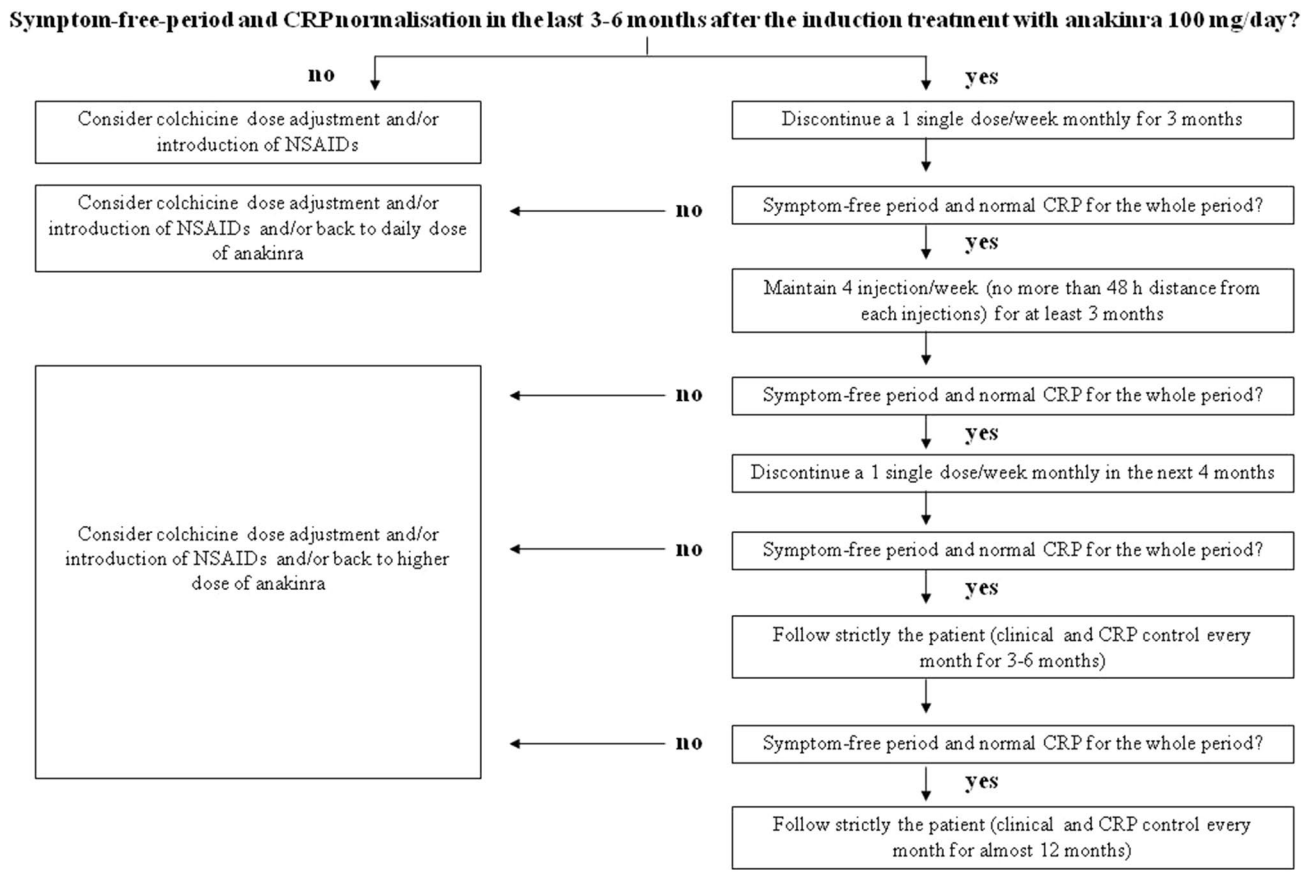

Fig. 3 Expert-opinion based proposal for guiding the gradual tapering of anakinra in patients with acute idiopathic recurrent pericarditis

particularly in the pediatric age indicating a pivotal pathogenic role of IL-1. Conversely, patients with mild or doubtful symptoms or normal or near normal levels of CRP are not good candidates for anti-IL-1 therapy. Similarly, anakinra seems less suitable for patients with idiopathic large pericardial effusion and normal CRP.

On the other hand, anakinra might be considered in selected IRP patients with raised CRP, in whom conventional therapy with NSAIDs and corticosteroids might be risky, such as: (1) anticoagulated patients, (2) patients with kidney or heart failure, at risk of sodium and water retention, (3) patients with gastrointestinal hemorrhages, and (4) patients with recent cardiac surgery.

Cost of therapy with anakinra

At present, one dose of 100 mg of anakinra costs 26.3 € (US$ 32.3) to the health system in Italy. One year of therapy for each patient costs about 6000–8000 €, considering progressive tapering and dose reduction. The economic balance should consider that these unfortunate patients have a long history of hospital admissions and school or work absenteeism that are generally reduced after starting anakinra.

Importance of a multidisciplinary care for refractory patients

Cardiologists are usually the first physicians dealing with IRP, and are usually in charge of the instrumental follow-up (ECG, echocardiography). Similarly, internists working in Emergency Units or emergency physicians often initially care for these patients. However, due to the immune-mediated pathogenesis of IRP, and its refractoriness to conventional drugs, other specialists are also usually involved. Indeed, rheumatologists and clinical immunologists should be considered for a multidisciplinary approach, especially when secondary forms are suspected or the use of immunosuppressants or anakinra is planned.

Conclusions and perspectives

The IL-1 pathway has emerged as pivotal in the pathogenesis of IRP [18], and a recent randomised controlled trial demonstrates that the IL1ra anakinra is a valuable therapeutic option to treat this condition in clinical practice [4, 5].

Anakinra has demonstrated its efficacy both in adults and in children, with a good safety profile [4, 41]. However, some points need to be clarified in the near future: (1) what kind of patients really needs treatment with anakinra? (2) Might this drug be considered as first line therapy in selected patients? (3) How long should this therapy be prolonged, and how and when should it be tapered or discontinued?

Despite these unanswered questions, anakinra is now gaining a more established role in the treatment of refractory forms of IRP. A multidisciplinary approach is warranted in most complicated cases, and cardiologists and internists must be confident with the use of anakinra in clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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