The autoinflammatory side of recurrent pericarditis: enlightening the pathogenesis for a more rational treatment

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Highlights

- Recurrent pericarditis is a troublesome and debilitating event subsequent to a first episode of acute pericarditis.
- The pathogenesis of recurrent pericarditis is still obscure, standing at a crossroad between autoimmune and autoinflammatory pathways.
- Several observations including the presence of anti-nuclear, anti-heart and anti-intercalated disk antibodies as well as the association with specific human leukocyte antigen haplotypes suggest the existence of autoimmune mechanisms in the pathogenesis of recurrent pericarditis.
- The clinical resemblance with autoinflammatory diseases, especially tumor necrosis factor receptor-associated periodic syndrome, familial Mediterranean fever and adult onset Still's disease, all marked by symptomatic serositis, high fevers and raised inflammatory parameters, support the involvement of innate immunity into the pathogenesis of recurrent pericarditis.
- Neutrophils and monocytes are key-effector cells capable of producing a large amount of interleukin-1 via inflammasome activation in patients with recurrent pericarditis.
- Anakinra is an effective therapeutic choice to manage refractory cases of recurrent pericarditis, though other anti-interleukin agents may enrich the therapeutic armamentarium currently available for this disorder in the near future.

The autoinflammatory side of recurrent pericarditis: enlightening the pathogenesis for a more rational treatment

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Ethical Statement

Not applicable for this work.

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ABSTRACT

Recurrent pericarditis (RP) is a troublesome and debilitating complication of acute pericarditis. Although the etiopathogenesis of this condition remains unknown, an intricate overlap of autoimmune and autoinflammatory pathways has been hypothesized to explain its beginning and recurrence over time. The majority of cases are defined as "idiopathic", reflecting our awkwardness to unravel the intimate mechanisms of RP. Given the possible occurrence of anti-nuclear, anti-heart and anti-intercalated disk antibodies as well as the association with peculiar human leukocyte antigen haplotypes, an autoimmune contribution has been claimed to specify the nature of RP. However, the most innovative pathogenic scenario of RP has been conferred to the innate immune system, mainly involving neutrophils and macrophages that produce a large amount of interleukin (IL)-1 via inflammasome activation. The clinical resemblance of RP with autoinflammatory diseases that may be marked by symptomatic serositis, high fevers and strikingly increased inflammatory parameters further suggests a similar inflammasome-mediated pathogenesis. Aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of therapy in RP, whereas colchicine is recommended on top of standard anti-inflammatory therapy, due to its role in inhibiting the IL-1 converting enzyme (caspase 1) within the inflammasome as well as the release of additional pro-inflammatory mediators and reactive oxygen species. With regard to treatment of RP refractory to NSAIDs and colchicine, blockade of IL-1 is the most relevant advance achieved in the last decade: the outstanding effect of the short-acting IL-1 receptor antagonist anakinra has been first recognized in the pediatric population,

giving a proof of its practical feasibility. Over a more recent time, a growing experience with anakinra deriving from both large and small studies has further confirmed that RP might be regarded as an IL-1-mediated disease. This review aims to provide a contemporary insight into the mechanisms leading to RP as well as into the most recent literature data showing the beneficial approach originating from IL-1 blockade in this intriguing disorder.

Keywords: Recurrent pericarditis, pericardial disease, pericardium, autoinflammation, autoinflammatory disease, interleukin-1, anakinra, personalized medicine, innovative biotechnologies

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1. RECURRENT PERICARDITIS: THE SIZE OF THE PROBLEM

Acute pericarditis accounts for about 5% of emergency department admissions due to chest pain, and the estimated recurrence rate of this disorder ranges from 15 to 50% [1] within 18 months after the first acute episode of pericarditis [2]. Recurrent pericarditis (RP) is a troublesome and debilitating complication of acute pericarditis that is defined as *recurrent* when a symptom-free interval of 4-6 weeks or longer occurs between the first acute episode and a relapse [3]. Moreover, RP should be differentiated from *incessant pericarditis*, in which symptoms persist for more than 4-6 weeks but less than 3 months, and *chronic pericarditis* that lasts for more than 3 months [1]. The overall incidence of RP can be estimated around 5-35/10^5 per year [4]. The cause of RP is believed to rely in a misdirected immune mechanism triggered by some microbial agents, mostly viruses, or by their antigens working as key-determinants contributing to both onset and recurrence of pericarditis [5]. Clinically speaking, chest pain, often sharp, improved by sitting up and leaning forward, is the most common symptom of both acute pericarditis and RP. Conversely, other clinical features including pericardial friction rub, electrocardiographic changes such as new widespread ST-elevation or PR segment depression and pericardial effusions may be present in a variable percentage of

patients [6]. About 80% of pericarditis are considered “idiopathic”, reflecting clinicians’ difficulty in unveiling the actual pathogenic mechanism underlying this disorder. However, an increasing knowledge of the pathways involving adaptive and innate immunity has allowed discriminating different subsets of patients with RP [7]. A clinical phenotype evolving to complete resolution of symptoms, though marked by symptomatic serositis with fever and remarkable increase of inflammatory parameters during acute attacks, tends to show a dramatic response to anti-interleukin (IL)-1 and suggests an autoinflammatory pathogenesis [8]. On the contrary, another phenotype of RP with a subacute course characterized by moderate increase of inflammatory markers, presence of serum autoantibodies including anti-nuclear antibodies (ANA), anti-heart antibodies (AHA) and anti-intercalated disk autoantibodies (AIDA) combined with autoimmune features such as arthralgias, sicca syndrome, Raynaud’s phenomenon and uveitis, would suggest more clearly an autoimmune working [9]. A third and last clinical phenotype of RP includes patients with mild attacks presenting a subacute course, weak elevation of inflammatory markers without autoimmune manifestations and without circulating autoantibodies [8]. Although elevation of inflammatory markers including C-reactive protein (CRP) is not specific for RP, this is important during the management of the disease. In this regard, atypical or subacute cases of RP may be disclosed by imaging techniques, such as computerized tomography scan or cardiac magnetic resonance, which help establishing diagnosis due to pericardial inflammation or edema on T2-weighted images, respectively [1]. More recently, the carcinoembryonic antigen cell adhesion molecule 1 and the major histocompatibility

complex class I chain-related protein A, have been identified as possible biomarkers of RP [10]. Conventional treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are the gold-standard therapies of RP, though these drugs often fail in definitely blocking an ongoing pericardial inflammation [11]. Clinical trials based on colchicine have shown its efficacy in controlling inflammatory attacks in both acute pericarditis and RP, suggesting inflammasome activation as a major contributor to their pathogenesis [2, 4]. More recently, the beneficial effects derived from IL-1 inhibition in the refractory forms of RP have reinvigorated the consideration of this disorder as a possible new autoinflammatory disease, characterized by imbalanced innate immunity [12]. This review aims at summarizing the most recent advances in RP, focusing on the pathogenic aspects related to the involvement of innate immunity as well as the growing experience with the main anti-IL-1 agents currently employed to manage this fascinating disorder.

2. AN INTERPLAY OF AUTOIMMUNE AND AUTOINFLAMMATORY PHENOMENA WITHIN THE PERICARDIUM

The pathogenesis of RP remains controversial as it stands at a crossroad between autoimmune and autoinflammatory pathways. In primis, a breakage in adaptive immunity pathways has been considered the starting point of pericarditis. Cardiotropic

viruses including Echovirus, Coxsackie B virus, Epstein-Barr virus, Cytomegalovirus, Adenovirus and Parvovirus B19 [13] as well as some peculiar bacteria such as *Mycobacterium tuberculosis* have been proposed as putative triggers capable of inducing a direct damage to the pericardium. In addition, other cardiac injuries such as surgery, infarction, irradiation, trauma or bleeding may contribute to the development of an autoimmune process leading to pericarditis [3]. The initial injury might expose or release cardiac autoantigens and stimulate an immune response activating B and T lymphocytes [14, 15]. In particular, naïve $CD4^+$ T cells may segregate into both Th1 and Th17 subsets with distinct effector functions and variable production of cytokines, including IL-6, IL-8 and interferon (INF)-γ [16]. Subsequently, these reactions may induce the production of AHA and AIDA perpetuating the damage within the pericardium [3]. In this regard, the evidence of an autoimmune hypothesis explaining RP derives from a study by Caforio et al. who assessed the concentrations of AHA and AIDA in about 67% of patients with RP. In particular, AIDA positivity was associated with a higher number of relapses, hospitalizations and refractory symptoms, whereas AHA positivity with longer duration of symptoms and higher number of recurrences [17]. Moreover, also ANA positivity further suggests the putative role of autoimmunity in RP. In fact, it is well-known that ANA are positive in a wide range of systemic autoimmune diseases, as systemic lupus erythematosus in which pericarditis can occur in 20-to-50% of patients, with a higher prevalence of pericardial involvement if demonstrated by autopsy [18]. Similarly to other autoimmune diseases, ANA positivity is not uncommon in patients with RP and may be found at a low positive titer in about

40% of cases [19]. However, as some authors highlight, autoantibodies are not unequivocal markers of an autoimmune pathogenesis of pericarditis, since they may be also regarded as a nonspecific epiphenomenon of pericardial inflammation [9]. In addition, the positive response to glucocorticoids [5] or immunosuppressants such as azathioprine and immunomodulatory treatments such as intravenous immunoglobulins (IVIg) represent other important clues supporting the hypothesis of an adaptive immunity imbalance in RP [3]. The relationship of RP with autoimmunity is also suggested by the presence of pro-inflammatory cytokines such as IL-6, IL-8 and INF-γ in the pericardial fluid, but not in the plasma, to highlight a local inflammatory reaction restricted to the pericardium [16]. Interestingly, some cytokine signatures may differentiate the etiology of pericardial inflammation: in this context, high tumor necrosis factor (TNF)-α and low transforming growth factor (TGF)β-1 levels have been found in viral pericarditis, whereas a low IL-6 concentration seems to characterize autoreactive pericarditis [20]. More recently, a similar pathogenic mechanism shared by RP and autoinflammatory diseases has been speculated. In particular, a dysregulation of the inflammasome, a large intracellular multiprotein platform with a central role in innate immunity, might lead to the overproduction of pro-inflammatory cytokines such as IL-1 and TNF-α, as well as to a pathological delay in turning off inflammation [21, 22]. The best characterized inflammasome has an NLR pyrin domain-containing 3 (NLRP3) sensor molecule that may be activated in several inflammatory diseases including gout, atherosclerosis, and also pericarditis [23]. Once the inflammasome has been 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 receptors, a large amount of IL-1 is released recruiting important effector cells which can enhance inflammation to the site of injury [23, 24]. Inflammatory signaling in cardiomyocytes usually occurs as an early response to myocardial injuries, and elevated levels of inflammatory mediators have been identified in patients with heart failure as a subverted expression of innate immunity. In particular, TLR signaling pathway downstream molecules are involved in the progression of inflammation [25]. TLR binding stimulates the adaptor molecules MyD88 and TRIF, which promote both the transcription of nuclear factor (NF)-κB and INF-regulatory-factor-1 (IRF1), which in turn stimulate the transcription and release of pro-IL-1 [26]. IRF1 activates an abundant release of reactive oxygen species and oxidized mitochondrial DNA, triggering inflammasome activation [27]. More recently, it has been suggested that bacteria inhibiting Ras homolog family member A (RhoA) GTPases are capable of disabling numerous downstream host-defence mechanisms, such as leukocyte migration and phagocytosis, and inducing IL-1β production through pyrin inflammasome activation. Physiologically, pyrin is inhibited by the activity of the small GTPase RhoA that binds the serine/threonine-protein kinases PKN1 and PKN2 and actin-binding proteins [28]. This mechanism may be involved in the pathogenesis of RP, explaining the beneficial effect of colchicine on the pyrin inflammasome, since colchicine is an established activator of the small GTPase protein RhoA [28]. The tangled interplay existing between autoimmune, autoinflammatory, environmental and genetic factors is also related to the consanguinity found in 10% of patients with RP,

suggesting a likely genetic background which might predispose to pericarditis [29]. More specifically, assessing human leukocyte antigen (HLA) haplotypes of 55 patients with RP, the existence of "predisposing" HLA alleles (HLA-A*02, Cw*07, and DQB1*0202) or even "protective" HLA alleles (HLA-DRB1*04 and -DQB1*0302) has been shown [30]. Interesting results from the same study have also shown that a significantly reduced number of naïve-T cells together with overexpression of activated CD8+ T effector cells are associated with a more active inflammatory response, more difficult to switch off, whereas a higher number of regulatory T cells combined with normal expression of naïve T cells and activated CD8+ T cells should suggest an inflammatory phenotype easier to control [30].

3. A PUTATIVE ROLE OF INNATE IMMUNITY IN RECURRENT PERICARDITIS

In acute pericarditis there are the disintegration and exfoliation of mesothelial cells lining the pericardial space. Indeed, the initial inflammatory cell response to different injuries is predominantly composed by neutrophils [5]. Neutrophils work through three major trajectories: (a) phagocytosis, (b) degranulation, and (c) release of neutrophil extracellular traps (NETs). Phagocytosis is central to the microbicidal function of neutrophils. Pathogens are initially engulfed into a plasma membrane-derived vacuole, "the phagosome", proceeding towards an active phagocytic process leading to the

destruction of the microorganism ingested [31]. Moreover, neutrophils actively synthesize and secrete a high number of pro-inflammatory mediators, including IL-1, IL-1 receptor antagonist, IL-6, IL-12, TGF-β, TNF-α, oncostatin M and B lymphocyte stimulator, which can subsequently activate both neutrophils themselves and other immune cells [32]. Finally NETs trap, a web-like structure composed of cytosolic and granule proteins assembled on a scaffold of decondensed chromatin, is able to neutralize several infectious agents preventing the dissemination of microorganisms. However, if dysregulated, NETs can contribute to the pathogenesis of immune-related diseases by modulating other immune cells, such as macrophages, to produce IL-6 and pro-IL-1β [33] mainly through TLRs 2 and 4 [34]. Neutrophils co-work also with platelets releasing chemokine heteromers, like CC-chemokine ligand 5 and platelet factor 4, which in turn promote further neutrophil adhesion, intravascular NETs, and secretion of granule proteins, such as cathelicidin and cathepsin G, enhancing the adhesion of monocytes to the endothelium [35, 36]. Neutrophils are critical at the site of inflammation for the recruitment of macrophages which produce a larger amount of pro-inflammatory cytokines, including IL-1β, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor and TNF-α [34], which set back neutrophil apoptosis and consequently further spread inflammation [37, 38]. Recently, with regard to pericarditis, attention has been paid to the purinergic P2X7 receptor (P2X7R), a nucleotide-gated ion channel largely expressed in monocytes and involved in triggering ATP-induced NLRP3 inflammasome activation [39]. There is increasing awareness that stressed cells due to a previous bacterial infection release soluble signals,

such as ATP, that activate monocytes and macrophages [40]. Extracellular ATP activates neighboring cells by paracrine or autocrine pathways. On this basis the P2X7R may function as an amplification device to spread the ATP wave, as its activation triggers further ATP release. Finally, macrophages stimulated by lipopolysaccharide and ATP release IL-1-containing microvesicles [41]. Additional evidence suggests that TNF-α upregulates monocyte P2X7R expression and function [42]. On this basis, TNF-α-induced P2X7R overexpression may represent a crucial process of such inflammatory mechanism, in which both TNF-α and IL-1β are involved [43]. The putative pathogenic pathways of neutrophils and macrophages in RP are depicted in Figures 1 and 2.

4. RECURRENT PERICARDITIS IN THE AUTOINFLAMMATORY DISEASES

Recurrent pericarditis has been described in the setting of different autoinflammatory diseases, a growing family of innate immunity dysfunction mainly caused by mutations in genes involved in the inflammatory response, on the whole marked by overexpression of several pro-inflammatory cytokines, especially IL-1 which has a master role in driving the clinical pictures of such disorders [44]. In general terms, these patients have mostly a disease onset in the pediatric age, but the presence of low-penetrance mutations may also give rise to atypical, unusual or milder manifestations starting in adulthood [45]. Despite all autoinflammatory diseases have distinct clinical

features, pericarditis may be the starting manifestation particularly for patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) [46], albeit an anecdotal case of RP has been also reported for mevalonate kinase deficiency [47]. TRAPS is the most frequent autosomal dominant autoinflammatory disorder, caused by mutations in the *TNFRSF1A* gene, encoding the type-1 receptor of TNF-α [48]: the intracellular accumulation of mutant receptors leads to enhanced sensitivity to exogenous stimuli and induces an exaggerated autocrine production of pro-inflammatory cytokines, including IL-1β, TNF-α and IL-6 by means of mitogen activated protein kinase stimulation [49]. Clinically, TRAPS patients can complain chest pain due to pericarditis, which sometimes may represent the only disease manifestation during attacks [50]. Interestingly, subjects carrying low-penetrance *TNFRSF1A* variants seem to have a higher rate of pericarditis than those with structural mutations. Moreover, a later disease onset as well as a more chronic disease course has been associated with such low-penetrance variants [51]. On this basis, patients with a positive family history for pericarditis, poor response to colchicine, higher number of pericarditis recurrences as well as patients needing supplementary immunosuppressive treatment should require specifically gene analysis for TRAPS, since low-penetrance *TNFRSF1A* mutations may be found in about 6% of these subjects [52]. The cardiovascular system may be also involved in FMF, the most common recessive autoinflammatory disorder worldwide, which is caused by mutations in the *MEFV* gene encoding for a protein of 781 amino acids known as pyrin (or marenostrin) [53, 54]. Pyrin negatively regulates IL-1 converting enzyme (caspase-1)

activation through a competitive binding with either procaspase-1 or apoptosis-associated speck-like protein (ASC), a key-adaptor molecule required for starting inflammation [44]. In response to bacterial toxins that inhibit downstream RhoA signaling pathways, pyrin induces inflammasome activation leading to the production of IL-1; additionally, disease-causing *MEFV* mutations inhibit downstream RhoA signaling and activate the pyrin inflammasome [55]. A pure pericardial involvement is rare in FMF [56], though RP may be the sole manifestation of this disorder at every attack [57, 58]. RP usually occurs late in the FMF course, and pericardial symptoms spontaneously resolve without sequelae [59]. Data from 2468 FMF patients collected in a nationwide registry in Turkey showed that about 2.4% of patients had presented at least 1 episode of pericarditis; additionally, RP was the initial and unique FMF manifestation in only 2 patients for whom diagnosis was established by genetic analysis [60]. Echocardiogram is extensively both sensitive and specific to detect pericarditis with pericardial effusion in FMF patients [61]: in this regard, the incidence of pericarditis during FMF attacks rises up to 3.6% if disclosed by echocardiography [62]. Interestingly, pericarditis has been related to some specific *MEFV* mutations, such as M694V and E148Q, in about 11% of FMF children presenting with chest pain and pericardial effusion on echocardiography [63]. Pericarditis can be also found in about 16% of patients suffering from adult onset Still's disease (AOSD), a rare multisystemic autoinflammatory disorder with unknown etiology [64]. Current evidence on AOSD pathogenesis suggests that environmental signals set fire to innate immune receptors, which in turn trigger the activation and secretion of several pro-inflammatory cytokines,

including IL-1β, IL-18 and IL-6. In particular, IL-1β and IL-18 seem to be responsible for some typical AOSD features such as fever, rash, arthritis, increased CRP and hyperferritinemia [65]. Recent findings report that pericarditis along with skin rash, splenomegaly and delayed diagnosis are significantly associated with the need for higher prednisone dosages to achieve remission [66]. Around 20% of AOSD patients with pericarditis may develop a pericardial effusion and even have cardiac tamponade [67]. In this regard, Pouchot et al. reported 23 cases of pericarditis due to AOSD among 62 patients (37%), and 3 of them developed cardiac tamponade [68]. More recently, 8 adults and 10 children with cardiac tamponade secondary to AOSD and systemic juvenile idiopathic arthritis, respectively, were reported: 4 children died, but there was no recurrence of tamponade in the remaining children and in all adults. In this respect, it is worth mentioning that cardiac tamponade may even occur as the first disease manifestation in both children with systemic juvenile idiopathic arthritis and adults with AOSD [69]. Compared to AOSD, it has been estimated that pericarditis occurs in 10% of patients with systemic juvenile idiopathic arthritis, while echocardiographic findings of pericardial disease can be detected in more than 30% of cases [70, 71].

5. **MANAGEMENT OF RECURRENT PERICARDITIS**

5.a **General hints for treatment of recurrent pericarditis**

The management of RP does not differ from therapy of a first episode of acute pericarditis. NSAIDs and aspirin remain the mainstay of treatment [72]. The effectively

used dosages are high, and the intravenous route can be used in hospitalized patients, especially to control an acute overwhelming chest pain [73]. Colchicine is the best-known prophylactic treatment for FMF attacks, and is generally recommended in all FMF patients regardless of the frequency and intensity of attacks typical of this disorder [74]: nowadays, colchicine is recommended as a standard anti-inflammatory therapy to improve remission rates and prevent recurrences of pericarditis in adults, though it is largely used also in children [75, 76]. Main colchicine mechanism of action is the ability to concentrate itself in white blood cells, especially granulocytes, blocking tubulin polymerization, thereby interfering with several cellular functions including phagocytosis, degranulation and chemotaxis [77]. Previous findings also suggest that colchicine is able to attenuate bacterial toxin-induced caspase-1 activation, IL-1 release and pyroptosis [73], whereas more recently it was shown by Park et al. that colchicine suppresses pyrin inflammasome activation [28]. The drug should be provided at weight-adjusted doses, usually 0.5 mg twice daily or once daily in individuals <70 kg or with impaired renal function (without a loading dose) to improve its tolerability [2]. Systemic corticosteroids constitute the second- or third-line treatments in acute pericarditis and RP, however in specific circumstances such as pregnancy, anticoagulation, advanced chronic kidney disease, heart failure, intolerance to NSAIDs and aspirin, or in the case of pericarditis associated with autoimmune diseases, they may be considered as treatment of choice. Corticosteroids may also be employed in patients with poor response to NSAIDs and colchicine, but at low weight-based doses (i.e., prednisone 0.2 to 0.5 mg/kg) since they may cause several drawbacks. Indeed, they can

favor, especially at high doses, the recurrences of pericarditis, promote steroid-dependence, reduce the efficacy of colchicine, and finally cause severe side effects such as diabetes, growth retardation and disfiguring striae rubrae, especially in children [1]. Immunotherapy represents an alternative choice for managing patients with RP. In particular, azathioprine, albeit being a slow-acting drug, is more effective in the long-term and consents to spare corticosteroids [78]. An immunomodulatory effect can be also obtained by IVIg administration, which may promote the clearance of potential infectious agents and modulate the immune system as well disease recurrence [79, 80].

5.b **Interleukin-1 blockade in recurrent pericarditis**

The progress in understanding molecular biology behind rare autoinflammatory diseases has largely clarified the pivotal role of IL-1 pathway in the inflammatory cascade of these protean conditions [81, 82]. IL-1 is mainly produced by innate immune cells, including macrophages, monocytes and dendritic cells [83]: the two major cytokines IL-1α and IL-1β elicit their pro-inflammatory effects by binding the IL-1 receptor domain in the cytoplasmic portion, then triggering signal transduction [84]. In particular, IL-1 has provided a rational and dramatically effective target in the treatment of cryopyrin-associated periodic syndrome, which is a clear-cut IL-1-mediated autoinflammatory disorder [85], and the IL-1 receptor antagonist anakinra working as a short-acting competitive inhibitor preventing IL-1α and IL-1β interaction with the IL-1 receptor has

shown brilliant results even in the management of neurologic autoinflammatory manifestations of patients with cryopyrin-associated periodic syndrome [86]. Anakinra is currently employed in the treatment of several monogenic and multifactorial autoinflammatory diseases in both adults and children [87, 88], and has been recently proposed as a therapeutic tool in managing refractory forms of pericarditis, strengthening the concept that RP may be more probably regarded as an IL-1-driven disorder [12]. In recent times, several interesting cases have been reported to support the effectiveness of anakinra in RP regardless of the underlying systemic disease [89-97]. Firstly, Picco et al. described 3 children with idiopathic RP in whom anakinra led to a brilliant therapeutic response. Interestingly, all these patients relapsed shortly after anakinra withdrawal, and experienced the same high rate of recurrence that had characterized the previous disease course. For the first time, the autoinflammatory side of idiopathic RP was suggested by this experience [98]. A few years later, Scott et al. reported 2 adults with idiopathic RP successfully treated with anakinra, reviewing other 16 patients (3 of whom underwent anakinra) treated with conventional therapy after failure of colchicine. Interestingly, anakinra and IVIg were the most effective treatments, with remission rates of 100% and 67% respectively, whereas cyclophosphamide and azathioprine were judged less effective [99]. The following year, a Greek experience reported 3 adults with idiopathic RP resistant or intolerant to standard therapies, who achieved a prompt clinical improvement along with normalization of inflammatory parameters after anakinra. As was observed by Picco et al., the discontinuation of anakinra was accompanied by recurrences in 2/3 patients

[100]. In 2014, Finetti et al. carried out a multicenter retrospective study including 15 patients with RP (12 children and 3 adults) who were corticosteroid-dependent and colchicine-resistant (14 out of 15 patients); 13 patients started anakinra during a disease flare, whereas 2 received anakinra while taking moderate-dose corticosteroids (0.7 mg/kg/day). All patients treated with anakinra during relapses showed a complete response, also confirmed by both decrease of inflammatory parameters and resolution of pericardial effusion within one week. In addition, all patients tapered corticosteroids progressively until stop within 2 months [101]. In the same year, Lazaros et al. performed a prospective open label study on 10 patients with idiopathic RP resistant and/or intolerant to previous treatments including aspirin, NSAIDs, colchicine, azathioprine and corticosteroids. Anakinra was highly effective in all cases, leading to rapid symptom relief, CRP normalization and decreased dosing or even discontinuation of corticosteroids. Although the authors observed a high recurrence rate (70%) after anakinra withdrawal, even higher if compared with the pediatric experience (43%) [101], probably caused by abrupt discontinuation of treatment, the resumption of anakinra led again to a quick resolution of symptoms [102]. One year later, a retrospective study aimed at evaluating the effectiveness of anakinra in 13 adults with RP refractory to conventional therapies found that anakinra was able to provide remarkable relief of symptoms in a high percentage of patients (92% of complete response *versus* 8% of partial response). Moreover, at a further follow-up (lasting around 2 years), about 84% of patients stopped concomitant NSAIDs, colchicine and corticosteroids. Of note, unlike the Greek study by Lazaros et al., only 5 patients (38%)

had a recurrence of symptoms after anakinra weaning. The drug was therefore resumed with good symptom control [103]. Recently, a multicenter cohort study including 110 patients has been carried out in order to explore the causes, clinical features, treatment and outcome of RP in pediatric patients. NSAIDs, corticosteroids and colchicine were the main drugs employed in the whole cohort. Corticosteroid-treated patients experienced more recurrences, and subsequently more hospitalizations. Anakinra was given to 12 children with refractory RP, resulting in a significant decrease of recurrence rates (from 4.29/per year at baseline to 0.14). Of note, in this work, for the first-time caution was recommended when anakinra was tapered, since the optimal length of therapy could not be defined yet. Moreover, the authors suggested to continue colchicine during or after anakinra discontinuation to further reduce the risk of recurrence [8]. Based on the medical literature encouraging the use of anakinra in RP, finally the first placebo-controlled randomized trial was performed in 2016. This study included 21 patients (enrolled at three Italian centers) who had RP along with elevation of CRP, colchicine resistance and corticosteroid-dependence. Relapses occurred in 9 out of 10 patients assigned to placebo and in only 2 of 11 patients assigned to anakinra. Moreover, anakinra compared to placebo was capable of reducing the risk of recurrence over a median of 14 months, allowing the discontinuation of corticosteroids. Among the key-messages of the study, the importance of selecting patients who might benefit from anakinra was clearly highlighted. In this regard, only patients with obvious signs of overt inflammation including high fever, increased CRP and pericardial effusion should be regarded as ideal candidates for this treatment. Contrarily, treatment with anakinra

might be ineffective [104]. Newly, Dagan et al. have reported a series of 7 patients with refractory corticosteroid-dependent RP successfully treated with anakinra for approximately 20 months. Previous treatments including NSAIDs, colchicine and azathioprine failed in achieving a permanent remission. After starting anakinra, a prompt clinical and laboratory response was obtained, allowing to taper prednisone (up to 5 mg/day) or withdraw both prednisone and colchicine. In addition, a complete prevention of recurrences by means of anakinra, in contrast to a median of 6 episodes while on other treatments, led also to reduce hospitalization-related economic burden [105]. In this regard, more recently, the IRAP (International Registry of Anakinra for Pericarditis) study, including 224 patients with corticosteroid-dependent and colchicine-resistant RP, has assessed both effectiveness and safety of anakinra in the largest real-world population. Overall, an 83% reduction in the recurrence rate of pericarditis was observed during anakinra. Moreover, compared to the period before starting anakinra, there was a reduction of 91% and 86% for emergency department admissions and requests of hospitalization, respectively. Interestingly, 135 patients (60%) discontinued the active treatment with anakinra, and 74% of them were still free from recurrences after 18-month follow-up. During follow-up, only 20 patients (8.9%) underwent pericardiectomy with subsequent discontinuation of anakinra. Of note, although at the time of enrollment 180 patients (80%) took glucocorticoids, after anakinra most patients were gradually tapered without any recurrence. Indeed, 61 patients (27%) remained on corticosteroid therapy at low dosages. The need to continue treatment with corticosteroids and anakinra in a not negligible percentage of patients further suggests

that the presence of a chronic inflammation in RP is likely caused by a complex interplay of autoinflammatory and autoimmune pathways. Similarly, NSAIDs were stopped in the majority of cases, whereas only 54 patients (24%) were still on NSAIDs. Conversely, most patients continued colchicine despite anakinra, suggesting the importance of this drug in preventing recurrences especially when anakinra is tapered. The results of the trial also pointed out how a longer full-dose treatment with anakinra as well as a longer tapering might be associated with lower rates of recurrences [106]. Overall, the analyzed studies dealing with the employment of anakinra in RP reveal how abrupt discontinuation of treatment is associated with higher rate of recurrences, which could be significantly reduced by adopting slow dose-tapering protocols. Beside anakinra, another anti-IL-1 agent like the human immunoglobulin G_1 anti-IL-1β monoclonal antibody canakinumab has proven its effectiveness in treating RP, although with contrasting results [107, 108]. In this regard, Kougkas et al. have described 3 patients with RP related to different systemic diseases who received canakinumab after failure on colchicine, methotrexate, corticosteroids and anakinra. Two patients diagnosed with AOSD experienced a prompt and longstanding remission by means of canakinumab (150 mg/monthly) with consequently corticosteroid discontinuation. On the contrary, the third patient with rheumatoid arthritis responded only partially to canakinumab (300 mg every 4 weeks), which was stopped due to the occurrence of two further relapses [107]. More recently, a child with corticosteroid-dependent RP who firstly developed a severe anaphylactic reaction caused by anakinra was successfully treated with canakinumab [109]. To date, clinical studies are completely missing in

adults with idiopathic RP. However, a preliminary experience on a pediatric cohort has suggested that the ability of canakinumab to control recurrences does not seem as high as that of anakinra, due to the active pathogenic role of IL-1α in RP, which instead is not blocked by canakinumab [108]. Interim data from an open-label 2 pilot study of the recombinant fusion protein rilonacept, blocking IL-1α and IL-1β signaling, in subjects with RP showed also prompt and clinically meaningful reduction in pain scores and CRP as early as after the first administration. Moreover, resolution of pericardial manifestations and improvement of patients' quality of life as well as feasibility to discontinue corticosteroids without relapses were also demonstrated [http://www.onlinejacc.org/content/73/9_Supplement_1/1261]. Of note, rilonacept is weekly administered as compared with anakinra, requiring daily administrations. This is an advantage over anakinra in terms of compliance and quality of life, provided that rilonacept will be proved as safe and effective as anakinra. On this basis, the pivotal phase 3 trial RHAPSODY aimed at evaluating both efficacy and safety of rilonacept in patients with RP using a double-blind placebo-controlled randomized-withdrawal design is actually recruiting participants (ClinicalTrials.gov Identifier: NCT03737110). Table 1 summarizes the main studies focusing on anti-IL-1 agents used in the general management of RP.

6. CONCLUSIVE REMARKS

RP is a troubling complication of acute pericarditis, especially in patients treated with corticosteroids at a first acute episode or when medical therapy has been reduced too quickly without waiting for a definite clinical improvement. An etiological evaluation should be performed at diagnosis or before starting treatment to discard any potentially serious causes requiring specific treatment. Most cases of RP are idiopathic, although two potential mechanisms, autoimmune and autoinflammatory, have been suggested to ideally explain its pathogenesis. Pericarditis may be found in autoimmune diseases suggesting that mechanisms of adaptive immunity play a relevant role for its beginning and recurrence over time. However, a rising body of evidence currently proves the involvement of innate immune system in the development of RP. In this regard, given the many clinical similarities between RP and autoinflammatory diseases, inflammasome activation has been identified as the main machinery responsible for IL-1 overproduction in pericardial inflammation [21, 22]. RP remains arduous to treat and stressful for the patient. Despite its overall long-term good prognosis, a proper treatment should be contemplated as soon as possible to avoid impairment of patient's quality of life due to recurrences, frequent hospitalizations and corticosteroid dependence [106]. Treatment is usually long and should be managed by monitoring both clinical improvement and possibly normalization of inflammatory markers. In addition, patients should be reassured during treatment explaining that disease recurrence does not worsen the final prognosis. Recent evidence has shown that anakinra is a treasurable therapeutic choice to manage RP, mostly in refractory cases that develop steroid-dependence and/or

colchicine-resistance [105]. It is already known that patients with a well-defined inflammatory pattern marked by chest pain, fever, increased CRP and pericardial effusion are likely the most fitting candidates for being treated with anakinra [104], though the overall duration of treatment and strategies adopted to outrun or stop this treatment remain yet unsolved issues. Finally, looking at the future, encouraging results in the management of RP derive from the experience with rilonacept that may further enrich the therapeutic armamentarium currently available for this disorder.

Author contributions

All authors contributed to the work. The first draft of the manuscript was written by Giuseppe Lopalco and Donato Rigante; all authors commented on the previous version of the manuscript. All authors read and approved the final manuscript.

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Figure captions

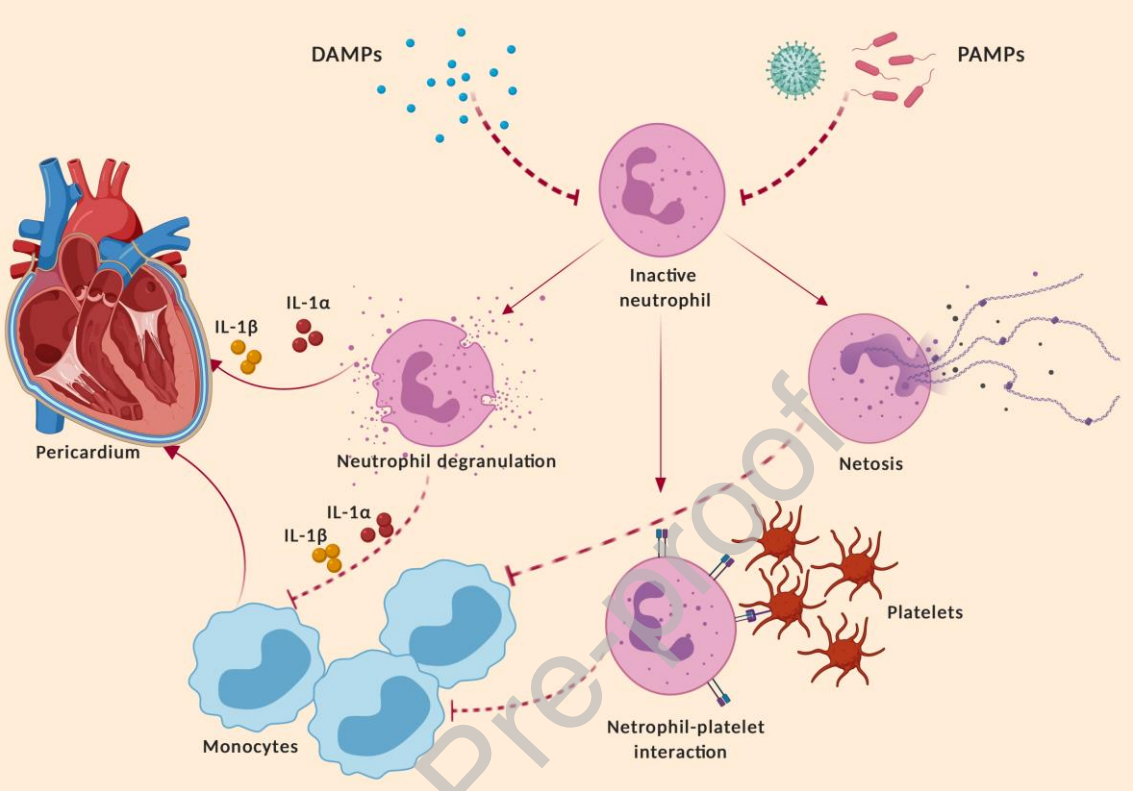

Figure 1 Putative role of neutrophils in the pathogenesis of recurrent pericarditis

Neutrophils activated by cellular sensors like pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) secrete a large amount of both interleukin (IL)-1α and IL-1β, which in turn can activate monocytes and enhance inflammation in the pericardium. Moreover, neutrophils co-work with platelets for the recruitment of monocytes at the site of inflammation. Finally, the release of neutrophil extracellular traps (Netosis) to neutralize infectious agents can activate monocytes to produce IL-6 and further pro-IL-1β

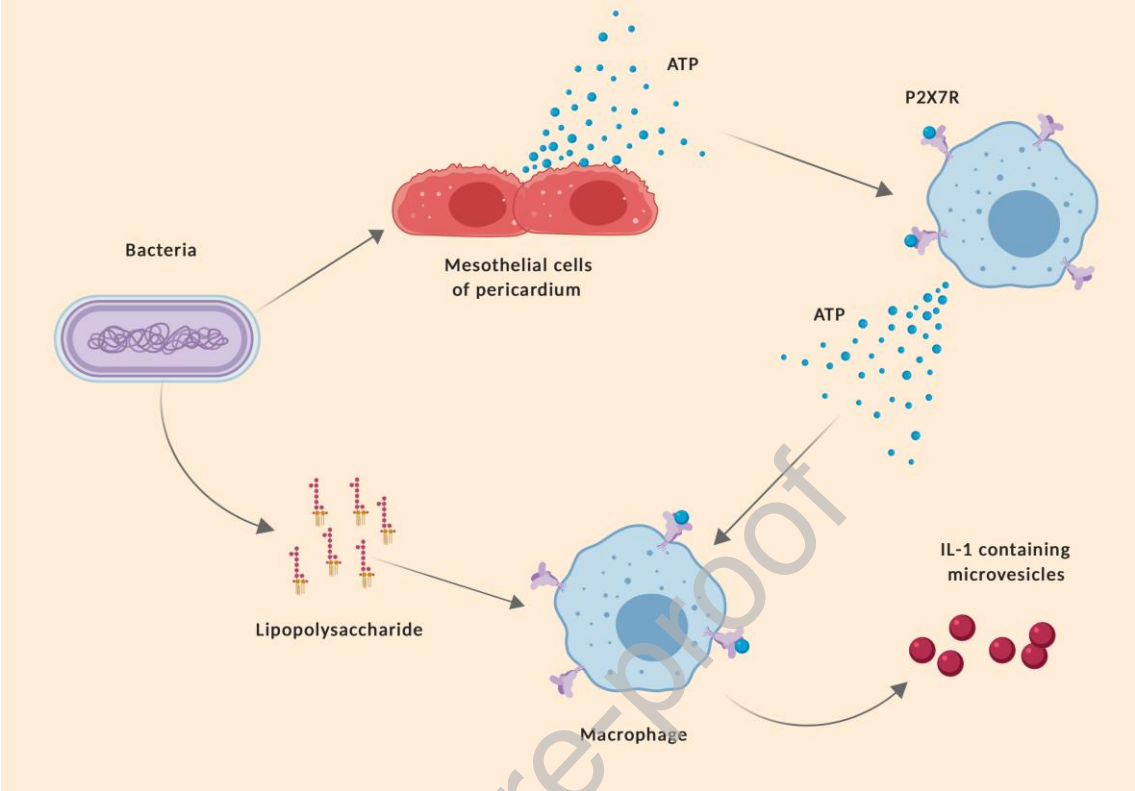

Figure 2 Macrophages and purinergic P2X7 receptor function in recurrent pericarditis

Mesothelial cells of the pericardium appear stressed due to a bacterial infection and release danger signals such as adenosine triphosphate (ATP) that activate monocytes/macrophages. In this context, the purinergic P2X7 receptor (P2X7R) may function as an amplification device to spread the ATP wave, as its activation triggers further ATP release. Finally, macrophages stimulated by lipopolysaccharide and ATP release interleukin (IL)-1-containing microvesicles

Table 1 Synoptic table reporting the main literature data dealing with anti-IL1 agents employed in the treatment of recurrent pericarditis

First author (year) [reference]	Patients number/age	Disease	Study	Anti-IL-1 agent dosage	Outcome	Side effects
Picco (2009) [98]	3 children	2 IRP, 1 Mhyre syndrome/IRP	Case series	ANA from 0.7 mg/kg/day to 1.25 mg/kg/day	Prompt resolution of the clinical symptoms with normalization of acute phase reactants, CCs tapering, relapse in all patients after anakinra withdrawal	NA
Scott (2011) [99]	2 adults	IRP	Case series	ANA 100 mg/day	Remission on anakinra and colchicine in 1 patient, dramatic response and steroid withdrawal without flares in the other patient	NA
Vassilopoulos (2012) [100]	3 adults	IRP	Case series	ANA 150 mg/day in 1 patient, ANA 100 mg/day in 2 patients	Dramatic clinical response with concomitant prompt normalization of acute phase reactants and steroid discontinuation in 2 patients	Increase in aminotransferase levels in 1
Finetti (2014) [101]	12 children, 3 adults	1 Mhyre syndrome/IRP, 1 Sotos syndrome/IRP, 13 IRP	Observational retrospective	ANA from 1 mg/kg/day to 2 mg/kg/day	Complete response within a few days, rapid CCs withdrawal	Skin reactions at the injection site in 5
Lazaros (2014) [102]	10 adults	IRP	Observational prospective	ANA 100 mg/day for 6 months followed by alternate day dosing for further 6 months	Rapid symptom relief, CRP normalization, tapering or discontinuation of CCs, 5/7 patients relapsed shortly after ANA discontinuation	Local reactions at the injection site in 6 patients, transient transaminase elevation in 1
Jain (2015) [103]	13 adults	12 IRP, 1 post-infarction pericarditis	Observational retrospective	ANA 100 mg once daily	Complete improvement of symptoms with ESR and CRP normalization within 2-to-5 days in 12, partial resolution in 1, discontinuation of NSAIDs, colchicine and CCs in 11	Transient injection site reaction in 4
Imazio (2016) [8]	12 children	IRP	Retrospective multicentre cohort study	ANA 1.0 mg/kg/day	Drop in the number of recurrences from 4.2 per year before to 0.1 per year after	NA
Brucato (2016) [104]	20 adults, 1 child	IRP	Randomized, double-blind placebo-controlled	ANA 100 mg/day in adults, 2 mg/kg/day up to 100 mg in children	Reduced risk of pericarditis recurrence and reduced incidence rate of recurrence following ANA	Local reaction at the injection site in 20, herpes zoster in 1, ischemic optic neuropathy in 1,

						elevation of transaminases in 3
Kougkas (2018) [107]	3 adults	2 AOSD, 1 RA	Case series	CANA 150 mg/monthly in AOSD; up to 300 mg/monthly in RA	Prompt and long-standing remission with consequent CCs discontinuation in 2 (with AOSD), partial response in RA	Not reported
Dagan (2019) [105]	7 adults	IRP	Observational retrospective	Anakinra 100 mg/ day in all patients, reduced to 100 mg/every other day in 1	Rapid response within a few days in all patients, prednisone discontinuation in 4 patients, reduction to low-dose in 2, CRP normalization in 6 and decrease in 1	Local reaction at the injection site in 2, herpes zoster in 1
Imazio (2019) [106]	224 adults	167 IRP, 28 post-cardiac injury syndrome, 21 autoimmune diseases, 5 AIDs, 2 pericarditis due to irradiation, 1 post-traumatic pericarditis	Observational cohort study	ANA starting dose of 100 mg/day followed by tapering	Reduction in pericarditis recurrences, emergency department admissions and hospitalizations, CCs sparing effect	Reaction at the injection site in 86, arthralgias/myalgias in 13, transaminase elevation in 7, infections in 6, neutropenia in 3, hypereosinophilia in 1, mild fever in 1, flushes and sweating in 1, perforated diverticulitis in 1, optic neuritis in 1
Caorsi (2019) [108]	55 children	IRP	Observational retrospective	ANA mean dosage of 1.67 mg/kg/day as first-line in 54 CANA 150 mg every 4 weeks in 5 (1 as first-line; 4 after ANA)	50/54 patients had a complete response to ANA combined with NSAIDs and glucocorticoids, colchicine withdrawal in the majority of patients, complete control in 2/5 following CANA, 2 patients discontinued CANA for inefficacy, 1 patient required low-dose CCs to control the disease	Poor compliance in 2, local reaction at the injection site in 1

Abbreviations: AIDs: Autoinflammatory diseases; AOSD: Adult onset Still's disease; RA: Rheumatoid arthritis; ANA: anakinra; CANA: canakinumab; CCs: corticosteroids; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IRP: Idiopathic recurrent pericarditis; NA: not applicable; NSAIDs: non-steroidal anti-inflammatory drugs