Interleukin-1 Antagonists for the Treatment of Recurrent Pericarditis

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Abstract
Although most patients with acute pericarditis will recover, a minority will have recurrent, debilitating episodes. In these patients, refractory symptoms result in high morbidity, and typically require a prolonged duration of anti-inflammatory treatment. Initially, the efficacy of colchicine in both recurrent pericarditis and periodic fever syndromes suggested the central role of the inflammasome in pericarditis. Subsequently, the success of interleukin-1 antagonists in autoinflammatory diseases prompted further investigation in recurrent pericarditis. In current clinical practice, interleukin-1 antagonists include canakinumab, anakinra, and rilonacept. Both anakinra and rilonacept have demonstrated efficacy in randomized trials of patients with recurrent pericarditis. The aim of the current review is to explain the biological rationale for interleukin-1 antagonists in recurrent pericarditis, highlight supporting clinical evidence, and emphasizing future areas of investigation.

Key Points
- Recurrent pericarditis causes significant morbidity and healthcare utilization.
- Recurrent pericarditis is thought to be an autoinflammatory condition caused by over-activity of the innate immune system.
- Interleukin-1 antagonists have been shown to rapidly resolve acute episodes and prevent further recurrences during treatment.

1 Introduction
The increased morbidity in recurrent pericarditis is due not only to painful and debilitating attacks, but also to the long-term adverse effects of treatment, especially using corticosteroids [1]. The majority of patients with acute pericarditis will have complete resolution; however, approximately 15–30% of patients will have a recurrence, defined as the relapse of pericarditis after a 4- to 6-week symptom-free interval [2, 3]. For acute pericarditis, the standard treatment is a combination of non-steroidal anti-inflammatories (NSAIDs) and colchicine, although corticosteroids are indicated in patients with an intolerance or a true allergy to NSAIDs, chronic kidney disease with creatinine clearance < 30 mL/min, the later stages of pregnancy, and pericarditis in the setting of an autoimmune disease [4, 5]. Corticosteroids can also be used in patients with symptoms that persist despite adequate doses of NSAIDs and colchicine; however, the use of corticosteroids has been consistently associated with higher rates of recurrence, particularly when given for a short duration or at a high dose [3, 6]. In addition, an incomplete response to NSAIDs and elevated inflammatory markers have been associated with an increased risk of recurrence [1, 2]. Traditionally, recurrences have been treated with a combination of NSAIDs, colchicine, and corticosteroids as needed with treatment durations of more than 6 months and often with prolonged tapers. During weaning of corticosteroids, patients may experience recurrences, and as a result, steroid-induced adverse effects are common [1, 7, 8].

For these reasons, a better understanding of the underlying pathophysiology of recurrent pericarditis and disease-specific therapies is needed. In particular, the recognition of idiopathic recurrent pericarditis as a disease of an inappropriate innate immune system response has emerged. Accordingly, interleukin-1 (IL-1) antagonists, therapies developed
for disorders of the innate immune system, have been studied in patients with recurrent pericarditis. This review will detail the use of IL-1 antagonists in recurrent pericarditis by answering the following questions:

1. What is the biological rationale for IL-1 antagonists in recurrent pericarditis?
2. What is the current evidence to support their use?
3. What are future potential applications of these medications?

2 Biological Rationale for the Use of Anti-Interleukin-1 Therapy for Recurrent Pericarditis

Interest in IL-1 antagonists for recurrent pericarditis was based on the success of colchicine in periodic fever syndromes and disorders of the innate immune system. In broad terms, immune responses are separated into the innate and the adaptive immune systems. The adaptive immune system is characterized by activation of B and T lymphocytes with signaling pathways largely driven by type 1 interferon [9]. Over-activity of the adaptive immune system causes autoimmune disorders with systemic lupus erythematosus (SLE) and Sjogren’s syndrome as quintessential examples. Alternatively, the innate immune system has distinct signaling pathways and causes different diseases.

Specifically, the innate immune system contains inflammasomes, multiprotein complexes that are activated by exogenous or endogenous danger signals. The most well-described inflammasome is the NLR pyrin domain-containing 3 (NLRP3) inflammasome. The NLRP3 inflammasome is composed of a sensor (NLRP3), a scaffold protein (ASC, apoptosis-associated speck-like protein containing a COOH-terminus caspase activation domain), and an effector, caspase-1 [10, 11]. When the inflammasome is activated, caspase-1 cleaves pro-IL-1β into its active form. Systemic secretion of IL-1β then recruits neutrophils, macrophages, and monocytes to the area of injury [9, 12]. Given the central role of the inflammasome, disorders of the innate immune system are referred to as autoinflammatory diseases [13].

Genetic mutations of the innate immune system have been linked to several rare periodic fever syndromes with characteristic relapses of frequency and length. For example, a gain of function mutation in the NLRP3 signaling pathway is the cause of a group of autoinflammatory disorders called cryopyrin-associated periodic syndromes (CAPS), characterized by fever and a wide variety of organ inflammation [12]. Activation of NLRP3 has been linked to several other inflammatory conditions including gout, atherosclerosis, and notably, viral pericarditis [14–16].

Mutations in the tumor necrosis factor signaling pathway are the cause of Tumor Necrosis Factor Associated Periodic Syndrome (TRAPS). Patients with TRAPS develop episodes of fever, myalgia, rash, and serositis every 5–6 weeks [12]. Several variations of TRAPS have been associated with recurrent pericarditis [17]. Familial Mediterranean Fever (FMF), another classic autoinflammatory disease, was the first disorder to suggest a link between autoinflammation and recurrent pericarditis. Familial Mediterranean Fever is characterized by relapses of fever, arthritis, and serositis, often including pericarditis [18, 19]. Familial Mediterranean Fever is caused by a mutation in the MEFV gene that codes for pyrin, a protein which activates caspase-1. Caspase-1 subsequently cleaves inactive pro-IL-1β into its active form [20, 21]. Colchicine was first described as a therapy for FMF in 1977 and has become a standard therapy for FMF with trials showing both a decrease in the frequency of attacks and markedly reducing the incidence of serum amyloid A (AA) amyloidosis [22–24] In fact, the success of colchicine in FMF provided motivation for the use of colchicine in idiopathic pericarditis [25–28].

Randomized trials have subsequently shown that colchicine halves the rate of first or subsequent recurrence in both acute and recurrent pericarditis [3, 6, 29]. Colchicine is thought to down-regulate the innate immune system by several mechanisms. Colchicine concentrates in neutrophils and negatively affects neutrophil chemotaxis, adhesion, and recruitment. Colchicine also suppresses the NLRP3 inflammasome, down-regulates the transcription factor nuclear factor kB and caspase-1 and inhibits ATP-induced release of IL-1β [23]. More recently, up-regulation of the NLRP3 inflammasome has been demonstrated in pericarditis. Concentrations of NLRP3 and downstream products caspase-1 and apoptosis speck-like protein have been shown to be higher in pericardial samples of patients with pericarditis compared to controls [30].

3 Anti-Interleukin-1 Therapies and Their Indications

The three anti-IL-1 therapies currently available are anakinra, canakinumab, and rilonacept. There are important differences in mechanism of action, pharmacokinetics, pharmacodynamics, and safety profiles between these drugs (Table 1 and Fig. 1). Anakinra was the first IL-1 antagonist developed and is a recombinant human IL-1 receptor antagonist, blocking both IL-1β and IL-1α activity [31, 32]. The typical dose of anakinra in adults is a 100 mg subcutaneously and is administered daily due to its short half-life of 2.64 hours [33]. The bioavailability of anakinra (80–92%) was only modestly different in patients of different body sizes,
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and therefore, there is no dose adjustment for body mass index or body weight [34]. Anakinra is renally cleared, and there is a stepwise decrease in drug clearance and increase in half-life with worsening kidney function. Rate of clearance of anakinra is 75% slower in patients with end-stage renal disease compared to healthy subjects, leading to a significantly longer half-life (2.64 vs 7.15 hours) [33]. Anakinra is used with caution in patients with creatinine clearance < 30 mL/min and alternative dosing regimens have been suggested [35].

Canakinumab is a human monoclonal antibody that binds circulating IL-1β and forms inactive IL-1β/canakinumab complexes. These large complexes are cleared slower than endogenous IL-1β and therefore total IL-1β serum concentrations are paradoxically increased. The bioavailability of canakinumab is 60–70%, largely limited by degradation from the reticuloendothelial system rather than poor tissue absorption. Canakinumab has long half-life (26.1 days) and is typically dosed at 4- or 8-week intervals. Canakinumab is cleared by the reticuloendothelial system with minimal clearance by the kidneys or liver and therefore does not require any dose adjustments. Body weight can affect dosing of canakinumab with dose reductions often indicated at < 40 kg [36].

Rilonacept is a dimeric fusion protein that consists of the extracellular binding portions of the IL-1 receptor and the IL-1 receptor accessory protein linked to the Fc portion of human IgG1 [37]. Rilonacept is often referred to as an “IL-1 trap” due its ability to bind circulating IL-1β and IL-1α. Rilonacept has a half-life of ~ 1 week allowing for weekly subcutaneous injections [38, 39]. The drug is cleared by the reticuloendothelial system, and there is no significant difference in half-life or clearance in patients with advanced kidney dysfunction or on hemodialysis [39]. The bioavailability of rilonacept is 45–50% [40, 41].

All three anti-IL-1 therapies have shown benefit in a variety of autoimmune inflammatory conditions and periodic fever syndromes. Anakinra is FDA approved for the use in CAPS, but has been used off-label effectively in FMF and TRAPS [42–44]. Canakinumab has broader approval for the use in

### Table 1: Mechanism of action, half-life, dosing, and common adverse effects for the IL-1 antagonists

| Drug         | Mechanism of action                           | Half-life      | Dosage                                    | Common adverse effects                                                                 |
|--------------|-----------------------------------------------|---------------|-------------------------------------------|----------------------------------------------------------------------------------------|
| Anakinra     | Interleukin-1 receptor antagonist             | 2.6 hours [33]| 100 mg daily (or 1 mg/kg/day) [33, 72]    | Injection-site reactions [59, 60, 71] Increased skin and respiratory infections [44, 51, 58–60] Transaminitis [51] Leukopenia [58, 60] |
| Canakinumab  | Human IgGκ monoclonal antibody to IL-1β       | 26.1 days [36]| 2–5 mg/kg/month [83, 84]                  | Increased skin and respiratory infections [46, 67, 68] Transaminitis [46, 53, 66, 67] Increased cholesterol and triglycerides [66] |
| Rilonacept   | Circulating IL-1 receptor trap                | 7 days [39]   | 320 mg loading dose followed by 160 mg weekly [76] | Injection-site reactions [48, 49, 55, 64] Increased skin and respiratory infections [48, 49, 55] Transaminitis [48, 49, 55, 70] Leukopenia [48, 55] Increased cholesterol and triglycerides [49] |

**IG** immunoglobulin, **IL** interleukin
periodic fever syndromes and is approved for CAPS, TRAPS, FMF, and hyperimmunoglobulin D syndrome [45–47]. Rilonacept is also approved for the treatment of CAPS [41, 48, 49]. All three therapies have been shown to significantly reduce flares and improve quality of life scores in these conditions. Systemic juvenile idiopathic arthritis and adult-onset Still’s disease are similar disorders of the innate immune system characterized by recurrent fever, rash, and arthritis. Anakinra, canakinumab, and rilonacept have all been shown to reduce flares, decrease the need for glucocorticoids, normalize serum inflammatory markers, and improve symptoms. However, only canakinumab is FDA approved for this indication [50–55].

Interleukin-1 antagonists have been used with variable success in other disorders thought to be related to activation of the innate immune system. Rheumatoid arthritis (RA) has classically been thought of as an autoimmune disorder, but recent evidence suggests there may be “mixed-patterns” of disease that also involve autoinflammation [56, 57]. Anakinra is FDA approved for use in patients with RA after several studies showed an improvement in symptoms, decreased glucocorticoid use, and slower radiographic progression of disease [58–61]. Gout, which is thought to be in-part related to activation of the innate immune system by uric acid crystals, has been treated successfully with all three anti-IL-1β therapies [62–64]. Anakinra was shown to have positive effects on vascular and myocardial function as assessed by vascular ultrasound and echocardiography in a small, randomized study of patients with RA [65]. More recently, canakinumab has been shown to reduce nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death when used in patients with prior myocardial infarction and elevated C-reactive protein (CRP) [66].

### 3.1 Safety

All three IL-1 antagonists have good long-term safety profiles, with subtle differences in their side effects. The majority of studies of anakinra, canakinumab, and rilonacept show an increase in infections compared to placebo, although this has been primarily driven by mild upper respiratory tract and skin infections. There was only a modest increase in serious infections for patients on IL-1 antagonists versus those not on IL-1 antagonists (1.6% vs 0.8%) [44, 46, 48, 49, 51, 53, 55, 58–60, 67–69]. Given that they have no effect on B and T lymphocytes, interleukin-1 antagonists are largely not considered to be immunosuppressive. A meta-analysis of the use of anakinra in more than 200,000 patients in a variety of indications found no increase in opportunistic infections, including reactivation of mycobacterial tuberculosis [32]. Similarly, rilonacept has not been associated with opportunistic infections [48, 55, 70]. Canakinumab has been associated with increased flares of herpes zoster and varicella zoster, but no other opportunistic infections [67]. In the clinical trials of anakinra in both pericarditis and non-pericarditis, the investigators temporarily discontinued anakinra in the setting of infection with no reports of permanent discontinuation for this reason. There is no clear guidance on the optimal timing to resume anakinra after an infection and it is largely at the discretion of the prescribing physician [61, 71, 72]. Recent guidance published on the use of anakinra in patients with pericarditis in the era of COVID-19 recommends patients undergo COVID-19 vaccination and continue their current treatment with anakinra [73, 74].

The incidence of injection-site reactions differs between all three therapies and is likely influenced by frequency of treatment. Anakinra, dosed daily, has the highest rate of injection-site reactions, occurring in up to 71% of patients [75]. The majority of injection-site reactions occur in the first month and between 5–7% of patients will discontinue anakinra for this reason [59, 60, 71]. Rilonacept, dosed weekly, has a lower rate of injection-site reactions, ranging from 15 to 60% [48, 49, 55, 64]. Canakinumab, dosed monthly, has a very low rate of injection-site reactions, ~2–8% [36, 68].

There have been discrepancies between the various trials of anti-IL-1 therapy on the effect on blood counts, liver functioning tests, and lipid levels. In two trials of patients with RA, anakinra was associated with a 1% incidence of leukopenia [58, 60]. However, this finding was not reproduced in other studies of RA, CAPS, and adult-onset Still’s disease [51, 61, 71]. There were no serious infections during these transient periods of leukopenia [58, 60]. Canakinumab has not been associated with hematologic changes [46, 53, 66, 67]. Two studies found decreases in white blood cell count, platelet count, and fibrinogen with use of rilonacept, but all values remained within normal limits and this was thought to be related to its anti-inflammatory effects [48, 55].

Anakinra was noted to cause elevations in alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin in patients with adult-onset Still’s disease, but this was not observed in patients with RA or CAPS [51, 58–61, 71]. Similarly, canakinumab was noted to cause elevations in liver chemistry tests in up to 29% of children and young adults with adult-onset Still’s disease, but not in patients with CAPS and coronary artery disease [46, 53, 66, 67]. Rilonacept was noted to cause mild elevations in AST and ALT in patients with both CAPS and systemic juvenile idiopathic arthritis (sJIA), though only one patient with sJIA had to permanently discontinue the drug for this reason [48, 49, 55, 70]. Overall, these observations are likely related to specific drug-disease interactions and not simply related to the drug.

Both canakinumab and rilonacept have been found to alter lipid levels. Canakinumab was associated with a 4–5% increase in total triglycerides in a trial of patients with
coronary artery disease [66]. In a study of patients with CAPS, rilonacept was associated with an increase in total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total triglycerides, although all values remained within normal limits [49].

The safety of IL-1 antagonists in the setting of malignancy remains unknown. With the exception of certain non-melanoma skin cancers, the majority of randomized trials of anakinra excluded patients with a history of malignancy [58, 59, 61]. The randomized trials of both anakinra and rilonacept in pericarditis excluded patients aged < 5 years from active malignancy [72, 76]. Of note, studies of long-term use of anakinra in RA have found a lower incidence of malignancy compared to the general population with the exception of melanoma and lymphoma; patients with RA have a higher incidence of lymphoma compared to the general population so it is unclear if this finding is a disease or drug effect [77]. A small, retrospective study of 122 patients with RA and a prior history of malignancy found no difference in recurrent malignancy in the patients taking anakinra compared to those on anti-TNF alpha agents or conventional disease-modifying agents [78]. Further investigation is warranted on the safety of IL-1 antagonists in patients with remote, recent, or active malignancy.

3.2 Current Evidence in Recurrent Pericarditis

3.2.1 Case Series

The first description of the successful use of anti-IL-1 therapy for recurrent pericarditis was published in 2009 with anakinra. In this series, three pediatric patients with at least 1 recurrence of idiopathic pericarditis and with no evidence of other autoimmune or autoinflammatory disorders were treated with daily anakinra. All three patients had rapid resolution of chest pain within 24 h and normalization of CRP within 5 days with doses of anakinra ranging from 1 to 1.25 mg/kg/day. The duration of treatment varied for each patient, ranging from 9 days to 3 months. However, all had recurrence of pericarditis within 2 months of discontinuing anakinra [79].

The first report of success with adults with anakinra was published in 2012 by Vassilopoulos et al. They described 3 adults with > 6 recurrences of idiopathic pericarditis who had failed weaning of corticosteroids and were started on 100–150 mg/day of anakinra. Similar to prior case reports, all patients had rapid improvement in pain and normalization of CRP shortly after initiation of anakinra. Two patients were treated with six months of therapy but had recurrence shortly after discontinuation. The third patient developed elevations in aminotransferases 6 times greater than the upper limit of normal requiring discontinuation of the drug. Of note, this patient had remained in remission for more than 15 months at the time of publication [80].

A common theme among the earlier case reports with anakinra was the absence of recurrence while on anakinra, but quick recurrences shortly after discontinuation. Camacho-Lovillo et al published a case in 2013 of a pediatric patient who was treated with 2 mg/kg/day of anakinra for 1 year only to have a recurrence within 4 weeks of discontinuation. This patient was subsequently restarted on anakinra and continued on treatment for more than 3 years without additional recurrences [81].

This high rate of recurrence after discontinuation of anakinra prompted investigators to treat for longer durations and to develop tapering schedules. In a case report published in 2013 of a pediatric patient with idiopathic recurrent pericarditis, treatment with anakinra at a dose of 0.7 mg/kg/day with indomethacin was continued for 10 months. Indomethacin was then discontinued and anakinra was reduced to 48-hour dosing. At the time of publication, the patient had been more than 12 months without recurrence [82].

Cases of canakinumab for the treatment of recurrent pericarditis have yielded mixed results. In 2015, Theodoropouloi et al described a pediatric patient who initially responded to anakinra. After 5 months of treatment, the patient was switched to 2 mg/kg/dose of canakinumab due to the convenience of monthly injections. Pericarditis recurred 1 week later. Despite concurrent use of both corticosteroids and higher doses of canakinumab (4 mg/kg/dose), the patient had two additional relapses. He was ultimately switched back to anakinra with resolution of symptoms [83].

Canakinumab was successfully used in a pediatric patient who developed an anaphylactic reaction to anakinra. This patient had been on 5 mg/kg/day of anakinra and colchicine for 6 months before being hospitalized for anaphylaxis shortly after an injection. He was started on 5 mg/kg/month of canakinumab and continued on colchicine. After 1 year without relapse, the frequency of canakinumab was decreased to every other month. There were no flares or adverse events during the two years of canakinumab therapy [84].

Canakinumab was attempted in two additional pediatric patients with an intolerance to anakinra without success. Case reports by Signa et al describe two patients, one with post-pericardiotomy recurrent pericarditis and one with idiopathic recurrent pericarditis, who both had rapid improvement with anakinra. One patient had to discontinue anakinra after injection-site reactions and was switched to 4 mg/kg/month of canakinumab with subsequent relapse. The second patient switched to 2.5 mg/kg/month of canakinumab due to poor compliance with the daily injections of anakinra. Shortly thereafter, the patient had a relapse requiring re-initiation of anakinra [85].
Canakinumab has been used successfully in a small series of patients with pericarditis due to other inflammatory syndromes. Chawla et al described a patient with RA and ulcerative colitis with recurrent pericarditis who failed anakinra, but responded to canakinumab [86]. Koukgas et al published a case series that describes two patients with adult-onset Still’s disease, recurrent pericarditis, and injection-site reactions to anakinra. These patients had more than 2 years without relapse on 150 mg/month of canakinumab [87]. Of note, these authors also describe a patient with seronegative RA for whom canakinumab did not cause durable remission. The difference in effectiveness for prevention of recurrence between anakinra and canakinumab may lie in their mechanism of action. Anakinra blocks both IL-1α and IL-1β activation of the IL-1 receptor whereas canakinumab exclusively acts on IL-1β (Fig. 1).

3.2.2 Observational Studies

The first observational study with anakinra was published in 2014 in 15 patients, 12 adults and 3 children. All patients had idiopathic recurrent pericarditis and were treated with a median of 12 months of anakinra at a dose of 1.3 mg/kg/day. All patients were able to discontinue colchicine, corticosteroids, and other anti-inflammatory agents by 2 months. Tapering of anakinra was attempted in 14 patients with various strategies. Some patients switched to every other day dosing whereas other patients had slow decreases in the number of treatments per week (e.g. 6 per week, then 5 per week, etc.). Overall, 6 patients had flares during tapering with a mean time to relapse of 8.5 months. Eight patients had no flares with a median follow up of 25.1 months with seven able to completely discontinue anakinra. There were no serious adverse reactions with 33 % having mild skin reactions [88].

Jain et al published a similar-sized observational study with comparable results. They included 13 patients with idiopathic recurrent pericarditis treated for 6 months with 100 mg/day of anakinra. Complete response was seen in 12 patients with a partial response in 1. All but 2 of the patients were able to be completely weaned off of corticosteroids with the remaining patients on low doses (< 5 mg/day prednisone). At the conclusion of the study, 11 of 13 patients remained on anakinra with 5 patients unsuccessfully weaned. There was no standard tapering strategy, but the authors noted that some patients’ doses decreased to 50 mg daily or 50 mg every other day [89]. Lazaro et al described a high recurrence rate after discontinuation of therapy in a study of 10 adults treated with 100 mg daily of anakinra for 6 months with a 6-month tapering period of every other day dosing. In their study, 70% of patients relapsed with a mean time to relapse of only 18 days [90].

A systematic review, which included the studies discussed above, was published in 2016. Among 24 patients with an average of 8.2 recurrences, the average dose of anakinra was 1.1 mg/kg/day with a maximum of 100 mg/day with a mean duration of therapy of 9.2 months. Anakinra was tapered in 65% of patients with recurrence in 26% [91]. To the best of our knowledge, there have been no observational studies of canakinumab or rilonacept in the treatment of recurrent pericarditis.

3.2.3 Prospective Trials

The Anakinra-Treatment of Recurrent Pericarditis (AIRTRIP) study was the first prospective, placebo-controlled trial evaluating the use anakinra in idiopathic recurrent pericarditis. In AIRTRIP, 21 patients with more than 3 recurrences, elevation of CRP, colchicine resistance, and corticosteroid dependence were treated with anakinra 2 mg/kg/day with a maximum dose of 100 mg for 2 months. Patients were then randomized to anakinra or placebo for an additional 6 months or until recurrence. All 21 patients had resolution of pain and inflammatory markers at the time of randomization. All patients were able to discontinue steroids by 6 weeks. After a median follow-up of 14 months, recurrence of pericarditis occurred in 9 of 10 patients assigned to placebo with a median event-free survival of 72 days. Only 2 of the 11 patients randomized to anakinra had recurrence, occurring a mean 76.5 days after randomization. Transient injection-site reactions occurred in 95% of patients during the initial 2 months [7]. AIRTRIP was the first randomized trial to show a dramatic improvement in recurrences with anakinra. Nonetheless, a key unanswered question was the optimal duration of therapy and tapering strategy.

The International Registry of Anakinra for Pericarditis (IRAP) study, published in 2020, is the largest investigation of anakinra in pericarditis. In this multicenter observational study, 224 consecutive patients with colchicine-resistant pericarditis with corticosteroid dependence were treated with anakinra. The primary endpoint was recurrence of pericarditis with a secondary outcome of a composite of emergency department visits, hospitalizations, corticosteroid use, and major adverse events. The etiology of pericarditis was idiopathic in 75%, post-cardiac injury in 13%, autoimmune in 9%, autoinflammatory in 2%, radiation-induced in 0.7%, and traumatic in 0.3%. Patients were treated with 100 mg daily of anakinra for a median of 6 months with a tapering period typically over 3 months. After a median treatment of 6 months, recurrences decreased from 2.33 to 0.39 per patient. There was a 91% reduction in emergency department visits and an 86% reduction in hospitalizations. Corticosteroid use decreased from 80% to 27%. Of the 224 enrolled patients, 135 were able to permanently discontinue anakinra, and after 18 months, 74% of this group remained free from recurrence. A longer duration of full-dose treatment

△ Adis
and a longer tapering duration were both associated with a decreased risk of recurrence [92].

Adverse events were reported in 44% of patients. Injection-site reactions were common, affecting 38% of patients, with 3 patients discontinuing treatment for this reason. Seven patients (3%) had transient elevations in aminotransferases and 3 patients (1%) had transient neutropenia, both of which did not require permanent discontinuation of anakinra. Infections were observed in 3% of patients, 2 with respiratory infections and 4 with skin infections. Overall, only 7 patients (3%) discontinued anakinra due to an adverse event [92].

The efficacy and safety of rilonacept was first demonstrated in a Phase II clinical trial published in 2020. This study enrolled adults and children with idiopathic or post-pericardiotomy recurrent pericarditis. Included patients had either active symptoms or were corticosteroid dependent. Patients were treated with a 320-mg loading dose of rilonacept then a 5-week period of 160 mg weekly. This was followed by the option to participate in an 18-week extension period. The primary end points for patients with an active flare were pain scores and improvement in CRP. The primary end point for the other patients was disease activity after tapering corticosteroids. The study enrolled 25 patients, 21 with idiopathic pericarditis and 4 with post-pericardiotomy pericarditis. Sixteen patients were having an active flare with 9 on corticosteroids. Patients with active chest pain had a significant improvement in pain scores after the loading dose that was maintained throughout the study period. The frequency of pericarditis episodes decreased from 3.9 to 0.18 per year. Corticosteroids were discontinued in 11 of 13 patients with the remaining patients on reduced doses [93].

The most common adverse events were injection-site reactions (60%), nasopharyngitis, arthralgia, and diarrhea. All injection-site reactions were considered mild, and no patient discontinued rilonacept for this reason. One patient, with a history of skin infections, discontinued rilonacept during the 6-week treatment phase after developing a skin abscess requiring intravenous antibiotics and surgical drainage. The majority of patients (23/25) opted to continue rilonacept into the 18-week extended period. There were mild increases in total cholesterol, HDL, LDL, and triglyceride levels [93].

Given the success in the Phase II clinical trial, rilonacept was evaluated in the larger Study to Assess the Efficacy and Safety of Rilonacept Treatment in Participants with Recurrent Pericarditis (RHAPSODY) Phase III clinical trial, published in 2021. This multicenter, double-blind, randomized withdrawal trial of rilonacept included adults and adolescents (aged ≥ 12 years) who presented with an acute episode of pericarditis with at least two prior recurrences despite treatment with NSAIDs, colchicine, and corticosteroids. All patients underwent a 12-week run-in period with rilonacept, which included 1 week for stabilization, 9 weeks to weak background therapy, and 2 weeks of monotherapy. The protocol was a loading dose of rilonacept 320 mg (or 4.4 mg/kg in patients aged < 18 years) followed by weekly injections of 160 mg (2.2 mg/kg for patients aged < 18 years). Patients whose pain scores were ≤ 2 and CRP ≤ 0.5 mg/dL were eligible to be enrolled in the withdrawal period. Patients were then randomized to continue weekly rilonacept or placebo. The primary end point was recurrence, defined as the return of pericarditis pain, increased CRP level, and other supportive evidence, such as a pericardial friction rub or new pericardial effusion [76].

RHAPSODY enrolled 86 patients in the run-in period, although only 61 were randomized because the study was stopped after accruing the pre-specified number of events. The majority of patients had idiopathic recurrent pericarditis (85%) with a minority having post-pericardiotomy pericarditis (15%). Recurrence occurred in 23 of 31 (74%) patients randomized to placebo versus 2 of 30 (7%) in those randomized to rilonacept. Of note, both recurrences in the rilonacept arm were related to interruptions in dosing. In placebo patients with a recurrence, all responded to bailout rilonacept with no further recurrences during the remainder of the study. As a result of the RHAPSODY trial, rilonacept became the first drug to be FDA approved for the treatment of recurrent pericarditis (Fig. 2) [94]. A summary of published data for anakinra, canakinumab, and rilonacept can be found in Table 2.

### 4 Future Applications of Interleukin-1 Antagonists

The success of IL-1 antagonists in recurrent pericarditis has generated interest in potential efficacy in other forms and etiologies of pericarditis. Specifically, IL-1 antagonists are promising therapies for patients with incessant or chronic pericarditis, a broader group of patients with post-cardiac injury syndromes, and certain patients with autoimmune recurrent pericarditis.

There has been limited investigation on the use of IL-1 antagonists for other forms of complicated pericarditis. Incessant pericarditis is defined as the persistence of symptoms for more than 4 weeks after an acute episode without a symptom-free interval and chronic pericarditis as the persistence of symptoms for more than 3 months. Effusive-constrictive pericarditis is a syndrome of both pericardial constriction and a pericardial effusion with the persistence of constrictive physiology despite drainage of the pericardial effusion [95, 96]. These syndromes are typically treated with NSAIDs, colchicine, and corticosteroids. As previously discussed, corticosteroids have numerous long-term adverse effects [1, 7].
To date, there have been two cases in the literature of the successful treatment of effusive-constrictive pericarditis with anakinra, one in a case of idiopathic pericarditis and one of RA. Both patients failed treatment with NSAIDs, colchicine, and corticosteroids. The patient with idiopathic pericarditis was treated with anakinra monotherapy and the patient with rheumatoid arthritis with a combination of anakinra and leflunomide. Both patients had improvement in pain and resolution of constrictive physiology [97, 98]. A small, prospective cohort study of patients with colchicine resistance and corticosteroid-dependent constrictive pericarditis showed that anakinra may reverse constrictive pathophysiology, and that the risk of constrictive pericarditis may be associated with an incessant rather than a recurrent course [99].
Table 2  Summary of case series, observational trials, and prospective trials for each IL-1 antagonist for the use in recurrent pericarditis

|                | Number of patients | Drug regimen | Study result                                                                                                                                                                                                 |
|----------------|--------------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Anakinra**   |                    |              |                                                                                                                                                                                                               |
| *Case Reports/Series* |                    |              |                                                                                                                                                                                                               |
| Picco et al. 2009 [79] | 3                | 1 mg/kg/day or 1.25 mg/kg/day | Rapid improvement of symptoms followed by relapse with 2 months after discontinuation                                                                                                                      |
| Vassilopoulos et al. 2012 [80] | 3                | 100-150 mg/day |  Rapid improvement of symptoms. Two patients had relapse shortly after discontinuation. One patient permanently discontinued anakinra due to elevations in aminotransferase |
| Camacho-Lovillo et al. 2013 [81] | 1                | 2 mg/kg/day | No recurrences on therapy with relapse 1 month after discontinuation                                                                                                                                          |
| Scardapane et al. 2013 [82] | 1                | 0.7 mg/kg/day | Improvement in symptoms with 10 months of treatment. No recurrences 12 months after discontinuation of anakinra                                                                                           |
| **Observational Trials** |                    |              |                                                                                                                                                                                                               |
| Finetti et al. 2014 [88] | 15               | 1.3 mg/kg/day | Treated with anakinra for 12 months followed by two tapering strategies. 6/15 patients had relapses                                                                                                          |
| Lazaros et al. 2014 [90] | 10               | 100 mg/day | Treated with anakinra daily for 6 months followed by 6 months every other day dosing with 7/10 relapsing                                                                                                                                 |
| Jain et al. 2015 [89] | 13               | 100 mg/day | All patients had response to therapy. 11/13 remained on anakinra with 5 having failed tapering                                                                                                                   |
| **Prospective Trials** |                    |              |                                                                                                                                                                                                               |
| Brucato et al. 2016 [72] | 21               | 2 mg/kg/day (max 100 mg/day) | Patients randomized to anakinra versus placebo after the 6-month run-in period were significantly less likely to have recurrence                                                                                       |
| Imazio et al. 2020 [92] | 224              | 100 mg/day | Significant reduction in number of recurrences, emergency department visits, and hospitalizations                                                                                                               |
| **Canakinumab** |                    |              |                                                                                                                                                                                                               |
| *Case Reports/Series* |                    |              |                                                                                                                                                                                                               |
| Theodoropouli et al. 2015 [83] | 1                | 2 mg/kg/month, 4 mg/kg/month | Relapse after switch from anakinra to canakinumab; symptoms refractory to higher dose of canakinumab                                                                                                       |
| Kougkas et al. 2018 [87] | 2                | 150 mg/month | Durable remission in two patients with adult-onset Still’s disease with recurrence pericarditis                                                                                                                                 |
| Epçaçan et al. 2019 [84] | 1                | 5 mg/kg/month | Patient had anaphylactic reaction to anakinra; switched to canakinumab with successful maintenance of remission                                                                                                 |
| Signa et al. 2020 [85] | 2                | 2.5 mg/kg/month, 4 mg/kg/month | Both patients relapsed shortly after starting canakinumab                                                                                                                                                    |
| Chawla et al. 2021 [86] | 1                | Not reported | Patient with rheumatoid arthritis and ulcerative colitis who responded to canakinumab after anakinra treatment failure                                                                                       |
| **Rilonacept** |                    |              |                                                                                                                                                                                                               |
| *Prospective Trials* |                    |              |                                                                                                                                                                                                               |
| Klein et al. 2020 [93] | 25               | 320 mg loading dose followed by 160 mg weekly | Phase II trial where patients had rapid resolution of symptoms and significant reduction in frequency of pericarditis episodes                                                                                      |
| Klein et al. 2021 [76] | 86               | 320 mg loading dose followed by 160 mg weekly | After run-in period on rilonacept, patients randomized to continue rilonacept versus placebo had significantly lower risk of recurrence                                                                       |

*a Mean dose*
Constrictive pericarditis, a syndrome of congestive heart failure caused by impaired filling of the heart from a stiff pericardium, has traditionally been thought to occur in patients with scarred and fibrotic pericardial tissue. However, cardiac MRI studies have shown that constrictive pericarditis is on an inflammatory spectrum with certain patients continuing to have active inflammation [100]. These patients have been successfully treated with traditional anti-inflammatory regimens and may also benefit from IL-1 antagonists. Additional investigation is needed to further evaluate the role of anti-IL-1 therapy in patients with these other forms of pericarditis [1].

Post-cardiac injury syndrome (PCIS) is a common cause of recurrent pericarditis. Post-cardiac injury syndromes can occur post-myocardial infarction, post-pericardiectomy, and after iatrogenic and non-iatrogenic trauma [101]. Although the incidence of post-myocardial infarction pericarditis is decreasing in the era of percutaneous coronary intervention, the incidence of iatrogenic post-traumatic pericarditis is on the rise with the increasing frequency of cardiac ablations. Post-cardiac injury syndrome is estimated to affect 9–29 % of adult cardiac surgery patients and up to 28.6% of patients with a radiofrequency ablation complicated by perforation [102]. The recurrence rate of pericarditis from PCIS is thought to be between 10 and 15 % [101, 102].

The exact pathophysiology of post-cardiac injury syndrome is unknown, although an autoimmune mechanism is favored for several reasons. First, the presence of anti-myocardial antibodies in patients with PCIS after myocardial injury suggests an immunological etiology [101]. In addition, the successful use of colchicine for the treatment of both acute and recurrent pericarditis associated with PCIS suggests an NLRP3-mediated process [103]. Finally, both the IRAP study and the RHAPSODY study included 13% and 14% of patients with PCIS, respectively. Although the cohort was small, there was no signal for decreased efficacy of anakinra and rilonacept in these studies [76, 92]. Despite a similar risk of recurrence (~ 15 %), PCIS is associated with a higher risk of progressing to constrictive pericarditis compared to idiopathic pericarditis (2–5% vs < 1%) [101]. Additional studies are needed to further elucidate the use of IL-1 antagonists in PCIS and whether, given the small differences in natural history of these conditions, different treatment regimens or durations are needed.

Recurrent pericarditis is a frequent manifestation in many rheumatologic conditions. Although disorders of the immune system are classically divided into autoimmune and autoimmune, there is often a substantial overlap [9]. Rheumatoid arthritis is traditionally thought to exist on this spectrum with elevations of both autoimmune and autoinflammatory signals. Moreover, there are high rates of pericardial involvement in RA [104]. Case reports have shown success with treating RA-associated recurrent pericarditis with both anakinra and canakinumab [86, 87]. Early use of anti-IL-1 therapy could be considered in patients with RA with pericardial involvement.

The use of IL-1 antagonists in other autoimmune conditions remains uncertain. Clinically relevant pericardial involvement is rare in scleroderma, inflammatory myositis, and Sjogren syndrome, but can occur in up to 25% of patients with SLE and 29% of patients with mixed connective tissue disease [105–108]. Systemic lupus erythematosus is considered to be a prototypical autoimmune disease with increased levels of interferon [9]. Interestingly, case reports suggest anakinra can be effective in treating both severe arthritis and recurrent fevers in SLE [109, 110]. A small case series of pericarditis from SLE suggests that colchicine can be an effective treatment and reduce the need for corticosteroids [111]. In 2021, Cafarelli et al. published the first case report of successfully treated SLE-associated pericarditis with anakinra [112]. These small studies suggest IL-1 may be involved in the pathophysiology of SLE, and IL-1 antagonists may have a role in treating SLE-associated pericarditis refractory to corticosteroids.

5 Gaps in Understanding

5.1 Duration of Treatment

As evidenced by the many case series, observational studies, and clinical trials, the proper duration of treatment for recurrent pericarditis is unknown. Multiple recurrences have traditionally been treated with courses of steroids for 6–12 months followed by long tapers [1]. The clinical trials of anakinra and rilonacept offer insight into duration of therapy, but were not designed to directly answer this question. In AIRTRIP, both arms of the study received 2 months of anakinra before being randomized to placebo or an additional 6 months of anakinra [72]. The inclusion of longer-term follow-up is an advantage of the IRAP study, and outcomes were generally better in patients treated for at least 3 months with at least 3 months of tapering. However, IRAP did not have a control group for comparison [92]. RHAPSODY also did not specifically address the appropriate duration of treatment [76].

Based on these studies, the optimal duration of IL-1 antagonists is at least 6 months and likely longer in many patients. Several studies have demonstrated that pericardial inflammation can persist despite improvement in both symptoms and normalization of serum inflammatory markers. An MRI-guided approach to tapering IL-1 antagonists could be considered; however, this approach warrants further investigation [113, 114].
5.2 Genetics

Genetics is an emerging area of interest in pericarditis. Numerous case reports and case series describing familial cases of pericarditis and pericarditis syndromes have been reported [115–119]. Although researchers have identified specific genes associated with higher rates of pericarditis in SLE and TRAP, no specific gene mutations have been identified in idiopathic recurrent pericarditis [120, 121]. The genetics of pericarditis have largely been unexplored and warrant further investigation.

5.3 Animal Models

The study of pericarditis has been limited by the absence of a reliable animal model. However, Mauro et al. recently published a mouse model [30]. This model was created by injected zymosan A, a known activator of the innate immune system, into the pericardium. Mice injected with zymosan A developed greater pericardial thickness on histology, larger pericardial effusions on echocardiography, and had higher expression of apoptosis-speck-like protein (ASC), a surrogate for NLRP3 inflammasome activation, compared to mice injected with saline. The authors then treated the mice with ibuprofen, colchicine, or anakinra. Ibuprofen reduced pericardial effusions, but not pericardial thickness or expression of ASC. Colchicine reduced pericardial effusions and ASC, but not pericardial thickening. Anakinra reduced all three surrogates of pericardial inflammation. This finding suggests that anti-IL-1 therapy provides a more potent block of pericardial inflammation compared to the traditional first-line therapies, NSAIDs, and colchicine. The development of this mouse model should lead to a greater understanding of the mechanisms of acute and recurrent pericarditis and aid the development of future therapeutics.

6 Conclusion

Recurrent pericarditis continues to be a challenging condition with high morbidity and frequent relapses. Until the development of IL-1 antagonists, treatment consisted largely of long courses of NSAIDs, colchicine, and corticosteroids with associated adverse effects. The link between pericarditis and the innate immune system dysregulation, largely spurred by the success of colchicine in periodic fever syndromes, led to significant interest in the use of IL-1 antagonists for the treatment of recurrent pericarditis.

The efficacy of anakinra for recurrent pericarditis was first demonstrated in several case reports and small case series. This success motivated larger clinical trials of both anakinra and rilonacept, which have shown that both drugs induce a rapid resolution of symptoms and inflammatory markers. Both trials showed a high rate of recurrence with placebo following the randomized withdrawal period, and the appropriate duration of therapy remains a pressing clinical question. Studies with IL-1 antagonists have largely included patients with idiopathic recurrent pericarditis and further research is needed to determine efficacy in other forms (e.g. acute, incessant, constrictive) and etiologies of pericarditis (e.g. PCIS, rheumatologic disorders). Despite these remaining gaps, IL-1 antagonists have revolutionized the treatment of recurrent pericarditis and should be strongly considered in patients who have failed traditional therapy with colchicine.
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