Interleukin-1 Blockers in Recurrent Pericarditis

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Diseases of the pericardium encompass a spectrum of conditions, including acute and recurrent pericarditis, where inflammation plays a pivotal role in the pathogenesis and clinical manifestations. Anti-inflammatory therapy indeed forms the cornerstone of treating these conditions: NSAIDs, colchicine, and corticosteroids (as a second-line treatment) are recommended by current guidelines. However, these medications come with several contraindications and are not devoid of adverse effects. There has been an increased focus on the role of the inflammasome and potential therapeutic targets. Recurrent pericarditis also shares numerous characteristics with other autoinflammatory diseases, in which interleukin-1 antagonists have already been employed with good efficacy and safety.

pericarditis anti-IL-1 drugs interleukin-1 (IL-1) autoinflammatory

1. Introduction

Pericardial diseases are a heterogeneous group of entities, ranging from acute pericarditis to asymptomatic pericardial effusion [1]. According to the latest update of the European Society of Cardiology (ESC) guidelines on pericardial diseases, published in 2015 [2], researchers define (a) acute pericarditis (AP) as an inflammatory pericardial syndrome, with or without pericardial effusion; (b) recurrent pericarditis (RP) as being identified by the presence of new signs and symptoms of pericardial inflammation after a first documented episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer; (c) incessant pericarditis as when pericarditis symptoms last more than 4–6 weeks, but less than 3 months, without remission; and (d) chronic pericarditis as when pericarditis symptoms manifest for more than 3 months.

The diagnosis of AP requires at least two of the following diagnostic criteria: typical chest pain; the finding of a pericardial friction rub; and new electrocardiographic findings, such as widespread ST elevation or PR depression (observed in up to 60% of cases), and the presence of pericardial effusion on echocardiogram (seen in up to 60% of cases) [2].

Precise epidemiological data for AP are lacking. The reported incidence in an urban area in Northern Italy was about of 27.7 cases per 100,000 person-years [3]. Recently, many epidemiologic studies have highlighted how SARS-CoV-2 infection increased the incidence of pericarditis at least 15 times over pre-COVID levels, although the condition remains rare [4].

Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and steroids (as second-line treatment) represent the mainstays of AP therapy [1][2]; however, up to 30% of patients with AP experience a recurrence, especially if not treated with colchicine, and up to 50% of recurrent patients can experience more than one recurrence [2].

To date, interleukin-1 (IL-1) antagonists (also called anti-IL-1 drugs or IL-1 blockers) are approved as a third line of therapy, only for cases of a non-infectious, steroid-dependent, and colchicine-refractory RP, with excellent results of efficacy and safety [2][5].

However, some recent evidence, although deviating from current guidelines, has shown interesting data regarding the use of these drugs as first- or second-line treatments in both recurrent and acute pericarditis, with preliminary good safety and efficacy results.

2. Interleukin-1 Blockers in Recurrent Pericarditis

2.1. Anakinra

Anakinra is a recombinant human IL-1 receptor antagonist (IL-1Ra), blocking both IL-1β and IL-1α activity [6][7]; due to its short half-life (about 2.6 h), the standard adult dose corresponds to daily administration of 100 mg subcutaneously [8].

Although only recently adopted in RP, Anakinra is approved by United States Food and Drug Administration (FDA) for the treatment of Rheumatoid Arthritis (RA), cryopyrin-associated periodic syndromes (CAPS), TRAPS, and FMF [9]. The use of Anakinra is allowed by the European Medicines Agency (EMA) for RA in combination with methotrexate when monotherapy with the latter has failed: CAPS, FMF (association with colchicine should be considered), and Still's disease [10]. Anakinra has also been approved for patients with COVID-19 pneumonia at risk of severe respiratory failure [11]

The first double-blind, placebo-controlled, randomized trial analyzing the use of Anakinra in RP was the Anakinra-Treatment of Recurrent Pericarditis (AIRTRIP) study [12]. Twenty-one patients with a clinical story of more than three pericarditis recurrences, laboratory evidence of CRP elevation above 1 mg/dL, colchicine resistance, and corticosteroid dependence received Anakinra 2 mg/kg/day (with a maximum dose of 100 mg) for 2 months. During this phase, all patients had pain resolution and CRP reduction, leading to the discontinuation of all anti-inflammatory drugs (including steroids) by 6 weeks [12]. Patients were then randomized to Anakinra or placebo for 6 months or until recurrence. After a median follow-up of 14 months, pericarditis recurred in 9 of 10 (90%) patients assigned to placebo and only in 2 of 11 (18%) patients treated with Anakinra. Side effects of Anakinra treatment were transient and minor, mostly injection site skin reactions, occurring in 95% of patients during the first 2 months of treatment (**Table 1**).

Table 1. Summary of studies on the use of anti-IL-1 drugs in recurrent pericarditis.

Drug	Study	Design	Year	Pts n.	Dose	Results	AE
Anakinra	AIRTRIP	PT	2016	21	2 mg/kg/day	↓ recurrence	ISR; ↑ALT; ↑AST
	IRAP	PT	2020	224	100 mg/day	↓ recurrence	ISR; A; M
Rilonacept	RHAPSODY II	PT	2020	25	320 mg LD and then 160 mg/week	↓ recurrence	ISR; I
	RHAPSODY III	PT	2021	86	320 mg LD 160 mg/week	↓ recurrence	ISR; URTI
Canakinumab	Theodoropoulou	CR	2015	1	2 mg/kg/month and then 4 mg/kg/month	Relapse	Unreported
	Kougkas	CR	2018	3	150/mg/month	Remission (2 Pts) Relapse (1 Pts)	Unreported
	Epçaçan	CR	2019	1	5 mg/kg/month	Remission	None
	Signa	CR	2020	2	2.5 mg/kg/month or 4 mg/kg/month	Relapse	Unreported
	Chawla	CR	2021	1	Unknown	Remission	Unreported

Later, in 2020, the IRAP (International Registry on Anakinra for Pericarditis) study, a multicenter observational work, confirmed the efficacy and safety of Anakinra in the treatment of 224 colchicine-resistant and steroid-dependent patients affected by RP with high CRP values [13]. Patients received 100 mg daily of Anakinra for a median treatment of six months. Response to Anakinra was rapid (within one week of treatment), with clinical benefit and CRP reduction, so that steroid therapy was gradually tapered to discontinuation in most patients. Pericarditis recurrences found a 6-fold reduction, with a 11-fold reduction of Emergency Department (ED) admissions and 7-fold reduction of hospitalizations. After 36 months from Anakinra initiation, 43% of patients had no recurrences, whereas 29% of patients had a single recurrence over the entire period.

Pts: Patients; n: number; AE: Adverse Effects; PT: Prospective Trial; LD: Loading Dose; CR: Case Report; ISR: Injection site reaction; A: Arthralgias; M: Myalgias; I: Infections; URTI: Upper Respiratory Tract Infection; ALT: Aminotransferase Alanine Transaminase; AST: Aspartate Transaminase; ↓: decrease; ↑: increase.

During the follow-up, 27% of patients still needed corticosteroid treatment. Regarding adverse events, injection site reactions were common, affecting 38% of patients, but only three patients had to discontinue treatment for this reason; 6% experienced arthralgias and myalgias, 3% showed transient transaminases elevation, 3% had infections, and 1% had transient neutropenia (**Table 1**); however, these three adverse effects did not require Anakinra discontinuation. As for the effective duration of treatment and tapering protocol, the IRAP study showed that Anakinra treatment longer than 3 months, followed by slow tapering of at least 3 months, was associated with a reduction in the risk of pericarditis recurrence [13].

Overall, AIRTRIP was the first trial to demonstrate a concrete improvement in RP with Anakinra, and the IRAP study assessed its use in a real-world clinical cohort. Although IRAP gave us more information about treatment duration and tapering, these two issues still need to be further explored.

2.2. Rilonacept

Rilonacept is a chimeric fusion protein constituted of the ligand-binding domain of human IL-1 receptor (IL-1R1) and the IL-1 receptor accessory protein (IL-1 RAcP) linked to the Fc portion of human IgG1. Circulating rilonacept acts as an “IL-1 trap”, binding both IL-1α and IL-1β, preventing their engagement with the cell surface receptor and downstream inflammatory cascade [14][15]. The Rilonacept half-life is about 7 days, allowing for weekly subcutaneous drug injections [16][17].

Approved for CAPS treatment by the FDA in 2008 [18], Rilonacept recently received FDA approval for treatment of RP after RHAPSODY (Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes Study) results from phase II (2020) and phase III (2021) trials [19].

RHAPSODY phase II was a multicenter, open-label study, which enrolled 25 adult patients with idiopathic or post-pericardiotomy RP, symptomatic (at least two pericarditis recurrences) and/or corticosteroid-dependent, with either active or non-active disease. Patients received a 320 mg s.c. Rilonacept loading dose, followed by weekly injections of 160 mg s.c. for 6 weeks; during an optional 18-week treatment-extension period, concomitant anti-inflammatory medications (colchicine, NSAIDs, corticosteroids) were prudently weaned off [19].

Patients with symptomatic RP and elevated CRP had rapid and sustained recovery after Rilonacept treatment, leading to a decrease in pericarditis annual recurrences and improvement in quality of life. Moreover, patients could stop or reduce the dose of at least one concomitant pericarditis medication, without a recurrence. In particular, most patients (84%) receiving corticosteroids at baseline could totally discontinue them, whereas the remaining 16% could reduce them. As for drug safety, 92% of the adverse events were mild–moderate in severity, mostly injection site reactions (**Table 1**).

The results were confirmed in phase III of the RHAPSODY study, a multicenter, double-blind, placebo-controlled randomized-withdrawal trial enrolling 86 patients (adults or adolescents older than 12 years) with symptomatic RP (with at least two previous recurrences) and elevated CRP (≥1 mg/dL), despite treatment with NSAIDs, colchicine, or steroid therapy.

The majority of patients (85%) had idiopathic RP, whereas post-pericardiotomy pericarditis affected the remainder [19]. During a 12-week run-in period, all patients received Rilonacept 320 mg subcutaneously, followed by a weekly maintenance dose of 160 mg. The run-in period included three periods: a 1-week stabilization period, a 9-week period to wean from pericarditis background therapy, and a 2-week Rilonacept monotherapy period. Among patients receiving Rilonacept monotherapy, 61 had clinical response criteria (CRP ≤ 0.5 mg/dL and weekly NRS score of ≤2) and entered the randomized-withdrawal period to either continue rilonacept or receive a placebo.

In the placebo arm, 23 of 31 (74%) patients experienced recurrence after Rilonacept discontinuation, and all responded to bailout Rilonacept, with no further recurrences; in the Rilonacept arm, 2 of 30 (7%) patients had pericarditis recurrence after temporary interruptions of drug administration.

Injection site reactions and upper respiratory tract infections represented the most common reported adverse events after Rilonacept injections (34% and 23% of participants, respectively), for which only four patients had to discontinue treatment during the run-in period (**Table 1**).

Overall, compared to the placebo, Rilonacept demonstrated its dramatic efficacy in treatment and prevention of RP in symptomatic patients. As for Anakinra, treatment duration and tapering strategies still represent key questions to explore.

2.3. Canakinumab

Canakinumab is a human monoclonal antibody selectively blocking circulating IL-1β, thus forming inactive complexes degraded by the reticuloendothelial system; it has a very long half-life (about 26 days), allowing a drug monthly administration [20]. Currently, Canakinumab is approved by the US FDA and EMA for the treatment of the following inflammatory conditions: CAPS, TRAPS, FMF, hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), Still's disease, and gouty arthritis [21][22].

To date, use of Canakinumab in RP is restricted to case reports in the current literature, offering us contrasting results (**Table 1**).

In 2015, Theodoropoulou et al. reported the use of Canakinumab in a pediatric patient with idiopathic RP, successfully treated with Anakinra for the previous 5 months. When switched to 2 mg/proKg of monthly Canakinumab injections, pericarditis recurred after 1 week and even two times more upon trying higher doses of Canakinumab (4 mg/proKg) and concurrent steroids [23]. Returning to Anakinra treatment led to the patient's symptoms recovery.

In 2018, Kougkas et al. described three adult patients with RP: two of them with Adult Onset Still Disease (AOSD), the third one with RA. These patients received Canakinumab after the failure of colchicine, methotrexate, corticosteroids, and Anakinra. Two patients with AOSD had remission after initiating Canakinumab 150 mg monthly, thus tapering corticosteroid therapy; however, the RA patient responded only partially to Canakinumab 300 mg monthly, then experienced two relapses [24].

One year later, Epçaçan and colleagues successfully adopted Canakinumab in a child with a clinical history of corticosteroid-dependent RP and anaphylactic reaction to Anakinra [25].

In 2020, Signa et al. reported the unsuccessful use of Canakinumab in two pediatric patients: the first one had RP after pericardiotomy, the second suffered from idiopathic RP. Both of them previously received Anakinra; the first patient discontinued Anakinra after injection site reactions and started Canakinumab 4 mg/kg, later developing

relapse. Similarly, the second patient interrupted Anakinra because of poor compliance, switching to 2.5 mg/kg of Canakinumab and relapsing shortly after [26].

Eventually, in 2021, Chawla et al. reported a Canakinumab response in a 31-year-old patient with RP and a past medical history of RA and ulcerative colitis (UC), who had failure with colchicine, prednisone, NSAIDs, Vedolizumab, Adalimumab, and Anakinra [27].

The major effect of Anakinra vs. Canakinumab in treating RP in pediatric patients may lie in the different mechanism of action of these two drugs: Anakinra blocks both IL-1α and IL-1β, whereas Canakinumab exclusively blocks IL-1β [28]. However, this seems no to be true for the patient in the Epçaçan study.

As for the (few) adult case series with RP, the autoimmunity and/or autoinflammatory background seems to influence the response to Canakinumab, with RA representing a negative prognostic risk factor compared to AOSD and CU.

2.4. Goflikicept

In 2023, Myachikova and colleagues published early data from an ongoing phase II/III double-blind, randomized-withdrawal, placebo-controlled study adopting a new IL-1 blocker named Goflikicept in patients with RP [29].

In the same way as Rilonacept, Goflikicept is a heterodimer fusion protein binding both IL-1α and IL-1β, with a ten-day half-life. The study by Myachikova et al. allowed enrollment of patients with at least one prior pericarditis recurrence, with either active or inactive pericarditis. Four different periods were analyzed: screening, run-in, randomized withdrawal, and follow-up.

In total, 22 patients participated in the study. The run-in phase found both CRP and chest pain reduction after Goflikicept treatment, consisting of a dosing regimen of 180 mg at day 0, 80 mg at day 7, and an additional dose of 80 mg at day 14. Colchicine and NSAIDs were stopped at day 14 of the run-in phase without tapering, and glucocorticoids were stopped by week 12. Afterwards, 20 patients were equally randomized to either the placebo or Goflikicept group; in the latter, a maintenance dose of 80 mg every two weeks was administered. Recurrence of pericarditis was defined by the presence of two of the following: significant pericardial chest pain, CRP arising, and new or worsening pericardial effusion. No recurrences occurred in the Goflikicept group within 24 weeks after randomization, with respect to 90% recurrences in the placebo group. The safety profile was similar to other IL-1 blockers [29].

While waiting for the final results of Myachikova and colleagues' study, Goflikicept appears to be an interesting new anti-IL-1 agent in the treatment of RP, although data are very preliminary.

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