Drug Design, Development and Therapy

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REVIEW

Clinical Utility of Rilonacept for the Treatment of Recurrent Pericarditis: Design, Development, and Place in Therapy

Panayotis K Vlachakis, Panagiotis Theofilis, Stergios Soulaidopoulos, Emilia Lazarou, Konstantinos Tsioufis, George Lazaros

First Cardiology Department, School of Medicine, Hippokration General Hospital, National and Kapodistrian University of Athens, Athens, 11527, Greece

Correspondence: George Lazaros, First Cardiology Department, School of Medicine, Hippokration General Hospital, National and Kapodistrian University of Athens, Vas. Sofias 114, Athens, 11527, Greece, Email glaz35@hotmail.com

Abstract: Recurrent pericarditis (RP) has been traditionally regarded as a "nightmare" for both clinicians and patients. Until approximately a decade ago, available treatments were thin on the ground with non-steroidal anti-inflammatory medications, glucocorticoids, colchicine, and classical immunosuppressants being the only options. The first important step in the tale of RP was the advent of colchicine in clinical practice, which has been shown to halve the rate of first and subsequent pericarditis recurrences. The second major breakthrough advance in this setting was the introduction of interleukin-1 inhibitors based on the recently unveiled autoinflammatory nature of pericarditis. At present, anti-interleukin-1 inhibitors available for clinical use in patients with refractory RP include anakinra and rilonacept, with the latter having obtained FDA approval for this indication. Apart from the remarkable efficacy and good safety profile which is a common feature of all anti-interleukin-1 compounds, rilonacept has the advantage of weekly administration (instead of daily compared to anakinra) which is important in terms of adherence to treatment and improved quality of life albeit at the expense of a higher cost. This review aims to summarize the available evidence on the role of rilonacept in the treatment of RP and the reduction of the recurrences risk.

Keywords: rilonacept, interleukin-1 blockers, NLRP3 inflammasome, recurrent pericarditis

Introduction

Recurrent pericarditis is a challenging pericardial syndrome due to its unpredictable course in terms of severity of relapses and variable duration of disease activity.[1] Recurrence is an inherent feature of pericarditis and in general of the inflammatory heart disease (namely pericarditis and myocarditis).[2,3]

After the first episode of pericarditis, a recurrent episode appears in 15–30% of the cases within 18–24 months after the target episode.[4] Occasionally 5–10% of the patients with recurrent pericarditis develop multiple episodes with a duration of disease activity in the most difficult cases of 4.7 years in average.[5–7] In the latter cases serious adverse events may appear due to the need for long-lasting treatments including aspirin and non-steroidal anti-inflammatory medications (NSAIDs), glucocorticoids, and immunosuppressants.[4]

As a result, the quality of life of the affected patients is severely impaired, and the consequences for health care systems are also a matter of concern due to the need for repeated hospitalizations, emergency department visits, and loss of working days.[8,9] Fortunately, colchicine, which is a milestone in the treatment of acute pericarditis, has been shown to halve the rate of both first and subsequent relapses with a good safety profile.[10–13]

It should be emphasized that recurrent pericarditis is an umbrella term which encompasses a wide spectrum of clinical manifestations. On the one hand, it includes patients with distant and easily managed relapses with first step medications (namely aspirin/NSAIDs) and those who, despite being glucocorticoid-dependent, require low doses of glucocorticoids

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(<5 mg of prednisone) which are generally well-tolerated.[4,14] On the other side of the spectrum, we may find the difficult-to-treat patient who requires high doses of glucocorticoids for disease control (>15 mg of prednisone) and depicts serious treatment-related adverse effects.[4,14]

Until approximately 10 years ago, the options for these refractory patients were very scant. Immunosuppressants and intravenous immunoglobulins could be employed unless contraindicated as steroid-sparing agents, with their results being controversial and not based on high quality data.[4] In recent years, the introduction of interleukin-1 (IL-1) inhibitors in everyday clinical practice constituted a paradigm shift in the treatment of glucocorticoid-dependent colchicine-resistant recurrent pericarditis.[15,16] Their use was justified by the recently described autoinflammatory nature of recurrent pericarditis (at least in a meaningful rate of cases) and, as it is well-known, IL-1 is the central cytokine underlying inflammation in these disorders.[17] According to the accumulated worldwide experience, these medications are extremely efficacious with a good safety profile in recurrent pericarditis.[18]

Nevertheless, the tale of refractory recurrent pericarditis has not yet reached an end. With the expanding use of IL-1 blockers, it has been noted that in many instances, it is not possible to wean patients from treatment, as relapses may reappear after abrupt discontinuation or during dose tapering.[18–25] Thus, what we have learned at present is that IL-1 blockers constitute valid treatments in terms of efficacy and safety. However, they are not able to definitively disrupt the vicious circle of the disease.

In this narrative review we will discuss in detail the rationale for the use of rilonacept, an IL-1 blocker, in glucocorticoid-dependent, colchicine-resistant pericarditis, its specific clinical indications and distinct features, the overall pros and cons of IL-1-based treatment of recurrent pericarditis, the gaps in knowledge, and the future perspectives.

The Role of Inflammation in Recurrent Pericarditis

Inflammation serves as the body's defense mechanism against pathogens and injury. However, inflammation is also implicated in cardiovascular disease pathophysiology. Most evidence in this field comes from atherosclerosis, where inflammation plays a crucial role in risk stratification through the use of biomarkers, as well as in treatment.[26] The impact of inflammation has also been demonstrated in other cardiovascular conditions such as heart failure and, more recently, acute and recurrent pericarditis. In pericarditis, an initial insult triggers an inflammatory cascade, leading to pericardial inflammation and subsequent symptoms like chest pain and fever.[16] However, in recurrent cases, this inflammatory response becomes exaggerated or prolonged, perpetuating the disease cycle. While acute inflammation is crucial for tissue repair and pathogen clearance, chronic inflammation can damage healthy tissue and contribute to disease progression. In recurrent pericarditis, persistent inflammation can lead to fibrosis and scarring of the pericardium, exacerbating symptoms and increasing the risk of complications such as constrictive pericarditis.

Pericarditis is often triggered by viruses or other stimuli capable of eliciting an inflammatory response following acute injury of the mesothelial cells. This response is subsequently intensified through the activation of the NLRP3 inflammasome, a complex molecular structure present in various immune cells, particularly macrophages and neutrophils.[27] Comprising three distinct elements, namely the NLRP3 sensor, the adaptor protein ASC (apoptosis-associated speck-like protein), and the effector protein caspase-1, this inflammasome facilitates the conversion of pro-IL-1β and pro-IL-18 into their active forms, along with the extracellular release of IL-1β and IL-18 via gasdermin D channels.[28]

Activation of the NLRP3 inflammasome typically occurs in two stages in most cells. Initially, a priming step is initiated upon tissue injury, where danger-associated molecular patterns (DAMPs) promote the transcription and translation of numerous proinflammatory genes, including those involved in the NLRP3 inflammasome.[28] Subsequently, the inflammasome is activated through the oligomerization of its three components, resulting in its characteristic stellate structure.[28]

In recent years, there has been growing evidence regarding the involvement of the NLRP3 inflammasome in the pathophysiology of pericarditis.[25] Indirect evidence supporting this notion has emerged, particularly from observations related to the use of colchicine as a primary treatment. Colchicine, renowned for its inhibition of microtubule

polymerization and neutrophil migration, has also been found to hinder the activation of the NLRP3 inflammasome by impeding microtubule assembly and the presentation of irritant agents to the inflammasome.

Further insights stem from studies like AIRTRIP and RHAPSODY trials which highlighted the efficacy of IL-1 blockade with anakinra and rilonacept, respectively, in reducing pericarditis recurrence risk among patients resistant to colchicine and dependent on glucocorticoids.[29,30] Recent research by Mauro et al has revealed heightened NLRP3 inflammasome activation within inflamed pericardial tissues, particularly during acute pericarditis episodes.[31] In both human samples and a mouse model of acute pericarditis, increased expression of inflammasome components was evident, correlating with pericardial inflammation. These findings, coupled with the observed reduction in ASC expression following treatment with colchicine, anakinra, or specific NLRP3 inhibitors, underscore the pivotal role of the NLRP3 inflammasome in acute and recurrent pericarditis pathogenesis. Consequently, targeting this inflammasome and its derivatives emerges as a promising therapeutic strategy for managing pericarditis effectively.

Recently, a meta-analysis of genome-wide association studies across five countries sheds more light on pericarditis pathogenesis.[32] It encompassed 4894 individuals diagnosed with pericarditis across various cohorts, revealing significant associations with two independent common intergenic variants situated at the interleukin 1 locus on chromosome 2q14. In particular, the lead variant was rs12992780 (T) - effect allele frequency 31%–40%; odds ratio of 0.83 (95% CI: 0.79 to 0.87), located downstream of IL 1B, while the secondary variant, rs7575402 (A or T) - EAF, 45%–55%; adjusted odds ratio of 0.89 (95% CI: 0.85 to 0.93). Notably, the lead variant, rs12992780, demonstrated a smaller odds ratio for recurrent pericarditis (0.76) compared to the acute form (0.86). In summary, this meta-analysis of genome-wide association studies showed an association of IL-1 gene locus with pericarditis, which is an important step forward for the comprehension of the genetic architecture of pericarditis. In specific, this study is suggestive of a genetic basis underlying autoinflammation in recurrent pericarditis which is important in terms of targeted therapies.

IL-1β is the main form of IL-1 in circulation and is responsible for systemic IL-1 effects such as fever, serositis, and increased acute phase reactants.[33] However, IL-1α has also a significant role in pericarditis pathophysiology. Primarily bound to cell membranes, IL-1α exerts localized inflammatory effects in the pericardium, which can lead to inflammation and occasionally fibrosis, potentially progressing to constrictive pericarditis in rare cases.[1,4,33,34] When pericardial cells are injured, they release preformed IL-1α, which, along with other alarmins, binds to receptors on leukocytes and endothelial cells, activating both Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs). This activation of IL-1α leads to the formation and activation of the NLRP3 inflammasome, perpetuating IL-1-mediated inflammation, a process known as the autoinflammatory mechanism of pericarditis. Examples of diseases driven by autoinflammatory mechanisms include familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and cryopyrin-associated periodic syndromes (CAPS).[1,4,34–36] These disorders are characterized by excessive IL-1 production due to dysregulated NLRP3 inflammasome activation.[1,4,34,37–41]

Overall, these findings provide crucial insights into the genetic underpinnings of pericarditis, particularly its recurrent subtype, and may bolster the development of targeted and personalized therapies involving IL-1-blocking drugs for more effective management of the condition, especially in patients with the autoinflammatory etiology.

Design and Development of Rilonacept

Pharmacological Properties

Rilonacept, also known as "IL-1 trap", comprises a dimeric fusion protein consisting of three components: IL-1 receptor accessory protein, the ligand binding-domain of the human IL-1 receptor, and the Fc portion of human immunoglobulin G1.[42] When circulating, rilonacept acts as a soluble decoy receptor, effectively binding to circulating IL-1α and IL-1β, and to a lesser extent, to the IL-1 receptor antagonist that naturally mitigates their inflammatory response.[43] This interaction inhibits the inflammatory cascade by preventing the interaction between IL-1β and cell surface receptors.[44] The mechanism of action of rilonacept is depicted in Figure 1.

The pharmacokinetic profile of rilonacept is characterized by slow subcutaneous absorption and a long elimination half-life (ranging from 154 to 184 hours), enabling convenient weekly dosing.[45] The administration regimen, as detailed

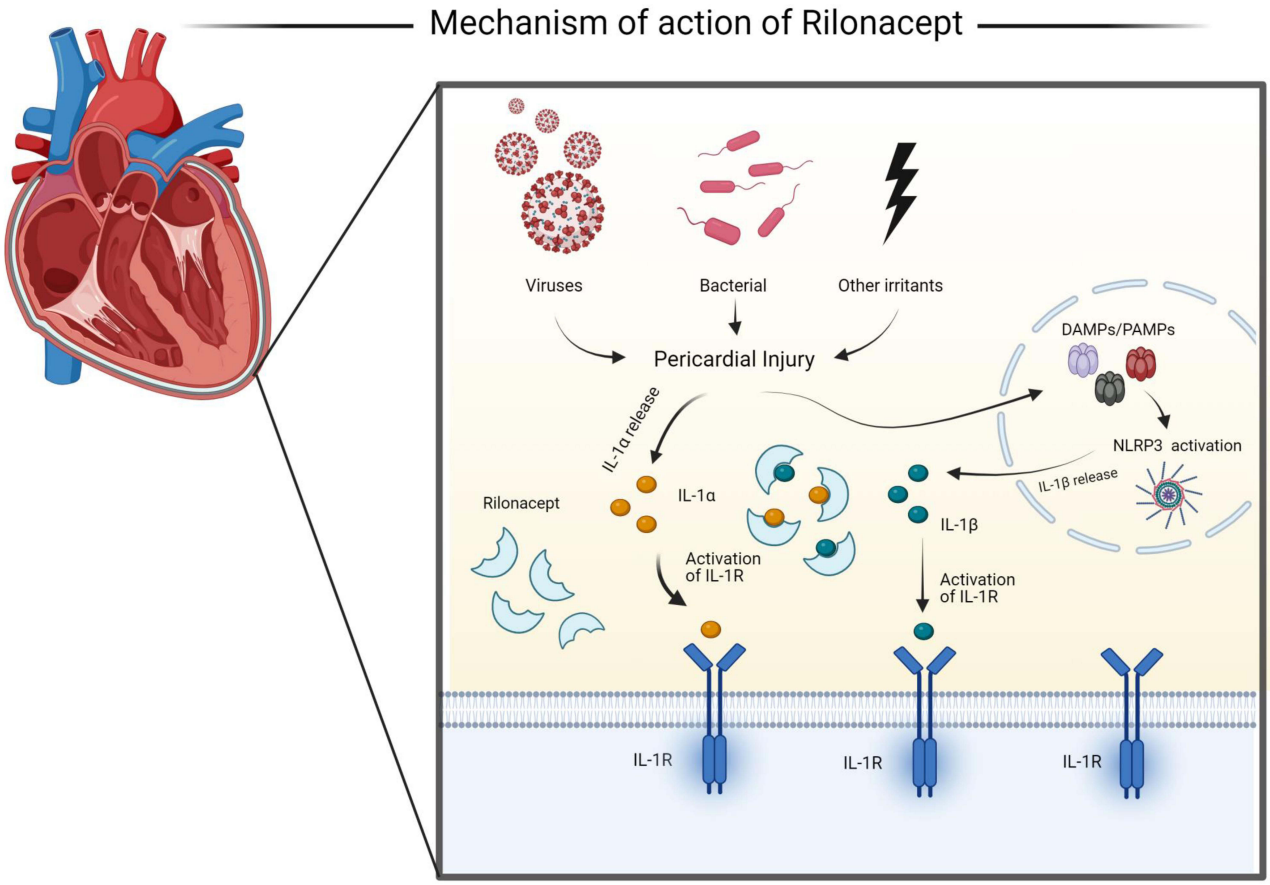

Figure 1 Mechanism of action of rilonacept (see text for details). Created with BioRender.com.

in clinical trials, involves an initial loading dose of 320 mg, administered as two separate injections of 160 mg each, on the same day at two different injection sites. Following the loading dose, maintenance therapy consists of a weekly injection of 160 mg. It is essential to commence the maintenance dose one week after the loading dose and adherence to a once-weekly dosing schedule thereafter.[30] Notably, the steady trough concentrations of the drug are not affected by factors such as gender, body weight, and age.[46] It is recommended that the rilonacept is stored in the refrigerator at a temperature between 2°C and 8°C (36–46°F), within its carton to shield it from light. So far, due to limited data, there have been no dosage adjustments recommended for patients with kidney or hepatic impairment.[47] Finally, drug–drug interactions are not documented with the usage of rilonacept.[48]

Contemporary Clinical Indications of Rilonacept

Rilonacept has demonstrated efficacy across various clinical diseases, including Cryopyrin-Associated Periodic Syndrome (CAPS), which involves excessive IL-1β release. CAPS includes familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), all sharing similar features, such as spontaneous generalized painful or itchy red rash, fever, flu-like symptoms, and increased white blood cell count.[49] Rilonacept has been approved by FDA (Food and Drug Administration) for patients aged 12 and older with CAPS and it significantly alleviates symptoms and reduces inflammatory markers in clinical trials, with favorable tolerability.[50,51] Additionally, literature data showed that rilonacept achieves a sustained disease remission, in Deficiency of the IL-1 Receptor Antagonist (DIRA), which is an autoinflammatory syndrome separate from CAPS.[52]

Moreover, rilonacept is currently being investigated for its potential use in systematic Juvenile Idiopathic Arthritis (sJIA). In a trial involving 24 patients with refractory sJIA, no significant differences in efficacy were noted between rilonacept and placebo during the blinded phase. However, during the open-label phase, patients receiving rilonacept experienced complete resolution of

symptoms, such as fever and rash within 3 months, with over 50% maintaining their response and more than 90% reducing or discontinuing glucocorticoids.[53] Moreover, rilonacept demonstrated in another trial including 71 children with active sJIA, a shorter time to response and a higher response rate at week 4 compared to the placebo arm, with the treatment being well tolerated.[54]

Additionally, the use of rilonacept in gout management has shown promise in reducing gout-related pain and inflammation by blocking IL-1β, a key mediator of gout inflammation.[55] In cases where standard therapies fail to improve relief, IL-1β inhibitors like rilonacept are recommended according to guidelines.[56,57] Clinical studies have reported favorable outcomes with rilonacept, demonstrating reduced frequency of gout flares and lower pain levels compared to placebo or other comparator medications.[55,58] Ongoing clinical investigations aim to expand rilonacept's uses and improve patient outcomes across various medical conditions.

Safety Profile

Based on available literature concerning its use in patients with pericarditis, as well as in various clinical disorders, rilonacept demonstrated generally good tolerability. The majority of adverse events is mild to moderate in severity. In the RHAPSODY (Rilonacept inHibition of interleukin-1 Alpha and beta for recurrent Pericarditis: a pivotal Symptomatology and Outcomes study) Phase II trial, the most common adverse reactions included transient injection site reactions (60%), with nasopharyngitis (16%), arthralgia (12%), and diarrhea (12%) also reported.[59] No adverse events led to drug discontinuation, and all were well managed conservatively. Notably, mild changes in lipid levels were observed in this study consisting of an increase in non-fasting total cholesterol, low-density lipoprotein cholesterol, and triglycerides, without however the need for therapy initiation. Nevertheless, no data on cardiovascular outcomes of rilonacept-related hyperlipidaemia were provided. In this line, it is recommended to monitor lipid profile in these patients and treat accordingly based on each patient's individual cardiovascular risk.[59]

The favorable safety profile observed in RHAPSODY phase II was corroborated in RHAPSODY Phase III, with the most common adverse reactions being injection site reactions (34%) and upper respiratory tract infections (23%), all of which were transient and mild to moderate in severity.[30] Discontinuation of rilonacept was warranted in four patients due to adverse events, including alopecia, extrinsic allergic alveolitis, systemic allergic reaction, and erythema.[30]

Regarding pregnancy, as many women with recurrent pericarditis are of childbearing age, robust data on the use of rilonacept during this period, as well as during lactation, is lacking. The only available data originates from animal studies, indicating a potential harmful effect on embryo-fetal development.[60] To date, there are no human studies investigating potential toxic effects, thus leading to its classification as a pregnancy category C drug. It should be used cautiously, only when the expected benefits outweigh the potential risks. Additionally, uncertainty persists regarding whether rilonacept is excreted during lactation.[60]

In addition, it is not recommended to use anti-IL-1 drugs concomitantly with TNF-α blocking agents due to the increased risk of immunosuppression and serious infections. The potential interaction of rilonacept with other drugs should be monitored, considering its potential to restore CYP450 enzyme production. Of note, completion of recommended vaccinations before rilonacept initiation is advised, while caution should be exercised with live vaccines.[60] Regarding COVID-19 vaccination, rilonacept's potential impact on vaccine-induced antibody formation remains speculative. However, its use in pericarditis patients treated with immunomodulator agents warrants further consideration, although preliminary data depicted no interferences.[61–63] Conversely, anti-IL-1 agents appear to be well tolerated in the context of COVID-19 infection, suggesting continued treatment if necessary for symptom control.[64]

Finally, there are theoretical concerns about a potentially weakened response against malignancies which apply to all immunomodulators, however the overall impact of rilonacept on the development of malignancies is at present unknown.[65] Recommended blood work while on rilonacept, includes a lipid profile as well as complete blood count.[66]

Rilonacept in Recurrent Pericarditis

Clinical Evidence

Rilonacept possesses unique attributes that could be advantageous in treating patients with recurrent pericarditis, notably its extended terminal half-life of 6 to 8 days. This prolonged half-life enables weekly subcutaneous (SC) administration,

potentially offering convenience and improved adherence to treatment regimens. The initial positive reports were derived from a single-arm, open-label, 24-week, Phase 2 trial in patients with symptomatic corticosteroid-dependent idiopathic or post-pericardiotomy recurrent pericarditis. Patients received standard treatment regimens consisting of NSAIDs, colchicine, and/or corticosteroids. Among the 25 enrolled patients, improvement in pericarditis symptoms and markers (imaging, electrocardiography, and inflammatory biomarkers) was noted, with successful withdrawal or tapering of corticosteroids.[59] In this trial, qualitative interviews with 10 recurrent pericarditis patients unveiled rilonacept's profound impact on health-related quality of life (HRQoL).[67] Indeed, rilonacept treatment demonstrated significant improvements in HRQoL, suggesting its potential as an alternative to corticosteroids. Notably, maintained or improved HRQoL was observed during the tapering or discontinuation of corticosteroids, without recurrence of the disease. This further underscores the importance of considering HRQoL outcomes in recurrent pericarditis management and highlights rilonacept as a promising therapeutic option for enhancing patient well-being while mitigating the need for corticosteroid reliance.

These encouraging findings prompted the pivotal Phase 3 trial, RHAPSODY.[30] This was a multicenter, double-blind, placebo-controlled, randomized trial that aimed to assess rilonacept's efficacy in treating the acute episodes, preventing recurrent events, and facilitating the tapering of corticosteroids without subsequent pericarditis recurrence. Patients aged ≥12 years experiencing recurrent pericarditis were eligible for inclusion if they exhibited a second recurrence of acute pericarditis, despite being on treatment with NSAIDs, colchicine, oral corticosteroids, or a combination thereof. Enrollment required a pain score of at least 4 on a numerical rating scale from 0 to 10 and a C-reactive protein level of at least 1 mg/dl within 7 days preceding the initial administration of the trial treatment. Subcutaneous rilonacept was given with a loading dose of 320 mg, followed by 160 mg weekly. The study's primary endpoint focused on the time to the first recurrence of pericarditis, with concurrent attention to safety considerations. During the run-in period, 81 patients were screened and among them 4 discontinued the drug. Following the latter period of time, a total of 61 patients were randomized. In the placebo group (31 patients), the median time to the first adjudicated recurrence was 8.6 weeks, while the number of recurrent events in the rilonacept group was insufficient for calculating a median time to recurrence. The median duration of the rilonacept exposure was 9 months. Rilonacept demonstrated a significantly reduced risk of recurrent pericarditis compared to placebo (hazard ratio: 0.04, 95% CI: 0.01 to 0.18, $P < 0.001$). Specifically, recurrence rates were 7% (2 out of 30 patients) in the rilonacept group and 74% (23 out of 31 patients) in the placebo group during follow-up. As mentioned above, rilonacept exhibited a favorable profile, with local skin irritation and upper respiratory tract infections being the most reported adverse effects, akin to those observed with anakinra. Based on this study results in March 2021, rilonacept was the first FDA approved IL-1 blocker for clinical use for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and pediatric patients 12 years and older.

Several subanalyses have derived from this trial. A secondary analysis evaluated patient-reported outcome questionnaire score changes.[9] During the trial, participants completed five questionnaires. Rilonacept significantly improved all scores during the run-in period. In the randomized withdrawal period, those on rilonacept maintained scores, while placebo recipients deteriorated upon recurrence, improving with rilonacept rescue, emphasizing its positive impact of the drug on HRQoL. In another post hoc analysis of the RHAPSODY trial, investigators examined transitioning to rilonacept monotherapy to streamline polypharmacy management in recurrent pericarditis.[68,69] Among patients initially on multidrug regimens, the mean time to rilonacept monotherapy was 7.9 weeks, without recurrence. Transitioning from various combinations, including NSAIDs, colchicine, and glucocorticoids, to rilonacept monotherapy was notably achieved without recurrence, indicating the feasibility of this approach in recurrent pericarditis management.

Recently, the results of the RHAPSODY long-term extension study were published.[70] According to the study findings, rilonacept's efficacy in reducing pericarditis recurrence was sustained over 24 additional months of treatment. Actually, a rate of 64% of the patients continued rilonacept, while 15% suspended treatment for observation, and 21% discontinued the study at the 18-month decision milestone. Among those continuing rilonacept, recurrence risk was significantly reduced compared to those suspending treatment. Specifically, among those who suspended rilonacept, 75% (6 out of 8) experienced a recurrence, with a median time to recurrence of 11.8 weeks (95% CI, 3.7 weeks to not

estimable).[70] This indicates that while rilonacept is effective during treatment, discontinuation unfortunately may lead to a high rate of relapses. Thus, it appears that rilonacept achieves a stable disease remission without however obtaining its definite cure. Most importantly, rilonacept is efficacious without the concerning side effects of glucocorticoids.[24] Notably, the data on the long extension arm are based on a limited number of patients having a large burden of disease and residual inflammation. It should be however emphasized that the recurrence rate among all subjects with recurrent pericarditis treated with rilonacept in real life, is unknown.

The Role of Rilonacept in the Treatment of Recurrent Pericarditis

The optimal selection of patients for anti-IL-1 therapy is crucial. Candidates for rilonacept should have recurrent pericarditis despite standard treatment, glucocorticoid dependency, and likely exhibiting an autoinflammatory phenotype with elevated C-reactive protein (CRP) levels, fever, and pleuropulmonary involvement.[30,71] Conversely, the role of rilonacept in pericarditis with normal or near normal CRP elevation has yet to be determined since the available data are scant.[17,72] Moreover, IL-1 blockers may be an alternative valuable option for patients with contraindications and/or intolerance to aspirin/NSAIDs, colchicine, or glucocorticoids.

Notably, the optimal duration of treatment with rilonacept in recurrent pericarditis is yet to be determined. Since the mean disease duration in cases of colchicine-resistant and glucocorticoid-dependent recurrent pericarditis may be as long as 5 years, rilonacept should be administered at full dose over a sustained period of time before attempting discontinuation.[7] At present, no data are available regarding optimal full dose treatment duration and the impact of dose tapering on pericarditis relapse.

The treatment algorithm on recurrent pericarditis outlined by the most recent 2015 European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases, recommends aspirin or NSAIDs (for weeks-months), along with colchicine, gastroprotection with proton pump inhibitors and exercise restriction as a first step approach (Figure 2). Upon plasma CRP values normalization, dose tapering is proposed by most experts. In case of treatment failure, the second step recommends administration of low to moderate

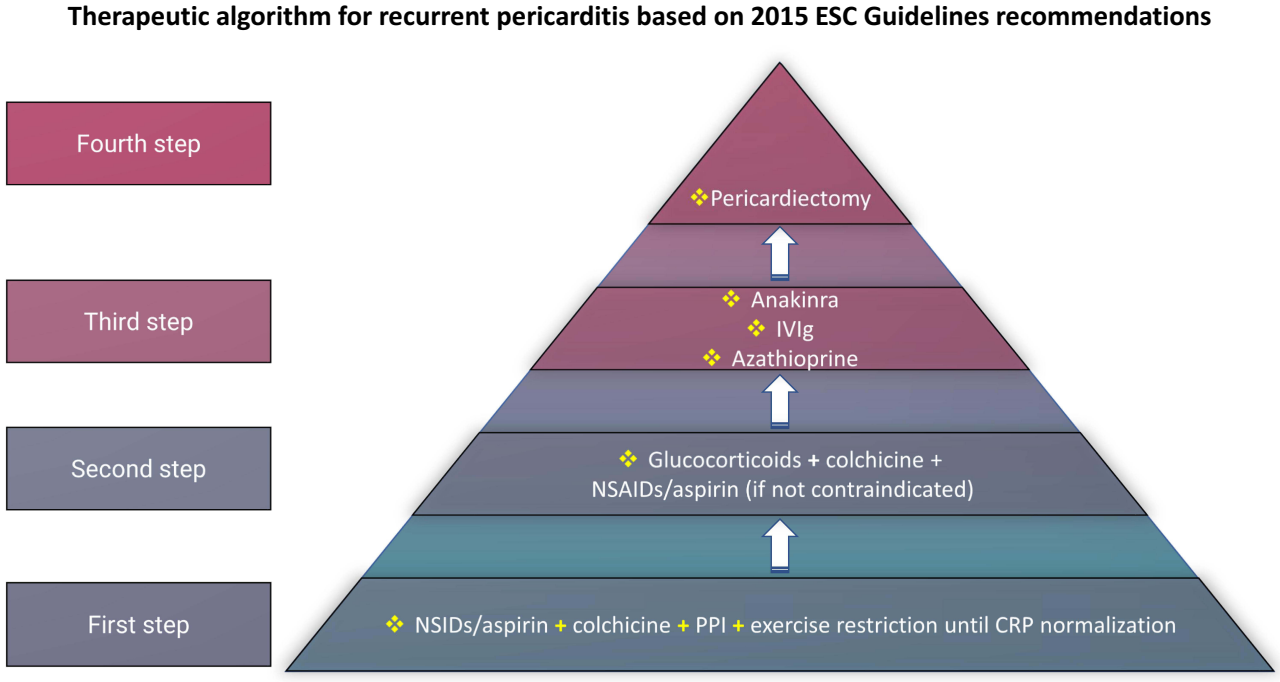

Figure 2 Therapeutic algorithm for recurrent pericarditis according to the 2015 ESC Guideline recommendations.
Abbreviations: ESC, European Society of Cardiology; CRP, C-reactive protein; IVIg, intravenous immunoglobulins; PPI, protein pump inhibitors.

doses of glucocorticoids (ie prednisone 0.2–0.5 mg/kg/day or equivalent), plus colchicine, plus NSAIDs/aspirin if tolerated and in the absence of contraindications to the latter medications (such as in advanced kidney disease, peptic ulcer, pregnancy beyond the 20th week of gestation, and eventually in anticoagulated patients).[4] In case of a further treatment failure, the third step in the ESC algorithm includes intravenous immunoglobulins (IVIg), azathioprine, and anakinra. It should be stressed that the contemporary evidence on IVIg and azathioprine is weak and at the time of 2015 ESC Guidelines publication contemporary data for IL-1 blockers were scant. However in the meantime, new evidence on recurrent pericarditis treatment has emerged and the landscape on this topic changed radically. Indeed, the publication of AIRTRIP, a double-blind, placebo-controlled, randomized withdrawal trial which tested anakinra in refractory recurrent pericarditis and a large international registry subsequently published, confirmed the excellent efficacy and the good safety profile of IL-1 blockers in patients with autoinflammatory phenotype.[18,28] Subsequently, similar results were reported in the RHAPOSDY trial which revealed an unprecedented reduction of pericarditis flares with rilonacept.[30]

Another IL-1 blocker, goflikicept, has been recently tested in patients with recurrent pericarditis in a phase II/III trial with open label, randomized placebo-controlled design. This drug which is administered twice a month has been proved very efficacious in the prevention of recurrences since no patient on the active medication arm depicted recurrences. In contrast, 9 out of 10 patients receiving placebo developed pericarditis recurrence during a 24-week observation period. Remarkably, no safety signals were identified.[73]

Taken together the results of the above-mentioned trials, IL-1 blockers have been consistently efficacious for the prevention of pericarditis relapses with a good safety profile, suggesting a drug class effect.

Finally, the ESC Guidelines algorithm recommend pericardiectomy as a fourth and last step in patients who cannot tolerate or fail to control disease with the above-mentioned medications, in centers with expertise in this procedure. The updated treatment strategy in cases of refractory recurrent pericarditis based on current evidence is summarized in Figure 3.

Future Directions

As already mentioned, the evidence on IL-1 blockade in patients with refractory recurrent pericarditis at the time of the latest 2015 ESC guidelines publication was scant. At present, however, ongoing research has provided convincing evidence on the striking efficacy and good safety profile of these medications and upgraded their role in the treatment of

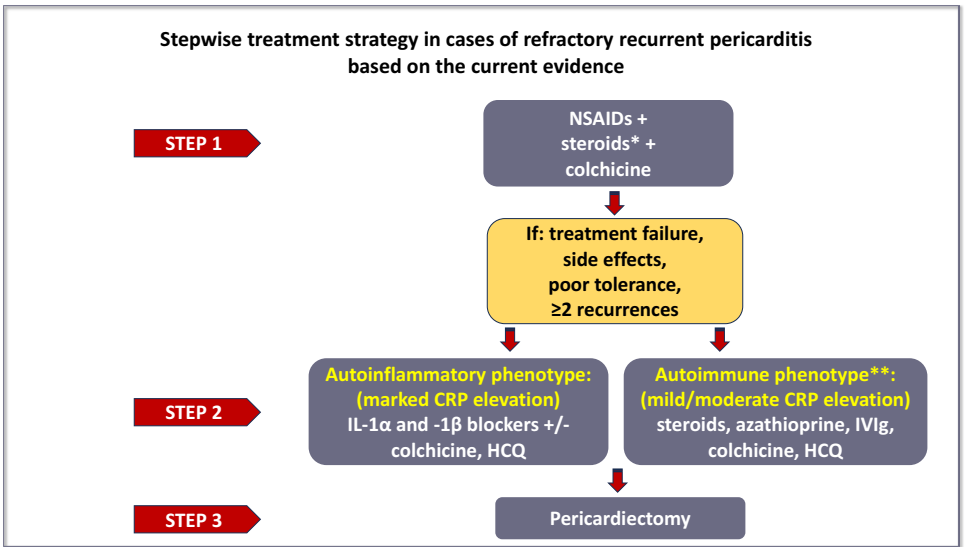

Figure 3 Stepwise treatment strategy in cases of refractory recurrent pericarditis based on current evidence.
Notes: *Low to moderate dose, **Monotherapy or drugs combination.
Abbreviations: CRP, C-reactive protein; IL, interleukin; IVIg, intravenous immunoglobulins; HCQ, hydroxychloroquine.

refractory pericarditis. The release of new Guidelines on pericardial syndromes has already been anticipated by the European Society of Cardiology for August 2025. In view of the contemporary evidence, the role and place in the updated treatment algorithm of IL-1 blockers and of rilonacept in specific which is the only medication of this class with FDA approval for this indication is eagerly awaited.

Establishing the optimal treatment duration for asymptomatic patients receiving rilonacept represents a clinical dilemma, given the absence of a standardized biomarker indicating recurrence risk post-treatment cessation. Towards this scope, cardiac MRI with its ability of tissue characterization may eventually guide treatment in refractory cases. In specific, drug discontinuation could be considered in the absence of pericardial edema in T2 weighted image (which is a marker of acute disease) and pericardial late gadolinium enhancement during the phase-sensitive inversion recovery technique.[74,75] However, the role of cMRI in this setting is yet to be determined.

Acquisition of data on the utilization of rilonacept in special populations such as pregnant or lactating women, patients with malignancies and patients with chronic kidney disease among others, is of similar importance. Ongoing research exploring molecular, cellular, and genetic methodologies is expected to shed more light regarding the selection of the optimal therapeutic strategy in refractory recurrent pericarditis.

Conclusions

The introduction of IL-1 blockers into clinical practice marks a significant advancement in treating patients with glucocorticoid-dependent and colchicine-resistant recurrent pericarditis. Rilonacept, based on accumulated experience, demonstrates high efficacy and a favorable safety profile in this context. Notably, rilonacept is the sole IL-1 blocker to have received FDA approval for recurrent pericarditis. In comparison to anakinra, prescribed for the same indication, rilonacept offers the advantage of weekly subcutaneous administration, greatly improving quality of life and compliance, albeit at a higher cost.

The ideal candidate for anti-IL-1 therapy is the patient with recurrent pericarditis on an autoinflammatory basis, with high CRP serum levels, high fever, neutrophil leukocytosis, pleuropulmonary involvement, frequent exacerbations, and resistant to conventional therapy. Moreover, they may be useful in difficult-to-treat patients when traditional therapies are ineffective, contraindicated, or not tolerated, such as gastrointestinal bleeding, decompensated heart failure, advanced chronic kidney disease, ischemic heart disease, elderly patients, uncontrolled hypertension, fluid overload, recent surgery (including cardiac surgery), and anticoagulated patients.

In patients with autoimmune phenotype characterized by modest/moderate CRP elevation, presence of autoantibodies, arthritis, Raynaud's phenomenon, and sicca syndrome, the therapy should be individualized.

Areas requiring further clarification in the near future include treatment protocols regarding duration and the necessity for tapering, as well as a more precise characterization of patient subgroups with recurrent pericarditis who are optimal candidates for this treatment.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lazaros G, Tousoulis D, Vassilopoulos D. Editorial commentary: recurrent pericarditis in the era of interleukin-1 inhibition. *Trends Cardiovasc Med*. 2021;31(5):275–276. doi:10.1016/j.tcm.2020.04.010
2. Lazarou E, Tsioufis P, Vlachopoulos C, Tsioufis C, Lazaros G. Acute pericarditis: update. *Curr Cardiol Rep*. 2022;24(8):905–913. doi:10.1007/s11886-022-01710-8
3. Kyto V, Sipila J, Rautava P. Rate and patient features associated with recurrence of acute myocarditis. *Eur J Intern Med*. 2014;25(10):946–950. doi:10.1016/j.ejim.2014.11.001
4. Adler Y, Charron P, Imazio M, et al. ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC)endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36(42):2921–2964. doi:10.1093/eurheartj/ehv318
5. Andreis A, Imazio M, Giustetto C, Brucato A, Adler Y, De Ferrari GM. Anakinra for constrictive pericarditis associated with incessant or recurrent pericarditis. *Heart*. 2020;106(20):1561–1565. doi:10.1136/heartjnl-2020-316898
6. Cremer PC, Kumar A, Kontzias A, et al. Complicated pericarditis: understanding risk factors and pathophysiology to inform imaging and treatment. *J Am Coll Cardiol*. 2016;68(21):2311–2328. doi:10.1016/j.jacc.2016.07.785

7. Brucato A, Brambilla G, Moreo A, et al. Long-term outcomes in difficult-to-treat patients with recurrent pericarditis. *Am J Cardiol*. 2006;98(2):267–271. doi:10.1016/j.amjcard.2006.01.086
8. LeWinter M, Kontzias A, Lin D, et al. Burden of recurrent pericarditis on health-related quality of life. *Am J Cardiol*. 2021;141:113–119. doi:10.1016/j.amjcard.2020.11.018
9. Brucato A, Lim-Watson MZ, Klein A, et al. Interleukin-1 trap rilonacept improved health-related quality of life and sleep in patients with recurrent pericarditis: results from the phase 3 clinical trial RHAPSODY. *J Am Heart Assoc*. 2022;11(20):e023252. doi:10.1161/JAHA.121.023252
10. Papageorgiou N, Briasoulis A, Lazaros G, Imazio M, Tousoulis D. Colchicine for prevention and treatment of cardiac diseases: a meta-analysis. *Cardiovasc Ther*. 2017;35(1):10–18. doi:10.1111/1755-5922.12226
11. Bayes-Genis A, Adler Y, de Luna AB, Imazio M. Colchicine in Pericarditis. *Eur Heart J*. 2017;38(22):1706–1709. doi:10.1093/eurheartj/ehx246
12. Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet*. 2014;383(9936):2232–2237. doi:10.1016/S0140-6736(13)62709-9
13. Imazio M, Brucato A, Cemin R, et al. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2023;369(16):1522–1528. doi:10.1056/NEJMoa1208536
14. Imazio M, Spodick DH, Brucato A, Trinchero R, Adler Y. Controversial issues in the management of pericardial diseases. *Circulation*. 2010;121(7):916–928. doi:10.1161/CIRCULATIONAHA.108.844753
15. Dong T, Klein AL, Wang TKM. Paradigm shift in diagnosis and targeted therapy in recurrent pericarditis. *Curr Cardiol Rep*. 2023;25(9):993–1000. doi:10.1007/s11886-023-01912-8
16. Imazio M, Lazaros G, Gattorno M, et al. Anti-interleukin-1 agents for pericarditis: a primer for cardiologists. *Eur Heart J*. 2022;43(31):2946–2957. doi:10.1093/eurheartj/ehab452
17. Brucato A, Imazio M, Cremer PC, et al. Recurrent pericarditis: still idiopathic? The pros and cons of a well-honoured term. *Intern Emerg Med*. 2018;13(6):839–844. doi:10.1007/s11739-018-1907-x
18. Imazio M, Andreis A, De Ferrari GM, et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: the IRAP (international registry of anakinra for pericarditis) study. *Eur J Prev Cardiol*. 2020;27(9):956–964. doi:10.1177/2047487319879534
19. Lazaros G, Tsioufis K, Vassilopoulos D. Interleukin-1 blockade for recurrent pericarditis: insights from the real-world experience. *J Pediatr*. 2023;258:113354. doi:10.1016/j.jpeds.2023.01.019
20. Caorsi R, Insalaco A, Bovis F, et al. Pediatric recurrent pericarditis: appropriateness of the standard of care and response to IL-1 blockade. *J Pediatr*. 2023;256:18–26e8. doi:10.1016/j.jpeds.2022.11.034
21. Finetti M, Insalaco A, Cantarini L, et al. Long-term efficacy of interleukin-1 receptor antagonist (anakinra) in corticosteroid-dependent and colchicine-resistant recurrent pericarditis. *J Pediatr*. 2014;164(6):1425–31e1. doi:10.1016/j.jpeds.2014.01.065
22. Lazaros G, Vasileiou P, Koutsianas C, et al. Anakinra for the management of resistant idiopathic recurrent pericarditis. Initial experience in 10 adult cases. *Ann Rheum Dis*. 2014;73(12):2215–2217. doi:10.1136/annrheumdis-2014-205990
23. Lazaros G, Antonatou K, Vassilopoulos D. The therapeutic role of interleukin-1 inhibition in idiopathic recurrent pericarditis: current evidence and future challenges. *Front Med*. 2017;4:78. doi:10.3389/fmed.2017.00078
24. Lazaros G, Tsioufis K, Vassilopoulos D. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N Engl J Med*. 2021;384(15):1474–1475. doi:10.1056/NEJMc2101978
25. Lazarou E, Koutsianas C, Theofilis P, et al. Interleukin-1 Blockers: a paradigm shift in the treatment of recurrent pericarditis. *Life*. 2024;14(3):305. doi:10.3390/life14030305
26. Dimitroglou Y, Aggeli C, Theofilis P, et al. Novel anti-inflammatory therapies in coronary artery disease and acute coronary syndromes. *Life*. 2023;13(8):1669. doi:10.3390/life13081669
27. Vlachakis PK, Theofilis P, Kachrimanidis I, et al. The role of inflammasomes in heart failure. *Int J Mol Sci*. 2024;25(10):5372. doi:10.3390/ijms25105372
28. Theofilis P, Oikonomou E, Chasikidis C, Tsioufis K, Tousoulis D. Inflammasomes in atherosclerosis-from pathophysiology to treatment. *Pharmaceuticals*. 2023;16(9):1211. doi:10.3390/ph16091211
29. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the airtrip randomized clinical trial. *JAMA*. 2016;316(18):1906–1912. doi:10.1001/jama.2016.15826
30. Klein AL, Imazio M, Cremer P, et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N Engl J Med*. 2021;384(1):31–41. doi:10.1056/NEJMoa2027892
31. Mauro AG, Bonaventura A, Vecchie A, et al. The role of nlrp3 inflammasome in pericarditis: potential for therapeutic approaches. *JACC Basic Transl Sci*. 2021;6(2):137–150. doi:10.1016/j.jacbts.2020.11.016
32. Thorolfsdottir RB, Jonsdottir AB, Sveinbjornsson G, et al. Variants at the Interleukin 1 Gene Locus and Pericarditis. *JAMA Cardiol*. 2024;9(2):165–172. doi:10.1001/jamacardio.2023.4820
33. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ Res*. 2020;126(9):1260–1280. doi:10.1161/CIRCRESAHA.120.315937
34. Khandaker MH, Espinosa RE, Nishimura RA, et al. Pericardial disease: diagnosis and management. *Mayo Clin Proc*. 2010;85(6):572–593. doi:10.4065/mcp.2010.0046
35. Cantarini L, Lucherini OM, Brucato A, et al. Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study. *Clin Res Cardiol*. 2012;101(7):525–531. doi:10.1007/s00392-012-0422-8
36. Cantarini L, Lucherini OM, Frediani B, et al. Bridging the gap between the clinician and the patient with cryopyrin-associated periodic syndromes. *Int J Immunopathol Pharmacol*. 2011;24(4):827–836. doi:10.1177/039463201102400402
37. Del Buono MG, Bonaventura A, Vecchie A, et al. Pathogenic pathways and therapeutic targets of inflammation in heart diseases: a focus on interleukin-1. *Eur J Clin Invest*. 2024;54(2):e14110. doi:10.1111/eci.14110
38. Toldo S, Mezzaroma E, Buckley LF, et al. Targeting the NLRP3 inflammasome in cardiovascular diseases. *Pharmacol Ther*. 2022;236:108053. doi:10.1016/j.pharmthera.2021.108053
39. Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. *Nat Rev Cardiol Apr*. 2024;21(4):219–237. doi:10.1038/s41569-023-00946-3

40. Cinteza E, Stefan D, Iancu MA, et al. Autoinflammatory recurrent pericarditis associated with a new NLRP12 mutation in a male adolescent. *Life*. 2023;13(11). doi:10.3390/life13112131
41. Peet CJ, Rowczenio D, Omoyinmi E, et al. Pericarditis and autoinflammation: a clinical and genetic analysis of patients with idiopathic recurrent pericarditis and monogenic autoinflammatory diseases at a national referral center. *J Am Heart Assoc*. 2022;11(11):e024931. doi:10.1161/JAHA.121.024931
42. Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov*. 2012;11(8):633–652. doi:10.1038/nrd3800
43. Van Tassell BW, Toldo S, Mezzaroma E, Abbate A. Targeting interleukin-1 in heart disease. *Circulation*. 2013;128(17):1910–1923. doi:10.1161/CIRCULATIONAHA.113.003199
44. Bettiol A, Lopalco G, Emmi G, et al. Unveiling the efficacy, safety, and tolerability of anti-interleukin-1 treatment in monogenic and multifactorial autoinflammatory diseases. *Int J Mol Sci*. 2019;20(8):1898. doi:10.3390/ijms20081898
45. Autmizguine J, Cohen-Wolkowiez M, Ilowite N, Investigators R. Rilonacept pharmacokinetics in children with systemic juvenile idiopathic arthritis. *J Clin Pharmacol*. 2015;55(1):39–44. doi:10.1002/jcph.372
46. Tombetti E, Mule A, Tamanini S, et al. Novel pharmacotherapies for recurrent pericarditis: current options in 2020. *Curr Cardiol Rep*. 2020;22(8):59. doi:10.1007/s11886-020-01308-y
47. Radin A, Marbury T, Osgood G, Belomestnov P. Safety and pharmacokinetics of subcutaneously administered rilonacept in patients with well-controlled end-stage renal disease (ESRD). *J Clin Pharmacol*. 2010;50(7):835–841. doi:10.1177/0091270009351882
48. Gupta M, Kaul S, Velazquez GR, et al. A brief overview of recurrent pericarditis management and the potential of rilonacept as a new therapeutic option. *Am J Cardiovasc Drugs*. 2022;22(1):27–33. doi:10.1007/s40256-021-00481-x
49. Cuisset L, Jeru I, Dumont B, et al. Mutations in the autoinflammatory cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France. *Ann Rheum Dis*. 2011;70(3):495–499. doi:10.1136/ard.2010.138420
50. Goldbach-Mansky R, Shroff SD, Wilson M, et al. A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. *Arthritis Rheum*. 2008;58(8):2432–2442. doi:10.1002/art.23620
51. Hoffman HM, Throne ML, Amar NJ, et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum*. 2008;58(8):2443–2452. doi:10.1002/art.23687
52. Garg M, de Jesus AA, Chapelle D, et al. Rilonacept maintains long-term inflammatory remission in patients with deficiency of the IL-1 receptor antagonist. *JCI Insight*. 2017;2(16). doi:10.1172/jci.insight.94838
53. Lovell DJ, Giannini EH, Reiff AO, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum*. 2013;65(9):2486–2496. doi:10.1002/art.38042
54. Ilowite NT, Prather K, Lokhnygina Y, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2014;66(9):2570–2579. doi:10.1002/art.38699
55. Schlesinger N, Pillinger MH, Simon LS, Lipsky PE. Interleukin-1beta inhibitors for the management of acute gout flares: a systematic literature review. *Arthritis Res Ther*. 2023;25(1):128. doi:10.1186/s13075-023-03098-4
56. FitzGerald JD, Dalbeth N, Mikuls T, et al. American college of rheumatology guideline for the management of gout. *Arthritis Care Res*. 2020;72(6):744–760. doi:10.1002/acr.24180
57. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76(1):29–42. doi:10.1136/annrheumdis-2016-209707
58. Terkeltaub RA, Schumacher HR, Carter JD, et al. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. *Arthritis Res Ther*. 2013;15(1):R25. doi:10.1186/ar4159
59. Klein AL, Lin D, Cremer PC, et al. Efficacy and safety of rilonacept for recurrent pericarditis: results from a phase II clinical trial. *Heart*. 2020;107(6):488–496. doi:10.1136/heartjnl-2020-317928
60. Arcalyst® (rilonacept) [package insert]. London, UK; Kiniksa Pharmaceuticals; 2021.
61. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403–416. doi:10.1056/NEJMoa2035389
62. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the bnt162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615. doi:10.1056/NEJMoa2034577
63. Brucato A, Trotta L, Arad M, et al. Absence of pericarditis recurrence in rilonacept-treated patients with COVID-19 and SARS-cov-2 vaccination: results from the RHAPSODY long-term extension. *CJC Open*. 2024;6(6):805–810. doi:10.1016/j.cjco.2024.02.002
64. Imazio M, Brucato A, Lazaros G, et al. Anti-inflammatory therapies for pericardial diseases in the COVID-19 pandemic: safety and potentiality. *J Cardiovasc Med*. 2020;21(9):625–629. doi:10.2459/JCM.0000000000001059
65. Wang TKM, Klein AL. Rilonacept (Interleukin-1 Inhibition) for the treatment of pericarditis. *Curr Cardiol Rep*. 2022;24(1):23–30. doi:10.1007/s11886-021-01621-0
66. Aldajani A, Imazio M, Klein A, Mardigyan V. How to use interleukin-1 antagonists in patients with pericarditis. *Can J Cardiol*. 2023;39(8):1132–1135. doi:10.1016/j.cjca.2023.02.071
67. Lin D, Klein A, Cella D, et al. Health-related quality of life in patients with recurrent pericarditis: results from a phase 2 study of rilonacept. *BMC Cardiovasc Disord*. 2021;21(1):201. doi:10.1186/s12872-021-02008-3
68. Brucato A, Wheeler A, Luis SA, et al. Transition to rilonacept monotherapy from oral therapies in patients with recurrent pericarditis. *Heart*. 2023;109(4):297–304. doi:10.1136/heartjnl-2022-321328
69. Lazaros G, Tsioufis C. Recurrent pericarditis: moving from the middle ages to renaissance. *Heart*. 2023;109(4):250–252. doi:10.1136/heartjnl-2022-321749
70. Imazio M, Klein AL, Brucato A, et al. Sustained pericarditis recurrence risk reduction with long-term rilonacept. *J Am Heart Assoc*. 2024;13(6):e032516. doi:10.1161/JAHA.123.032516
71. Bizzi E, Picchi C, Mastrangelo G, Imazio M, Brucato A. Recent advances in pericarditis. *Eur J Intern Med*. 2022;95:24–31. doi:10.1016/j.ejim.2021.09.002

72. Fava A, Cammarata M, Adamo L. May rilonacept use in lupus pericarditis. *Clin Exp Rheumatol*. 2024;42(5):1115–1117. doi:10.55563/clinexprheumatol/pb3hzb
73. Myachikova VY, Maslyanskiy AL, Moiseeva OM, et al. Treatment of idiopathic recurrent pericarditis with goflikicept: phase II/III study results. *J Am Coll Cardiol*. 2023;82(1):30–40. doi:10.1016/j.jacc.2023.04.046
74. Antonopoulos AS, Vrettos A, Androulakis E, et al. Cardiac magnetic resonance imaging of pericardial diseases: a comprehensive guide. *Eur Heart J Cardiovasc Imaging*. 2023;24(8):983–998. doi:10.1093/ehjci/jead092
75. Imazio M, Mardigyan V, Andreis A, Franchin L, De Biasio M, Collini V. New developments in the management of recurrent pericarditis. *Can J Cardiol*. 2023;39(8):1103–1110. doi:10.1016/j.cjca.2023.04.008