IJC Heart & Vasculature 61 (2025) 101841

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Pericarditis at the crossroads: Unlocking the next wave of therapies

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ARTICLE INFO

Keywords:
Pericarditis
Therapy
anti-IL-1 agents
Anakinra
Rilonacept

ABSTRACT

Pericarditis is an inflammation of the pericardial sac with different aetiologies. While often self-limited, up to 30 % of cases recur or become chronic, causing significant morbidity. Traditional treatments – nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids – have important limitations, including steroid dependence, high recurrence rates, and side effects. Accordingly, new targeted immunomodulatory therapies are under investigation to improve outcomes in refractory pericarditis. This review outlines the epidemiology and burden of pericarditis, current management and its shortcomings, and the rationale for novel therapies. We then discuss emerging therapeutic agents in development (biologics and small molecules), focusing on phase II/III candidates. The central role of interleukin-1 (IL-1) and related inflammasome pathways in pericardial inflammation provides a strong rationale for these targeted treatments. Key trials of IL-1 inhibitors (anakinra, rilonacept, canakinumab, goflikicept) have demonstrated dramatic reductions in recurrence rates, validating IL-1 as a therapeutic target. Other innovative approaches – such as NLRP3 inflammasome inhibitors and a cannabinoid-based agent – offer the prospect of oral, steroid-sparing therapy. We highlight the current challenges in developing these therapies, including heterogeneous disease causes, safety concerns, and trial design issues. Overall, the therapeutic pipeline for pericarditis is robust and poised to transform management. In the coming years, integration of targeted biologics and small molecules alongside conventional anti-inflammatories may significantly improve outcomes in recurrent pericarditis, moving towards more precise and effective treatment strategies.

1. Introduction

Pericarditis is a syndrome of pericardial inflammation that accounts for approximately 0.1–0.2 % of hospital admissions [1,2]. Its aetiologies are diverse and geographically variable. In high-income countries, most cases are idiopathic (presumed viral), whereas in low-resource regions tuberculous pericarditis predominates (accounting for 70–80 % of cases, and up to 90 % in HIV-positive patients) [3]. Other recognised causes include post–myocardial infarction pericarditis (Dressler's syndrome, occurring in ~7–12 % of acute MI cases), post-cardiac surgery syndromes (incidence 5–30 %), connective tissue diseases (e.g. lupus), malignancy, uraemia, radiation, and certain medications [1]. In practice, however, 70–90 % of recurrent pericarditis cases are ultimately labelled idiopathic, reflecting diagnostic gaps in identifying an underlying cause.

Recurrent pericarditis (RP) is defined by return of symptoms after a symptom-free interval of ≥4–6 weeks. About 15–30 % of patients experience at least one recurrence after an initial episode [4]. Notably, once a patient has a first recurrence, the risk of further recurrences is high (approximately 50 % in the absence of colchicine therapy) [5,6]. Persistent or chronic pericarditis (symptoms >3 months) can develop, and roughly half of patients with multiple recurrences become steroid-dependent with ongoing symptoms. Pericarditis flares cause substantial burden: around 60 % of patients with RP report severe pain and about 50 % have impaired work capacity [2,7]. Although often considered benign, recurrent pericarditis can lead to serious complications if inadequately treated – including large pericardial effusions, cardiac tamponade, or constrictive pericarditis, especially with incessant course [8]. Thus, recurrent pericarditis is not always a benign condition; each relapse entails diminished quality of life and increased

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https://doi.org/10.1016/j.ijcha.2025.101841
Received 15 September 2025; Received in revised form 24 October 2025; Accepted 4 November 2025
Available online 8 November 2025

healthcare costs.

These clinical realities have created a strong impetus for more effective therapies. The pathogenesis of pericarditis often involves intense inflammation mediated by IL-1 and related cytokines, suggesting that targeted anti-inflammatory treatments could improve disease control [2,9]. As discussed below, recent evidence indeed validates the IL-1 pathway as an attractive therapeutic target in pericarditis, and multiple novel agents are in development.

2. Pathophysiology and rationale for targeted therapy

Pericarditis can arise from both innate (autoinflammatory), and adaptive (autoimmune) immune mechanisms, which frequently overlap. For example, a viral infection can activate innate inflammasome pathways, while connective tissue diseases can generate pericardial autoantibodies – and both processes may coexist in the same patient. A key insight from recent research is the central role of the interleukin-1 (IL-1) family of cytokines in driving pericardial inflammation [1,2,9]. Injured or infected cells release danger signals (pathogen- or damage-associated molecular patterns) that trigger assembly of the NLRP3 inflammasome in macrophages. This leads to caspase-1 activation and cleavage of pro–IL-1β into active IL-1β, as well as release of IL-1α from dying pericardial mesothelial cells. IL-1α and IL-1β bind to IL-1 receptors, unleashing a downstream inflammatory cascade (including IL-6, TNF-α and prostaglandin-mediated pain) and recruiting leukocytes to the pericardium [9]. The result is a self-amplifying loop of inflammation that can produce recurrent flares and persistently elevated inflammatory markers.

Autoimmune phenomena also play a role in many cases. Pericardial autoantibodies are detectable in roughly 50 % of idiopathic or recurrent cases, indicating an overlap of innate and adaptive immunity [10,11]. Thus, pericarditis across varied aetiologies is characterised by a robust inflammatory cascade – often with IL-1 as a proximal mediator. Blocking this pathway is a logical therapeutic strategy. Indeed, clinical use of IL-1 inhibitors (such as anakinra, rilonacept, and goflikicept) has yielded dramatic improvements in patients with refractory pericarditis [12–15]. These successes validate the rationale of targeting the IL-1 axis and upstream inflammasome in order to interrupt the cycle of pericardial inflammation.

3. Current management and unmet needs

The first-line management of acute and recurrent pericarditis is well established in current guidelines [1]. High-dose NSAIDs (e.g. ibuprofen 600–800 mg three times daily) or aspirin (e.g. 1–2 g three times daily for post-myocardial infarction pericarditis) are recommended to control inflammation and pain. Colchicine (0.5–0.6 mg once or twice daily) is advised as an adjunct in all acute and recurrent cases, as it accelerates resolution and approximately halves the recurrence rate (Number Needed to Treat ≈10) [1,4–6]. Despite this, up to 20–30 % of patients on NSAIDs plus colchicine still experience relapse [2]. Furthermore, colchicine causes dose-limiting gastrointestinal side effects (primarily diarrhoea) in about 10–15 % of patients, which can impair adherence [4–6].

Corticosteroids are reserved as a second-line therapy for cases refractory to NSAIDs and colchicine or for specific indications (e.g. autoimmune or uremic pericarditis). However, steroid use in pericarditis is problematic. Even moderate or low doses of prednisone (0.2–0.5 mg/kg/day) have been linked to higher recurrence rates and prolonged disease course [16,17]. Inappropriate exposure to corticosteroids during an acute episode significantly increases the likelihood of recurrence up to 50 % in steroid-treated patients [18]. Many patients become corticosteroid-dependent, with flares occurring whenever the dose is tapered. Long-term steroid therapy also incurs well-known adverse effects (osteoporosis, hyperglycaemia, weight gain, infections), underscoring the need to avoid chronic steroids in pericarditis management in the absence of specific indications [1,19,20].

A variety of other immunomodulatory agents have been used off-label in refractory pericarditis, although evidence is limited to small series. Azathioprine and methotrexate have been administered in steroid-dependent cases in an effort to spare corticosteroids, but their efficacy in preventing recurrences is uncertain [21]. Likewise, intravenous immunoglobulin (IVIG) has been tried in severe autoimmune-associated pericarditis (such as lupus pericarditis) or after failure of conventional therapies with anecdotal success [22]. In extreme cases of incessant or constrictive pericarditis, surgical pericardiectomy may be considered, though it is a last resort due to its invasiveness and usually not considered in Europe [1].

Despite these available therapies, a substantial subset of patients has inadequate disease control or unacceptable medication side effects. An appreciable proportion of pericarditis patients remain dependent on steroids or suffer frequent relapses despite NSAIDs and colchicine. This situation highlights a clear unmet need for more effective and steroid-sparing treatments. In the United States alone, recurrent pericarditis is estimated to affect on the order of 20,000 patients per year [2]. These patients would greatly benefit from safer and more targeted therapies. The emerging therapeutic agents aim to fill this gap by targeting specific immune pathways (such as IL-1 or the inflammasome) that drive pericardial inflammation – mechanisms that were not addressable with traditional anti-inflammatory drugs [23].

4. What's next: The market landscape

Historically, the management of pericarditis relied on inexpensive, generic medications, and there were no therapies specifically approved for this condition, but colchicine in some European countries (e.g. Italy, Austria). This landscape is now changing with the advent of IL-1 targeted treatments. Industry analyses estimate the global market for pericarditis therapies (including all treatments) to be approximately USD 3.6–4.1 billion in 2025, with growth projected to exceed USD 6–7 billion by 2035 (around 5 % compound annual growth) [24]. North America is expected to remain the largest regional market, reflecting its advanced healthcare infrastructure and research activity, followed by Europe and parts of Asia [24]. The launch of rilonacept – the first drug approved specifically for recurrent pericarditis in the US – in 2021 set an important precedent and has begun to expand the market for targeted pericarditis therapies [25]. Anakinra continues to be used off-label, although it lacks a formal pericarditis indication.

Several factors make this a particularly dynamic niche. The high unmet medical need and the significant morbidity associated with recurrent pericarditis mean that patients and clinicians are willing to adopt new therapies despite their cost. Indeed, orphan drug designation has been granted to IL-1 inhibitors for recurrent pericarditis in some jurisdictions, providing incentives and market exclusivity to developers. Commercial reports indicate that rilonacept sales for pericarditis were approximately USD 416 million in 2024, representing only around 13 % of eligible patients in the US receiving this therapy. This suggests substantial room for growth as awareness increases and additional therapies come to market. Biologic agents targeting IL-1 (from companies like Kiniksa/Regeneron) currently dominate the emerging pericarditis therapeutics space, but novel oral agents (e.g. from Ventyx and Cardiol Therapeutics) may soon broaden the options available. As these new treatments are approved, the share of pericarditis patients receiving specialized therapy is expected to rise accordingly.

5. Emerging therapeutic agents

Research efforts in pericarditis are focused on translating recent pathophysiological insights into better treatments. Several objectives are guiding current investigations:

- **Targeted immunomodulation:** Validating that blocking specific cytokines (such as IL-1 or IL-6) or inflammasome components can control pericardial inflammation more effectively than broad anti-inflammatories.
- **Steroid-sparing therapy:** Demonstrating that adding targeted agents (e.g. IL-1 inhibitors) allows safe tapering and discontinuation of corticosteroids in patients who would otherwise be steroid-dependent.
- **Broadening indications:** Determining whether therapies proven in idiopathic or post-cardiac injury pericarditis will also benefit secondary forms (e.g. pericarditis associated with autoimmune disease, malignancy, or tuberculosis).
- **Safety profiling:** Establishing the long-term safety of new immunomodulators, particularly regarding infection risk and tolerability, given the need for prolonged therapy in some patients.
- **Biomarkers and imaging:** Identifying reliable markers of pericardial inflammation (e.g. C-reactive protein, serum-amyloid A, interleukin levels) and advanced imaging techniques (e.g. cardiac MRI) to guide treatment selection and monitor disease activity.
- **Clinical endpoints:** Reaching consensus on standardized outcome measures for trials (such as time to recurrence, symptom scores, and recurrence-free survival) to facilitate regulatory approval of new treatments.

Early successes with IL-1 inhibitors have spurred a wave of clinical trials for novel agents. The most active area of development involves IL-1 pathway antagonists, but other innovative approaches are also under investigation.

6. IL-1 targeted therapies

Interleukin-1 has emerged as a pivotal therapeutic target in recurrent pericarditis. The first drugs to specifically address this pathway have shown remarkable efficacy.

Anakinra (Kineret) is a recombinant IL-1 receptor antagonist given as a daily subcutaneous injection. The double-blind AIRTRIP trial demonstrated that anakinra dramatically reduced recurrences in steroid-dependent recurrent pericarditis (recurrence in 18 % on anakinra vs 90 % on placebo) [12]. Although anakinra is not formally approved for pericarditis, it has been used off-label for years in refractory cases and is supported by observational studies and *meta*-analyses showing rapid symptom improvement and tapering of corticosteroids in many patients [13].

Rilonacept (Arcalyst) is a dimeric fusion protein that acts as a soluble IL-1 receptor trap, binding both IL-1α and IL-1β. In the phase III RHAPSODY trial for recurrent idiopathic pericarditis, weekly subcutaneous rilonacept almost eliminated recurrences: only ~7 % of rilonacept-treated patients had a new recurrence versus 74 % of patients on placebo [14]. Rilonacept was approved by the FDA in 2021 as the first therapy specifically indicated for recurrent pericarditis.

Canakinumab (Ilaris), a human monoclonal antibody against IL-1β, is another agent being explored. While not yet studied in large trials for pericarditis, there are case reports of canakinumab inducing remission in recurrent pericarditis [26].

Goflikicept (RPH-104) is a novel IL-1α/β trapping fusion protein similar in concept to rilonacept. It binds IL-1α/β with high affinity. A recent trial in Russia (phase II/III) reported that goflikicept significantly reduced recurrence rates in patients with recurrent pericarditis [15]. This agent is currently in mid-stage development and could expand IL-1 targeted options.

Another upcoming IL-1 pathway therapy is KPL-387 (Kiniksa Pharmaceuticals), a long-acting monoclonal antibody against the IL-1 receptor. KPL-387 is designed for monthly dosing and is planned to enter a phase 2/3 trial for steroid-dependent recurrent pericarditis in 2025 [27]. If successful, it could offer a more convenient alternative to daily anakinra while targeting the same pathway. Nevertheless, KPL-387 monthly dosing must be proven safe, not just efficacious, and a careful evaluation of the balance between costs, convenience and safety is mandatory for this new agent.

7. NLRP3 inflammasome inhibitors and other approaches

Targeting the upstream triggers of IL-1 production is another promising strategy. The NLRP3 inflammasome, which governs IL-1β activation, is a prime target. VTX2735 is an oral small-molecule inhibitor of NLRP3 currently entering phase II trials for recurrent pericarditis. By preventing inflammasome assembly, VTX2735 is intended to suppress IL-1 production at its source, potentially controlling inflammation without the need for biologic drugs. Early preclinical results and initial clinical data in other autoinflammatory disorders lend support to this approach [28].

A first-in-class therapy taking a similar upstream approach is CardiolRx (CT-100), a proprietary cannabidiol derivative that modulates the NLRP3 inflammasome. In a phase II study of recurrent pericarditis, oral CardiolRx was associated with a marked reduction in pericarditis flares, and a pivotal phase III trial (MAVERIC) is now underway to confirm its efficacy. As an oral, non-immunosuppressive agent, CardiolRx could represent a major advance if its benefits are confirmed [29].

Other immunomodulatory approaches are also being considered. Blockade of interleukin-6 (e.g. with tocilizumab) has a theoretical anti-inflammatory benefit in pericarditis, although no formal trials have been conducted to date, and only case reports have been published in non-idiopathic cases [30,31]. Overall, the emerging therapies pipeline is heavily focused on IL-1 and inflammasome inhibition, reflecting the central role of these pathways in pericardial inflammation. However, ongoing research should also focus on alternative pathogenetic pathways. Table 1 and Fig. 1 summarize current and new therapeutic targets in pericarditis.

8. Challenges in drug development

Despite the promising progress, several challenges must be addressed to ensure successful development and implementation of novel pericarditis therapies. One major issue is the heterogeneity of pericarditis. Patients differ in their underlying causes (idiopathic vs post-cardiac injury vs autoimmune vs neoplastic), clinical course, and dominant immune pathways. Most trials to date have enrolled relatively homogeneous populations (idiopathic or post-surgical pericarditis with elevated C-reactive protein, but excluded other aetiologies, such as infectious for post-myocardial infarction), and it remains uncertain whether the impressive efficacy of IL-1 blockade will generalise to other forms such as autoimmune-related or cancer-associated pericarditis. Future studies will need to include more diverse patient cohorts or stratify by aetiology to ensure that new therapies benefit a broad spectrum of pericarditis cases.

Clinical trial design for pericarditis also poses difficulties. Recurrent pericarditis is an episodic disease with flares that can remit spontaneously, so defining clear endpoints (such as time to recurrence or sustained remission) can be challenging. Trials must ensure adequate follow-up duration (often 6–12 months) to capture meaningful differences in recurrence rates, given that flares may occur late. Placebo-controlled designs are still needed to rigorously prove efficacy, but withholding effective therapy can be ethically problematic in patients with frequent, painful relapses. Consensus on standardized outcome measures (symptom scores, biomarker normalization, recurrence-free survival, quality-of-life indices) will facilitate comparison across studies and satisfy regulatory requirements for approval.

Safety and tolerability are paramount concerns when introducing long-term immunomodulatory therapy for a condition like pericarditis. Any immunosuppressive treatment carries an infection risk: IL-1 inhibitors, for instance, can exacerbate latent infections (they are

Table 1
Competitive environment: phase II/III pericarditis therapies.

Agent (Developer)	Modality/Structure	Mechanism	Indication	Development phase
Rilonacept (Arcalyst)(Regeneron/ Kiniksa)	Fusion protein (IL-1 trap)	Binds IL-1α/β	Recurrent pericarditis (RP)	Approved (Phase III)
Anakinra (Kineret)(Sobi)	Recombinant IL-1R antagonist	Blocks IL-1 receptor	Recurrent pericarditis (off-label)	Approved for RA; Phase IV use in RP
Canakinumab (Ilaris)(Novartis)	IL-1β monoclonal antibody	Neutralizes IL-1β	Recurrent pericarditis (RP)	Phase II
Goflikicept (RPH-104)(R-Pharm)	Fusion protein (IL-1 trap)	Binds IL-1α/β (high affinity)	RP (phase II/III Russia)	Phase II/III
CardiolRx (CT-100–004)(Cardiol Therapeutics)	Oral small molecule (CBD derivative)	Modulates NLRP3 inflammasome	RP (cannabidiol-based therapy)	Phase III (MAVERIC)
KPL-387(Kiniksa)	Human monoclonal (IgG)	IL-1 receptor antagonist	RP (steroid-dependent)	Phase II/III planned (2025)
VTX2735(Ventyx Biosciences)	Oral small molecule	NLRP3 inflammasome inhibitor	RP (oral NLRP3 inhibitor)	Phase II (2024/25)

SC: subcutaneous; IL: interleukin; IgG: immunoglobulin G. Indication refers to the targeted pericarditis population (typically recurrent/idiopathic forms).

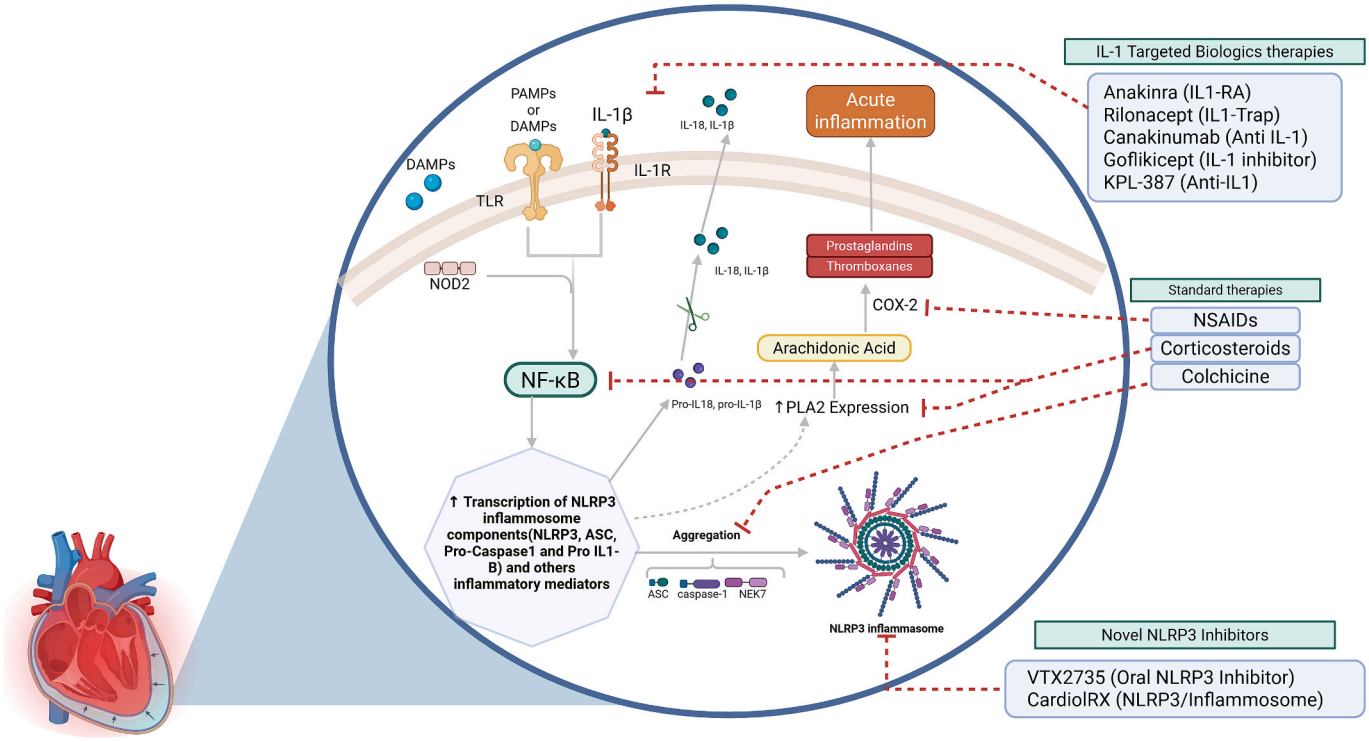

Fig. 1. Old, new and emerging therapeutic targets for acute and recurrent pericarditis. The figure summarize different mechanisms of action of conventional and novel therapies for recurrent pericarditis. Rilonacept and Anakinra are now on-market (phase IV) after trials, whereas most others are experimental. Several of the emerging therapies (e.g. VTX2735, CardiolRx, KPL-387) aim to offer oral or less immunosuppressive alternatives to the existing IL-1 biologics.

contraindicated in active tuberculosis, a consideration in regions where TB pericarditis is prevalent). Long-term safety data remain limited beyond the relatively short follow-up of current trials. Careful screening and monitoring for infections will be necessary as these therapies are used in broader populations, given the risk that IL-1 inhibitors could exacerbate latent infections (e.g. active tuberculosis, for which they are contraindicated).

Other potential issues include immunogenicity or hypersensitivity reactions to biologics, injection site reactions, and possible off-target effects for oral small molecules. Demonstrating acceptable safety profiles over longer durations (beyond the relatively short follow-up of current trials) will be critical.

There are also practical and regulatory challenges. Recurrent pericarditis is an orphan disease, making it difficult to recruit large patient populations for trials. Multi-centre international collaboration is often required to achieve adequate sample sizes for phase III studies. Even if a drug proves effective, its high cost may limit accessibility; payers could demand evidence of substantial benefit (such as steroid-free remission or prevention of hospitalisations) compared to inexpensive conventional therapy. Even with effective new drugs, their high cost compared to inexpensive conventional therapies may limit accessibility. The necessity for cost-effectiveness considerations is mandatory, particularly within European healthcare systems. Cost considerations need to be taken into account when recommending treatment strategies. Moreover, special subgroups remain underrepresented in trials. For example, acute post-infarction pericarditis (Dressler's syndrome) and active tuberculous pericarditis are usually managed with established therapies (aspirin and anti-tuberculous therapy, respectively) and have not been included in studies of IL-1 blockers, yet these patients might also benefit from novel anti-inflammatory drugs. Addressing these subpopulations—through dedicated trials or registry data—will be important for a truly comprehensive approach to pericardial disease.

Another important issue of ongoing clinical trials is the necessity for consensus on standardized outcome measures—such as time to recurrence, symptom scores, recurrence-free survival, and quality-of-life indices—to facilitate comparison across studies and meet new regulatory approval requirements.

9. Conclusion and future directions

The advent of targeted immunotherapies marks a new era in the management of pericarditis. IL-1 inhibition, in particular, has proved to be a game-changer for refractory recurrent pericarditis, with clinical trials showing that agents like rilonacept can virtually abolish recurrences during treatment. Emerging therapies, including next-generation IL-1 blockers and inflammasome inhibitors, promise to further improve patient outcomes. Ongoing studies are evaluating whether these treatments can reduce or eliminate the need for corticosteroids and provide durable remission after therapy withdrawal.

Key questions remain to be answered. Long-term safety data are still limited, and careful post-marketing surveillance will be needed as these therapies see broader use. It is also crucial to determine whether the benefits observed in idiopathic or post-cardiac injury pericarditis extend to other forms such as autoimmune or malignant pericarditis. As evidence grows, clinical practice guidelines will need to incorporate these novel agents and provide recommendations on patient selection, optimal timing, and duration of therapy.

In the coming years, it is likely that targeted therapies will become integrated into routine care for difficult cases of pericarditis. For example, one could envision combination regimens – such as an IL-1 inhibitor added to NSAIDs and colchicine – being used for patients with multiple recurrences to break the cycle of inflammation. Trials are even being considered to use IL-1 inhibitors in a first episode of pericarditis to prevent recurrent disease, but cost-effectiveness considerations are warranted, especially in European healthcare systems. The development of biomarkers and advanced imaging (e.g. cardiac MRI) to gauge pericardial inflammation may facilitate a more personalized treatment approach, helping identify which patients are most likely to benefit from specific immunotherapies. Paediatric pericarditis and prevention of long-term complications (like constrictive pericarditis) are additional areas where research is needed. Genetic insights, such as the recognition of autoinflammatory gene mutations in some idiopathic pericarditis patients [32,33], could also guide future therapy or inspire new drug targets.

Overall, the outlook for patients with recurrent pericarditis is increasingly optimistic. A robust pipeline of biologics and small molecules is poised to supplement or replace the traditional anti-inflammatory drugs that have long been the mainstay of therapy. By strategically targeting the inflammatory pathways at the heart of pericarditis, these emerging treatments have the potential to transform a once-chronic, relapsing disease into one that can be predictably controlled – or even cured – with minimal toxicity.

Grant support

None.

CRediT authorship contribution statement

Massimo Imazio: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Francesco Venturelli:** Writing – review & editing, Visualization, Validation, Data curation, Conceptualization. **Maria Cristina Tomat:** Writing – review & editing, Visualization, Validation, Data curation, Conceptualization. **Giulio Savonitto:** Writing – review & editing, Validation, Data curation, Conceptualization. **Davide Stolfo:** Writing – review & editing, Visualization, Validation, Data curation, Conceptualization. **Valentino Collini:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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