

Recurrent pericarditis: Why IL-1 blockade is changing the game

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Recurrent pericarditis presents a persistent challenge for clinicians, often trapping patients in a debilitating cycle of inflammation, pain, and repeated hospitalisations. The standard anti-inflammatory therapies, while effective in acute episodes, frequently fail to prevent subsequent recurrences, leaving a significant unmet need for more durable prophylactic strategies. Interleukin-1 (IL-1) blockade has emerged as a targeted approach to disrupt the underlying inflammatory pathways driving this chronic condition.

KEY TAKEAWAYS

- **The Pivot:** Interleukin-1 inhibition offers a specific mechanism to prevent recurrent pericarditis, moving beyond broad anti-inflammatory agents.
- **The Data:** Clinical studies demonstrate a reduction in recurrence rates with IL-1 blockade compared to placebo or conventional therapy.
- **The Action:** Consider IL-1 inhibitors for patients with frequent, steroid-dependent, or colchicine-resistant recurrent pericarditis to break the cycle of inflammation.

Recurrent pericarditis is characterised by repeated episodes of pericardial inflammation, often manifesting as chest pain, dyspnoea, and pericardial effusions. This condition significantly impairs quality of life and can lead to substantial healthcare utilisation. The underlying pathophysiology involves an aberrant inflammatory response, with increasing evidence pointing to the central role of interleukin-1 (IL-1) in driving this inflammation.² Patients often experience multiple recurrences, sometimes requiring prolonged courses of corticosteroids, which carry their own burden of adverse effects.

The typical presentation of recurrent pericarditis involves a patient who has experienced at least one prior episode of acute pericarditis, followed by a symptom-free interval of 4 to 6 weeks, and then a subsequent recurrence. This pattern can repeat multiple times, leading to chronic, debilitating symptoms. The diagnosis relies on clinical criteria, including chest pain characteristic of pericarditis, pericardial friction rub, new or worsening diffuse ST-segment elevation or PR depression on ECG, and pericardial effusion. Elevated inflammatory markers, such as C-reactive protein (CRP), are also commonly observed during acute episodes and can guide treatment response. For a deeper dive into managing steroid-dependent cases, see our article on steroid-dependent pericarditis.

The Inflammatory Cascade in Pericarditis

The pathogenesis of pericarditis, particularly its recurrent forms, is complex but increasingly understood to involve dysregulation of the innate immune system.² Viral infections are a common trigger for initial acute pericarditis, but

in recurrent cases, an autoimmune component often plays a significant role. The pericardium, a serous membrane surrounding the heart, becomes inflamed, leading to fluid accumulation and pain. This inflammation is mediated by various cytokines, with IL-1 emerging as a key driver.²

Interleukin-1 is a potent pro-inflammatory cytokine that exists in two main forms, IL-1 alpha and IL-1 beta. Both are involved in initiating and amplifying inflammatory responses. In recurrent pericarditis, elevated levels of IL-1 beta have been detected in the pericardial fluid and serum of affected patients, suggesting its direct involvement in the disease process. This cytokine promotes the release of other inflammatory mediators, recruits immune cells to the pericardium, and contributes to the pain and tissue damage characteristic of the condition. Blocking this specific pathway offers a more targeted approach than broad immunosuppression.²

Current Treatment Paradigms and Unmet Needs

Standard-of-care for acute pericarditis typically involves non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine. Colchicine, in particular, has demonstrated efficacy in reducing recurrence rates and is a cornerstone of therapy.¹ However, a substantial proportion of patients either do not respond adequately to colchicine, cannot tolerate it due to gastrointestinal side effects, or continue to experience recurrences despite optimal dosing.³ For more on the role of colchicine, consider our piece on colchicine in acute pericarditis.

Corticosteroids are often used in patients who do not respond to NSAIDs and colchicine, or in those with severe inflammation. While effective in rapidly suppressing inflammation and alleviating symptoms, corticosteroids are associated with numerous adverse effects, including weight gain, hypertension, diabetes, osteoporosis, and increased susceptibility to infections. Prolonged steroid use can also lead to steroid dependency, where patients experience a flare-up of symptoms upon tapering the dose, creating a vicious cycle that is difficult to break. This dependency highlights a critical unmet need for steroid-sparing therapies that can effectively prevent recurrences without the systemic side effects of long-term corticosteroid use.^{2,3} The Oxford Handbook of Clinical Medicine provides a concise overview of these management strategies.

Rilonacept: A Targeted Approach to IL-1 Blockade

Rilonacept is a recombinant fusion protein that acts as an IL-1 trap. It binds to both IL-1 alpha and IL-1 beta, preventing them from interacting with their receptors and thereby inhibiting the downstream inflammatory cascade. This targeted mechanism of action offers a precise way to address the specific inflammatory driver in recurrent pericarditis, theoretically leading to fewer systemic side effects compared to broad immunosuppressants.

The drug is administered via subcutaneous injection, typically on a weekly basis. Its long half-life allows for less frequent dosing compared to some other biologic agents. The rationale for using rilonacept in recurrent pericarditis stems directly from the understanding of IL-1's role in the disease.^{2,4} By neutralising this key cytokine, rilonacept aims to prevent the inflammatory flares that characterise recurrent episodes, offering a prophylactic benefit rather than merely treating acute symptoms.²

Clinical Evaluation of Rilonacept

Clinical studies evaluating rilonacept in recurrent pericarditis have focused on its ability to prevent recurrence and reduce corticosteroid dependence.³ These trials typically enrol patients with a history of multiple pericarditis episodes, often those who are already on corticosteroids or have failed conventional therapies.³ The primary endpoints in such studies

usually include the time to first pericarditis recurrence, the proportion of patients free from recurrence, and the ability to taper corticosteroids without a flare.

Patients receiving rilonacept have demonstrated a reduced risk of pericarditis recurrence compared to those on placebo or conventional therapy.^{1,3} This reduction in recurrence translates into fewer hospitalisations and emergency department visits, significantly improving patient quality of life.³ The drug also facilitates corticosteroid tapering, allowing many patients to discontinue steroids entirely without experiencing a flare.³ This steroid-sparing effect is particularly valuable given the long-term complications associated with corticosteroid use. The mechanism of action and clinical utility of rilonacept in this context are further explored in our article, *Rilonacept: Blocking IL-1 to break the cycle of recurrent pericarditis*.

Safety Profile and Considerations

The safety profile of rilonacept has been generally favourable.³ The most common adverse events reported in clinical trials include injection site reactions, upper respiratory tract infections, and nasopharyngitis.³ These are typically mild to moderate in severity. Serious infections are a concern with any immunosuppressive therapy, but the incidence with rilonacept has been low. Clinicians must monitor patients for signs of infection and exercise caution in those with a history of recurrent infections or underlying immunocompromise.

But, as with all biologics, there is a theoretical risk of malignancy, though this has not been a prominent signal in studies of rilonacept for pericarditis. Liver enzyme elevations have also been observed in some patients, necessitating periodic monitoring of liver function tests. The long-term safety data are still accumulating, but the targeted nature of IL-1 blockade suggests a potentially better safety profile than broad immunosuppressants.² The decision to initiate rilonacept requires a careful weighing of its benefits against these potential risks, particularly in patients with comorbidities.

Where it Falls Short and Future Directions

While rilonacept offers a significant advance, it is not without limitations. The cost of biologic therapies is substantial, which can be a barrier to access for many patients. The need for regular subcutaneous injections also requires patient education and adherence, which can be challenging for some individuals. The long-term effects of chronic IL-1 blockade, particularly regarding immune surveillance and susceptibility to rare infections, still require further investigation.

The optimal duration of rilonacept therapy remains an open question. Some patients may achieve sustained remission after a period of treatment, while others might require indefinite therapy to prevent recurrences. Identifying biomarkers that predict response to therapy or guide treatment duration would be a valuable area for future research. While rilonacept has shown efficacy in steroid-dependent and colchicine-resistant patients, its role in earlier stages of recurrent pericarditis, or in combination with other therapies, warrants further exploration. The trial was not powered to detect differences in rare subgroups, and that gap matters for clinicians managing complex cases. Whether benefits extend to broader groups of patients, such as those with very infrequent recurrences, remains unclear.

CLINICAL IMPLICATIONS

For patients trapped in the cycle of recurrent pericarditis, rilonacept represents a genuine step forward. The ability to effectively prevent recurrences and, to liberate patients from chronic corticosteroid dependence, addresses a major clinical pain point. This shift means fewer hospitalisations, less debilitating pain, and a

significant improvement in quality of life, which for many, has been severely compromised for years. Clinicians managing these complex cases now have a targeted therapeutic option that moves beyond the broad, often side-effect-laden, immunosuppression of corticosteroids. The data supports its use in patients who are frequently recurring, steroid-dependent, or intolerant to colchicine. Integrating this biologic into practice will require careful patient selection, monitoring for potential adverse effects, and navigating the practicalities of administration and cost.

The pharmaceutical industry's focus on specific inflammatory pathways, rather than general immunosuppression, is a welcome development. But the high cost of biologics remains a significant hurdle for widespread adoption, placing a burden on healthcare systems and potentially limiting access for patients who could benefit most. Future research should focus on identifying predictors of response and optimal treatment duration to ensure resources are allocated effectively.

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