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REVIEW

# A Comprehensive Clinical Evaluation of Rilonacept in the Treatment of Recurrent Pericarditis: A Systematic Review

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**Objective:** Recurrent pericarditis (RP) is a rare cardiac condition characterized by recurrent inflammation, in which interleukin-1 (IL-1) is a key mediator. Despite increasing use of IL-1 inhibitors, comprehensive evaluations of rilonacept for RP are very limited, especially in China, where RP was newly listed as a rare disease in 2023. This review addresses the current gap by systematically assessing the efficacy, safety, cost-effectiveness, innovativeness, suitability, and accessibility of rilonacept in the management of RP, providing evidence-based guidance for clinical practice.

**Methods:** A systematic literature review (PROSPERO registration: CRD42024609978) was conducted across six electronic databases (three international databases, PubMed, Ovid/Embase, The Cochrane Library; three Chinese platforms, CNKI, Wanfang, VIP) from their inception to September 30, 2024. The search protocol incorporated both controlled vocabulary (MeSH terms) and free-text terms specific to rilonacept and RP. Studies were included if they investigated rilonacept for the treatment of RP, and fulfilled all predefined inclusion/exclusion criteria. The retrieved literature underwent comprehensive analysis focusing on efficacy, safety, cost-effectiveness, innovativeness, suitability, and accessibility of rilonacept in RP management.

**Results:** Five clinical studies were identified but no pharmacoeconomic studies were found. All patients experienced a decrease in pericarditis pain to 0.4–0.6 points and a decrease in C-reactive protein levels to 0.22 mg/dL after treatment. The median time to reach therapeutic endpoints was approximately 5–7 days, with significantly reduced recurrence rates and markedly improved quality of life. The treatment demonstrates excellent long-term tolerability. It addresses a critical clinical need, offers convenient administration, and exhibits promising innovation, appropriateness, and accessibility. While its economic feasibility requires post-marketing analysis, the drug shows considerable potential for future clinical application.

**Conclusion:** Rilonacept is effective, tolerable, innovative, and suitable in the treatment of RP, while also showing promise in improving its cost-effectiveness and accessibility. Further comparative and cost-effectiveness studies are needed to fully define the therapeutic role of rilonacept in the RP treatment paradigm.

**Keywords:** rilonacept, recurrent pericarditis, IL-1, systematic review, clinical comprehensive evaluation

## Introduction

Recurrent pericarditis (RP) refers to the recurrence of pericarditis after the initial acute episode has resolved. It is generally non-hereditary and typically presents as recurring chest pain. Research indicates that pericardial tissue damage leads to excessive secretion of Interleukin-1 (IL-1), perpetuating the inflammatory cycle of pericarditis.[1] The IL-1 family, comprising crucial inflammatory mediators, plays a central role in the pathogenesis of various autoinflammatory diseases when abnormally expressed. Following pericardial tissue injury, overproduction of IL-1α and IL-1β is observed, resulting in excessive IL-1 signaling and subsequent downstream pro-inflammatory responses.[2]

General therapies for RP include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS), and colchicine.[3] These treatments improve the clinical course in some patients, but long-term administration is associated with a high risk of dependency and resistance, with CS particularly linked to increased adverse effects and elevated recurrence rates.[4] In recent

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years, as understanding of the inflammatory mechanisms underlying pericarditis advances, targeted IL-1 antagonist therapies (IL-1 blockers or inhibitors) are increasingly demonstrating therapeutic advantages. IL-1 antagonists are now recommended for the treatment of IL-1-mediated autoinflammatory diseases.[5–9] Currently, only three IL-1 inhibitors are available globally, including anakinra, rilonacept, and canakinumab.[5,7,8] Nevertheless, notable differences exist among the three IL-1 inhibitors in terms of mechanism of action, indications, and efficacy. Anakinra is an IL-1 receptor antagonist that primarily blocks the binding of both IL-1α and IL-1β to their receptor, but it requires daily subcutaneous injections and may cause local adverse reactions and tolerability issues in some patients.[10] Canakinumab is a monoclonal antibody that specifically neutralizes IL-1β. Although it is convenient to use by infrequent injection, its cost is high, and its use in pericarditis is limited.[11] Rilonacept acts as a decoy receptor that uniquely binds both IL-1α and IL-1β with high affinity, effectively blocking IL-1 signal transduction and reducing inflammatory responses.[12] Clinical trials demonstrate that rilonacept significantly reduces RP recurrence and alleviates symptoms.[4,13] It is the sole approved drug for RP treatment and has recently received approval in China in December 2024 for two indications: cryopyrin-associated periodic syndrome (CAPS) and RP in adults and children aged 12 and above.

In 2023, RP is listed as a rare disease in China's "Second List of Rare Diseases" potentially accelerating the entry of IL-1 blockers such as rilonacept into the domestic market. This development is expected to address the medication challenges faced by RP patients in China. However, systematic reviews of rilonacept for the treatment of RP remain limited, and no comprehensive evidence-based evaluations are available in China. This study aims to conduct a systematic, multi-dimensional clinical comprehensive evaluation of rilonacept in the treatment of RP through evidence-based pharmaceutical research. The primary objective is to provide evidence-based support for clinical decision-making and drug accessibility, ultimately improving treatment accessibility for RP patients in China.

## Materials and Methods

This study adheres to the "Guidelines for Comprehensive Clinical Evaluation of Pharmaceuticals (2021 Trial Version)"[14] to assess the efficacy, safety, cost-effectiveness, innovation, appropriateness, and accessibility of rilonacept through a systematic literature review. For evaluation dimensions lacking applicable literature, supplementary data is sourced from clinical guidelines, drug labels, and third-party pharmaceutical market databases, including Yaorongyun and Yaozhi. The methodology employed in this research ensures a comprehensive and rigorous evaluation of rilonacept.

### Protocol and Registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42024609978).

### Search Strategy

A comprehensive literature search was conducted across six electronic databases: PubMed, Ovid/Embase, The Cochrane Library, and Chinese databases (CNKI, Wanfang, and VIP). The search period extends from the inception of each database to September 30, 2024. For international databases, we used a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to rilonacept and RP. For Chinese databases, corresponding Chinese terms were used. The search strategy was adapted for each database, considering their specific indexing systems and search capabilities. To ensure comprehensive coverage of the available literature, only Chinese and English databases were searched, thereby excluding other languages from the scope of retrieval. Additionally, we manually searched the reference lists of included studies and relevant reviews to identify any potentially eligible studies that might have been missed by the electronic search. Grey literature, including conference proceedings and unpublished reports, was also considered to minimize publication bias. The detailed search strategy for each database, including all search terms and combinations, is provided in the supplementary material (Table S1).

## Inclusion and Exclusion Criteria

Literature inclusion criteria were: (1) the study disease is RP; (2) the study drug is rilonacept, with no restrictions on control measures; (3) publicly published randomized controlled trials (RCTs), clinical studies, cohort studies, cross-sectional studies, case-control studies, and case reports including 3 or more cases, pharmacoeconomic studies; (4) no language restrictions, no regional restrictions.

Exclusion criteria for literature review were as follows: (1) non-clinical studies, including basic experimental research, animal studies, and in vitro studies; (2) literature types such as reviews, conference articles, book chapters, and other types of literature; (3) studies reporting data from the same population or duplicate publications; (4) articles without full-text access.

## Literature Screening and Data Extraction

Bibliographic management was performed using EndNote X9 (Clarivate, Philadelphia, PA, USA), where duplicate citations were systematically identified and eliminated from the search results in the aggregated database. Two researchers (Yue Yu and Jiajing Chen) independently screened the literature according to the inclusion and exclusion criteria. In case of disagreement, a third researcher (Zhao Zhao) was consulted for joint determination. Two researchers, (Yue Yu and Jiajing Chen), independently conducted data extraction utilizing a standardized form that had been pre-tested for reliability. The extracted information includes the basic characteristics and results of the included studies, such as: (1) Article title, publication year, and first author; (2) Sample size and baseline characteristics of the intervention and control groups; (3) Intervention and control measures; (4) Outcome indicators, loss to follow-up, and handling; (5) Study treatment-related indicators, such as randomization method, blinding, and bias. After independent data extraction, the researchers cross-verified their findings to ensure both accuracy and completeness. Any discrepancies were resolved through discussion or, if needed, by consulting a third researcher (Zhao Zhao). Regular team meetings were convened throughout the process to address challenges and maintain consistent interpretation of study data among all team members.

## Literature Quality Assessment

Standardized assessment instruments specific to each study design were employed to conduct a comprehensive evaluation of the methodological rigor of the included studies. For the included RCTs/clinical studies, the risk of bias assessment tool from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[15] is used to evaluate study quality. For the included pharmacoeconomic studies, the CHEERS 2022 checklist[16] is employed for evaluation. Two reviewers (Moting Qian and Zhao Zhao) independently assessed the methodological quality, with any disagreements resolved through discussion or consultation with a third reviewer (Yufei Zhang). The assessment outcomes guided the interpretation of study findings and contributed to evaluating the overall strength of evidence in this systematic review.

# Results

## Literature Search Results

A total of 257 articles on RP were retrieved. Five articles ultimately met the criteria: one open-label single-arm Phase II clinical study (NCT03980522),[4,17] and one randomized controlled Phase III clinical trial and its long-term extension study (NCT03737110).[18–20] No economic studies were identified. The literature screening process is illustrated in Figure 1, and the basic characteristics of the included studies are presented in Table 1.

The quality assessment of the included literature is presented in Figure 2. Due to its open-label design, the phase II clinical study (Klein 2020 and Lin 2021) could not avoid potential bias on subjective indicators such as patient self-ratings. Additionally, not all patients underwent magnetic resonance imaging and echocardiography, potentially introducing selection bias. The phase III clinical study (Klein 2021 and Brucato 2022) is of higher quality. The long-term extension study of the phase III trial (Imazio 2024) was designed as an open-label study, allowing patients to voluntarily choose between continuing treatment, suspend treatment and stay in observation, or discontinuing from the study.

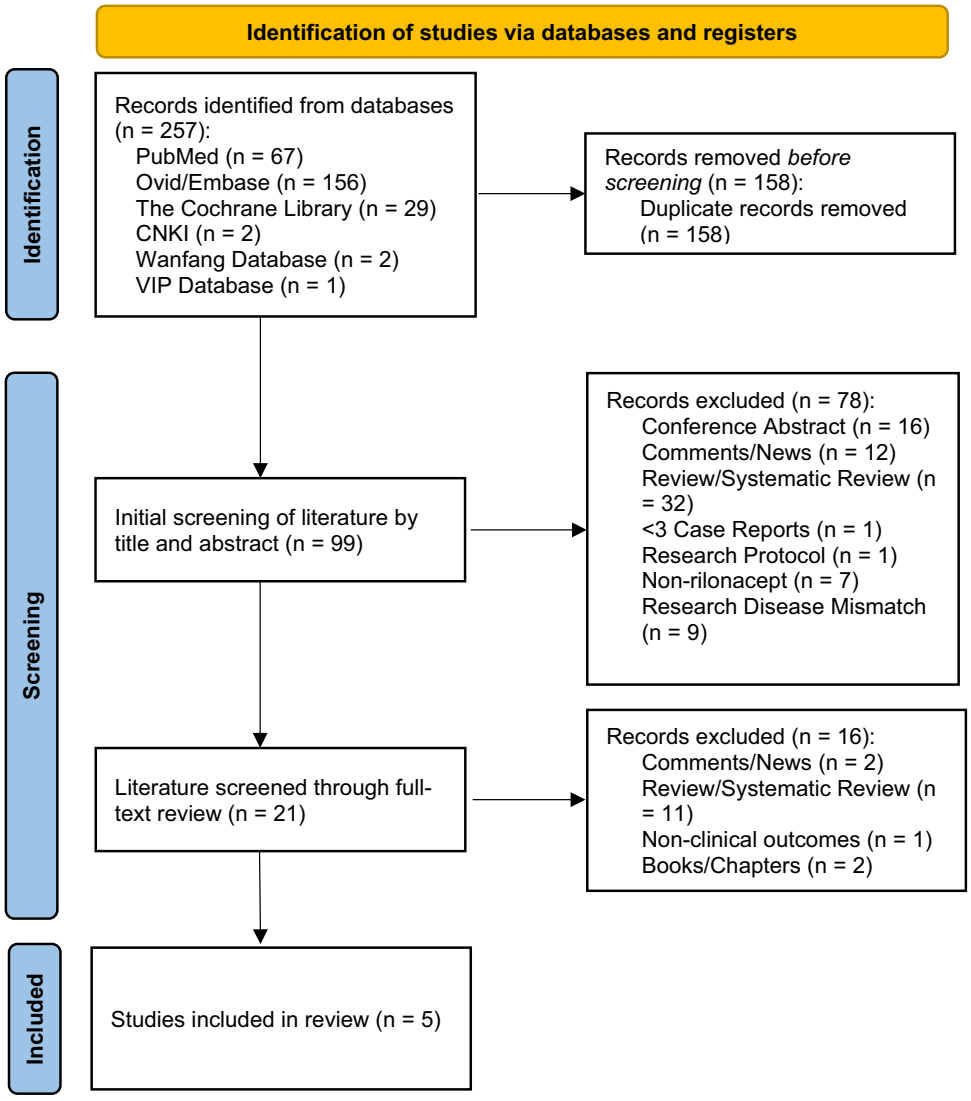


**Figure 1** PRISM flow diagram of the systematic review conducted. PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[21]
**Abbreviations**: CNKI, China National Knowledge Infrastructure; VIP, China Science and Technology Journal Database.

Consequently, the study could not avoid the risk of allocation concealment bias and its potential impact on subjective outcome measure scores. Overall, the quality of the literature is relatively good.

# Efficacy

## Indications

Rilonacept received orphan drug designation for the treatment of RP by the European Medicines Agency[22] and the US Food and Drug Administration[23] in 2021. In December 2024, it was approved for the RP indication in China, becoming the first and so far the only approved drug for this condition. It is indicated for patients aged 12 and above, including both children and adults.

## Clinical Study Efficacy Results

The two included RCT studies (NCT03980522, NCT03737110) involved a total of 111 patients, with an average of 90.5% Caucasian and 58.5% female. The mean age was 42.8±10.5 years in the phase II study and 44.7±16.1 years in the phase III study. Most patients in the phase II study were using two or more traditional anti-inflammatory drugs at baseline. The phase III study included screening, run-in, randomized-withdrawal, and long-term extension periods, with

**Table 1** General Information of the Included Studies

| Study | Country | Center | Sample Size(T/C[a]) | Intervention | Control Measures | Follow-Up Duration | Efficacy Outcomes | Safety Outcomes |
|---|---|---|---|---|---|---|---|---|
| Klein,[4] 2020 | The United States | Multi-center | 25/0 | Rilonacept 2x160mg loading dose, followed by 160mg per week (2.2 mg/kg in pediatric patients); | None | 6-24weeks | Active pericarditis patients: ①②③④⑤⑥Corticosteroid-dependent patients: ③④⑤⑥⑦ | ⑧⑨⑩ |
| Lin,[17] 2021 | | | | | | | ①②⑤ | / |
| Klein,[18] 2021 | The United States, Australia, Israel, Italy | Multi-center | Run-in period: 86/0 Randomized trial period: 30/31 | Run-in period: Rilonacept 320mg (4.4mg/kg in pediatric patients) loading dose, followed by 160mg per week (2.2mg/kg in pediatric patients); Randomized-withdrawal period: Rilonacept 160mg per week (2.2mg/kg in pediatric patients); | Placebo | Averaged 36 weeks[b] | Run-in period: ⑪ ⑫ ⑬ ⑭Randomized-withdrawal period: ⑮ ⑯ | ⑧⑨⑩ |
| Brucato,[19] 2022 | | | | | | | ①⑰ ⑱ ⑲ ⑳ | / |
| Imazio,[20] 2024 | | | 74/0 | Within 18 months from the most recent pericarditis event: Rilonacept 160mg weekly; 18 months after the most recent pericarditis event: Options include continuing with rilonacept open-label, suspending rilonacept for observation, or discontinuing from the study; | None | 24 months | Within 18 months from the most recent pericarditis event: ①②③⑥⑮ | ⑧ |
| | | | | | | | 18 months after the most recent pericarditis event: ①②③⑥⑮ | |

**Notes**: [a]T/C: treatment and control. [b]Includes a 12-week run-in period. ① Pericardial pain numeric rating scale (NRS) scores; ② C-reactive protein (CRP) levels; ③ Other pericarditis symptoms; ④ Health-related quality of life (physical and mental aspects); ⑤ Concomitant use of corticosteroids or not; ⑥ Changes in the use of other concomitant medications for pericarditis; ⑦ Disease activity after the tapering and discontinuation of corticosteroids; ⑧ Treatment-emergent adverse events; ⑨ Safety clinical laboratory testing included local haematology, chemistry, urinalysis and central laboratory lipid panel; ⑩ Physical examinations included vital signs, weight and height; ⑪ The time to pain response (rolling mean numerical rating scale score of ≤ 2 on 3 consecutive days); ⑫ The time to normalization of the CRP level; ⑬ The time to prespecified treatment response; ⑭ The time by which the patients discontinued standard therapy and were receiving rilonacept monotherapy; ⑮ Recurrence events; ⑯ The percentage of patients who had a persistent clinical response at the week-16 assessment, the percentage of days with no or minimal pericarditis pain (numerical rating scale score ≤ 2) through week 16, and the percentage of patients with absent or minimal pericarditis symptoms (score of 0 or 1), according to the patient's global impression of pericarditis severity rating scale (scores range from 0 to 6, with higher scores indicating greater severity of symptoms), at the week-16 assessment; ⑰ Health-related quality of life assessed with the SF-36v2; ⑱ General health status score assessed using the EQ-5D Visual Analogue Scale (EQ VAS); ⑲ Sleep impact assessed by the Insomnia Severity Index (ISI); ⑳ Global pericarditis symptom severity assessed by the Patient Global Impression of Pericarditis Symptom Severity (PGIPS).

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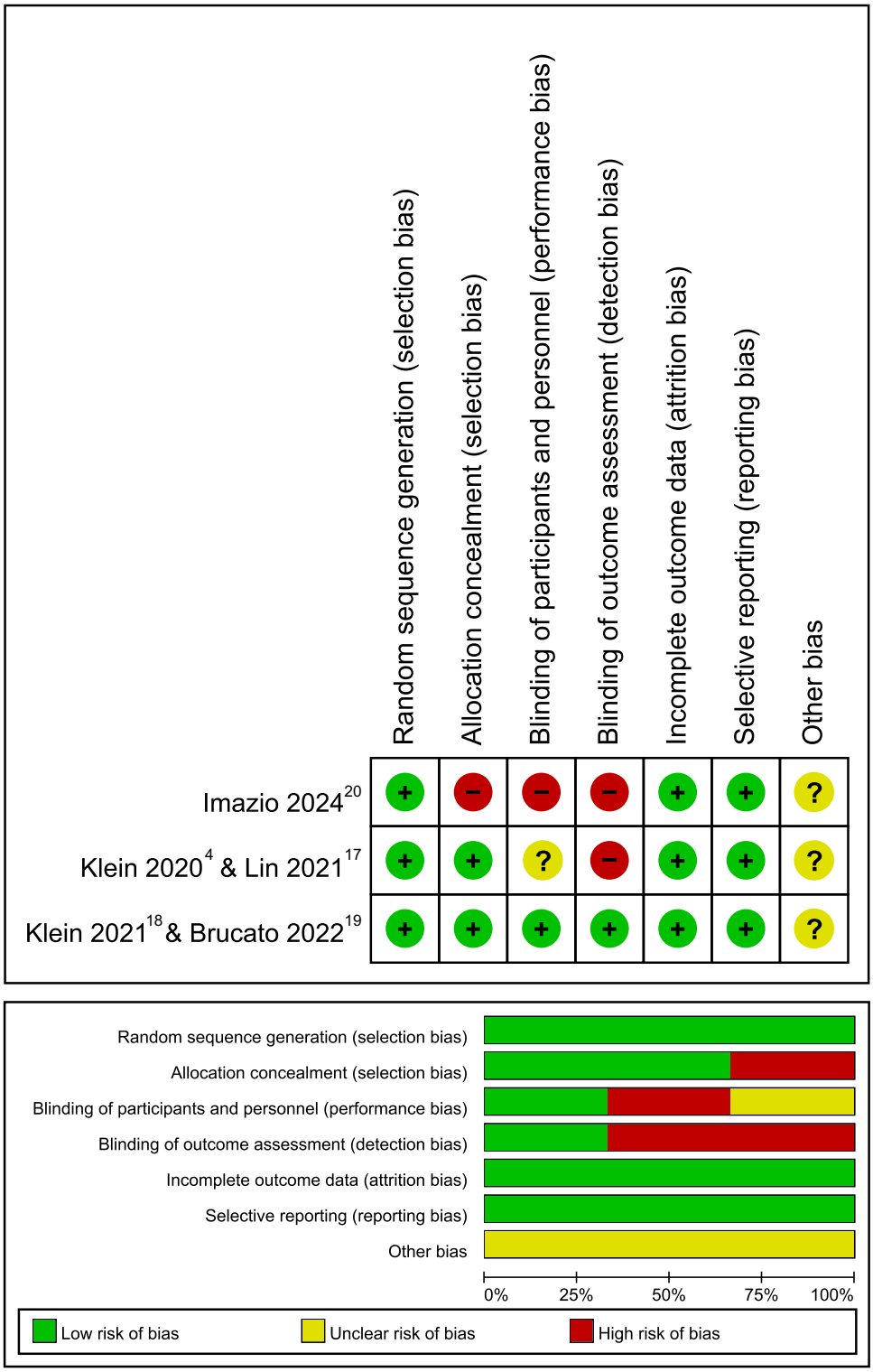


**Figure 2** Risk of Bias Assessment: (**a**) Summary Table and (**b**) Cross-study Analysis Overview.

all the patients who had been taking glucocorticoids discontinued them and transitioned to receive rilonacept monotherapy during the run-in period. Bailout rilonacept was used as rescue medication for qualifying recurrence events. In the long-term extension study, concomitant oral medications were allowed except steroids.

In the phase II study, relief of pericarditis pain was observed as early as after the first loading dose. The overall pericarditis pain score decreased from a baseline of 4.5 to 0.7, with effects sustained through the 18-week extension study. C-reactive protein (CRP) levels decreased from a baseline of 4.62 mg/dL to 0.38 mg/dL during the 6-week follow-up period, and to 0.22 mg/dL at the end of the extension period. Among all patients, those with RP (active pericarditis) showed a significant decrease in pain score from 4.6±1.82 to 0.4±0.91 (ES= −2.89; 95% CI: −3.90 to −1.88) and in CRP levels from 3.84±5.30 mg/dL to 0.24±0.36 mg/dL (ES= −0.94; 95% CI: −1.89 to −0.20) by the end of the extension study. Stable patients previously dependent on CS had lower baseline pain scores (1.4±1.51), which decreased to 0.6 ±1.19 (ES= −0.58; 95% CI: −1.56–0.39) at the end of study, with CRP levels slightly decreasing from 0.19±0.11 mg/dL to 0.12±0.06 mg/dL (ES= −0.78; 95% CI: −1.76 to 0.21). A pronounced reduction in the frequency of pericarditis recurrence was observed across all patients, and each patient was afforded the opportunity to either reduce or completely discontinue the use of at least one concomitant medication, and overall health status, quality of life, and physical health scores improved significantly.

During the run-in period of the phase III study, the median time to pain relief with rilonacept was 5 days (95% CI: 4–6), median time to CRP normalization was 7 days (95% CI: 5–8), and median time to predetermined efficacy was 5 days (95% CI: 4–7). Approximately 7.9 weeks were required to taper off and subsequently discontinue the existing medications, followed by a transition to rilonacept monotherapy (95% CI: 7.0–8.1). All quality of life-related scores improved significantly ($P < 0.001$), with pain improvement being the most notable (Cohen's d = 2.63), followed by patient-rated pericarditis symptom severity (Cohen's d = 1.82). During the randomized-withdrawal period, rilonacept significantly reduced the risk of pericarditis recurrence compared to placebo (HR 0.04; 95% CI: 0.01–0.18; $P < 0.001$). The fraction of patients free from insomnia exhibited an upward trend, ascending from roughly 30% at the run-in baseline stage to in excess of 70% when it came to the randomized withdrawal week 24 or the conclusion of the study. Among them, 74 patients participated in the long-term extension study of the Phase III trial, with an average age of 44.2 years and 54.1% being female. Within 18 months following the most recent episode of pericarditis recurrence, the annual incidence rate of RP for all patients was 0.04 cases per patient per year, with CRP levels maintained at a low level, regardless of the use of non-steroidal anti-inflammatory drugs (NSAIDs). Eighteen months after the most recent pericarditis event, 64% (33/52) of patients continued to use rilonacept, with only 1 case (1/33; 3.0%) of recurrence, which was associated with a deliberate interruption of rilonacept treatment 4 weeks prior to the surgery. The annual recurrence rate was 0.18 (95% CI, 0.06–0.41) events per patient per year; whereas among the 8 patients who discontinued treatment and stayed in observation, 75% (6/8) experienced recurrence, with an annual recurrence rate of 2.18 (95% CI, 0.80–4.75) events per patient per year. Among these patients, 4 patients did not achieve resolution even after taking NSAIDs.

The overall risk of recurrence in the continuous treatment group was reduced by 98% compared to the observation group after treatment discontinuation (HR 0.02; P<0.0001).

In summary, rilonacept is currently the only approved drug for RP. In the treatment of RP, it not only reduces pericarditis symptoms and lowers recurrence risk but also allows for safe reduction and discontinuation of corticosteroids, and transition to rilonacept monotherapy. It significantly improves patients' quality of life in various aspects, especially in pain and sleep quality.

## Safety

### Label Warnings

Rilonacept inhibits IL-1 activity, potentially modulating immune responses. It is not recommended for use with other drugs targeting IL-1 or tumor necrosis factor (TNF) due to increased risk of infection. It is not recommended in patients with active or chronic infections. Treatment should be discontinued immediately if severe infection occurs.

Elevated lipid levels were observed in some patients during clinical trials. Regular lipid monitoring is recommended after treatment initiation.

### Clinical Study Safety Results

Among 111 patients in both studies, 99 (89.2%) experienced adverse events, with over 95 (85.6%) being mild to moderate. The most common adverse events were injection site reactions (44/111, 39.6%) and upper respiratory tract

infections (19/111, 17.1%). The longest follow-up period was 56 weeks. A total of seven serious adverse events were documented, yet none of them led to any long-term ramifications. Among these, one incident transpired within the placebo group, and there were no fatalities reported. In the phase III investigation, four patients ceased the treatment protocol during the run-in phase owing to the occurrence of adverse events. During the randomized trial phase, mild to moderate adverse events manifested in 80.0% (24 out of 30) of the participants within the rilonacept cohort and 41.9% (13 out of 31) of those in the placebo group. The relatively high incidence rate within the placebo group intimates that the observed adverse events might be correlated with individual patient idiosyncrasies and the progression of the disease, rather than being exclusively ascribed to the investigational drug. Overall, rilonacept demonstrates exemplary safety parameters, with special attention needed for injection site reactions and infection risk during initial use.

## Economic Considerations

No economic evaluation literature was found for rilonacept. In clinical studies,[18] patients had an average of 2.6 previous recurrences, with an annualized recurrence rate (including initial occurrence) of about 3.9 times/year. Recent research findings suggest that rilonacept exhibits a comparatively superior efficacy rate in contrast to other available treatment modalities.[24] In the conducted trials, patients who received rilonacept treatment demonstrated an annualized recurrence rate approaching zero, thereby manifesting its potent capacity to effectively preclude the recurrence of pericarditis. Considering that a single hospitalization for RP patients can cost $20,000 to $30,000,[25] the attenuation of recurrence frequency holds the potential to engender a substantial diminution in medical expenditures, both for patients and at the societal level. While the monthly treatment expenditure for rilonacept may potentially reach $20,000,[26] the typical treatment duration approximates one year.[27] Notably, the actual patient financial burden can be substantially moderated by regional pricing variations and comprehensive insurance coverage mechanisms.

However, the long-term clinical data available for rilonacept is currently limited. Moreover, there is a lack of specific economic evaluation parameters, including costs, willingness to pay, and quality-adjusted life years, which precludes the possibility of conducting a comprehensive cost-effectiveness analysis of rilonacept at this time. Furthermore, pharmacoeconomic assessment for Chinese patients will require further research after domestic pricing structures are defined, insurance coverage protocols are clarified, and local clinical implementation is validated.

## Innovativeness

Rilonacept is the first and so far the only approved treatment for RP, providing an effective solution for patients facing recurrent, painful episodes. It has significant innovative and clinical value. The drug was approved for market launch in China in December 2024, expected to address the urgent treatment needs of RP patients in China and contribute to promoting independent research and innovation in drug development within this therapeutic area.

## Suitability

Rilonacept does not require administration at specific time of the day and is given once weekly via subcutaneous injection, allowing for home self-administration. Compared to daily dosing requirement of anakinra, rilonacept has a less frequent dosing strategy which may improve patient compliance. However, rilonacept is a lyophilized powder that requires reconstitution with sterile water before each use, which requires patients to have higher administration skills compared to pre-filled syringes.

## Accessibility

RP has been listed as a rare disease in China's "Second List of Rare Diseases".[28] As the only globally approved treatment for RP, rilonacept's launch in China will significantly improve treatment accessibility for Chinese RP patients and address the issue of drug availability at an early stage. Although rilonacept is priced high internationally, its pricing in China is yet to be determined. Considering China's insurance and tax support policies for rare disease medications, patient affordability is expected to improve.

## Discussion

This study provided a comprehensive evaluation of rilonacept for RP treatment based on clinical trials and currently available data, assessing its efficacy, safety, economic value, innovativeness, suitability, and accessibility. The comprehensive evaluation revealed that rilonacept demonstrates significant therapeutic advantages, with notable strengths in clinical effectiveness, safety profile, and innovative treatment approach. Moreover, its potential for broader clinical application suggests a promising therapeutic strategy in managing the target condition. It shows good potential in terms of pharmacoeconomic potential, which will require further comprehensive analysis after its domestic market launch.

Notably, current clinical guidelines recommend CS as second or third-line treatment for RP patients when NSAIDs and colchicine are ineffective.[9,29] Prolonged corticosteroid administration is associated with substantial systemic adverse effects,[30] while abbreviated therapeutic regimens with accelerated dose reduction may potentially precipitate disease recurrence.[9,31,32] Clinical and laboratory results suggested that rilonacept can successfully reduce or discontinue the use of standard anti-inflammatory drugs, demonstrating sustained suppression of inflammatory biomarkers and prolonged clinical remission.[33] This indicates that rilonacept monotherapy could potentially serve as an alternative to CS as a potentially paradigm-shifting primary therapeutic intervention. RP imposes a significant disease burden on patients, and rilonacept can markedly improve clinical symptoms, reduce recurrence frequency, and thereby enhance patients' quality of life. Moreover, potentially minimizing polypharmacy and enabling pharmaceutical optimization, especially corticosteroids, helping to improve patient compliance and reduce the chances of drug interactions and adverse reactions.[34,35] However, while rilonacept offers promising efficacy and convenient administration, its high cost and currently limited availability, particularly in many healthcare systems outside the United States, remain significant barriers to its widespread adoption. Additionally, long-term real-world safety data are still lacking, and although injection site reactions are generally mild, other rare or cumulative adverse effects may emerge as use increases. Current evidence remains circumscribed by placebo-controlled trials, necessitating definitive head-to-head comparative investigations to conclusively establish therapeutic superiority over conventional treatment modalities.

Rilonacept and anakinra are both dual-target IL-1 inhibitors targeting IL-1α and IL-1β, providing more comprehensive control of RP recurrence compared to single-target drugs (such as the IL-1β inhibitor canakinumab). Rilonacept achieves predetermined efficacy faster than anakinra, with similar adverse reaction rates[36] and lower dosing frequency. However, given methodological disparities in study designs, including variations in follow-up periods and baseline recurrence characteristics, further research is needed to validate comparisons between the two. Additional real-world studies and health-economic analyses will be required to determine whether rilonacept's therapeutic advantages can justify its cost in different healthcare settings, and whether results from largely Western studies can be generalized to Asian populations.

There are several strengths in our study. Firstly, it offers a multidimensional assessment of rilonacept. This comprehensive approach provides a well-rounded view of the drug's clinical value and potential impact. Additionally, the review adheres to established guidelines (PRISMA) and employed a systematic search strategy across multiple databases, including both English and Chinese sources. The quality of the included studies was assessed using standardized tools (Cochrane risk of bias tool), enhancing the reliability of the findings. It offers valuable insights for clinicians and policymakers, particularly in the context of China's rare disease policies and potential drug approval.

This study also has several limitations. Due to the rarity of RP, few studies were included and each of them had small sample sizes, leading to potential sample heterogeneity. Some of the included studies were not placebo-controlled, which might potentially influence the evaluation of efficacy outcomes, which were predominantly reliant on subjective scoring metrics, and there was a likelihood of selection bias among the patients undergoing examinations. Furthermore, non-Chinese and non-English literature was excluded due to language limitations, potentially resulting in the inadvertent exclusion of certain studies. In addition, the reliance on published aggregate data and the absence of dedicated meta-analytical or subgroup analyses further limit our ability to provide comparative efficacy and relative rankings among available treatments. Lastly, the study population was predominantly Caucasian, perhaps attributable to the geographical distribution of the conducted studies. It is also noted that the levels of inflammatory markers exhibit a correlation with

race and socioeconomic status.[37,38] Consequently, the extrapolation of these results to Asian populations demands additional substantiating evidence to validate its applicability and generalizability.

## Conclusion

Rilonacept, as the only approved therapy for RP globally, has demonstrated consistent and clinically meaningful benefits in reducing recurrence rates and improving symptom control across clinical trials. However, its relatively high cost and limited accessibility remain challenges to its widespread application. Further comparative and pharmacoeconomic studies, especially in diverse populations such as those in China, are needed to fully establish its therapeutic role and cost-effectiveness.

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## Disclosure

The authors report no conflicts of interest in this work.

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