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REVIEW

Comprehensive Clinical Analysis of Rilonacept in the Treatment of Cryopyrin-Associated Periodic Syndromes: A Systematic Review

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Objective: Cryopyrin-associated periodic syndromes (CAPS), a group of interleukin-1 (IL-1) mediated autoinflammatory disorders, were incorporated into China's "Second List of Rare Diseases" in 2023. Notably, rilonacept, an IL-1 inhibitor approved in the United States since 2008, has been a key treatment for CAPS. However, comprehensive analysis of its efficacy and safety are limited. This systematic review aims to assess rilonacept for CAPS treatment and provide evidence-based therapeutic recommendations.

Methods: We used medical subject headings terms and free-text keywords related to rilonacept and CAPS to perform a systematic literature search. This search covered databases including PubMed, Ovid/Embase, The Cochrane Library, and Chinese databases (CNKI, Wanfang, and VIP) from their inception to September 30, 2024. A multidimensional systematic review was then conducted, collating the efficacy, safety, cost-effectiveness, innovativeness, suitability, and accessibility of rilonacept in treating CAPS.

Results: Out of 1223 screened publications, three clinical studies including two sequential randomized controlled trials were selected based on the established criteria. Notably, no economic evaluations were identified. Treatment with rilonacept resulted in a reduction of approximately two points in key symptom scores for patients, with significant improvements in all outcome measures such as the number of flare days and high-sensitivity C-reactive protein levels. Adverse reactions were mostly mild to moderate, and with favorable long-term tolerability. Rilonacept meets current clinical needs due to its ease of use, demonstrating strong innovativeness and suitability. Its cost-effectiveness and accessibility warrant further examination post-market entry, yet it exhibits considerable potential for widespread use.

Conclusion: Rilonacept demonstrates significant effectiveness in treating CAPS with a favorable overall safety profile. It shows high innovativeness and acceptable suitability, with the potential for improved cost-effectiveness and accessibility. We anticipate that the effective treatment of CAPS with rilonacept will encourage further clinical and fundamental research, offering valuable insights for the treatment of other autoinflammatory diseases.

Keywords: rilonacept, cryopyrin-associated periodic syndromes, interleukin-1 systematic review, clinical comprehensive summary

Introduction

Autoinflammatory diseases (AIDs) represent a diverse group of primary immunodeficiency disorders, typically classified as rare diseases. These conditions often result from monogenic mutations that lead to dysregulation of pro-inflammatory cytokines. Among the various inflammatory factors involved in AIDs, the interleukin-1 (IL-1) family plays a particularly crucial role.[1,2] The IL-1 family is an important class of inflammatory factors, and their abnormal expression is closely associated with the pathogenesis of various AIDs. IL-1α and IL-1β are the crucial members of this family, and genetic mutations can lead to excessive production of IL-1α and IL-1β or a deficiency in natural IL-1 receptor antagonists. This results in excessive IL-1 signaling, which may trigger downstream pro-inflammatory responses.[3]

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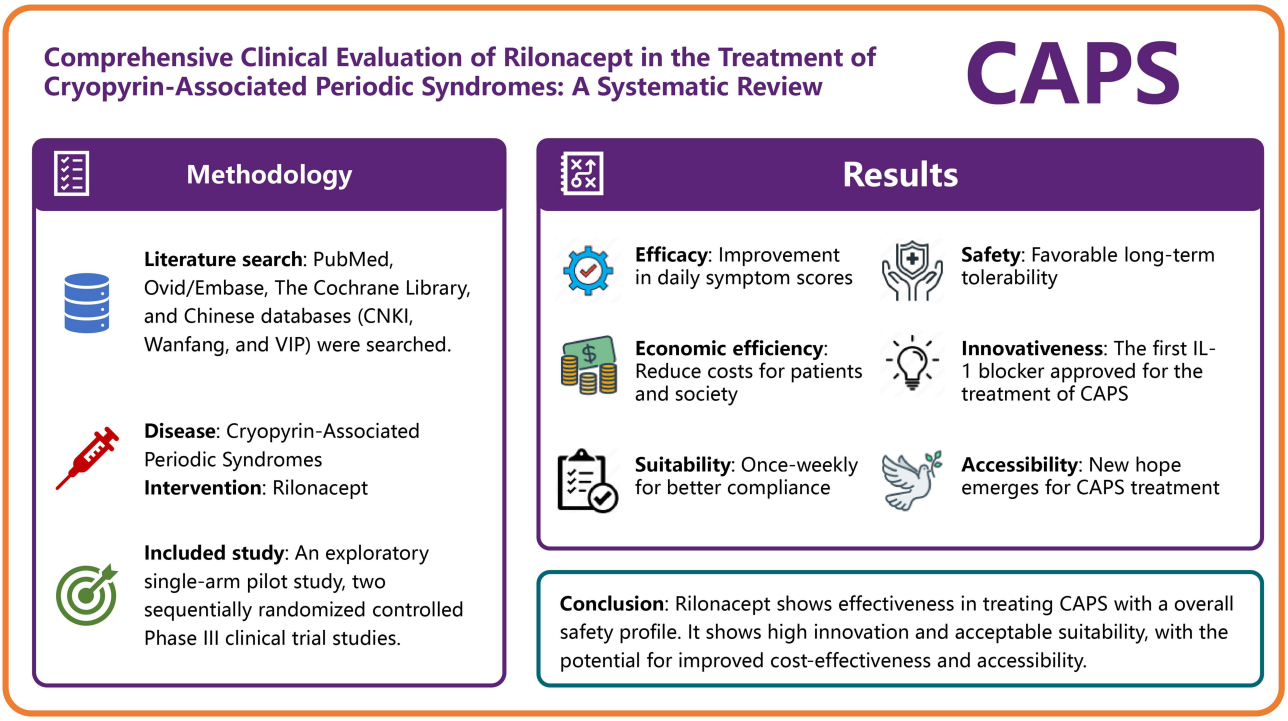
Graphical Abstract



Cryopyrin-associated periodic syndromes (CAPS) are one of the primary inflammatory disorders mediated by IL-1. The NLRP3 gene encodes a critical component of the NLRP3 inflammasome, a molecular platform that regulates the activation of pro-inflammatory cytokines such as IL-1β in response to various stimuli.[4] Mutations in the NLRP3 gene disrupt its regulatory function, leading to excessive inflammasome activation and overproduction of IL-1β, which are key drivers of inflammation in CAPS.[5–7] This condition manifests through symptoms like fever, joint pain, and urticaria, and can lead to severe complications including hearing loss and growth abnormalities, with potential life-threatening outcomes.[8,9] CAPS is categorized into three subtypes, increasing in severity: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular (CINCA) syndrome/neonatal-onset multisystem inflammatory disease (NOMID).[10] Notably, CAPS was recognized in China's second list of rare diseases in 2023. Despite its low prevalence and limited epidemiological data, the frequent documentation of case reports highlights its complexity and severity.[11–14] In China, the large population implies that even rare diseases can affect a significant number of individuals, thus posing a substantial clinical challenge.

To address IL-1 driven AIDs, IL-1 receptor antagonists are recommended as they offer a means to mitigate the side effects and resistance associated with traditional anti-inflammatory drugs like corticosteroids and colchicine.[9,15] Currently, three IL-1 antagonists—anakinra, rilonacept, and canakinumab—are available globally, with rilonacept and anakinra accessible in mainland China. Rilonacept, a soluble recombinant dimeric fusion protein, includes the extracellular ligand-binding domains of the human IL-1 type I receptor (IL-1RI) and the IL-1 receptor accessory protein (IL-1RAcP). By acting as a soluble decoy receptor, it effectively sequesters IL-1α and IL-1β, thereby blocking IL-1 signaling and reducing downstream inflammatory responses.[16,17] Furthermore, its long half-life allows for once-weekly injections, which significantly improves patient compliance.[18] Rilonacept has been approved in the United States for the treatment of CAPS, IL-1 receptor antagonist deficiency, and recurrent pericarditis.[18] In China, injectable rilonacept was included in the "List of Clinically Urgent New Overseas Drugs (First Batch)" in 2018. However, its application in CAPS treatment, especially within the Chinese population, remains unexplored, necessitating a comprehensive clinical summary.

This study aims to systematically review the effectiveness of rilonacept in treating CAPS from multiple perspectives. By providing evidence-based insights, it seeks to guide clinical decision-making and facilitate drug accessibility. Ultimately, the study is expected to advance the rational use of rilonacept and other IL-1 blockers, thereby addressing the therapeutic challenges faced by CAPS patients in China in a timely manner.

Materials and Methods

In accordance with the China's "Guidelines for Comprehensive Clinical Evaluation of Drugs (2021 Trial Version)",[19] this study systematically summarizes the efficacy, safety, cost-effectiveness, innovativeness, suitability, and accessibility of rilonacept through a structured literature review. When relevant literature was not available for certain analysis dimensions, supplementary information was extracted from clinical guidelines, drug package inserts, and reputable third-party pharmaceutical market databases, including Yaorongyun (https://www.pharnexcloud.com) and Yaozhi (https://www.yaozh.com). This approach ensures a comprehensive summary by integrating a wide range of data sources to address gaps and support the analysis's robustness.

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: CRD42024585479).

Search Strategy

A comprehensive literature search was conducted across six electronic databases: PubMed, Ovid/Embase, The Cochrane Library, and Chinese databases (CNKI database, Wanfang database, and VIP database). The search covered the period 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 CAPS. For Chinese databases, corresponding Chinese terms were used. The search strategy was adapted for each database, taking into account their specific indexing systems and search capabilities. No language restrictions were applied to ensure comprehensive coverage of the available literature. 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

The literature selection process adhered to predefined inclusion and exclusion criteria. Studies were included if they: (1) focused on CAPS as the primary condition of interest; (2) involved interventions using rilonacept, without restrictions on comparator or control measures; (3) were publicly available research, including randomized controlled trials (RCTs), observational clinical studies, cohort studies, cross-sectional studies, case-control studies, case series with three or more cases, and pharmacoeconomic analyses; and (4) had no restrictions on language of publication or geographical location. Conversely, studies were excluded if they: (1) were basic experimental research, animal studies, or other non-clinical investigations; (2) represented secondary literature such as systematic reviews, meta-analyses, conference abstracts, and book chapters; (3) were duplicate publications or studies utilizing the same population dataset; or (4) lacked full-text availability after exhaustive search efforts. These criteria were designed to ensure a comprehensive yet focused review of relevant literature on CAPS and rilonacept interventions while maintaining methodological rigor and minimizing potential biases.

Literature Screening and Data Extraction

The search results from the databases were imported into EndNote (EndNote X9; Clarivate, Philadelphia, PA, USA), and duplicates were removed. Two researchers (Tian Zhang and Yue Yu) independently screened the literature based on the predefined inclusion and exclusion criteria. Any disagreements were resolved through consultation with a third researcher

(Jiajing Chen). Data extraction was performed independently by two researchers (Tian Zhang and Yue Yu) using a standardized, pre-piloted form. Extracted data included basic study characteristics (article title, publication year, first author), sample information (sample size and baseline characteristics of participants in intervention and control groups), intervention details, outcome data (primary and secondary outcome measures, loss to follow-up, methods for handling missing data), and methodological features (randomization techniques, blinding procedures, potential sources of bias). Following the independent extraction, the researchers cross-checked their data to ensure accuracy and completeness, resolving discrepancies through discussion or, when necessary, consultation with a third researcher (Zhao Zhao). Regular team meetings were held throughout the process to address challenges and ensure consistent interpretation of study data across all team members.

Literature Quality Assessment

The methodological quality of the included studies was rigorously evaluated using standardized assessment tools appropriate to each study design. For RCTs and clinical studies, we employed the Cochrane Risk of Bias tool (RoB 2) from the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0.[20] This tool assesses potential biases across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For pharmacoeconomic studies, we plan to use the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist,[21] which evaluates the completeness and transparency of reporting in health economic studies across six main categories. Two reviewers (Moting Qian and Yufei Zhang) independently conducted the quality assessments, with any discrepancies resolved through discussion or consultation with a third reviewer (Tian Zhang). The results of these assessments will be used to inform the interpretation of study findings and to evaluate the overall strength of evidence in our systematic review.

Results

Literature Search Results

A total of 1223 articles related to CAPS were initially retrieved, of which three studies met the criteria. Among them, one study[22] was an exploratory single-arm pilot study (NCT00094900), while the other two studies originated from a sequentially randomized controlled Phase III clinical trial (NCT00288704)[23] and its long-term open-label extension study.[6] No economic evaluations were identified. The literature selection process is illustrated in Figure 1.

The characteristics of the studies included in this research are presented in Table 1. Three studies, published between 2008 and 2012, were all conducted in the United States. Goldbach-Mansky et al performed an open-label trial involving five patients diagnosed with FCAS. The intervention protocol initiated with a weekly dose of 100 mg, with provisions for dose escalation to 160 mg or 320 mg weekly. In instances of dose increase, patient follow-up was extended to 2 years.[22]

Hoffman et al conducted a multicenter, sequential study in 2008, enrolling 47 adult patients with CAPS who participated in two consecutive Phase III trials.[23] The first study comprised a 6-week randomized, double-blind comparison of weekly subcutaneous injections of rilonacept (160 mg) versus placebo. The second study was structured in two parts: Part A consisted of 9 weeks of single-blind rilonacept treatment, followed by Part B, a 9-week randomized, double-blind, placebo-controlled withdrawal period.

In a subsequent study published in 2012, Hoffman et al conducted a 72-week open-label extension trial involving 101 CAPS patients.[6] This extended study aimed to analyze the long-term efficacy of rilonacept in ameliorating CAPS symptoms, as well as to assess its safety and tolerability profiles during prolonged treatment.

The quality assessment of the included studies is presented in Figure 2. The pilot study by Goldbach-Mansky et al[22] and the long-term open-label extension study by Hoffman et al[6] utilized unblinded designs, potentially introducing bias in subjective outcome measures and overestimating treatment efficacy. The pilot study's small sample size (n=5) limits result generalizability, though it provides valuable preliminary data for subsequent larger-scale randomized controlled trials (RCTs). The extension study underwent multiple protocol amendments, potentially introducing selection bias due to data collection from only a subset of participants. In contrast, the Phase III clinical trial (Hoffman et al, 2012)[6]

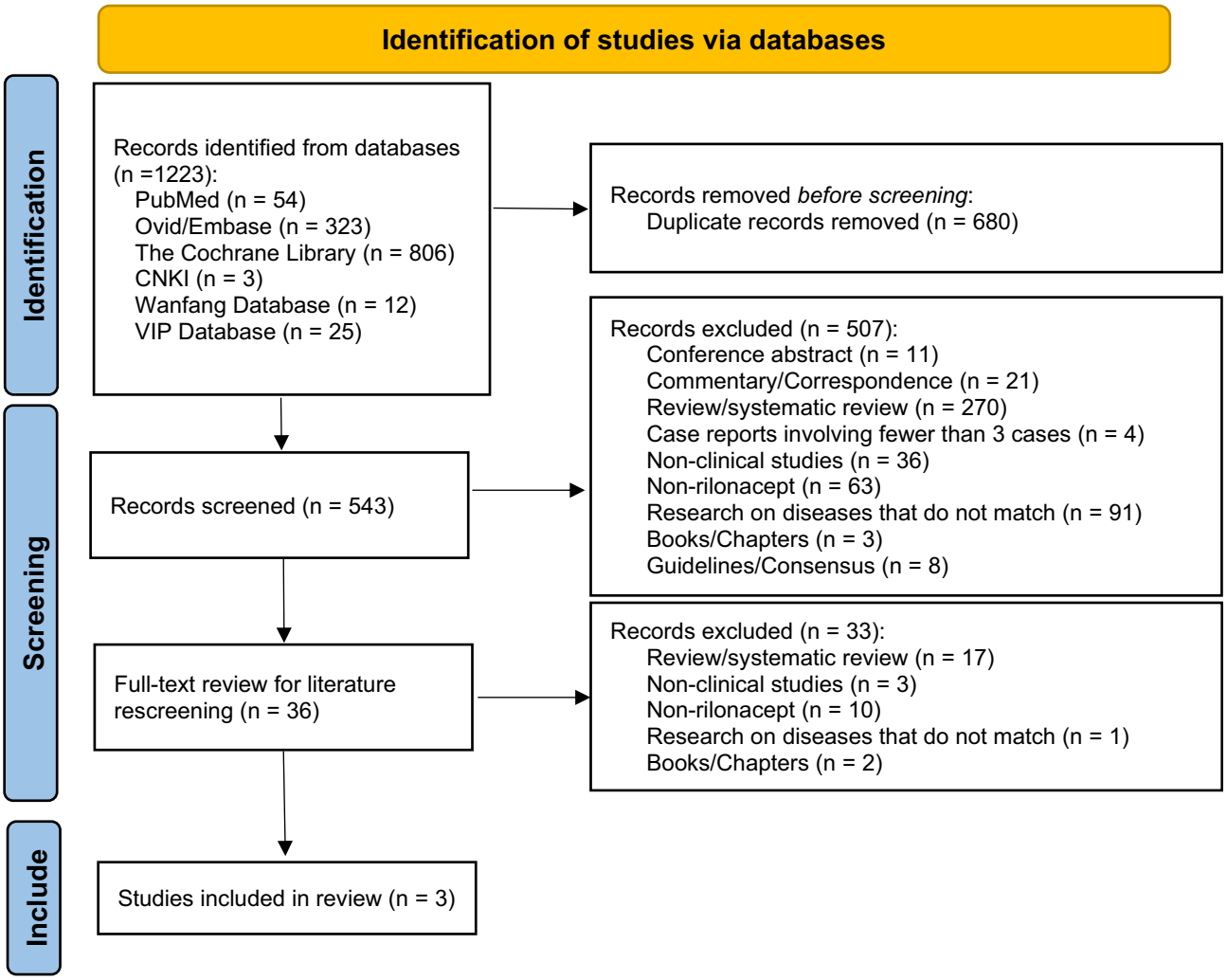


Figure 1 PRISM flow diagram of the systematic review conducted.
Notes: PRISMA figure adapted from Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100.[24]
Abbreviations: CNKI, China National Knowledge Infrastructure; VIP, China Science and Technology Journal Database.

demonstrates high methodological quality. Despite these limitations, the overall quality of the included literature is deemed satisfactory.

Efficacy

Instructions

In 2008, the US Food and Drug Administration (FDA) approved rilonacept for the orphan drug indication in the treatment of CAPS, making it the first approved medication for CAPS, indicated for patients aged 12 and older, including

Table 1 General Information of the Included Studies

Study	Country	Sample Size (T/C[a])	Study Design	Intervention	Control Measures	Follow-up Duration	Efficacy Outcomes	Safety Outcomes
Goldbach-Mansky 2008[18]	The United States	5/0	Single-center	100 mg per week, titrated up to 160 mg or 320 mg per week	None	8–42 weeks; 2 years if dosage increased	①②③④⑤⑥⑦⑧⑨⑩⑪	⑫

(*Continued*)

Table 1 (Continued).

Study	Country	Sample Size (T/C[a])	Study Design	Intervention	Control Measures	Follow-up Duration	Efficacy Outcomes	Safety Outcomes
Hoffman 2008[19]	The United States	47-participants sequential study Study 1: 23/24 Study 2A: 46/0 Study 2B: 22/23	Multi-center	Study 1: Loading dose of 2×160 mg, followed by 160 mg weekly; Study 2: 160 mg weekly;	Study 1: Placebo; Study 2A: None; Study 2B: Placebo;	Study 1: 6 weeks; Study 2: 9 weeks;	②[b]③⑬ ⑭	⑮ ⑯ ⑰ ⑱ ⑲ ⑳
Hoffman 2012[20]	The United States	101/0	Multi-center	160 mg weekly (for children: 2.2 mg/kg, maximum of 160 mg)	None	72 weeks	②[a]③⑬ ⑭	⑮ ⑯ ⑰ ⑱ ⑲ ⑳

Notes: [a]T/C: treatment and control. [b]This study measures high-sensitivity C-reactive protein (hsCRP). The study evaluates various parameters: ① Erythrocyte Sedimentation Rate (ESR), ② C-Reactive Protein (CRP) level, ③ Serum Amyloid A (SAA) level, ④ Patient symptom clinical diary scores, ⑤ Time to relapse, ⑥ Overall health status assessment (patient self-assessment and physician evaluation), ⑦ Pain and fatigue scores, ⑧ Number of swollen and tender joints, ⑨ Quality of life (SF-36), ⑩ Health assessment (questionnaire), ⑪ IL-6 level, ⑫ Incidence of adverse events, ⑬ Disease activity questionnaire score, ⑭ Physician-assessed patient disease activity score, ⑮ Physical examination and vital signs results, ⑯ Tuberculin skin test results, ⑰ Chest radiography results, ⑱ Electrocardiogram (ECG) results, ⑲ Routine laboratory test results, and ⑳ Anti-Linaclotide antibody levels.

both children and adults.[25] In 2009, the European Medicines Agency (EMA) also approved rilonacept for the orphan drug indication for CAPS.[26] However, the pharmaceutical company voluntarily withdrew the product from the market for commercial reasons in 2012.[27] Nonetheless, in 2021, rilonacept was re-approved in the European Union for a new idiopathic pericarditis indication.

Efficacy Outcomes of Clinical Research

A total of 106 patients were included in the study, of which three had MWS and the remainder presented with FCAS. All enrolled patients were Caucasian, with 66% female, and ages ranged from 12 to 78 years. All eight pediatric patients were enrolled during the extension study. The average age of patients in the extension study was 43.6 ± 18.1 years.

The five patients in the pilot study[22] demonstrated a significant average improvement in daily symptom scores compared to baseline (3.48 ± 0.93), with an average reduction of 3.09 ± 1.03 points, representing approximately an 81% decrease in symptoms ($P < 0.05$). There were significant improvements in three key inflammatory markers: erythrocyte sedimentation rate (ESR) decreased by 58% ($P < 0.01$), high-sensitivity C-reactive protein (hsCRP) levels decreased by 88% ($P < 0.001$), and serum amyloid A (SAA) protein levels decreased by 95% ($P < 0.001$). Overall health scores, pain scores, and tender joint counts also showed significant improvements.

In the Phase III study,[23] patients in the rilonacept group experienced an average change from baseline in key symptom scores of −2.6 (a group mean change of −84%), while the placebo group showed only a change of −0.3 (a group mean change of −13%). The rilonacept group demonstrated significant improvements across all efficacy measures: 96%, 87%, and 70% of patients in the rilonacept group achieved at least 30%, 50%, and 75% improvement in key symptoms, respectively, compared to only 29%, 8%, and 0% of patients in the placebo group ($P < 0.0001$). There were also significant improvements in the number of days with multi-symptom and single-symptom disease flares ($P < 0.0001$), single symptom scores ($P < 0.0001$), physician and patient global assessments of disease activity ($P < 0.0001$), limitations on daily activities ($P = 0.006$), as well as hsCRP levels ($P < 0.0001$) and SAA levels ($P = 0.006$). In the subsequent open-label extension study, patients in the placebo group who discontinued treatment showed significant declines in all previously mentioned efficacy endpoints, whereas those in the intervention group who continued rilonacept treatment maintained their therapeutic benefits ($P \leq 0.01$).

The subsequent 72-week extension trial[6] revealed that the overall average key symptom score for all patients decreased by 2.3 points. The number of days with multi-symptom flare-ups reduced from a baseline of 7.3 days to 0.6 days, and the days with single-symptom flare-ups decreased from a baseline of 12.7 days to 1.5 days.

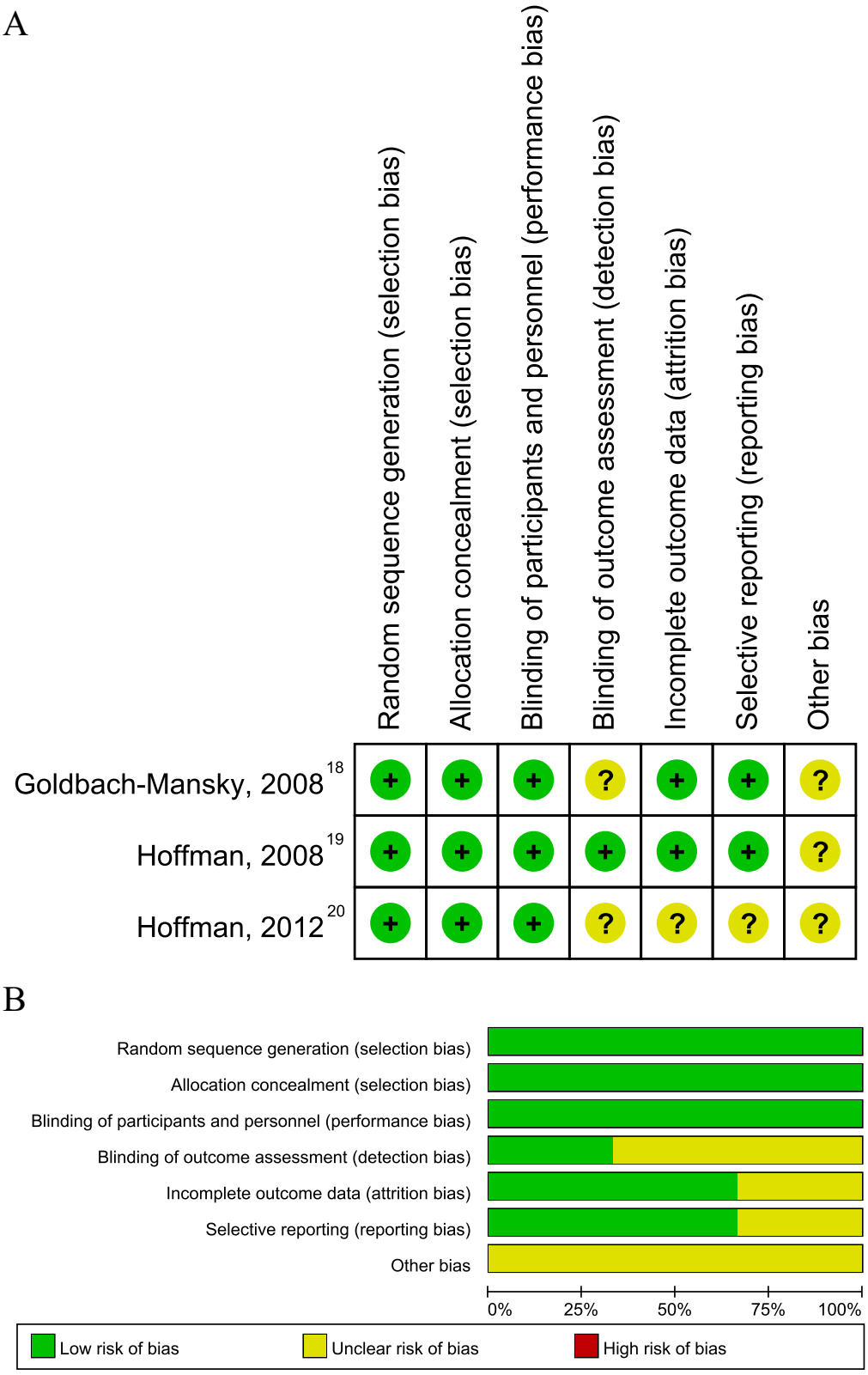


Figure 2 Risk of Bias Assessment: (**A**) Summary Table and (**B**) Cross-study Analysis Overview.

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In summary, rilonacept is the first approved medication for CAPS, with a long-standing market presence. Studies have demonstrated that it significantly improves patients' disease symptoms, reduces flare frequency, enhances quality of life, and decreases inflammatory markers.

Safety

Package Insert Warnings

The package insert for rilonacept indicates that, as an IL-1 blocker, the drug may potentially affect immune responses. Therefore, it is not recommended to use rilonacept in combination with other medications that act on IL-1 or tumor necrosis factor (TNF) to avoid an increased risk of infections. It is also not recommended for patients with active or chronic infections. If a patient develops a serious infection, the medication should be discontinued immediately.

Clinical Study Safety Results

Among the 106 patients, 95 (89.6%) experienced adverse events, with over 89% of these being mild to moderate in severity. The most common adverse events were injection site reactions (75 out of 106, 70.8%) and upper respiratory infections (28 out of 106, 26.4%).[6,22,23] In the randomized controlled trial,[23] 54% (13 out of 24) of placebo group patients experienced adverse reactions, compared to 74% (17 out of 23) in the intervention group. However, the incidence of injection site reactions and upper respiratory infections in the intervention group was about three times that in the placebo group. The relatively high incidence of adverse events in the placebo group suggests that the observed adverse events during the trial may be related to individual patient variability and the inherent fluctuations of CAPS itself, rather than solely attributable to the investigational drug. Nonetheless, the likelihood of major adverse reactions being related to the investigational drug is relatively high.

In the pilot study with a follow-up of up to 24 months,[22] no serious adverse events were reported. During the randomized controlled trial and its 72-week extension study,[6] there were a total of ten serious adverse events, including the deaths of two patients, which were not related to the investigational drug. Additionally, two patients discontinued treatment due to elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The remaining patients demonstrated good long-term safety with the use of rilonacept.

In summary, rilonacept demonstrates a favorable overall safety profile with good long-term tolerability. However, during the initial phase of treatment, special attention should be paid to patients' injection site reactions and potential infection risks.

Economic Efficiency

No literature has been found evaluating the economic efficiency of rilonacept. The frequency of flares in CAPS patients is influenced by the risk of exposure to triggers, which limits their daily activities. The studies on rilonacept directly report its impact on symptom scores, focusing on the improvement of clinical symptoms rather than just inflammation levels, including hsCRP and SAA.[28] By reducing the number of disease flare days and enhancing patients' activity capabilities, significant savings on direct and indirect costs can be achieved for both patients and society. Although the average monthly treatment cost for rilonacept can be as high as $20,000 to $30,000,[4,29] actual expenses may be much lower due to variations in pricing, insurance coverage, and discounts offered by pharmaceutical companies. In terms of price, some research suggests that the monthly cost of anakinra is significantly lower than that of rilonacept;[4] however, this data is over ten years old. Given the current cost of over $1400 per injection of anakinra in the US (based on the price guide from Drugs.com: https://www.drugs.com/price-guide/kineret) and the daily dosing requirement, its monthly cost may be comparable to that of rilonacept.

Additionally, the weekly subcutaneous injection regimen of rilonacept helps reduce the number of medical visits and eliminates the need for inpatient treatment. Compared to daily medication, it reduces the frequency of administration, which can significantly lower both the direct medical expenses and indirect costs for patients over the long term, while also potentially improving the overall cost-effectiveness of the treatment.

However, due to the current lack of sufficient long-term clinical trial data and key economic evaluation parameters such as patients' willingness to pay and quality-adjusted life years (QALYs), a comprehensive cost-effectiveness

assessment of rilonacept cannot yet be conducted. To analyze the economic value of rilonacept among Chinese patients, it is necessary to further clarify its pricing strategy, insurance coverage, and real-world effectiveness in the Chinese market, which will allow for more in-depth research and analysis. For example, in the future, the cost-effectiveness assessment of rilonacept can be conducted by collecting data on long-term clinical outcomes, real-world evidence, and incorporating health economic models such as Markov models or decision tree analysis to evaluate its economic value more comprehensively.

Innovativeness

Rilonacept is the world's first IL-1 blocker approved for the treatment of CAPS. It offers an effective solution for addressing the clinical needs of CAPS patients, such as managing disease flares, improving mobility, and controlling symptoms, showcasing significant innovation and clinical value. In 2023, a Category 3.1 import new drug application for rilonacept was submitted in China. Rilonacept received marketing approval in China on November 27, 2024 (Approval No. SJ20240045).[30] Following its approval and market launch, this agent now provides an additional therapeutic option for Chinese patients with CAPS and contributes to advancing domestic research and innovation in this therapeutic area, addressing more clinical needs.

Suitability

Rilonacept, administered as a once-weekly subcutaneous injection that patients can self-administer at home, offers a convenient dosing regimen compared to daily medications, potentially improving treatment adherence and quality of life for patients. However, rilonacept is supplied as lyophilized powder, which requires reconstitution with sterile water prior to each injection. This process presents some inconvenience compared to pre-filled syringes and requires patients to have certain technical skills in preparation and aseptic handling.

Accessibility

The growing national focus on rare disease populations and the incorporation of CAPS into the China's national rare disease catalog are anticipated to accelerate the regulatory approval process for associated therapies, potentially expediting the resolution of drug accessibility challenges. Once rilonacept enters the Chinese market, it will significantly enhance treatment accessibility for patients in China, providing more treatment options. Although rilonacept is priced relatively high internationally, its pricing in the Chinese market has yet to be determined. Considering that anakinra is priced slightly lower domestically than internationally, along with China's supportive insurance and tax policies for rare disease medications, rilonacept's domestic pricing is expected to be set at a reasonable level, thereby improving affordability for CAPS patients.

Discussion

This study conducted a comprehensive multidimensional analysis of rilonacept for the treatment of CAPS, by integrating clinical trial data and other relevant information. The findings indicate that rilonacept demonstrates favorable efficacy, safety, innovativeness, and suitability, making it a promising option for CAPS management. Additionally, it shows potential in terms of cost-effectiveness and accessibility. However, the pricing of rilonacept could influence its overall value proposition, suggesting the need for further in-depth analysis once it enters clinical practice in China.

IL-1 receptor antagonists have demonstrated significant efficacy in the treatment of CAPS. Previous studies have shown that these antagonists effectively inhibit leukocyte count increases and serum IL-6 levels, thereby preventing cold-induced acute inflammation in FCAS.[31] Similarly, research on anakinra, another IL-1 receptor antagonist, has shown substantial improvement in the inflammatory symptoms of patients with MWS.[32] Notably, rilonacept was the first medication approved by the US FDA for CAPS treatment and has been in clinical use for an extended period, underscoring its critical role in this therapeutic area.[4] Through a comprehensive review of existing studies, this study highlights rilonacept's substantial impact on ameliorating disease symptoms, reducing attack frequency, enhancing quality of life, and lowering inflammation levels in patients. Our findings further emphasize the pivotal role and value

of rilonacept as a a highly targeted and effective therapeutic option, laying the groundwork for future advancements in managing autoinflammatory syndromes.

Rilonacept is generally well-tolerated and exhibits good long-term safety, although attention should be paid to injection site reactions and infection risks, particularly during initial treatment stages. A prospective, single-center, open-label study supported these findings by demonstrating rapid clinical response and good tolerability in Schnitzler syndrome without serious adverse events or significant laboratory changes.[16] Similarly, in some studies, changes in blood cell counts and lipid levels were observed in certain patients, but did not adversely affect the treatment outcomes.[6,33] The reduction in blood cell counts could be a class effect of IL-1 antagonists, related to the correction of the inflammatory state.[34,35] During acute inflammatory responses, total cholesterol levels may decrease, and increased cholesterol levels have been noted with anti-inflammatory cytokine drugs, indicating inflammation reduction.[36] These observations reinforce that rilonacept effectively reduces inflammation levels. Importantly, because IL-1 blockade typically suppresses immune responses, rilonacept should not be combined with other IL-1 inhibiting drugs, such as TNF inhibitors, to avoid serious infections.[33]

Overall, rilonacept demonstrates significant cost-effectiveness, innovation, and accessibility in the treatment of CAPS. From an economic perspective, rilonacept shows potential long-term cost-effectiveness despite high initial costs, primarily through reduced hospitalizations and improved quality of life. While comprehensive cost-effectiveness analyses for IL-1 inhibitors in CAPS are lacking, studies on similar conditions provide insights. A cost-effectiveness analysis of anakinra in the treatment of rheumatoid arthritis demonstrated potential cost-effectiveness in certain scenarios, particularly for patient's refractory to conventional therapies.[37] The study estimated anakinra's incremental cost-effectiveness ratio to range between 106,000 and 604,000 pounds per quality-adjusted life year.[37] While this range is broad, it provides a reference framework for assessing the economic impact of IL-1 inhibitors in chronic inflammatory diseases. Similarly, the Phase 3 trial demonstrated rilonacept's efficacy in suppressing pericarditis episodes and reducing recurrence risk, suggesting potential reductions in healthcare resource utilization and associated costs.[38] In addition, as an IL-1 inhibitor, rilonacept provides innovative advantages through targeted therapy that was previously unattainable. Its once-weekly subcutaneous injection promotes patient compliance, demonstrating strong appropriateness.

In terms of accessibility, as China has been continuously improving its medical insurance policies for rare diseases in recent years, such as including some orphan drugs in the medical insurance catalog and conducting specialized centralized procurement for orphan drugs, rilonacept is expected to increase its accessibility through these channels.[39] This aims to ensure its availability and coverage within the national healthcare system, meeting patient expectations.

This study has several strengths. Firstly, it compiles data from multiple authoritative databases, such as The Cochrane Library, PubMed, and Embase, enhancing data richness and representativeness. Secondly, stringent inclusion criteria and clear exclusion criteria were applied, ensuring high-quality studies with minimal bias, thus improving result reliability. Thirdly, the study combines quantitative and qualitative analyses, integrating statistical data with descriptive insights for a comprehensive assessment of efficacy, safety, and tolerability. Finally, a multidimensional analysis was conducted, considering factors such as efficacy, safety, innovation, economic efficiency, and accessibility, ensuring a thorough assessment.

However, the study also has limitations. Firstly, due to the rarity of CAPS, the studies included were limited, with small patient sample sizes and the exclusion of infants. Secondly, the absence of placebo control in some studies might affect outcomes assessed by subjective ratings. Lastly, since the study population was predominantly Caucasian, and inflammation marker levels can vary with race and socioeconomic status,[40,41] the applicability of these results to Asian populations requires additional evidence.

Conclusion

In conclusion, rilonacept demonstrates substantial overall clinical value and holds significant potential for value enhancement in the treatment of CAPS. To fully validate and enrich the evidence base for its comprehensive value, further clinical studies, real-world evidence, and economic evaluations are essential. These efforts will not only confirm

rilonacept's efficacy and safety but also provide deeper insights into its long-term benefits and cost-effectiveness, ultimately guiding its optimal integration into clinical practice.

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Author Contributions

All authors made significant contributions to the work reported, involving conception, study design, execution, data acquisition, analysis, and interpretation. They participated in drafting, revising, or critically reviewing the article, and provided final approval for the version to be published. The authors have collectively agreed on the journal to which the article has been submitted and have committed to being accountable for all aspects of the work, ensuring the integrity and accuracy of the research.

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Disclosure

There is no conflict of interest in publishing this article.

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