Earlier Rilonacept Use in Recurrent Pericarditis Reduces Subsequent Recurrence Burden and Treatment Escalation: Outcomes from the RESONANCE Patient Registry

Paul C. Cremer, MD[1], Michael S. Garshick, MD[2], Sushil A. Luis, MBBS, PhD[3], Ajit Raisinghani, MD[4], Brittany Weber, MD, PhD[5,6], Vidhya Parameswaran, MPH[7], Allan L. Klein, MD[8], John F. Paolini, MD, PhD[7], on behalf of the RESONANCE Study Group

[1]Northwestern University, Chicago, United States of America; [2]NYU Langone Health (Cardio-Rheumatology Program, Center for the Prevention of Cardiovascular Disease), New York, United States of America; [3]Mayo Clinic (Department of Cardiovascular Medicine, Mayo Clinic, Rochester), Rochester, United States of America; [4]UC San Diego Health (Division of Cardiology, Department of Medicine, Sulpizio Cardiovascular Center), San Diego, United States of America; [5]Brigham and Women's Hospital (Division of Cardiovascular Medicine, Department of Medicine), Boston, United States of America; [6]UT Southwestern Medical Center, Dallas, United States of America, [7]Kiniksa Pharmaceuticals Corp., Lexington, Massachusetts; [8]USA Cleveland Clinic, Cleveland, United States of America

Real-world data from RESONANCE demonstrate that earlier use of rilonacept in recurrent pericarditis minimizes recurrences and provides a streamlined long-term disease management strategy

BACKGROUND

Recurrent Pericarditis (RP)

- Recurrent pericarditis (RP) is an IL-1-mediated chronic autoinflammatory disease[1,2]
- The rilonacept (IL-1α and IL-1β cytokine trap) development program was designed to address the well-known concerns of prolonged glucocorticoid use and was informed by contemporaneous evidence implicating IL-1 in RP pathophysiology[3-5]
- The Phase 3 trial RHAPSODY demonstrated that rilonacept was effective in treating RP and in reducing recurrence risk not only as a third-line agent (after glucocorticoids) but also as a second-line agent (instead of glucocorticoids), supporting authorization by the FDA as the only approved treatment for RP[3,4]
- The multi-center REgiStry Of the NAtural history of recurreNt periCarditis in pEdiatric and adult patients (RESONANCE) showed that in the first 3 years after rilonacept availability in RP, second-line treatment choice in the US shifted from glucocorticoids to IL-1 pathway inhibition[6]
- Based on the weight of clinical trial evidence, the 2025 ACC Concise Clinical Guidance (CCG) on the Diagnosis and Management of Pericarditis recently elevated IL-1 pathway inhibition to second-line (glucocorticoid-sparing) therapy after first-line NSAIDs/colchicine[7]

RESONANCE Patient Registry

- The REgiStry Of the NAtural history of recurrent periCarditis in pEdiatric and adult patients (RESONANCE) (NCT04687358) was developed to quantify trends in contemporary real-world clinical practice in RP to inform disease understanding and management strategies
- RESONANCE, the largest multi-center US-based observational registry, has been collecting long-term data from US-based pericardial-disease-dedicated programs since 2021[6]
- RESONANCE employs a hybrid data collection approach: up to 1-year retrospective data (the year prior to enrollment) are combined with prospective data into a single seamless real-world observation period
- Patients with RP diagnosis were enrolled into either:
  - Active (recurrence ≤3 years of enrollment, and on treatment at enrollment)
  - Inactive (prior RP diagnosis but with no episodes and not on treatment within 3 years prior to enrollment)

Hypothesis

- Rilonacept initiation earlier in the RP disease course reduces recurrence burden and escalation to next-line therapy versus conventional (first-line or second-line) oral therapies (i.e., NSAIDs/colchicine and/or glucocorticoids)

METHODS

Data Analysis

- Data for this interval analysis were collected from patients with ≥2 years of RESONANCE observation between March 2020 until the data cutoff (DCO) date (Jan 15, 2026).
- Data analyzed include general RP disease data [e.g., date of RP diagnosis, disease duration at DCO, medication history (e.g., medications prescribed prior to rilonacept and reasons for second-line treatment transition), and number of recurrences.
- Investigator-assessed pericarditis recurrences were reviewed in the context of standardized pericarditis recurrence event adjudication criteria used by the Clinical Endpoint Committee (CEC) in the RHAPSODY program, including available contemporaneous objective clinical indicators such as patient-reported chest pain, serum C-reactive protein [CRP], and/or cardiac imaging[3].
  - Annualized recurrence rate (ARR) was calculated per RP treatment regimen (e.g., NSAIDs ± colchicine, rilonacept, and glucocorticoids) as total number of investigator-assessed pericarditis recurrences (unadjudicated) divided by total patient-years (PY) while receiving that treatment.
  - Of 347 investigator-assessed pericarditis recurrences analyzed; 18.2% (n=63) met RHAPSODY adjudication criteria (See Table 2).
- Normally distributed data are presented as mean ± standard deviation (SD); all other data are presented as median [Q1, Q3] and n (%).

RESULTS

TABLE 1. Demographics and Patient Characteristics

Characteristics	All Patients (n=261)	First-line Rilonacept (n=6)	Remained on First-Line NSAIDs ± Colchicine* (n=83)	Transitioned to Second-Line IL-1 Pathway Inhibition (n=76)	Transitioned to Second-Line Rilonacept (n=52)	Transitioned to Second-Line Anakinra (n=24)	Transitioned to Second-Line Glucocorticoids (n=96)
Age at DCO†, years; median [Q1, Q3]	54 [43, 61]	57 [51, 67]	51.5 [47.5, 56]	54 [49, 63]	57 [50.5, 61]	53 [48, 57]	55 [43, 59]
Female, % (n)	62.1% (162)	50% (3)	57.8% (48)	67.1% (51)	60.5% (46)	48% (12)	61.5% (59)
Etiology, % (n) Idiopathic/ viral PPS Other	 85.8% (224) 8.8% (23) 5.4% (14)	 83.3% (5) 0% (0) 16.7% (1)	 84.3% (70) 13.3% (11) 2.4% (2)	 84.2% (64) 10.6% (8) 5.3% (4)	 86.5% (44) 7.7% (4) 7.7% (4)	 83.3% (20) 16.7% (4) 0% (0)	 88.5% (85) 4.2% (4) 7.3% (7)
Disease Duration at RP diagnosis‡, years; median [Q1,Q3]	0.3 [0.15, 0.5]	0.2 [0.1, 0.4]	0.3 [0.1, 0.6]	0.3 [0.15, 0.7]	0.3 [0.15, 1]	0.3 [0.2, 0.7]	0.2 [0.1, 0.6]
Disease Duration at last observation‡, years; median [Q1,Q3]	5.3 [2.8, 6.2]	3.9 [2.5, 4.6]	5.2 [3.9, 6.3]	5.3 [3.8, 6.7]	5.3 [3.7, 6.2]	4.9 [2.7. 5.3]	5.4 [3.1, 7.2]
Length of RESONANCE observation, years; median [Q1,Q3]	3.5 [2.9, 4.2]	3.4 [2.1, 4.1]	3.2 [2.4, 4.9]	3.5 [2.8, 4.4]	3.7 [2.2, 4.9]	3.4 [2.1, 5]	3.7 [2.6, 4.9]

*Patients remaining on NSAIDs ± Colchicine who did not escalate therapy to 2nd-line treatment.
†Age at DCO (Jan 15, 2026).
‡Pericarditis disease duration calculated as time from incident acute episode to last follow-up (ongoing disease) or to disease resolution (no flares while off all RP therapy ≥6 months)
DCO; data cutoff date; PPS, post-pericardiotomy syndrome; RP, recurrent pericarditis.

TABLE 2. Recurrence Rates Before and After Treatment Escalation

First-Line Therapy Upon RP Diagnosis	Second-Line Therapy After First-Line NSAIDs ± Colchicine[a]	First-Line Therapy Duration Median [Q1, Q3], Years	Second-Line Therapy Duration Median [Q1, Q3], Years	Annualized Recurrence Rate* (events/ PY)		Relative Risk Difference [P-value]	Reasons for Second -Line Treatment Transition
				On First-Line Therapy	On Second-Line Therapy		
Rilonacept[b] (n=6)	N/A	1.7[c] [0.9, 2.1]	N/A	0	N/A	N/A	N/A
NSAID ± Colchicine (n=83)	N/A	2.3 [1.6, 3.2]	N/A	0.76[d,e]	N/A	N/A	N/A
NSAID ± Colchicine	IL-1 Pathway Inhibition[b] (n=76)	1.9 [0.6, 3.7]	1.9 [1.4, 2.5]	0.93[d,f]	0.11[g]	-88.2% [<0.001]	Chest pain/ recurrence (n=67) Intolerance to prior therapy (n=3) Unknown (n=6)
NSAID ± Colchicine	Rilonacept[b] (n=52)	1.5 [0.5, 3.7]	2.1[h] [1.6, 2.5]	1.03[d,i]	0.014[j]	-98.6% [<0.001]	Chest pain/ recurrence (n=49) Intolerance to prior therapy (n=2) Unknown (n=2)
NSAID ± Colchicine	Anakinra[b] (n=24)	2.7 [0.8, 3.9]	1.4 [1.1, 2.6]	0.8[d,k]	0.5[l]	-37.5% [0.012]	Chest pain/ recurrence (n=21) Intolerance to prior therapy (n=2) Unknown (n=2)
NSAID ± Colchicine	Glucocorticoids[b] (n=96)	0.6 [0.1, 2]	0.7[m] [0.4, 0.9]	1.21[d,n]	2.04[o]	+68.6% [<0.001]	Chest pain/ recurrence (n=71) Intolerance to prior therapy (n=22) Unknown (n=7)

*ARR: total number of investigator-assessed pericarditis recurrences (e.g., chest pain + elevated CRP + EKG changes + friction/rub) divided by the total PY of follow-up. Of 347 investigator-assessed pericarditis recurrences analyzed, 18.2% (n=63/347) were confirmed by having met RHAPSODY adjudication criteria.
[a]Known reasons for second line treatment included chest pain/recurrence and/or intolerance to prior therapy.
[b]Primary therapy in treatment regimen.
[c]One patient transitioned from 1L rilonacept to 2L glucocorticoids due to pregnancy.
[d]Including 1* recurrence episode after management of incident episode with NSAIDs and/or colchicine and/or glucocorticoids.
[e]8% of events confirmed by chest pain+ RHAPSODY adjudication criteria; 6% did not meet RHAPSODY adjudication criteria; 86% had no CRP value ≤ 30 days of each event.
[f]16% of events confirmed by chest pain + RHAPSODY adjudication criteria; 14% did not meet RHAPSODY adjudication criteria, 71% had no CRP value ≤ 30 days of each event.
[g]37% of events confirmed by chest pain + RHAPSODY adjudication criteria, 16% did not meet RHAPSODY adjudication criteria, 47% had no CRP value ≤ 30 days of each event.
[h]1 pt transitioned to anakinra due to allergic reaction to rilonacept, 1pt transitioned to GCafter16.2months on therapy due to pt preference, 3 pts suspended rilonacept after 14 months (median) of therapy - investigator assessed pericarditis recurrences 1.2 months (median) after cessation (n=3) were managed with GC; 1 pt re-initiated rilonacept after 5.6 mo on GC.
[i]13% of events confirmed by chest pain+ RHAPSODY adjudication criteria, 17% did not meet RHAPSODY adjudication criteria; 70% had no CRP value ≤ 30 days of each event.
[j]50% of events did not meet RHAPSODY adjudication criteria, and 50% did not have a CRP value ≤ 30 days of each event All events were associated with dose interval elongation.
[k]18% of events confirmed by chest pain + RHAPSODY adjudication criteria, 7% did not meet RHAPSODY adjudication criteria; 74% had no CRP value ≤ 30 days of each event.
[l]35% of events confirmed by chest pain+ RHAPSODY adjudication criteria, 12% did not meet RHAPSODY adjudication criteria, and 53% had no CRP value ≤ 30 days of each event. 100% of events were associated with dose interval elongation.
[m]69% of GC-treated pts (n=66/96) escalated to 3L therapy, of whom 42% (n=28) transitioned to rilonacept (96% due to prior events on GC; 4% unknown), 12% (n= 8) to anakinra (all due to prior events on GC), and 45% (n=30) to NSAIDs/colchicine (67% due to prior events on GC; 17% intolerance; 17% patient preference).
[n]19% of events confirmed by chest pain+ RHAPSODY adjudication criteria, 15% did not meet RHAPSODY adjudication criteria, 66% had no CRP value ≤ 30 days of each event.
[o]41% of events confirmed by on chest pain+ RHAPSODY adjudication criteria, 8% did not meet RHAPSODY adjudication criteria; 52% had no CRP value ≤ 30 days of each event. 83% and 17% of events were associated with tapering and breakthrough, respectively.

RESULTS/DISCUSSION

- The analysis set at DCO included 261 patients (median age, 54 years; 62.1% female; 85.8% had idiopathic/viral etiology, and 8.8% had post-pericardiotomy syndrome; median disease duration at last observation 5.3 yrs; median observation period 3.5 yrs; **Table 1**).
- Of the patients initiating first-line NSAIDs ± colchicine (n=255), only 32.5% (n=83) remained on NSAIDs ± colchicine throughout the observation period and of these, 68.7% (n=57) increased the NSAID/colchicine dose.
- In total, 67.5% (n=172) advanced to second-line therapy (IL-1 pathway inhibition [44.2%; n=76] or GC [55.8%; n=96]*).
- Second-line rilonacept significantly reduced ARR versus prior NSAIDs ± colchicine (0.014 vs 1.03; 98.6% reduction; P<0.001), whereas second-line GC significantly increased ARR versus prior NSAIDs ± colchicine (2.04 vs 1.21; 68.6% increase; P<0.001; **Table 2**).
- Patients receiving second-line rilonacept treatment had significantly lower recurrence rates compared to those receiving second-line glucocorticoid treatment (ARR: 0.014 vs. 2.04, P=0.0016; **Table 2**).
  - The consistent reductions in recurrence risk during rilonacept treatment suggests that IL-1α/IL-1β pathway inhibition enabled continued targeted immunomodulation without interruption, leading to successful long-term disease control.
- Rilonacept-treated patients had the lowest escalation rate to next-line therapies (10.3% [6/58]), whereas 80.0% of patients on first-line NSAIDs ± colchicine (n=204/255) and 68.8% of patients on second-line glucocorticoids (n=66/96) escalated to next-line therapies.

*Rilonacept became commercially available in RP in April 2021; 47.9% (46/96) initiated GC prior to April 1, 2021, and 52.1% (50/96) initiated GC on or after April 1·2021

Limitations

- All data were derived from an interval analysis of an unlocked database from an ongoing registry; as such, data may be missing, incomplete, and/or may change with future data cleaning
- Pericarditis recurrences, hospitalizations and medication history which occurred prior to the 1-year retrospective observation period were not entered into the registry database and were not evaluated
- Suspected RESONANCE pericarditis recurrences were initially identified based upon investigator assessment, but only events confirmed based on clinical outcomes measures (i.e., pain, CRP ≥1 mg/dL, ECG, pericardial effusion, and pericardial friction rub) were used in this RESONANCE analysis; while robust, the most rigorous adjudication process has been the formal adjudication of suspected pericarditis recurrences performed by the independent CEC in RHAPSODY
  - Investigator-assessed pericarditis recurrence rates in this analysis may be an overestimate relative to actual confirmed event rates based on standardized adjudication criteria in controlled trials (e.g., RHAPSODY)
  - Missing/absent confirmatory data (e.g., CRP, imaging) due to variations in clinical practice may limit quantitative comparisons to rigorous clinical trial endpoints
- The inclusion of established pericardial-disease-dedicated programs, with principal investigators experienced in the management of RP, may limit generalizability
  - Findings derived from these institutions set the benchmark for best practices and inform clinical guidance within RP
  - However, further education or resourcing may be needed for implementation in community practice centers following the example of these established pericardial-disease-dedicated centers

CONCLUSIONS

- Second-line rilonacept (reflected in the 2025 ACC CCG) was superior to second-line glucocorticoids (consistent with the 2025 ESC Guidelines) in reducing recurrence rates, affirming the evidence-based shift to a glucocorticoid-sparing paradigm and the need for prompt escalation to effective 2nd-line therapies to improve patient outcomes.
- Less than one-third of patients who initiated first-line NSAIDs ± colchicine remained on NSAIDs ± colchicine throughout the observation period, of whom greater than two-thirds of these patients required dose increases.
- High rates of dose intensification, treatment escalation, and suboptimal disease control observed with first-line NSAIDs ± colchicine are important considerations when evaluating IL-1 pathway inhibition use earlier in the disease course to minimize recurrence burden and streamline long-term disease management.

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