Multi-Year Recurrent Pericarditis Disease Duration in Italian Patients: Clinical Outcomes After Cessation of Long-Term IL-1 Pathway Inhibition Provide Insights for Chronic Management

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BACKGROUND

Recurrent Pericarditis (RP)

- RP is a chronic autoinflammatory disease mediated by interleukin-1 (IL-1).[1]
- RP negatively impacts quality of life, and refractory disease requires treatment over a number of years.[1-3]
- Rilonacept, an IL-1α and IL-1β cytokine trap, is the only FDA-approved treatment for RP, supported by data from the pivotal trial, RHAPSODY.[3]
- The tools to guide treatment duration at the individual patient level are limited.

RHAPSODY

- In the Phase 3 trial RHAPSODY (randomized-withdrawal [RW] period and 2-year long-term extension [LTE]), rilonacept reduced the risk of recurrence over long-term treatment (96% and 98%, respectively).[3,4]
- Among LTE patients suspending rilonacept after 18 months of treatment, 75% (6/8) experienced recurrence.
- At the conclusion of the LTE, after a median of 28 months of rilonacept treatment (non-US patients), Italian patients (n=17) returned to standard management (rilonacept was not commercially available in Italy).

Purpose

Assess RP disease persistence and time to recurrence after study completion and rilonacept cessation/washout by retrospective medical record review of clinical outcomes in Italian RHAPSODY patients.

METHODS

Study Design

- Medical records of 17 Italian patients from 3 Italian centers were examined after RHAPSODY completion.
  - Prior to Last Study Visit, patients received the last rilonacept dose; treatment ceased per protocol without taper.
  - Patients transitioned to individualized standard management; clinicians elected to observe prospectively without empiric prophylactic treatment with colchicine (inflammasome inhibitor) or steroids.
- Medical record data were collected for the 18-month period after the last visit in the RHAPSODY LTE - June 2022 for all patients (defined as T_0), until November 2023 (data cutoff) (**Figure 1**).
  - All patients signed informed consent for retrospective chart review and data collection.

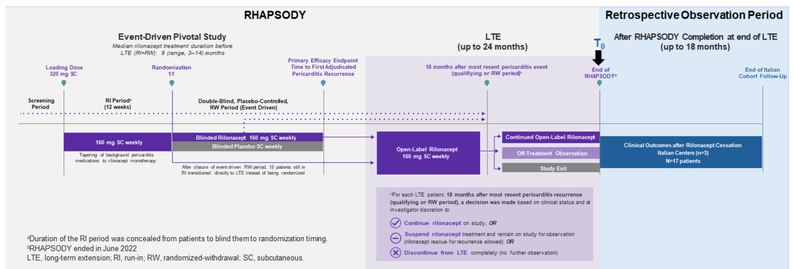
Medical Record Review of Clinical Outcomes

- **Primary outcome:** incidence of pericarditis recurrence (investigator-adjudicated post-hoc using RHAPSODY criteria: pericarditis pain NRS score ≥4, C-Reactive Protein (CRP) ≥1 mg/dL within 7 days of increased pain).
- **Secondary outcomes:** time to recurrence; proportion of patients requiring re-initiation of IL-1 pathway inhibition.
- **Safety outcomes:** post-trial serious adverse events (SAEs) (e.g., death, constriction, or tamponade).

Data Analysis

- Normally distributed data are presented as mean ± standard deviation (SD); all other data are represented as median [Q1-Q3] and n (%).
- Statistical analyses: For all analyses Mann-Whitney test was used at a (two-sided) significance level of 0.05.

FIGURE 1. STUDY DESIGN



RESULTS

DURING RHAPSODY – ITALIAN COHORT

TABLE 1. BASELINE DEMOGRAPHICS & DISEASE CHARACTERISTICS

RHAPSODY Baseline (at trial entry, prior to rilonacept initiation)	N = 17
Age, years, median (Q1-Q3)	49 (19-58)
Female sex, n (%)	8 (47.1%)
Cause of pericarditis, n (%)	
Post-cardiac injury syndrome	1 (5.9%)
Idiopathic	16 (94.1%)
Disease duration at baseline, months (Q1-Q3)	18 (11-27)
Total number of pericarditis episodes prior to baseline (including index & qualifying episode), median (Q1-Q3)	4 (4-6)
Pericarditis treatment before trial entry, n (%)	
NSAIDs	11 (64.7%)
Colchicine	10 (58.8%)
Steroids	11 (64.7%)
Other	2 (11.8%)
C-Reactive Protein level at qualifying episode, mg/dL, median (Q1-Q3)	2.1 (1.7-15.2)

TABLE 2. RW AND LTE PERIOD: RANDOMIZATION AND CLINICAL OUTCOMES

During RHAPSODY	N = 17
Patients who completed the run-in and entered the RW portion, n (%)	12 (70.6%)
Patients randomized to rilonacept, n (%)	5/12 (41.7%)
Patients randomized to placebo, n (%)	7/12 (58.3%)
Patients who completed the run-in and entered the LTE directly, n (%)	5 (29.4%)
Pericarditis recurrences during RW portion, n (%)	5/12 (41.7%)*
Patients Randomized to Rilonacept, n (%)	1/5 (20.0%)**
Patients Randomized to Placebo, n (%)	4/7 (57.1%)***
Pericarditis recurrences during LTE among patients (2/17) who suspended treatment at 18MDM€ for observation, n (%)	2/2 (100%)

*Patients who flared reinitiated rilonacept and remained on-treatment for the rest of the RW period
**Recurrence associated with temporary interruption of rilonacept; RW: randomized-withdrawal; LTE: long-term extension
***RW period closed prior to 1 of these patients reaching the median time to flare
€ At the 18-month decision milestone (18MDM), 15/17 remaining patients chose to remain on treatment without interruption

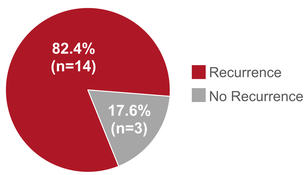
POST-RHAPSODY OBSERVATION PERIOD – ITALIAN COHORT (T_0 TO END OF FOLLOW-UP)

TABLE 3. DISEASE CHARACTERISTICS* AT RHAPSODY LAST STUDY VISIT (T_0)

At RHAPSODY last study visit (T_0)	N = 17
Total duration of continuous rilonacept treatment until T_0, months, median (Q1-Q3)	28 (27-30)
Total disease duration at T_0, months, median (Q1-Q3)	48 (41-56)
Patients stopping rilonacept at end of trial without taper, n (%)	17 (100%)
Patients receiving prophylactic oral treatment (e.g., NSAIDs, colchicine, steroids) after rilonacept cessation, n (%)	0 (0%)

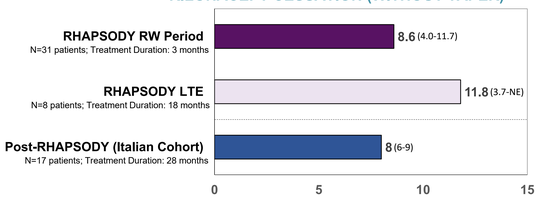
*At last study visit of RHAPSODY, all patients were in Clinical Response, i.e., no pain, normalized CRP, and on rilonacept monotherapy

FIGURE 2. PROPORTION OF PATIENTS WHO EXPERIENCED POST-TRIAL PERICARDITIS RECURRENCE*



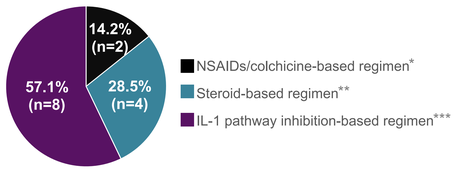
*Median (Q1-Q3) CRP levels during recurrences were 3.1 mg/dL (1.4-6.2)

FIGURE 3. TIME TO PERICARDITIS RECURRENCE* AFTER RILONACEPT CESSATION (WITHOUT TAPER)



*Data presented as median (Q1-Q3); NE: Not estimable

FIGURE 4. MEDICAL MANAGEMENT FOR POST-TRIAL OFF-TREATMENT RECURRENCES



* 5 patients started NSAIDs and/or colchicine, of whom 3 failed: 2 required steroid therapy, 1 required IL-1 pathway inhibition
** 1 patient started steroids directly, 1 patient started colchicine + steroids simultaneously; the remaining 2 started steroids after having failed NSAIDs and/or colchicine
*** Includes 1 patient who failed NSAIDs and subsequently initiated IL-1 pathway inhibition

- Patients requiring re-initiation of IL-1 pathway inhibition (n=8) vs others (n=6) had:
  - Longer overall disease duration
    - 56 months (Q1-Q3: 47-84) vs 42 months (Q1-Q3: 34-48), p=0.008
  - Higher plasma CRP concentrations at RHAPSODY baseline
    - 5.9 mg/dL (Q1-Q3: 4.0-17.8) vs 2.5 mg/dL (Q1-Q3: 1.6-4.2), p=0.021
- Neither recurrence frequency nor time to recurrence was significantly related to baseline demographics or disease characteristics
  - n=14 with recurrence vs n=3 without recurrence; p>0.05

DISCUSSION

- 17 Italian patients completed RHAPSODY after 48 months of disease duration and after 28 months of continuous monotherapy rilonacept treatment.
  - At trial completion, all patients were in Clinical Response with normal CRP.
  - There were no clinical or imaging biomarkers to indicate persistent disease.
- At trial completion, per protocol, patients stopped rilonacept treatment without taper or prophylactic therapy (i.e., no prophylactic colchicine or steroid use) for expectant observation.
- ~80% of these patients (14/17) subsequently experienced an off-treatment pericarditis recurrence, with increased pain and CRP>1 mg/dL but no hospitalizations or other complications.
- Baseline demographics or disease characteristics (disease duration, CRP levels) were not predictive of recurrence after rilonacept cessation.
- Time to pericarditis recurrence after rilonacept cessation (8 weeks) in the Italian cohort was consistent with the two prior observations from RHAPSODY also in which rilonacept was stopped without taper or empiric prophylactic oral therapy.
  - 8.6 weeks (RW); 11.8 weeks (LTE)
  - A two-week prodrome of increasing pain intensity was noted prior to reaching adjudication thresholds.[5]
- 57% of patients with recurrence required re-initiation of IL-1 pathway inhibition.
  - While 36% of patients with recurrence attempted management with NSAIDs/colchicine, only 14% of patients with recurrence were successfully managed with NSAIDs/colchicine.
  - Of patients who failed NSAIDs and/or colchicine rescue (3/14), 2 received steroids, and 1 received IL-1 pathway inhibition.

LIMITATIONS

- Patients were not randomized to interventions given the retrospective nature of the study.
- Cardiac magnetic resonance imaging data were not available for the majority of patients in the study.

CONCLUSIONS

- **RP is a severe persistent disease even after 4 years, as evidenced by the 80% recurrence rate following treatment cessation after 28 months of IL-1 pathway inhibition.**
- **A strategy of inflammasome inhibition alone was insufficient for managing pericarditis recurrences in these patients with long disease duration and systemic inflammation, necessitating re-initiation of advanced therapy.**
- **Time to pericarditis recurrence (approximately 2 months) after rilonacept cessation without taper was consistent with previous RHAPSODY data and predicted by the gradual washout pharmacokinetics of once-weekly rilonacept.[3,4]**
- **Three independent implementations of rilonacept cessation without taper confirm that this simpler evidence-based strategy of expectant management quickly and safely identified patients with persistent disease requiring continued treatment, an advance over once-daily IL-1 inhibitors, where complex tapering and empiric prophylactic colchicine bridge regimens have been used.[3,4]**
- **Further studies could quantify ideal treatment duration and individualized prospective criteria for treatment cessation after prolonged remission on IL-1 pathway inhibition.**

ACKNOWLEDGEMENTS

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DISCLOSURES

Massimo Imazio served on an advisory board for Kiniksa Pharmaceuticals; Lucia Trotta, Emanuele Bizzi, Massimo Pancrazi, Enrico Tombetti have no disclosures to report; Sheldon Wang, JoAnn Clair, & John F. Paolini are shareholders and employed by Kiniksa Pharmaceuticals; Allan L. Klein reports grants and consultant fees from Kiniksa Pharmaceuticals, Cardiol Therapeutics, and Pfizer; Antonio Brucato reports institutional funding from Kiniksa Pharmaceuticals as an investigative site, an unrestricted research grant from Sobi and Acarpia and travel and accommodation for advisory committee from Sobi and Kiniksa.

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