Cardiac Magnetic Resonance Imaging Paralleled Recurrent Pericarditis Clinical Response to Rilonacept Treatment Over 18 Months: a RHAPSODY Subgroup Analysis

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BACKGROUND

- Recurrent pericarditis (RP) is a chronic autoinflammatory disease with a median duration of 3 years and requires prolonged treatment.[1]
- Pericardial inflammation and disease activity/propensity can be assessed with high sensitivity by cardiac magnetic resonance (CMR) imaging, including late gadolinium enhancement (LGE).[2]
- In the phase 3 trial RHAPSODY, rilonacept, the interleukin 1 (IL-1) α and β cytokine trap, effectively resolved active pericarditis recurrences and reduced risk of recurrence during long-term treatment.[3]
  - In patients treated with rilonacept, greater LGE at baseline was associated with faster time to recurrence upon rilonacept suspension (randomization to placebo) after 12 weeks of treatment.[2]
- Longitudinal assessment by serial CMR imaging may be valuable for assessing clinical improvement, predicting patient outcomes, and helping to guide clinical decision-making in RP.[4]
- We present clinical and serial CMR data from patients who reached the 18-month decision milestone (18MDM) in the RHAPSODY long-term extension (LTE).

PURPOSE

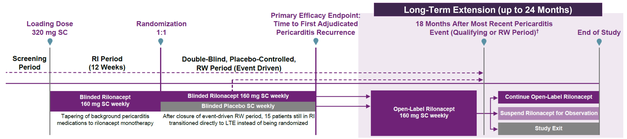
- To assess the utility of serial CMR imaging for guiding clinical decision-making in patients with RP.

METHODS

Study Design

- RHAPSODY was a phase 3, double-blind, placebo-controlled, randomized-withdrawal trial that enrolled 86 patients with a history of 2 or more pericarditis recurrences and an active recurrence.[3]
  - CMR was performed at selected study sites at prespecified time points to assess for changes in pericardial inflammation.
- At the end of the double-blind randomized-withdrawal period, patients could receive open-label rilonacept for up to 24 months in the LTE **(Figure 1)**.
- At the 18MDM (18 months after the most recent of either the qualifying pericarditis recurrence or randomized-withdrawal period flare) the investigator decided if each patient continued rilonacept treatment on study, suspended rilonacept but remained on study for off-treatment observation, or discontinued the study without further observation.

FIGURE 1. RHAPSODY STUDY DESIGN, INCLUDING PATIENTS IN THE CMR SUBSTUDY



18MDM, 18-month decision milestone; RI, run-in; RW, randomized-withdrawal; SC, subcutaneous.
Assessments at 18MDM: cardiac magnetic resonance, pain by numeric rating scale, C-reactive protein; electrocardiogram, effusion (echocardiogram), pericardial friction rub, Patient Global Impression of Pericarditis Severity, Physician Global Assessment of Pericarditis Activity.

Assessments

- LTE recurrences were investigator-assessed; individual clinical outcomes measures (pain by numeric rating scale [NRS], C-reactive protein [CRP], electrocardiogram [ECG], presence/absence of pericardial effusion by echocardiography, presence/absence of pericardial friction rub, Patient Global Impression of Pericarditis Severity, Physician Global Assessment of Pericarditis Activity) were collected and available for post-hoc review.
- CMR imaging results were assessed by an independent imaging core lab blinded to clinical data.
  - Pericardial thickness (mm) was assessed on black blood imaging.
  - Pericardial edema (T2-short tau inversion recovery [STIR] fat saturation) and LGE were based on prespecified criteria **(Table 1)**.

TABLE 1. GRADING CRITERIA FOR PERICARDIAL EDEMA AND LGE

Grade	Definition
None	No signal detected
Trace	Increased signal limited to <50% of cardiac circumference at 1 of 3 ventricle levels (base/mid-cavity/apex)
Mild	Increased signal involving >50% of cardiac circumference at 1 of 3 ventricle levels (base/mid-cavity/apex)
Moderate	Increased signal involving >50% of cardiac circumference at 2 of 3 ventricle levels (base/mid-cavity/apex)
Severe	Increased signal in >50% of cardiac circumference at all 3 ventricle levels (base/mid-cavity/apex)

RESULTS

RHAPSODY LTE Overall Clinical Outcomes Summary (Entire Study)

- There was a 98% reduction in risk of pericarditis recurrence among patients continuing rilonacept after the 18MDM vs those who suspended treatment for off-treatment observation (hazard ratio, 0.02; P<0.0001).[5]
  - Continued rilonacept after 18MDM (n=33): 1/33 (3.0%) had an investigator-assessed recurrence (NRS 8, CRP 7.5 mg/dL; met RHAPSODY event adjudication criteria) 23.4 weeks into the LTE, associated with an intentional 4-week rilonacept treatment interruption 2 weeks before elective surgery.
  - Suspended rilonacept at 18MDM for off-treatment observation (n=8): 6/8 (75.0%) had an investigator-assessed recurrence (NRS >7, CRP >1 mg/dL; met RHAPSODY event adjudication criteria); median (IQR) time to recurrence after suspension was 11.8 (3.7 to not estimable) weeks.
  - Discontinued rilonacept at 18MDM (n=11): During the post-treatment 6-week safety follow-up, 5 additional investigator-assessed pericarditis recurrences (NRS ≥6; CRP ≥1.9 mg/dL; met RHAPSODY adjudication criteria) were reported, at 3 weeks (n=1) and at 6 weeks (n=4).

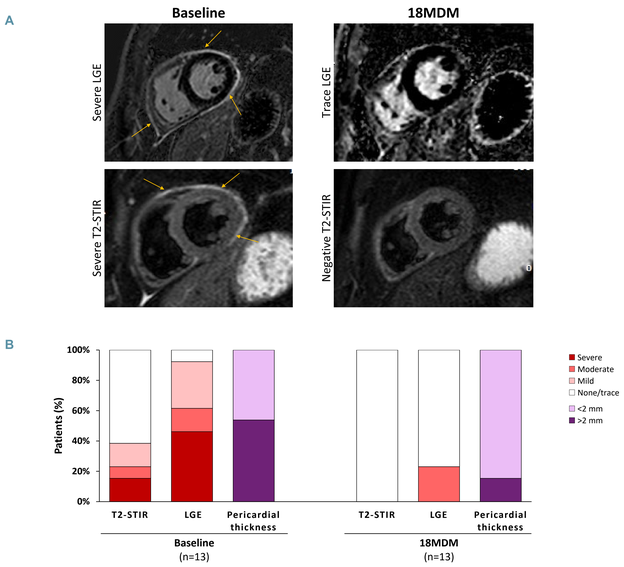
LTE Patient Disposition and CMR Substudy Analysis Datasets

- 74 patients entered the LTE:
  - 52/74 (70.3%) in the entire LTE reached the 18MDM:
    - 28/52 (53.8%) patients had CMR at the 18MDM
    - 13/52 (25.0%) patients had CMR at both baseline and 18MDM

CMR Endpoints: Change from Baseline to 18MDM

- Representative LGE and T2-STIR CMR images from the same patients at baseline and 18MDM are shown in **Figure 2A**.
  - Of the 13 patients with CMR data at both baseline and 18MDM, 12/13 (92.3%) showed improvement in LGE, T2-STIR, and pericardial thickness from baseline to 18MDM (**Figure 2B**) while on rilonacept treatment:
    - At baseline:
      - 5/13 (38.4%) patients had elevated T2-STIR
      - 12/13 (92.3%) patients had LGE
      - 7/13 (53.8%) patients had pericardial thickness of >2 mm
    - At 18MDM:
      - 13/13 (100%) patients had normal T2-STIR
      - 10/13 (76.9%) patients had no LGE
      - 11/13 (84.6%) patients had normal pericardial thickness (<2 mm)

FIGURE 2. (A) REPRESENTATIVE LGE AND T2-STIR (FAT SATURATION) IMAGES WITH GRADING FROM A PATIENT SHOWING IMPROVEMENT FROM BASELINE TO 18MDM (ARROWS INDICATE PERICARDIAL LGE/PERICARDIAL EDEMA). (B) CHANGE FROM BASELINE TO 18MDM FOR ALL PATIENTS WITH DATA AT BOTH BASELINE AND 18MDM.

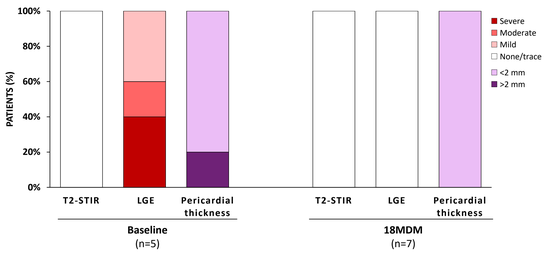


18MDM, 18-month decision milestone; LGE, late gadolinium enhancement; STIR, short tau inversion recovery

CMR Endpoints at 18MDM and Clinical Outcomes After 18MDM

- Of the 28 substudy patients with CMR data at 18MDM, all had CRP levels <1 mg/dL, absent pericardial rub, normal ECG, and no pericardial effusion at 18MDM
  - 14 substudy patients continued rilonacept after 18MDM:
    - CMR at 18MDM: LGE: 12 none/trace, 1 mild, 1 moderate
    - Clinical outcomes after 18MDM: no pericarditis recurrences while on treatment
    - Clinical outcomes post-study: After cessation of rilonacept treatment at end of study, following 28 and 25 months of total rilonacept treatment, 2/14 (14.3%) patients had a recurrence recorded at the 6-week post-treatment safety follow-up visit. Both patients had demonstrated no LGE at 18MDM (while on treatment).
  - 7 substudy patients suspended rilonacept at 18MDM for off-treatment observation:
    - CMR at 18MDM: LGE: all normal; T2-STIR: all normal; pericardial thickness <2 mm (**Figure 3**)
    - Clinical outcomes after 18MDM: 5/7 (71.4%) had recurrences within 1-4 months after rilonacept suspension despite receiving prophylactic colchicine (n=2)
  - 7 substudy patients discontinued the study after 18MDM:
    - CMR at 18MDM: LGE: 4 none/trace, 1 mild, 2 moderate
    - Clinical outcomes post-study: no pericarditis recurrences off treatment within the 6-week safety follow-up period

FIGURE 3. CMR RESULTS AT BASELINE AND 18MDM FOR PATIENTS WHO SUSPENDED RILONACEPT FOR OFF-TREATMENT OBSERVATION



18MDM, 18-month decision milestone; CMR; cardiac magnetic resonance; CRP, C-reactive protein; ECG, electrocardiogram; LGE, late gadolinium enhancement; STIR, short tau inversion recovery.
Of 8 patients who suspended rilonacept for off-treatment observation at 18MDM, CMR was not assessed for 3 at baseline and 1 at 18MDM. All 8 patients were negative for symptoms, CRP, ECG, echo/effusion, and exam/rub at 18MDM.

- **Together, these results suggest absence of pericardial LGE while on treatment lacks predictive value for risk of future pericarditis recurrence after rilonacept cessation/suspension.**

LIMITATIONS

- This study was limited by a small number of patients with available CMR data.
- The protocol did not stipulate specific CMR or conditions that had to be met for the 3 different management decisions at 18MDM.
- Recurrence events during the LTE were investigator-assessed and were not externally adjudicated.
- For those who discontinued the study at 18MDM, potential events occurring after the 6-week safety follow up period had ended would have been outside of the observational gaze of the trial, so these observed event counts may be an underestimate.

CONCLUSIONS

- **Previous RHAPSODY data (RI/RW period) demonstrated that higher levels of residual pericardial LGE are associated with faster time to recurrence upon treatment suspension.**
- **T2-STIR and LGE were present during acute flares at baseline, and rilonacept treatment reduced T2-STIR and LGE at 18MDM.**
- **Absence of LGE after 18 months on treatment did not predict reduced recurrence risk upon subsequent suspension of rilonacept therapy.**
- **Larger prospective studies are warranted to further elucidate CMR parameters for guiding RP treatment duration decisions and informing associated clinical outcomes.**

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors would like to acknowledge Nate Connors, PhD from Acumen Medical Communications for medical writing assistance. Paul C Cremer: grants and personal fees from Kiniksa Pharmaceuticals; grants from Novartis Pharmaceuticals; and personal fees from SOBI Pharmaceuticals outside the submitted work. Antonio Brucato: unrestricted research grant from SOBI and ACARPIA; travel and accommodation for advisory committee from SOBI and Kiniksa. Antonella Insalaco: travel and accommodation for advisory committee from SOBI. David Lin: advisory board for Kiniksa Pharmaceuticals. Sushil A. Luis: consultant for Kiniksa Pharmaceuticals, Cardiol Therapeutics and Medtronic. Deborah H Kwon: funding from the National Heart, Lung, and Blood Institute of the National Institute of Health. Christine Jellis: none. Massimo Imazio: scientific advisory board for Kiniksa Pharmaceuticals. Allan L. Klein: research grant and scientific advisory boards for Kiniksa Pharmaceuticals and Cardiol Therapeutics, scientific advisory board for Pfizer, consultant to Kiniksa Pharmaceuticals. Allison Curtis, JoAnn Clair, Sheldon Wang: employees of Kiniksa Pharmaceuticals. John F. Paolini: Employee and shareholder of Kiniksa Pharmaceuticals; inventor on patents/patent applications covering the use of rilonacept for the treatment of recurrent pericarditis.
This study was sponsored by Kiniksa Pharmaceuticals.

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