Neutrophil to lymphocyte ratio for tracking inflammation and recurrence in patients with recurrent pericarditis: post hoc assessment of a phase 3 trial, RHAPSODY

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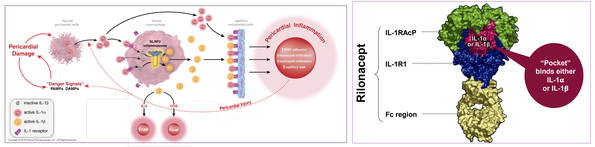
BACKGROUND

Recurrent Pericarditis (RP)

- Chronic, debilitating autoinflammatory disease often requiring months to years of treatment[1-3]

Role of IL-1

- Interleukin 1 (IL-1) has been implicated as a key mediator of recurrent pericarditis[4-8]



Rilonacept

- Once-weekly IL-1α and IL-1β cytokine trap
- Phase 3 clinical trial RHAPSODY (NCT03737110) demonstrated efficacy and safety of rilonacept in patients with RP[9]
  - RHAPSODY data helped support FDA approval of the first therapy for RP[10]

Measures of RP

- Measurement of inflammation in patients with RP is essential for disease monitoring
- C-reactive protein (CRP), a standard acute phase reactant for monitoring inflammation in rheumatic diseases, is elevated during acute pericarditis episodes and normalizes with treatment and episode resolution
- However, patients with RP often require months to years of therapy, indicating persistence of underlying auto-inflammation which is not reflected in the normalized CRP while on treatment
  - A similar "flooring effect" is reported with CRP in patients with rheumatoid arthritis[11-12]

Neutrophil to lymphocyte ratio

- Neutrophil to lymphocyte ratio (NLR) has prognostic value in some inflammatory diseases[12-13]
- NLR, a measure of immune system equilibrium, is an indicator of poor prognosis in myocardial infarction, coronary artery disease, atherosclerosis and chronic obstructive pulmonary disease[14]
- While no threshold for NLR elevation has been established in patients with RP, an NLR of 1 to 3 is generally considered normal, and a recent study found that normal NLR in adult, non-geriatric, healthy patients is between 0.78 and 3.53[15]
- Although CRP is used fairly widely, it isn't readily available in all locations and circumstances; we aimed to test the utility of neutrophil to lymphocyte ratio as an indicator of inflammation in RP, considering the broad availability of cell counts with routine blood draws.

RHAPSODY[9,16]: Global, Double-blind, Placebo-controlled, Randomized Withdrawal Phase 3 Study

Inclusion Criteria:

- Presenting with at least 2nd pericarditis recurrence; pain NRS ≥4, CRP≥1 mg/dL
- NSAIDs/Colchicine/Corticosteroids in any combination
- Multiple etiologies

Definition of Clinical Response

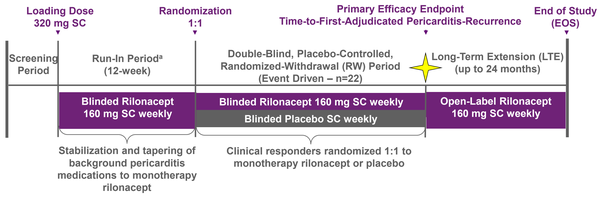
- Weekly average of daily pericarditis pain of ≤2.0
- CRP level ≤0.5 mg/dL
- On monotherapy study drug without a recurrence

Primary Efficacy and Key Secondary Endpoints

- Time to first pericarditis recurrence
- Percentage of patients with persistent clinical response

Post Hoc Analysis

- NLR change from Run-In (RI) Baseline (BL) to wk 12 after rilonacept initiation
- Time to pericarditis recurrence in patients randomized to placebo with baseline neutrophil to lymphocyte ratio (NLR) of ≤4 versus >4



[a]The duration of the run-in period was concealed from patients so that they were blinded to the timing of randomization

OBJECTIVE

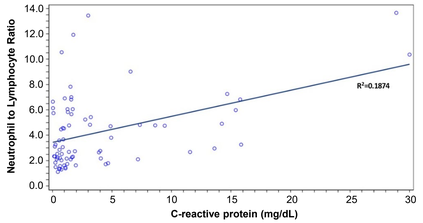
To explore NLR for monitoring RP by examining its association with inflammatory state, response to IL-1 antagonism, and pericarditis recurrence in a controlled study population.

RESULTS

No strong association between NLR and CRP during acute RP episodes (Baseline)

- In the 86 patients enrolled in the study,
  - Mean CRP at qualifying: 6.2 mg/dL; 100% (86/86) had elevated CRP (≥0.5 mg/dL)
  - Mean CRP at baseline: 3.7 mg/dL; 80% (68/85) had elevated CRP (≥0.5 mg/dL)
- At baseline, NLR was not strongly associated with CRP
- At baseline, 36% (27/74) of patients had NLR>4

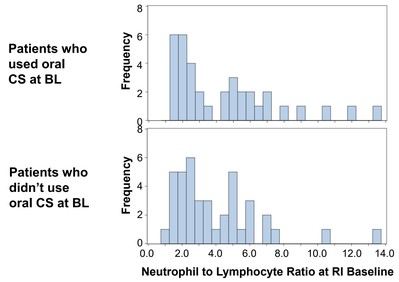
FIGURE 1. SCATTER PLOT OF BASELINE C-REACTIVE PROTEIN VERSUS NLR IN ALL PATIENTS*



*Of 86 patients enrolled, 76 had NLR at baseline and 74 had both NLR and CRP on the same day at baseline

Corticosteroid use did not impact NLR in this group of patients

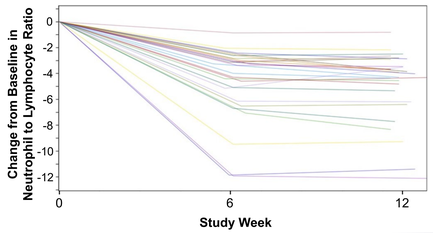
FIGURE 2. FREQUENCY OF PATIENT NLR LEVEL AT BASELINE IN THOSE WHO USED ORAL CS AT BASELINE AND THOSE WHO DID NOT



NLR decreased after rilonacept treatment during the run-in period

- Rilonacept initiation resulted in decrease in NLR by week 6, the first timepoint collected after baseline

FIGURE 3. NLR CHANGE FROM BASELINE IN INDIVIDUAL PATIENTS WITH BASELINE NLR>4 DURING TREATMENT WITH RILONACEPT DURING THE RI PERIOD

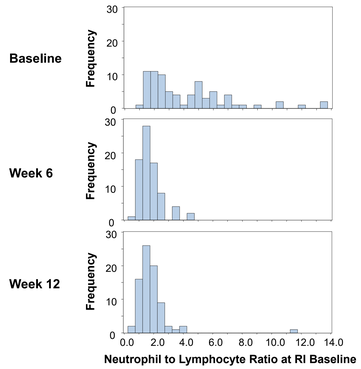


Treatment with rilonacept resulted in normalization* of NLR to ≤4 during the run-in period

- Of the patients with NLR >4 at baseline, 90.3% normalized* to ≤4 by week 6 (28 of 31‡ patients)
- Of patients with NLR >4 at baseline, 100% normalized* to ≤4 by week 12 (30 of 30‡ patients)

*Normalized defined as NLR≤4
‡In order to be considered for each analysis, patients were required to have NLR data at baseline and at the specific final timepoint, i.e., week 6 or week 12.

FIGURE 4. FREQUENCY OF PATIENT NLR LEVEL AT RI BASELINE, WEEK 6, AND WEEK 12



Patients with NLR >4 at baseline had shorter time to recurrence after randomization to placebo as well as more recurrences

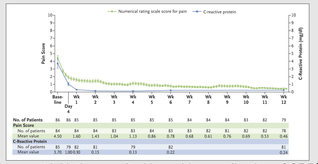
- The trend of more recurrences and shorter time to recurrence in those with baseline NLR>4 suggests that higher NLR could be indicative of a higher degree of inflammation at baseline
- Event rate and time to event was not associated with NLR level reached by week 12 of treatment (data not shown)

TABLE 1. RISK OF RECURRENCE AND TIME TO RECURRENCE IN PATIENTS WITH BASELINE NLR≤4 AND BASELINE NLR>4.

Outcomes	BL NLR≤4 n=14*	BL NLR>4 n=12*	Statistical Analyses
Number (%) of patients with recurrence	10 (71.4)	11 (91.7)	HR: 0.56 95% CI: 0.22, 1.39 p<0.1983
Median (95% CI) time-to-recurrence (weeks)	7.9 (3.7, 32.1)	5.2 (2.1, 15.0)	

*Placebo patients with NLR at Run-in Baseline. Of 86 patients enrolled, 76 had NLR at baseline, and 74 had both NLR and CRP on the same day at baseline. Of these, 52 were randomized (26 to rilonacept and 26 to placebo)

Mean (SE) Numerical Rating Scale Scores for Pain and C-Reactive Protein Levels over the 12-Week Run-In Period.



- Rilonacept initiation resulted in rapid normalization of CRP[9]
- Median (95% CI) time to CRP normalization was 7 (5, 8) days[9]

From New England Journal of Medicine, Klein and Imazio et al, Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent Pericarditis, 384, 31-41. Copyright 2021 Massachusetts Medical Society. Reprinted with permission.

CONCLUSIONS

In this post hoc analysis of RHAPSODY:

- A significant number of patients had elevated NLR at baseline (36% with NLR>4), although there was no association of magnitude of NLR at baseline with CRP
- Treatment with rilonacept resulted in reduction of NLR consistent with treatment response (NRS and CRP) during the run-in phase; NLR had normalized in 90.3% of patients by week 6 (the earliest timepoint available after baseline)
- Patients with high NLR at baseline trended towards poorer outcomes after randomization to placebo when compared to those with lower NLR at baseline, including:
  - Trend of increased risk of recurrence (91.7% with NLR >4 vs 71.4% with NLR≤4)
  - Trend of shorter time to recurrence (5.2 weeks with NLR >4 vs 7.9 weeks with NLR≤4)
- While Acute Phase Reactants like CRP remain the most rapid and sensitive measure of inflammation and treatment response, NLR may be a readily accessible supplementary method to monitor disease activity in patients with recurrent pericarditis. Further validation is needed.

LIMITATIONS

- Patient subgroups are small in this post hoc analysis
- NLR was more widely available at the baseline timepoint than at the time of qualifying episode. NLR at the baseline visit is likely to differ from that recorded for the qualifying pericarditis episode; to allow for the completion of screening procedures, the investigator was permitted to treat each patient with standard-of-care medications temporarily during the interval between presentation with the qualifying episode and the baseline visit or trial enrollment.

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John F. Paolini reports personal fees and other from Kiniksa Pharmaceuticals and is a patent inventor on pending patent applications licensed to Kiniksa Pharmaceuticals covering methods of using rilonacept for treating recurrent pericarditis.
Bryan Abadie and Joshua Saef have nothing to disclose.

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