Health-related Quality of Life in Patients With Recurrent Pericarditis: Results From a Phase 2 Study of Rilonacept

David Lin (✉ David.Lin@allina.com)

Minneapolis Heart Institute, Minneapolis, Minnesota, USA <https://orcid.org/0000-0001-5076-8737>

Allan Klein

Cleveland Clinic

David Cella

Northwestern University

Anna Beutler

Kiniksa Pharmaceuticals Ltd

Fang Fang

Kiniksa Pharmaceuticals Corp

Matt Magestro

Kiniksa Pharmaceutical Corp

Paul Cremer

Cleveland Clinic

Martin M. LeWinter

University of Vermont Medical Center

Sushil Allen Luis

Mayo Clinic

Antonio Abbate

Virginia Commonwealth University

Andrew Ertel

Medstar Heart and Vascular Institute

Leighann Litcher-Kelly

Adelphi Values

Brittany Klooster

Adelphi Values <https://orcid.org/0000-0002-2018-8982>

John F. Paolini

Kiniksa Pharmaceuticals Corp.

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Abstract

Background: Impact of recurrent pericarditis (RP) on patient health-related quality of life (HRQoL) was evaluated through qualitative patient interviews and as an exploratory endpoint in a Phase 2 trial evaluating the efficacy and safety of rilonacept (IL-1 α /IL-1 β blocker) to treat RP.

Methods: Qualitative interviews were conducted with ten adults with RP to understand symptoms and HRQoL impacts, and the 10-item Patient-Reported Outcomes Measurement Information System Global Health (PROMIS Global) v1.2 was evaluated to determine questionnaire coverage of patient experience. The Phase 2 trial enrolled participants with active symptomatic RP (A-RP, n=16) and corticosteroid-dependent participants with no active recurrence at baseline (CSD-RP, n=9). All participants received rilonacept weekly for 6 weeks during a base treatment period (TP) plus an optional 18-week extension period (EP). Concomitant medications, including corticosteroids (CS), were tapered, if possible, during EP. HRQoL was assessed using the PROMIS Global, and patient-reported pain and blood levels of c-reactive protein (CRP) were also collected at Baseline and follow-up periods.

Results: Information from qualitative interviews demonstrated that PROMIS GH concepts are relevant to adults with RP. From the Phase 2 trial, both participant groups showed impacted HRQoL at Baseline [mean PROMIS Global Physical Health (GPH) and Global Mental Health (GMH), were lower than population norm average]. In A-RP, GPH/MPH improved by end of base TP and were sustained through EP (similar trends were observed for pain and CRP). Similarly, in CSD-RP, GPH/MPH improved by end of TP and further improved at EP, during CS tapering or discontinuation, without disease recurrence (low pain scores and CRP levels continued during the TP and EP).

Conclusion: This is the first study demonstrating impaired HRQoL in RP. Rilonacept treatment was associated with HRQoL improvements using PROMIS GH scores. Maintained/improved HRQoL during tapering/withdrawal of CS without recurrence suggests that rilonacept may provide an alternative to corticosteroids.

Trial Registration: ClinicalTrials.gov; NCT03980522; 5 June 2019, retrospectively registered; <https://clinicaltrials.gov/ct2/show/NCT03980522>

Introduction

Pericarditis, or inflammation of the pericardium, has a variety of etiologies but is most commonly referred to as idiopathic. The primary symptom of pericarditis is debilitating chest pain. Pericarditis is considered recurrent if symptoms and inflammation recur at least 4 weeks after an initial acute episode. Recurrent pericarditis (RP) affects approximately 15–30% of patients who have an acute episode of pericarditis, and up to 50% of patients who experience one recurrence will experience two or more. There are currently no FDA-approved therapies for pericarditis or RP; however, exploratory therapy with nonsteroidal anti-inflammatory drugs [NSAIDs] and colchicine is a standard often used successfully to treat the first pericarditis episode or initial recurrence. Treatment options are limited and there is a high unmet medical

need for patients who have inadequate response (i.e., continued recurrence or incomplete symptom resolution) to or who cannot tolerate standard therapy.

While the impact of RP on patients' health-related quality of life (HRQoL) has been reported in the literature [1–4] and is thought to be due to the primary symptom of the condition (e.g., chest pain) and the resulting uncertainty and anxiety of new recurrences, impact to HRQoL has not been explicitly evaluated in previous clinical research. In addition, corticosteroids are widely used to treat RP [5], putting patients at risk for steroid-dependence [6]; comorbidities associated with chronic corticosteroid use may also lead to adverse impacts on HRQoL [7, 8].

Both qualitative and quantitative research approaches were used to explore the HRQoL impacts experienced by adults with RP and how those impacts may change in response to treatment. Qualitative interviews were conducted with ten adults with RP to document the patient experience of RP symptoms and HRQoL impacts (known as concept elicitation interviews). Results from these interviews were used to develop a conceptual model of RP. In addition, a Phase 2 clinical trial of rilonacept (an IL-1 α /IL-1 β blocker) for the treatment of RP included a HRQoL patient-reported outcome (PRO) questionnaire as an exploratory endpoint. Therefore, the objective of these two streams of research is to evaluate HRQoL in patients with RP; specifically, to confirm whether the concepts assessed with the HRQoL PRO questionnaire used in the Phase 2 clinical trial are relevant to patients with RP (based on patient reports during the qualitative interviews) and to evaluate the effect of rilonacept treatment on physical and mental aspects of HRQoL.

Methods

The sections below describe the methodology used for both the qualitative interviews with patients and the clinical trial study design relevant to the current research objective.

Methods for qualitative patient interviews to develop a patient-centric conceptual model

To understand the patient experience of RP, one-on-one telephone interviews were conducted with adults with a confirmed diagnosis of RP.

Participants for qualitative interviews

The qualitative interview study was approved by a centralized independent review board (IRB) and following approval, potentially eligible participants were identified from clinical sites through review of medical records. Key inclusion criteria for the qualitative study included: age 18 years or older and a clinical diagnosis of RP (either idiopathic or due to post-pericardiotomy syndrome, adult onset Still's Disease, or Dressler's Syndrome), defined as the first episode of acute pericarditis (as defined by the 2015 European Society of Cardiology [ESC] Guidelines for the Diagnosis and Management of Pericardial

Diseases) [9] followed by at least one pericarditis recurrence after a symptom-free interval of at least 4–6 weeks. Key exclusion criteria for the study included: individual was currently enrolled in another clinical interventional study for RP; individual had a diagnosis of RP that was secondary to specific prohibited etiologies, including tuberculosis, neoplastic, purulent, or radiation, post-thoracic blunt trauma, myocarditis, or systemic autoimmune diseases (with the exception of adult onset Still's Disease).

Potentially eligible participants were presented with study information by a recruiting clinician (or his/her representative), and once participants provided a signed informed consent form, the clinical site completed a screening document to determine participants' eligibility. Participant interviews were scheduled once eligibility was confirmed.

Interview conduct

One-on-one, 60-minute telephone interviews with ten adults aged 18 to 75 years with RP were conducted. Interviewers used a semi-structured interview guide to facilitate the conversation and included open-ended questions to understand the patient experience of RP and its treatments, specifically, what signs, symptoms, and HRQoL impacts are experienced in relation to RP from the patient perspective.

Interview guide questions included:

- “Could you please start by telling me about the first signs or symptoms of [participant's term for RP] you noticed?”
- “Does the [patient-reported sign/symptom] have any impact on your daily life? If so, how?”
- “Have there been any changes to your daily life because of [participant's term for RP]? If so, can you please describe?”

Data handling and analysis

Interviews were audio-recorded after obtaining participant consent, transcribed and anonymized. These transcripts were coded and qualitatively analyzed using the ATLAS.ti software program. The goals of transcript coding were to organize and catalog participants' descriptions of the characteristics of RP, in order to develop a patient-centric conceptual model of RP signs, symptoms, and impact concepts. A conceptual model is a heuristic classification scheme that links a specified disease state or condition to its proximal and increasingly distal health outcomes [10], acts as a framework for understanding a disease and/or its treatment, specifies the potentially relevant outcomes for a program of research, and informs the selection of measurement concepts to foster the development of questionnaires, outcomes, and endpoints. Specifically, to characterize the specific applicability of the Patient Reported Outcome Measurement Information System Global Health (PROMIS GH v1.2) [10] questionnaire (described below) for capturing the HRQoL impacts experienced by patients with RP, conceptual mapping was conducted to compare the concepts within the conceptual model against PROMIS GH v1.2 individual items.

Methods for the Phase 2 study KPL-914-C001

The methodology of the Phase 2 clinical trial of rilonacept for the treatment of RP (clinicaltrial.gov: NCT03980522) is provided in detail in Klein and colleagues (in press). To summarize, this was a multicenter, open-label, single-active-arm Phase 2 study which enrolled adults with RP who either were having an active recurrence at baseline or who were not having an active recurrence but were dependent on corticosteroids. All participants received weekly subcutaneous (SC) injections of rilonacept for 6 weeks during the treatment period (TP) and were invited to continue weekly SC injections for up to 18 weeks in the extension period (EP).

Participants

Adults (18–75 years of age) with RP (idiopathic or post-pericardiotomy syndrome etiology) were enrolled and stratified into one of two participant groups: (1) those with an active recurrence at baseline (with at least two additional prior recurrences; A-RP), or (2) those without an active recurrence who were dependent on corticosteroids (and had had at least three prior recurrences; CSD-RP). Participants in the A-RP group had either evidence of elevated c-reactive protein (CRP) at baseline or did not have elevated CRP potentially due to concomitant medications (such as corticosteroids) but had evidence of pericardial inflammation by cardiac Magnetic Resonance Imaging. Participants in the CSD-RP group had corticosteroid-dependent disease (based on information from the investigator regarding prior recurrences when taking medication) and did not have active pericarditis symptomatology or elevated CRP at baseline.

Assessments

Weekly in TP, and then monthly blood levels of CRP, were evaluated to measure inflammation from baseline to the end of the EP for all participants. In addition, two PRO questionnaires were completed by all participants during the clinical trial. They included:

1. A single-item 11-point numeric rating scale (NRS) for average pericarditis pain intensity with a 24-hour recall window (with 0 = no pain to 10 = pain as bad as it could be) [11–13] was completed weekly in TP and monthly in EP from baseline to the end of the EP.
2. The 10-item PROMIS GH v1.2 questionnaire was also completed by participants at up to five time points during the clinical trial to assess HRQoL [14]. The analyses presented here focused on the following three most critical timepoints: baseline (Day 0), end of TP (Week 6), Final Visit (end of EP). Items 1–7 ask participants to think about their general health and are rated on a five-point response scale (with higher number associated with better quality of life). Items 8–10 ask participants to report on the emotional problems, fatigue, and pain over last seven days, with Items 8 and 9 rated on a five-point response scale (with higher scores associated with better quality of life), and Item 10 rated on a 0–10 NRS (with higher scores associated with more pain). Two domain scores are created from the 10-item scale, the global physical health (GPH), and the global mental health (GMH). The GPH is scored by averaging together the global03 (physical health), global06 (physical function), global07 (pain) and global08 (fatigue) items. The GMH is scored by averaging together the global02 (quality of life), global04 (mental health), global05 (satisfaction with discretionary social activities),

and global10 (emotional problems) [14]. The published US-generalized normative scores for both of these domains are a mean score of 50, and a standard deviation of 10 [14].

Procedure and Analyses

All participants received rilonacept SC injections weekly for 6 weeks until the end of TP and were invited to continue weekly SC injections (at the same dose) during an optional 18-week EP. For those on other concomitant medications for RP at baseline (participants in both the A-RP and CSD-RP groups), including corticosteroids, the option to taper was offered during the EP. Participants completed the PRO questionnaires (PROMIS and Pain NRS) at study visits, including telephone and site visits. Blood levels for CRP were also assessed during clinical site visits or via visiting nurse or local contract laboratory; CRP was analysed via a central laboratory.

The analyses presented in the results are descriptive, given the small sample size of the clinical trial and the single-active arm design. Specifically, results are reported as Means and Standard Deviations, with ranges of values for each participant group. While participants were asked to complete the HRQoL questionnaire at multiple time points in the clinical trial, the analyses focus on the baseline, (Day 0), end of base TP (Week 6), and Final Visit at end of EP timepoints. In addition, the descriptive analyses also include the weekly pericardial pain NRS scores and CRP blood levels that were collected at study visits.

Results

Qualitative patient interviews:

Qualitative interviews were conducted via telephone with ten adults diagnosed with RP to understand the patient experience of the condition, including the signs, symptoms, and health-related quality of life impacts. Participants were recruited from three clinical sites in the US. The mean age of the participants was 58.5 years (SD = 11.5), and six participants (60.0%) were female. Clinicians reported that participants exhibited the following RP types: idiopathic (n = 4, 40.0%), post-pericardiotomy syndrome (n = 4, 40.0%), adult-onset Still's Disease (n = 1, 10.0%), or Dressler's syndrome (n = 1, 10.0%). The majority of participants reported taking over-the-counter or prescription anti-inflammatory medications (n = 7, 70.0%), and half reported that they had previously taken corticosteroids (n = 5, 50.0%) for their RP.

A total of 13 symptoms and 34 impacts across 11 domains were reported by participants during these qualitative interviews and were organized into a conceptual model (Fig. 1). All participants reported experiencing chest pain (n = 10, 100.0%), with seven (n = 7, 70.0%) stating it is the most bothersome symptom, and five (n = 5, 50.0%) reporting it is the most important symptom to improve. After chest pain, the next most frequently reported signs or symptoms reported by at least half of participants, were tiredness (n = 8, 80.0%), shortness of breath (n = 7, 70.0%), fever (n = 6, 60.0%), and heart palpitations (n = 5, 50.0%). The most frequently reported impacts (reported by at least half of the participants) were inability to exercise (n = 8, 80.0%), disrupted sleep (n = 7, 70.0%), fear (n = 6, 60.0%), inability to go to

social events (n=6, 60.0%), interruption of daily activities (n = 6, 60.0%), absenteeism (n = 5, 50.0%), and impaired ability to do housework (n = 5, 50.0%).

In order to confirm that the assessment of HRQoL completed by participants in the Phase 2 clinical trial captured concepts relevant to adults with RP, concepts reported during the qualitative interviews were mapped to the ten items of the PROMIS Global Health v1.2 questionnaire. Table 1 shows the results of this exercise, with representative patient quotes from the qualitative interviews for each of the items of the PROMIS GH questionnaire. In particular, adults reported symptoms and HRQoL impacts during the interviews, that are included in the PROMIS GH questionnaire, such as pain, social and emotional impacts, and physical functioning.

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Phase 2 study rilonacept

Twenty-five participants were enrolled in a multicenter, open-label, single-active-arm Phase 2 clinical trial of rilonacept, with an average age of 42.8 ± 10.5 years ($\pm$ indicates standard deviation; range 26–62); most were female (n = 15, 60.0%) and white (n = 22, 88.0%). Participants had a mean number of prior recurrences of 2.6 (range 1–8), and average duration of disease of 2.2 ± 1.9 years (range 0.2 to 7.9 years), and average number of pericarditis episodes per year of 3.9 ± 3.7 (range 0.54-15). Based on their baseline symptoms and signs of pericardial inflammation, there were two groups of participants: those experiencing an active recurrence (A-RP; n = 16), and those who were corticosteroid-dependent but not acutely symptomatic at baseline (CSD-RP; n = 9). See Table 2 for the demographics and health characteristics of these two participant groups.

Table 2
Demographics and health characteristics of Phase 2 clinical trial sample

Characteristic	Active recurrence (A-RP) N = 16	Not symptomatic, Corticosteroid-dependent (CSD-RP) N = 9
Age (years) (Mean $\pm$ standard deviation [SD] [range])	39.8 $\pm$ 10.52 (26–58)	48.2 $\pm$ 8.56 (36–62)
Gender (% female)	75.0% (n = 12)	33.3% (n = 3)
Race (% white)	81.3% (n = 13)	100% (n = 9)
BMI (kg/m²) (Mean $\pm$ SD [range])	31.99 $\pm$ 7.51 (23.4–52.7)	28.97 $\pm$ 4.68 (22.5–34.3)
Duration of disease (years) (Mean $\pm$ SD [range])	2.6 $\pm$ 2.13 (0.2–7.9)	1.4 $\pm$ 0.97 (0.6–3.4)
Number of prior recurrences (median, [range])	2 (1–8)	3 (2–5)
Baseline NRS (Pain Rating 0–10; Mean $\pm$ SD [range])	4.6 $\pm$ 1.82 (2–8)	1.4 $\pm$ 1.51 (0–5)
Baseline CRP values (mg/dL) (Mean $\pm$ SD [range])	3.8 $\pm$ 5.30 (0.09–19.84)	0.19 $\pm$ 0.11 (0.05–0.36)
Concomitant medications at baseline		
Aspirin (n [%])	0 (0%)	2 (22.2%)
NSAID (n [%])	7 (43.8%)	5 (55.6%)
Colchicine (n [%])	12 (75.0%)	8 (88.9%)
Corticosteroids (CS) (n [%])	6 (37.5%)*	9 (100.0%) [†]
*4/6 (66.7%) discontinued CS and 1/6 (16.7%) tapered CS by end of EP; 1/6 (16.7%) did not enter EP.		
[†] 7/9 (77.8%) discontinued CS and 1/9 (11.1%) tapered CS by end of EP; 1/9 (11.1%) did not enter EP.		

Scores from the PROMIS GH questionnaire items and domains were evaluated for each of the participant groups over time (baseline, end of TP, and end of EP). Figure 2 shows the baseline scores for the two domains of the PROMIS GH health questionnaire. For both the A-RP and CSD-RP groups, average scores for these domains are below the US normative average score of 50. Additionally, Table 3 shows a trend for improvement in some item and domain scores for both the A-RP and CSD-RP groups.

Table 3
PROMIS Global Health item and domain scores over time (mean $\pm$ standard deviation), by participant group

PROMIS GH item/ domain*	A-RP			CSD-RP		
	Baseline (n = 16)	End of TP visit (n = 15)	End of EP visit (n = 15)	Baseline (n = 7)	End of TP visit (n = 9)	End of EP visit (n = 8)
Global Physical Health (GPH)	39.94 $\pm$ 8.94	51.35 $\pm$ 7.96	51.32 $\pm$ 6.56	43.30 $\pm$ 5.31	45.09 $\pm$ 4.06	46.81 $\pm$ 9.27
<i>Item 3: physical health</i>	2.6 $\pm$ 0.96	3.2 $\pm$ 1.01	3.5 $\pm$ 0.83	2.8 $\pm$ 0.46	3.1 $\pm$ 0.33	3.0 $\pm$ 0.93
<i>Item 7: physical activities</i>	3.3 $\pm$ 1.39	4.4 $\pm$ 1.06	4.1 $\pm$ 1.03	3.4 $\pm$ 0.74	3.3 $\pm$ 0.87	3.8 $\pm$ 1.04
<i>Item 9: fatigue</i>	3.1 $\pm$ 0.96	3.7 $\pm$ 0.49	3.7 $\pm$ 0.82	3.1 $\pm$ 0.69	3.2 $\pm$ 0.44	3.4 $\pm$ 1.06
<i>Item 10: pain</i>	4.8 $\pm$ 1.88	0.6 $\pm$ 1.18	0.5 $\pm$ 1.13	1.7 $\pm$ 1.60	1.0 $\pm$ 1.32	1.4 $\pm$ 2.50
Global Mental Health (GMH)	44.50 $\pm$ 10.48	50.13 $\pm$ 11.33	50.54 $\pm$ 11.00	46.49 $\pm$ 7.77	47.91 $\pm$ 5.51	50.66 $\pm$ 6.30
<i>Item 2: quality of life</i>	3.0 $\pm$ 1.03	3.6 $\pm$ 1.06	4.0 $\pm$ 1.00	3.3 $\pm$ 1.04	3.6 $\pm$ 0.73	3.4 $\pm$ 0.74
<i>Item 4: mental health</i>	3.3 $\pm$ 1.13	3.7 $\pm$ 1.23	3.6 $\pm$ 1.12	3.4 $\pm$ 0.74	3.6 $\pm$ 0.73	3.9 $\pm$ 0.83
<i>Item 5: social activities and relationships</i>	3.1 $\pm$ 1.34	3.7 $\pm$ 1.18	3.6 $\pm$ 1.12	3.1 $\pm$ 0.83	3.3 $\pm$ 0.50	3.6 $\pm$ 0.92
<i>Item 8: emotional problems</i>	3.1 $\pm$ 1.41	3.5 $\pm$ 1.36	3.4 $\pm$ 1.12	3.4 $\pm$ 0.98	3.3 $\pm$ 0.71	4.0 $\pm$ 0.53
Items that are not included in above domains						
<i>Item 1: general health</i>	2.9 $\pm$ 0.72	3.5 $\pm$ 0.83	3.6 $\pm$ 0.91	2.9 $\pm$ 0.64)	3.1 $\pm$ 0.33	3.1 $\pm$ 0.64
<i>Item 6: social activities and roles</i>	3.1 $\pm$ 1.09	3.5 $\pm$ 1.25	3.5 $\pm$ 1.13	2.9 $\pm$ 0.99	3.1 $\pm$ 0.93	3.5 $\pm$ 0.93
*For Items 1–9, higher scores indicate improvement, and for Item 10, lower scores indicate improvement. Scoring for Item 10 is adjusted when calculating the GPH.						

For participants in the A-RP group, increases in the average scores for items of the PROMIS GH questionnaire that assess general health, quality of life, and physical health indicate improvement over the study period. In addition, for the A-RP group, the average score of the PROMIS GH pain item shows the largest decrease over the study period, with a mean score of nearly 5 on the 0–10 NRS at baseline,

and less than 1 at end of EP. At baseline, both the physical and mental domain scores (GPH/MPH) were lower than the normative average of 50, but by end of TP mean scores for the GPH were above the US norm (and remained above at end of EP), and mean scores for the GMH were at the US norm (and remained at the normative average at end of EP).

For participants in the CSD-RP group, there were some increases (improvements) on the PROMIS GH items assessing mental health, social activities and relationships, social activities and roles, and emotional problems, but the average scores for the other items did not change. Similar to the A-RP group, average scores for the CSD-RP group were also below the US norm for both the GPH and GMH domains at baseline. For the GMH domain, average scores were at the normative average at the end of EP.

Figure 3 also shows the change in the GPH and GMH domain scores over the study period, and the relationship between these HRQoL scores and patient-reported pericardial pain and serum marker of inflammation (CRP). For the A-RP group, pain scores and CRP levels decrease over the study period, while HRQoL scores increase. For the CSD-RP group, pericardial pain and CRP (low at baseline, as expected as these participants entered the trial while not in active flare) remain low over the course of the study even while tapering and discontinuing corticosteroids, while HRQoL scores increase over time.

Please note that participants who completed the EP and were taking corticosteroids at Baseline (all participants in the CSD-RP [$n = 8$], and 83.3% [$n = 5/6$] of participants in the A-RP), were able to taper and/or discontinue using corticosteroids by the end of the EP (i.e., the end of the study) without recurrence or pericarditis symptomatology (e.g., patient-reported pericardial pain) or inflammation (e.g., elevated CRP level).

Discussion

While a substantial negative impact of RP on patients' HRQoL has traditionally been assumed, to our knowledge this is the first analysis using qualitative and quantitative methods to explore the ways that symptoms of pericarditis recurrence impact patients' quality of life. The results from the baseline timepoint of the Phase 2 clinical trial align with the assumption of patients' decreased HRQoL, showing that scores on the GMH and GPH of the PROMIS GH questionnaire were on average lower than normative scores for both the A-RP and CSD-RP groups. In addition, the improvement in HRQoL scores over the course of the study tracks with improvements in patient-reported pericardial pain and CRP levels for the A-RP group, and with the tapering and discontinuing corticosteroids for the CSD-RP group while pericardial pain and CRP remained stable and low while on rilonacept treatment. Therefore, these results show that RP negatively impacts patients' quality of life physically and emotionally, and that improvements in quality of life may be associated with improvement in disease symptomatology and a decrease in pericardial inflammation, in particular, while patients receive targeted treatment.

Furthermore, results from qualitative interviews, where adults with RP spoke about the unpredictable nature of the condition, supported that pericarditis recurrences impact patient physical and mental health.. Specifically, using the qualitative data, a conceptual model of RP was developed, and HRQoL

concepts included in the concept model (e.g., ability to carry out daily activities, impacts on mood, and limitation on social activities), were mapped against the ten items of the PROMIS GH v1.2 questionnaire (included in the Phase 2 clinical trial of rilonacept), which demonstrate that this questionnaire is assessing concepts that are relevant to adults with RP.

Limitations include the small sample sizes for both the qualitative interviews and the clinical trial, the single-active-arm design of the clinical trial, and the relatively short duration (24 weeks) of the clinical trial compared to the overall duration of this chronic disease. In addition, while the inclusion criteria for the qualitative interview study were intended to be similar to those of the clinical trial, they were less restrictive (i.e., adults interviewed did not experience as many recurrences as the participants in the clinical trial). Nevertheless, these results provide preliminary support for the importance of including a multidimensional assessment of HRQoL for future clinical research of RP. It is also important to consider that some HRQoL impacts may be dependent on age and gender, therefore given the age range of the participants who completed the qualitative interviews and the Phase 2 clinical trial, the resulting conceptual model should be considered representative of adult RP.

Strengths include leveraging qualitative results to support the importance of the item- and domain-level scores of the PROMIS GH v1.2 questionnaire to adults with RP. The representative patient quotes help contextualize how participants may be interpreting each item of the PROMIS GH questionnaire. In addition, the means for the GH domain scores at baseline in the rilonacept clinical trial provides evidence of the impact RP has on patients' HRQoL, as they are lower compared to population norm scores. These findings are consistent with other clinical studies reporting lower PROMIS GH questionnaire scores and associated impacts in physical, mental, and social domains in cardiac and vascular populations [15–17]. The increase in both the physical and mental component scores over the course of the study for both the A-RP and CSD-RP, in conjunction with improvements and/or stable pericardial pain scores and CRP levels, shows that HRQoL scores may also be responsive to treatment as the patient's condition improves.

Conclusions

Given the exercise restrictions that patients are expected to adhere to following a diagnosis of RP and the anxiety associated with the unpredictability of recurrences, it is important to evaluate both physical and emotional impacts of the condition. As more clinical trials move to incorporate patient-centric outcomes to evaluate treatments not only in terms of resolution of a physiological indicator of disease but also to ensure that patients feel and function better, future clinical trials of adults with RP should include HRQoL PRO questionnaires. In addition, future studies should explicitly examine the effect of concomitant medications, including corticosteroids, and their independent impact on patient HRQoL.

The results of this pilot study demonstrate an early signal of a positive impact of rilonacept on clinical outcome measures and improvements in patient HRQoL over the study time period which tracked with improvements in pericardial pain and inflammation. For those participants in the CSD-RP group, who

were weaning off corticosteroids while taking rilonacept, patient-reported pericardial pain and CRP levels were stable, while HRQoL scores improved over the course of the study, without recurrences.

Abbreviation

A-RP active recurrence of pericarditis at baseline

CRP c-reactive protein

CSD-RP active recurrence of pericarditis at baseline dependent on corticosteroids

EP extension period

ESC European Society of Cardiology

GMH global mental health

GPH global physical health

HRQoL health-related quality of life

IRB independent review board

NRS numeric rating scale

NSAIDs nonsteroidal anti-inflammatory drugs

PRO patient-reported outcome

PROMIS GH Patient Reported Outcome Measurement Information System Global Health

RP recurrent pericarditis

SC subcutaneous

TP treatment period

Declarations

Ethics approval and consent to participate

Ethics approval for the qualitative interviews was granted by Sterling IRB under IRB ID# 6406.

Ethics approval for the Phase 2 study was granted by the central IRB Aspire under IRB ID# KPL-914-C001 as well as by site-specific local IRBs as applicable.

Consent for publication

N/A

Availability of data and materials

Data will be made available upon reasonable request.

Competing interests

David Lin: None

Allan Klein: Research grant, scientific advisory board Kiniksa Pharmaceuticals, Ltd., advisory board Swedish Orphan Biovitrum AB, advisory board Pfizer, Inc., modest.

David Cella: Consultant for Kiniksa Pharmaceuticals, Ltd., modest.

Anna Beutler: Kiniksa Pharmaceuticals, Ltd. consultant.

Fang Fang: Kiniksa Pharmaceuticals, Corp. employee.

Matt Magestro: Kiniksa Pharmaceuticals, Corp. employee.

Paul Cremer: Advisory board Swedish Orphan Biovitrum AB, advisory board Kiniksa Pharmaceuticals, Ltd., modest.

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Authors' contributions

Study design: JFP, AB, AK, PC, LLK (qualitative interview study), BK (qualitative interview study)

Study investigator: AK, MLW, DL, PC, SAL, AA, AE, SN

Enrolled patients: AK, MLV, DL, PC, SAL, AA, AE, SN.

Collection and assembly of data: AB, FF, AK, PC, SAL, LLK (qualitative interview study), BK (qualitative interview study)

Data analysis: JFP, AB, FF, AK, PC, LLK (qualitative interview study), BK (qualitative interview study)

Data interpretation: All authors

Manuscript preparation: JFP, MM, LLK, BK

Manuscript review and revisions: All authors

Final approval of manuscript: All authors

Independent data access and analysis: throughout the writing of this paper, all authors had the ability to query any aspect of the data either directly or through independent analysis and retain this ability until publication. Anna Beutler, John Paolini, and Fang Fang had full access to all the data in the study and take responsibility for its integrity and the data analysis.

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References

1. Imazio M, Gribaudo E, Gaita F. Recurrent Pericarditis. *Progress in cardiovascular diseases*. 2017;59(4):360-8.
2. Lotan D, Wasserstrum Y, Fardman A, Kogan M, Adler Y. Usefulness of Novel Immunotherapeutic Strategies for Idiopathic Recurrent Pericarditis. *Am J Cardiol*. 2016;117(5):861-6.
3. Soler-Soler J, Sagristà-Sauleda J, Permanyer-Miralda G. Relapsing pericarditis. *Heart*. 2004;90(11):1364.
4. Raatikka M, Pelkonen PM, Karjalainen J, Jokinen EV. Recurrent pericarditis in children and adolescents: report of 15 cases. *J Am Coll Cardiol*. 2003;42(4):759-64.
5. Imazio M, Brucato A, Cumetti D, Brambilla G, Demichelis B, Ferro S, et al. Corticosteroids for Recurrent Pericarditis. *Circulation*. 2008;118(6):667-71.
6. Assolari A, Maestroni S, Cumetti D, Valenti A, Parisi F, Brucato A. Clinical management and therapy of idiopathic recurrent pericarditis. *Clinical Management Issues*. 2018;12.
7. Judson MA, Chaudhry H, Louis A, Lee K, Yucel R. The effect of corticosteroids on quality of life in a sarcoidosis clinic: the results of a propensity analysis. *Respir Med*. 2015;109(4):526-31.
8. McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet*. 2018;391(10119):451-61.
9. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*. 2015;36(42):2921-64.
10. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA*. 1995;273(1):59-65.
11. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19.
12. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S240-52.
13. Mannion AF, Balague F, Pellise F, Cedraschi C. Pain measurement in patients with low back pain. *NatClin PractRheumatol*. 2007;3(11):610-8.
14. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *QualLife Res*. 2009;18(7):873-80.

15. Charles E, Mehaffey J, Hawkins R, Burks S, McMurry T, Yarboro L, et al. Meaningful Patient-centered Outcomes 1 Year Following Cardiac Surgery. *Annals of Surgery*. 2019;1.
16. Lam KH, Kwa VIH. Validity of the PROMIS-10 Global Health assessed by telephone and on paper in minor stroke and transient ischaemic attack in the Netherlands. *BMJ open*. 2018;8(7):e019919-e.
17. Ahmad FS, Kallen MA, Schifferdecker KE, Carluzzo KL, Yount SE, Gelow JM, et al. Development and Initial Validation of the PROMIS®-Plus-HF Profile Measure. *Circ Heart Fail*. 2019;12(6):e005751.

Figures

Figure 1

Patient-centric conceptual model for recurrent pericarditis *Khandaker MH, Espinosa RE. Nishimura RA, et al. Pericardial disease diagnosis management. Mayo Clin Proc. 2010;85(6):572-593

Figure 2

Mean PROMIS GPH/MPH at Baseline for A-RP and CSD-RP A-RP, active symptomatic recurrent pericarditis; CSD-RP, corticosteroid-dependent recurrent pericarditis with no active recurrence; GPH, Global Physical Health; GMH, Global Mental Health; PROMIS GH, Patient-Reported Outcomes Measurement Information System Global Physical Health.

Figure 3

PROMIS GH domain scores, pericardial pain, and c-reactive protein levels over time by participant group BL, baseline; CRP, c-reactive protein; D, day; EoEP, end of extension period; NRS, numeric rating scale; W, week.

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