Corticosteroid Tapering and Discontinuation in a Phase 2 Study of Rilonacept in Recurrent Pericarditis

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BACKGROUND

- Recurrent pericarditis (RP) is characterized by the recurrence of pericarditis signs and symptoms after a symptom-free period of ≥4 to 6 weeks[1] and affects 15% to 30% of patients after a first episode[2,3]
- Conventional treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids (CS)[4]
  - ESC guidelines[1] recommend NSAIDs and colchicine as first-line treatment, with CS added to NSAIDs and colchicine as escalation to triple therapy in case of no or incomplete response
  - CS are often used long-term in patients (pts) with RP[1]
  - CS are associated with substantial comorbidities[5, 6]
    - Cushingoid appearance, weight gain, increased risk for infection, skin fragility, corticosteroid induced diabetes, risk of adrenal insufficiency upon withdrawal, muscle weakness, elevated blood pressure, mood instability, and compression fractures due to osteoporosis[7]
    - Some CS-related morbidities may be irreversible or require a surgical intervention, as in the case of avascular necrosis or cataracts
- Treatment with CS with fast tapering may be associated with an increased risk of pericarditis recurrences[8]
- Interleukin-1 (IL-1) is a family of cytokines which mediate the pathophysiology of recurrent pericarditis (**Figure 1**)
  - Tissue damage caused by inflammation as a result of IL-1α and IL-1β in the pericardium stimulates additional IL-1α and IL-1β, thereby creating a self-perpetuating cycle of pericardial inflammation
- Rilonacept inhibits IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β, thus preventing their interaction with IL-1 cell surface receptors (**Figure 2**)

Figure 1. Role of IL-1α and IL-1β in the Autoinflammatory Cycle of Recurrent Pericarditis[9, 10]

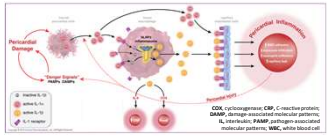
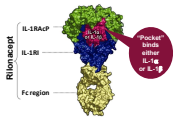


Figure 2. Rilonacept is an IL-1α/IL-1β inhibitor



IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein; IL-1RI, IL-1 receptor subtype 1.

METHODS

Phase 2 Study

Study Objectives

- Evaluate the efficacy and safety of rilonacept in patients with RP, assessing:
  - Improvement of pericarditis symptomatology with rilonacept
  - Feasibility of weaning from CS while receiving rilonacept in patients with CS-dependent RP
  - Disease activity after CS taper in patients with CS-dependent RP
  - Safety of rilonacept

Study Design

- Open-label, single-active-arm, 5-part pilot study
- Eligible patients were adults (18 to 75 y) or children (≥6 to <18 y) with RP due to idiopathic or PPS etiology, presenting with at least a third pericarditis episode or with at least 3 prior episodes if not in an active episode but CS-dependent at the time of enrollment
- All patients at study entry were allowed concomitant NSAIDs and/or colchicine and/or CS (in any combination) as long as the dosages were stable for ≥7 days; CS-dependent patients must have been on CS at enrollment

Treatment and Procedures

- In the 6-week open-label base treatment period (TP):
  - Adults (≥18 y) received a loading dose of 320 mg (2 × 160 mg) rilonacept, administered via SC injection on day 0, followed by 160 mg SC weekly for 5 additional doses
  - No changes in concomitant medications were allowed during the TP unless medically indicated
- In the optional 18-week treatment extension period (EP), during which weekly rilonacept continued with the same schedule, investigators were given the option to wean patients from concomitant medications, including CS
- Patients who completed both the TP and the EP received rilonacept for 6 months

Efficacy Assessments

- Primary endpoints: Patients with active pericarditis: pain numeric rating scale (NRS) and C-reactive protein (CRP) levels at baseline and on treatment; patients with CS-dependent non-active pericarditis: disease activity during and after CS taper
- Secondary endpoints: Use of concomitant CS; changes in the use of other concomitant medications for pericarditis

Safety Assessments

- Adverse events (AEs) were recorded with the level of severity and relationship to study drug based on investigators' judgement

Patients on Corticosteroids or Colchicine at Baseline[a]

- In this retrospective analysis, patients were divided into groups based on their use of therapies at baseline
  - CS-failure group: patients with active pericarditis despite ongoing treatment with CS at enrollment; prior history of at least 2 pericarditis episodes[b]
  - CS-dependent group: patients with no active episode of pericarditis but defined by Investigator as dependent on CS to control their disease; history of at least 3 pericarditis episodes
  - Colchicine-failure group: patients with active pericarditis despite ongoing treatment with colchicine enrolled in the study before escalating to CS therapy[c]
- Analyses of CS tapering dose and duration excluded patients who did not enroll in the 18-week EP; other analyses (baseline demographics, efficacy, etc) included these patients

[a]For continuous variables (e.g., change from baseline), summary statistics were calculated as mean and median; for categorical variables, frequency and percentage were calculated
[b]Patients could be on any other standard of care medication in addition to CS to be included in this group, including colchicine
[c]Patients could be on any other standard of care medication, with the exception of CS, to be included in this group

RESULTS

Baseline Patient Demographics and Characteristics

- Out of 25 patients enrolled in the study, 2 discontinued before entering the EP
  - 1 patient with active pericarditis discontinued during the TP (SAE of subcutaneous abscess; resolved with standard management)
  - 1 CS-dependent patient declined to enter the EP
- Out of 23 patients who completed the 24 weeks of study, 57% (n=13) of patients were receiving CS at baseline
  - CS-dependent: 35% (n=8); all except one patient were also receiving colchicine
  - CS-failures (active pericarditis): 22% (n=5); all patients were also receiving colchicine
- Out of 23 patients who completed the 24 weeks of study, 30% (n=7) were colchicine-failures (active pericarditis, no CS)

Table 1. Baseline Demographics

General Characteristics	All Patients	CS-failure	CS-dependent w/o active pericarditis	Colchicine-failure
Unique patients, n	25	6	9	7
Mean age (range), yrs	42.8 (26-62)	32.3 (26-42)	48.2 (36-62)	42.6 (26-58)
Sex (male/female)	10/15	0/6	6/3	2/5
Race (white/African American)	22/3	4/2	9/0	7/0
Mean # previous pericarditis recurrences[a] (range)	2.6 (1-8)	1.8 (1-3)	3.3 (2-5)	2.7 (1-8)
Mean disease duration (range), yrs	2.2 (0.2-7.9)	2.9 (1.0-5.6)	1.4 (0.6-3.4)	2.9 (0.2-7.9)

[a]Index and current pericarditis episodes (if applicable) were not included

Table 2. Clinical Characteristics

	CS-failure n = 6	CS-dependent w/o active pericarditis n = 9	Colchicine-failure n = 7
Mean NRS[a] (SD)	5.7 (2.3)	1.4 (1.5)	4.3 (1.3)
Mean CRP (SD), mg/dL	4.6 (7.6)	0.2 (0.1)	4.2 (4.2)

[a]11-point numeric scale, ranging from zero (0, no pain) to ten (10, pain as bad as possible); CRP, C-reactive protein; NRS, numeric rating scale;

Corticosteroid Dose at Baseline in All Patients

- In CS-failure patients with active pericarditis, mean baseline dose of prednisone was 20.6 mg per day
- In CS-dependent patients without an active pericarditis episode, mean baseline dose of prednisone was lower, at 8.5 mg per day
- The only CS used in the study for pericarditis treatment was prednisone

Table 3. Baseline CS Dose in All Patients[a]

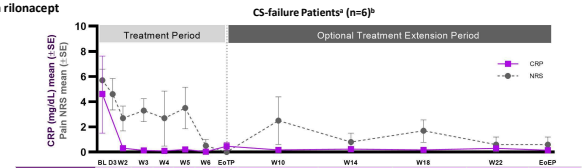
	CS-failure n = 6	CS-dependent w/o active pericarditis n = 9
Prednisone dose (mg/day)		
Mean (SD)	20.6 (19.6)	8.5 (8.9)
Median (range)	11.3 (1.0-50.0)	5.0 (2.5-30.0)

[a]Safety population

RESULTS, continued

All CS-failure patients who completed the 24-week study experienced resolution of the acute pericarditis episode and were able to taper or discontinue CS without pericarditis recurrence while on treatment with rilonacept

Figure 3. All CS-failure patients experienced rapid, sustained, and clinically meaningful reductions in pericarditis pain and CRP with rilonacept



	# Patients on CS	BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	6	6	6	6	5	5	5	5	3	2	1	1	1
	CRP Mean	4.6	0.3	0.1	0.1	0.2	0.03	0.5		0.2	0.2	0.2	0.3	0.1
PAIN NRS	# of Patients	6	5	6	6	3	6	4	3	4	4	3	5	5
	Pain Mean	5.7	4.6	2.7	3.3	2.7	3.5	0.5	0.0	2.5	0.8	1.7	0.6	0.6

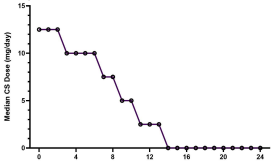
[a]Patients with active pericarditis episodes who were on CS at enrollment (safety population); results were similar in patients who failed CS and entered the EP (EP population; n=5)
[b]One CS-failure patient discontinued during the TP due to an SAE; EoTP, end of treatment period; EoEP, end of extension period;

Table 4. CS dose and duration prior to enrollment in CS-failure patients who completed the EP (n=5)[a]

	Time on CS prior to enrollment (days)	CS dose at enrollment (mg/day)	CS dose at end of study (mg/day)
Patient 1	29	10	0
Patient 2	>320	1	0
Patient 3	19	12.5	0
Patient 4	9	30-40[b]	0
Patient 5	13	50	30

[a]One CS-failure patient discontinued during the TP due to an SAE
[b]Patient was on 40 mg/day from day -9 to day -4, then on 30 mg/day until enrollment

Figure 4. Median CS dose in CS-failure patients who completed the EP (n=5)[a]

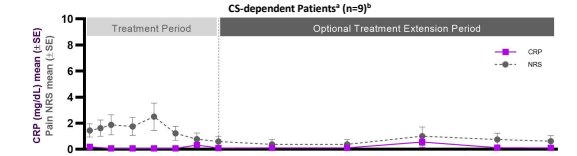


[a]One CS-failure patient discontinued during the TP due to an SAE

- Of 5 CS-failure patients who completed the 24 weeks of study
  - 4 patients discontinued CS during the EP
  - 1 patient reduced CS dose from 50 mg/day at baseline to 30 mg/day at final visit
- There were no pericarditis recurrences during CS taper/discontinuation while on rilonacept treatment

All CS-dependent patients without active pericarditis who completed the study tapered and/or discontinued CS use with no pericarditis recurrence while on treatment with rilonacept

Figure 5. All CS-dependent patients without active pericarditis tapered and/or discontinued CS use with no pericarditis recurrence while on treatment with rilonacept



	# Patients on CS	BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	9	9	9	9	9	9	9	9	8	8	2	1	1
	CRP Mean	0.19	0.07	0.07	0.07	0.07	0.07	0.33	0.09	0.10	0.11	0.56	0.12	0.12
PAIN NRS	# of Patients	9	8	8	8	4	9	9	5	8	8	4	8	8
	Pain Mean	1.4	1.6	1.9	1.8	2.5	1.2	0.8	0.6	0.4	0.4	1.0	0.8	0.6

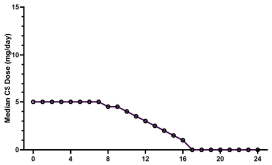
[a]All CS-dependent patients without active pericarditis (safety population); results were similar in CS-dependent patients who entered the EP (EP population; n=8)
[b]One CS-dependent patient did not enter the EP; EoTP, end of treatment period; EoEP, end of extension period;

Table 5. CS dose and duration prior to enrollment in CS-dependent patients who completed the EP (n=8)[a]

	Time on CS prior to enrollment (days)	CS dose at enrollment (mg/day)	CS dose at end of study (mg/day)
Patient 1	35	5	0
Patient 2	17	2.5	0
Patient 3	51	30	2.5
Patient 4	33	8	0
Patient 5	23	4	0
Patient 6	63	3	0
Patient 7	259	15	0
Patient 8	142	5	0

[a]One CS-dependent patient did not enter the EP

Figure 6. Median CS dose during the study in CS-dependent patients who completed the EP (n=8)[a]

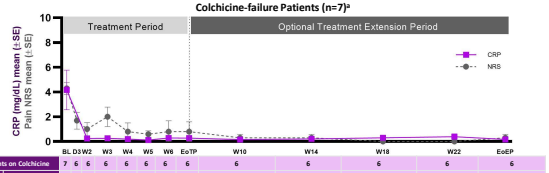


[a]One CS-dependent patient did not enter the EP

- 7 out of the 8 CS-dependent patients who completed the EP (87.5%) successfully stopped CS with no pericarditis recurrence while on treatment with rilonacept
- 1 remaining patient successfully tapered from 30 mg/day at baseline to 2.5 mg/day by completion of the EP with no pericarditis recurrence while on treatment with rilonacept

All colchicine-failure patients had rapid, sustained, and clinically meaningful reductions in pericarditis pain and CRP with initiation of rilonacept

Figure 7. All colchicine-failure patients had rapid, sustained, and clinically meaningful reductions in pericarditis pain and CRP with initiation of rilonacept



	# Patients on Colchicine	BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	7	6	6	6	6	6	6	6	6	6	6	6	6
	CRP Mean	4.2	0.3	0.3	0.2	0.1	0.3	0.3		0.2	0.2	0.3	0.4	0.2
PAIN NRS	# of Patients	7	6	7	7	4	7	6	5	7	7	5	6	7
	Pain Mean	4.3	1.7	1.0	2.0	0.8	0.6	0.8	0.8	0.3	0.3	0.0	0.0	0.3

[a]Patients with active pericarditis episodes who were on colchicine and not CS at enrollment (safety population)
EoTP, end of treatment period; EoEP, end of extension period;

- Of the 7 colchicine-failure patients (active pericarditis episode despite colchicine and enrolled in lieu of CS initiation) who completed the EP:
  - 6 out of 7 patients experienced successful treatment of the acute episode and no pericarditis recurrence while on treatment with rilonacept
  - 1 patient experienced a mild recurrence during the TP, 5 days duration, with NRS pain increase from 0 to 2 and CRP of 0.10 mg/dL, not requiring addition of new medication to treat pericarditis; patient stayed on rilonacept treatment until the end of the study with no other recurrence
  - 1 discontinued colchicine during the study, while the remaining 6 patients did not decrease colchicine dose. This investigator decision to not discontinue concomitant colchicine may be related to anticipation of a potential post-study recurrence in patients with long-standing RP once fixed-duration rilonacept treatment had been completed

Annualized incidence of pericarditis episodes decreased across all groups of patients during rilonacept treatment

Table 6. Annualized Incidence of Pericarditis Episodes Prior to and During the Study

	CS-failure n = 6	CS-dependent w/o active pericarditis n = 9	Colchicine-failure n = 7
Prior to the study[a]			
Pericarditis episodes per year, mean (SD)	1.9 (1.3)	4.2 (2.6)	5.7 (5.9)
During the study[b]			
Patients with pericarditis episodes, n	0	0	1[c]
Pericarditis episodes per year, mean (SD)	0	0	0.3 (0.8)

[a]Episodes at enrollment include index, prior recurrences, and current episode;
[b]Episodes during the study include recurrences during TP and EP combined. Pericarditis recurrence during the study was based on Investigator's judgement;
[c]Patient had a mild pericarditis recurrence in TP, 5 days duration, with NRS pain increase from 0 to 2, CRP 0.10 mg/dL, not requiring addition of new medication to treat pericarditis;
CS-dep, corticosteroid-dependent; PPS, post-pericardiotomy syndrome

Rilonacept was generally well-tolerated: majority of AEs were mild

- There were 2 serious treatment-emergent AEs in patients presenting with an active pericarditis episode, both of which resolved
  - 1 serious adverse event (SAE, subcutaneous abscess) in week 5 of TP in a patient with a history of skin infections, still receiving concomitant prednisone at the dose of 10 mg/day. The abscess resolved with standard management; patient discontinued rilonacept.
  - 1 patient with atypical chest pain (not related to study drug) continued rilonacept treatment
- AEs observed with rilonacept treatment are consistent with the known safety profile of rilonacept
- The most common AEs were injection site reactions (12 patients out of 25 [48%]), nasopharyngitis, arthralgia, and diarrhea

CONCLUSIONS

- CS-failure patients with active pericarditis treated with rilonacept experienced rapid, sustained, and clinically meaningful reductions in pericarditis pain and CRP and tapered or discontinued CS use without pericarditis recurrences while on rilonacept treatment
- CS-dependent patients tapered or discontinued CS without pericarditis recurrences while on rilonacept treatment
- Colchicine-failure patients with active pericarditis treated with rilonacept experienced rapid, sustained, and clinically meaningful reductions in pericarditis pain and CRP
  - 6 out of 7 patients did not taper off colchicine. This investigator decision to not discontinue concomitant colchicine may be related to anticipation of a potential post-study recurrence in patients with long-standing RP once fixed-duration rilonacept treatment had been completed
- Safety data from this study are consistent with the known safety profile of rilonacept
- These data suggest a potential corticosteroid-sparing effect of rilonacept, i.e., supporting a reduction in corticosteroid dose or obviating the need for corticosteroid use while on treatment in the study. Novel therapies are needed which could eliminate or reduce the risk of significant corticosteroid-associated morbidity in recurrent pericarditis.

Results from this study support the design of RHAPSODY, a double-blind, placebo-controlled randomized withdrawal (RW) pivotal Phase 3 study with an open-label extension, designed to evaluate the efficacy and safety of rilonacept treatment in patients with RP

Interpretation of efficacy and safety outcomes is limited by small number of patients in each study part, open-label study design, and single-active-treatment arm design

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Arcalyst® (rilonacept, Regeneron, Tarrytown, NY) is approved in the US for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS); Arcalyst® is a registered trademark of Regeneron;

Rilonacept is being investigated for the treatment of RP by Kiniksa Pharmaceuticals, Ltd.

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