MHIF FEATURED STUDY:

Exact Trial

OPEN AND ENROLLING:

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Refractory Angina	Jay Traverse, MD Ben Sun, MD	Jake Jensen – Jacob.Jensen@allina.com | 612-863-3818 Kari Thomas – Kari.M.Thomas@allina.com | 612-863-7493	Xylocor Therapeutics, Inc

DESCRIPTION: an early phase, non-randomized, study evaluating direct administration of a modified adenovirus vector expressing multiple isoforms of the VEGF (human vascular endothelial growth factor) gene.

The route of administration will be one-time intramyocardial injections directly into the free wall of the left ventricle via TECAP.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- Diagnosis of Chronic angina due to obstructive coronary artery disease
  - CCS Angina class II-IV
- History of reversible left ventricular ischemia

Exclusion:

- Current electrocardiographic abnormalities that would interfere with ST-segment analysis
- Severe Congestive heart failure defined as NYHA III or IV, or LVEF less than 25%

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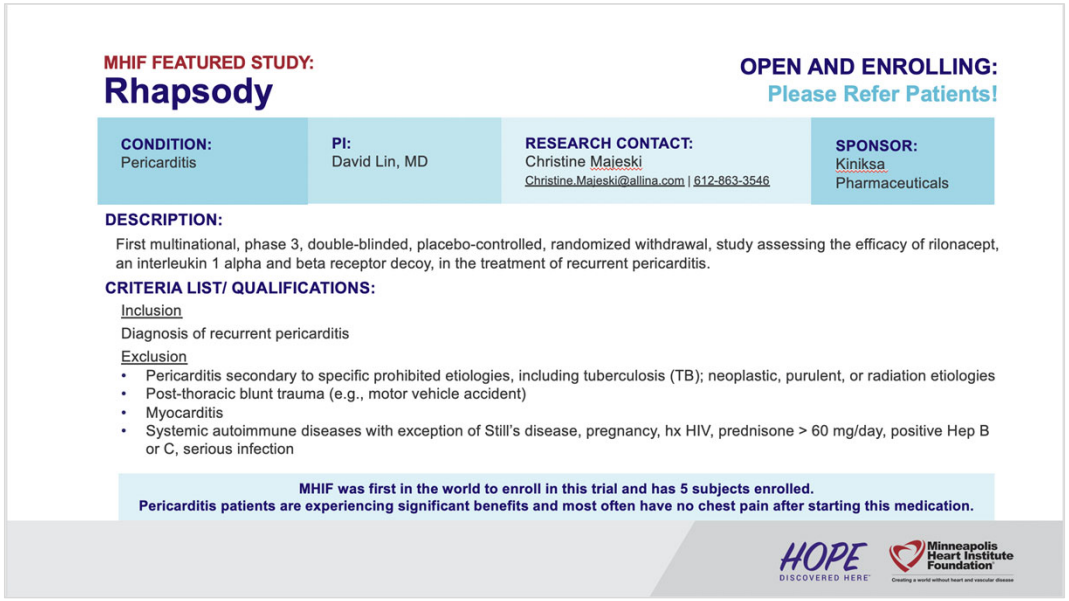
Spotlight on the Rhapsody Team!

Congratulations to Dr. Lin, Christine Majeski, RN, and team for success with the Rhapsody trial!



MHIF FEATURED STUDY:

Rhapsody

OPEN AND ENROLLING:
Please Refer Patients!

CONDITION:	PI:	RESEARCH CONTACT:	SPONSOR:
Pericarditis	David Lin, MD	Christine Majeski Christine.Majeski@allina.com | 612-863-3546	Kiniksa Pharmaceuticals

DESCRIPTION:

First multinational, phase 3, double-blinded, placebo-controlled, randomized withdrawal, study assessing the efficacy of rilonacept, an interleukin 1 alpha and beta receptor decoy, in the treatment of recurrent pericarditis.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion

Diagnosis of recurrent pericarditis

Exclusion

- Pericarditis secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies
- Post-thoracic blunt trauma (e.g., motor vehicle accident)
- Myocarditis
- Systemic autoimmune diseases with exception of Still's disease, pregnancy, hx HIV, prednisone > 60 mg/day, positive Hep B or C, serious infection

MHIF was first in the world to enroll in this trial and has 5 subjects enrolled.
Pericarditis patients are experiencing significant benefits and most often have no chest pain after starting this medication.

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Key Accomplishments:

- First enroller worldwide
- 2nd Highest enroller worldwide
- Poster presentation at AHA 2019:

  Real-world clinical characteristics and recurrence burden of patients diagnosed with recurrent pericarditis in the U.S.

We are proud of MHIF for researching treatment opportunities for a patient population with limited options.

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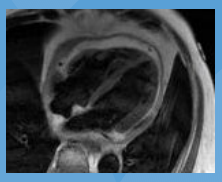
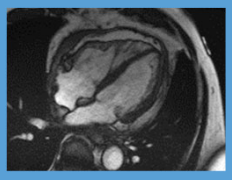
Diagnosis and Management of Pericarditis





David Lin, MD
Minneapolis Heart Institute
02/24/20

- Disclosures:
  - none

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Objectives

- Etiology/Epidemiology
  - Focus on idiopathic
- Diagnosis, clinical and use of imaging
- Complications
- Treatment including novel therapies
- Constriction

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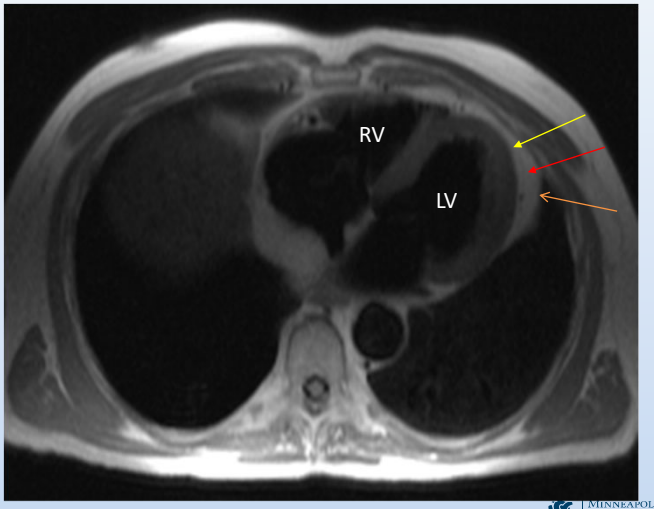
Introduction

- Double wall sac containing the heart and roots of the great vessels and vena cava.
  - *Visceral (epicardium)*
  - *Parietal*
  - Fixes the heart to the mediastinum
  - ≤ 3mm in thickness on CMR
  - Well innervated, inflammation trigger pain
  - Contains 15-50cc serous fluid. ? Lubrication for the heart
  - Facilitate cardiac chamber coupling?
  - Protect against infection?
  - Not essential for normal cardiac function

Introduction



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Introduction

- Anatomical studies suggest that normal parietal pericardium is ≤ 1mm.
- Overestimation by CMR?
  - Motion/chemical shift artifact at fat-fluid interface (measure thickness on black blood imaging, not SSFP)
  - Limited spatial resolution
  - At times normal pericardium can be difficult to delineate and appears “pencil thin”
- Markedly thickened pericardium is evident

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Introduction

- Most patients with pericarditis has a benign course and when treated with NSAIDS, symptoms resolve within days to weeks.
- Significant minority, however, can develop adverse events and be debilitated by recurrent attacks.

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Epidemiology

Etiology	AP patients (N = 17,168)
Idiopathic, n (%)	12,993 (75.7)
Non-idiopathic,[1,2] n (%)	4,175 (24.3)
Metastatic neoplasm	1,141 (6.6)
Autoimmune	1,109 (6.5)
Systemic lupus erythematosus	343 (2.0)
Rheumatoid arthritis	273 (1.6)
Ulcerative colitis	107 (0.6)
Crohn's disease	90 (0.5)
Still's disease	12 (0.0)
Cardiac syndromes/procedures	853 (5.0)
Post-pericardiotomy syndrome	81 (0.5)
Metabolic	361 (2.1)
Bacterial	360 (2.1)
Traumatic	298 (1.7)
Fungal	235 (1.4)
Parasitic	7 (0.0)
Other[2]	229 (1.3)

Real-World Clinical Characteristics and recurrence Burden of Patients Diagnosed with Recurrent Pericarditis in the US, Lin et al , AHA abstract, 2019

- In developed countries, 70-80% of pericarditis are idiopathic or presumed post viral. Often preceded by GI or flu like syndrome.
- Account for 0.2% of all CV in-hospital admission.
- 5% of all ER admissions for chest pain.

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Epidemiology

- Seasonal pattern with distinct late winter peak is seen with acute pericarditis, consistent with certain viral infection.
- No pattern seen for recurrence, suggest it's not due to re-infection.
  - Immunogenic background?
  - Incomplete treatment?

Seasonal patterns of acute and idiopathic and recurrent pericarditis, Hammer et al, Clinical Cardiology, 2017;40:1152-1155

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Epidemiology

- Post cardiac injury has become more prevalent
  - Post pericardiotomy syndrome (PPS)
  - Post traumatic (mostly iatrogenic, ablation, PPM, TAVR, PCI)
  - MI (decreasing with early revascularization)
- Presumed immune pathogenesis triggered by initial pericardial damage.
  - Can have latent period of a few weeks
- Overall complication rates are low.
- Treatment approach is similar to idiopathic pericarditis.
  - Lower dose of NSAIDS due to concomitant antiplatelet or anticoagulant

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Diagnosis

Pericarditis	Definition and diagnostic criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: (1) pericarditic chest pain (2) pericardial rubs (3) new widespread ST-elevation or PR depression on ECG (4) pericardial effusion (new or worsening) Additional supporting findings: - Elevation of markers of inflammation (i.e. C-reactive protein, erythrocyte sedimentation rate, and white blood cell count); - Evidence of pericardial inflammation by an imaging technique (CT, CMR).
Incessant	Pericarditis lasting for >4–6 weeks but <3 months without remission.
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer[a].
Chronic	Pericarditis lasting for >3 months.

- Diagnosis (2/4 criteria)
  - Sharp and pleuritic pain, improves with sitting and leaning forward
  - Pericardial rub (<30%)
  - ST elevation/PR depression (~ 60%)
  - Pericardial effusion
- Supportive:
  - Markers of inflammation (CRP, ESR, WBC)
  - Imaging (CMR, CT)

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

European Heart Journal (2015) 36, 2921–2964

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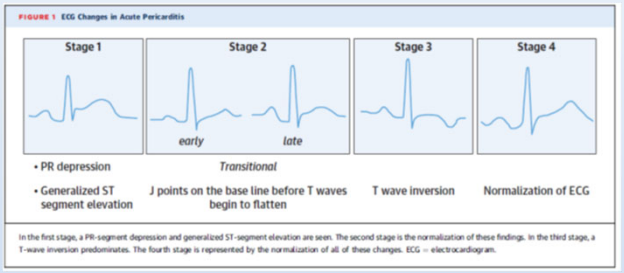
Diagnosis



Management of Acute and Recurrent Pericarditis, Chiabrando et al, *JACC*; 75:1,2020, 76-92

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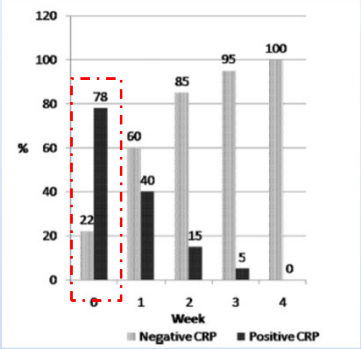
Diagnosis

- No specific biomarkers



Imazio et al, Circulation, 2011, 123:1092-1097

Only *3.5%* had persistently normal CRP with no previous treatment (repeat testing within 24-48 hours in those with initial negative CRP)

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Diagnosis

- ~ *30%* develops TnI elevation. Likely due to epicardial involvement.
- Unlike ACS, is *NOT* a negative prognostic marker.
- Concentration correlate with magnitude of ST elevation.

Table 2. Complications and Clinical Events During a Mean Follow-Up of 24 Months (Range 8 to 30 Months)

	Serum cTnI (ng/ml) (n = 118)		
	≤0.1 (n = 80)	>0.1 (n = 38)	p Value
Recurrent pericarditis	15 (18.8%)	7 (18.4%)	NS
Cardiac tamponade	0	0	NS
Constrictive pericarditis	1 (1.3%)	0	NS
Residual left ventricular dysfunction	0	0	NS
Congestive heart failure	0	0	NS
Dilated cardiomyopathy	0	0	NS

cTnI = cardiac troponin I.

Cardiac TnI in acute pericarditis, Imazio et al, JACC, 2003;42:2144-8

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Diagnosis

- Routine identification of the putative virus is *NOT* recommended.
  - Enterovirsuses (echo, coxsackie)
  - Herpesviruses (EBV, CMV, HHV6)
  - Adenovirus, parvovirus B19
- Search is often exhaustive and does not change prognosis or management.
- *No* correlation of serum viral antibodies to PCR analysis from pericardial tissue or fluid.
- Avoid routine *ANA* testing as low titer levels are common and nonspecific.

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Diagnosis

Table 14 **First and second level investigations for pericarditis**

Level	Investigation
1st level (all cases)	Markers of inflammation (i.e. ESR, CRP, white blood cell count). Renal function and liver tests, thyroid function. Markers of myocardial lesion (i.e. troponins, CK). ECG Echocardiography Chest X-ray
2nd level (if 1st level not sufficient for diagnostic purposes)	CT and/or CMR Analysis of pericardial fluid from pericardiocentesis, or surgical drainage, for (i) cardiac tamponade or (ii) suspected bacterial, neoplastic pericarditis, or (iii) symptomatic moderate to large effusions not responding to conventional anti-inflammatory therapy. Additional testing should be directed to specific aetiologies according to clinical presentation (presence of high risk clinical criteria).

CK = creatine kinase; CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate.

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

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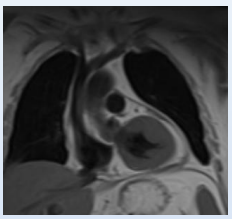
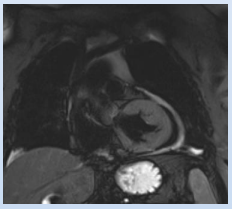
Diagnosis

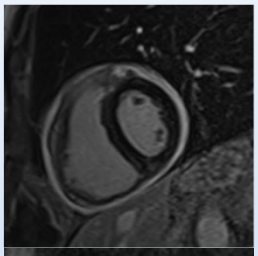
LGE

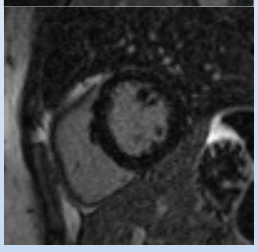
T1

T2



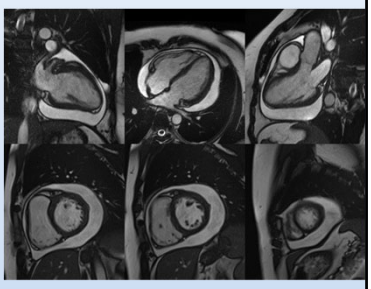






NO LGE

SSFP



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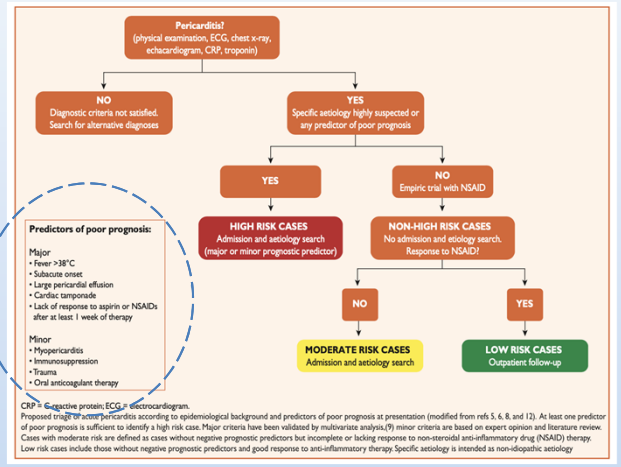
Diagnosis



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Diagnosis

Predictors of poor prognosis:

Major
- Fever >38°C
- Subacute onset
- Large pericardial effusion
- Cardiac tamponade
- Lack of response to aspirin or NSAIDs after at least 1 week of therapy

Minor
- Myopericarditis
- Immunosuppression
- Trauma
- Oral anticoagulant therapy

- Increased risk of short term complications.
- Likelihood of specific disease
- Tamponade is rare, occurs in the beginning of the disease.

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Treatment

Acute pericarditis

Drug	Usual dosing*	Tx duration*	Tapering*
Aspirin	750–1000 mg every 8h	1–2 weeks	Decrease doses by 250–500 mg every 1–2 weeks
Ibuprofen	600 mg every 8h	1–2 weeks	Decrease doses by 200–400 mg every 1–2 weeks
Colchicine	0.5 mg once (<70 kg) or 0.5 mg b.i.d. (≥70 kg)	3 months	Not mandatory, alternatively 0.5 mg every other day (< 70 kg) or 0.5 mg once (≥70 kg) in the last weeks

* Exercise restriction and GI protection.
  - for athletes 3 months
  - others shorter period until remission with normalization of diagnostic tests

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

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Treatment

TABLE 3 Randomized Clinical Trials in Acute and Recurrent Idiopathic Pericarditis With Colchicine Added to Aspirin

Trial (Year)	Indication	Blinding	Patients	Treatment Duration	Primary Endpoint	Results
COPE trial (2005)	Acute pericarditis	No	120 patients	3-4 weeks (A), 3 months (A + C)	Recurrence	33.3% in A vs. 11.7% in A + C (P = 0.009)
CORE trial (2005)	Recurrent pericarditis	No	84 patients	3-4 weeks (A), 6 months (A + C)	Recurrence	50.6% in A vs. 24% in A + C (P = 0.02)
CORP trial (2011)	Recurrent pericarditis	Yes	120 patients	A/Ib: 3-4 weeks; Pl or C: 6 months	Recurrence	55% in A vs. 24% in A + C (P < 0.001)
ICAP trial (2013)	Acute pericarditis	Yes	240 patients	A/Ib: 3-4 weeks; Pl or C: 3 months	Incessant or recurrent pericarditis	37.5% in A vs. 16.7% A + C (P < 0.001)
CORP-2 trial (2014)	Recurrent pericarditis (2 or more events)	Yes	240 patients	A/Ib/In: 3-4 weeks; Pl or C: 6 months	Recurrence	42.5% in A vs. 21.6% in A + C (P = 0.0009)
CAFE-AIP trial (2019)	First episode of acute pericarditis (not secondary to cardiac injury or connective tissue disease)	No	110 patients	Group 1: A/Ib/In: 3-4 weeks; group 2: A/Ib/In: 3-4 weeks + C: 3 months	Recurrence	13.5% in A/Ib/In vs. 7.8% in A/Ib/In + C (P = 0.34)

A = aspirin; C = colchicine; CAFE-AIP = Colchicine Administered in the First Episode of Acute Idiopathic Pericarditis; COPE = COlchicine for acute PEricarditis; CORE = COlchicine for REcurrent pericarditis; CORP = Colchicine for Recurrent Pericarditis; CORP-2 = Efficacy and Safety of Colchicine for Treatment of Multiple Recurrences of Pericarditis; Ib = ibuprofen; ICAP = Investigation on Colchicine for Acute Pericarditis; In = indomethacin; Pl = placebo.

Management of Acute and Recurrent Pericarditis, Chiabrando et al, *JACC*; 75:1,2020, 76-92

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Treatment

- ~ 15% has myocardial involvement.
- Myopericarditis (primarily pericarditis with concomitant myocardial involvement).
  - Definition of myocardial involvement?
- CMR to confirm the diagnosis
- Without LV dysfunction, treatment is the same
  - Consider reducing NSAIDs dose
- Berg et al, *Open Heart*, 2019, retrospective study of 45 patients with myopericarditis confirmed by CMR. No difference in major adverse CV events when treated with or without NSAIDS.

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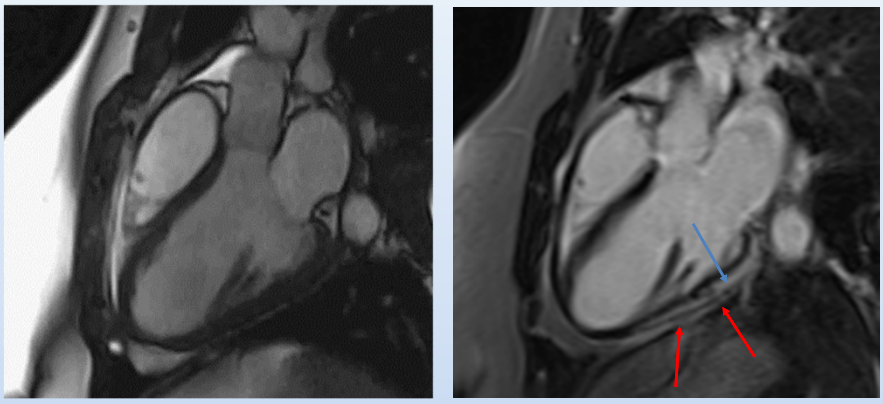

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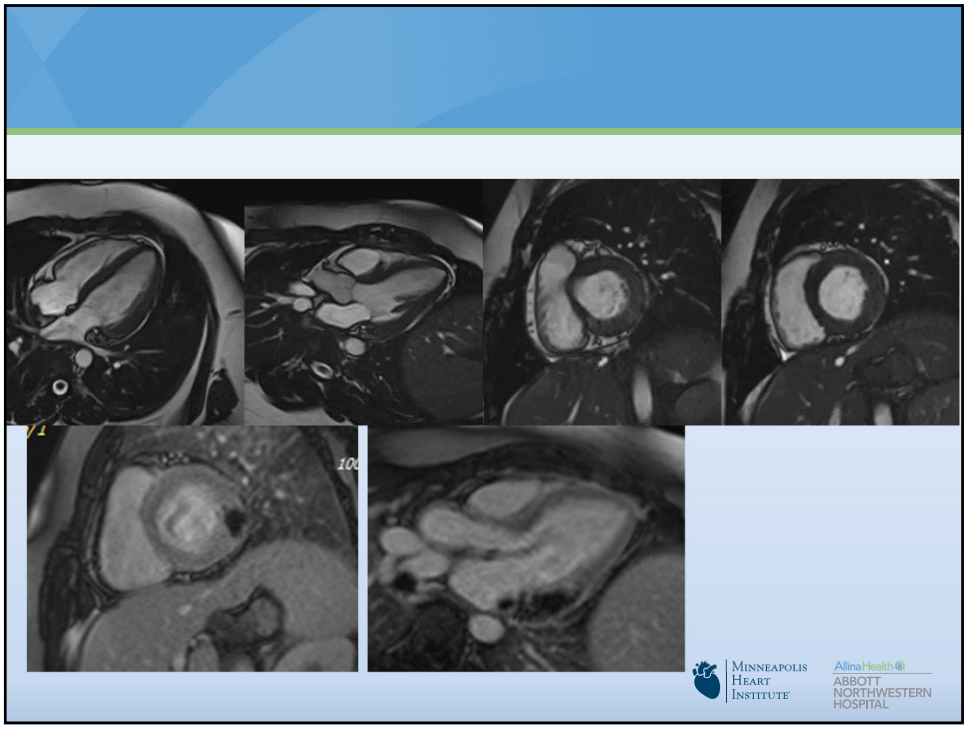
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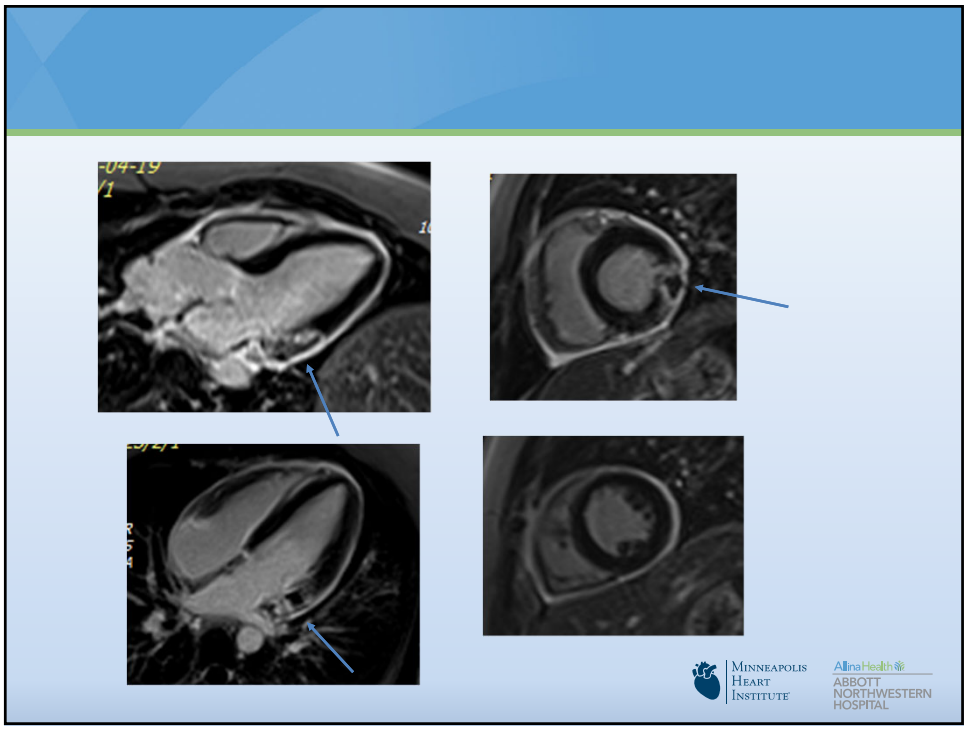
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Diagnosis

- 76 patients with surgically proven pericardial disease, 94% of patient with recurrent pericarditis has LGE of pericardium in CMR. Young et al, Int J Cardiovascular Imaging 2012;28:1099-109

Usefulness of cardiac magnetic resonance for recurrent pericarditis, Imazio et al, AJC 2020;125:146-151

Diagnostic accuracy of CMR criteria for the diagnosis of recurrent pericarditis (as percentage and 95% confidence interval)

CMR criteria	Se	Spe	PPV	NPV	LR+	LR-
(1) Pericardial thickening	28.9 (21.1-37.6)	98.4 (94.5-99.8)	94.9 (82.799.4)	58.1 (51.2-64.7)	18.5 (4.6-75.1)	0.7 (0.6-0.8)
(2) Pericardial edema (T2w)	68 (59.1-75.9)	100 (97.2-100)	100 (95.8-100)	75.7 (68.6-82)	N.A.*	0.3 (0.2-0.4)
(3) Pericardial LGE	64.8 (55.9-73.1)	99.2 (95.7-100)	98.8 (93.5-100)	73.8 (66.6-80.2)	83 (11.7-587)	0.4 (0.3-0.5)
(4) Pericardial effusion	52.3 (43.3-61.2)	89.8 (83.3-94.5)	83.8 (73.8-91.1)	65.3 (57.8-72.3)	5.2 (3-8.9)	0.5 (0.4-0.6)
Pericardial edema and LGE	72.7 (64.1-80.2)	99.2 (95.7-100)	98.9 (94.2-100)	78.4 (71.3-84.5)	93 (13.2-657)	0.3 (0.2-0.4)

*Using presence of pericardial edema at CMR as diagnostic test, 0 false positive results were obtained; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive values; Se, sensitivity; Spe, specificity.

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Acute vs Recurrent

TABLE 1 Definitions of Pericarditis According to the Time of Presentation

	Definition
Acute	Event lasting <4 to 6 weeks
Incessant	Event lasting >4 to 6 weeks without remission
Recurrent	New signs and symptoms of pericardial inflammation after a symptom-free interval of 4 to 6 weeks
Chronic	Pericarditis lasting >3 months

Management of Acute and Recurrent Pericarditis, Chiabrando et al, *JACC*; 75:1,2020, 76-92

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Recurrent Pericarditis

- Presumed immune mediated phenomenon, more so than recurrent infection.
- Factors associated with increased recurrence risk:
  - Previous steroid use
  - Frequent prior recurrence
  - Female gender

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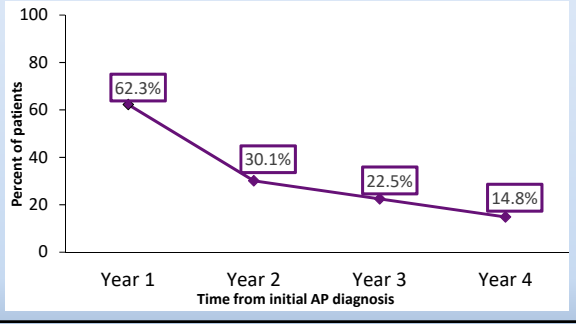
Recurrence Episodes among RP Patients with ≥4 Years of Follow-up

Outcomes	RP patients (N = 512)
Recurrences within 4 years of the initial AP diagnosis, n (%)	
≥2 recurrences	184 (35.9)
≥3 recurrences	93 (18.2)
≥4 recurrences	50 (9.8)



Real-World Clinical Characteristics and recurrence Burden of Patients Diagnosed with Recurrent Pericarditis in the US, Lin et al , AHA abstract, 2019

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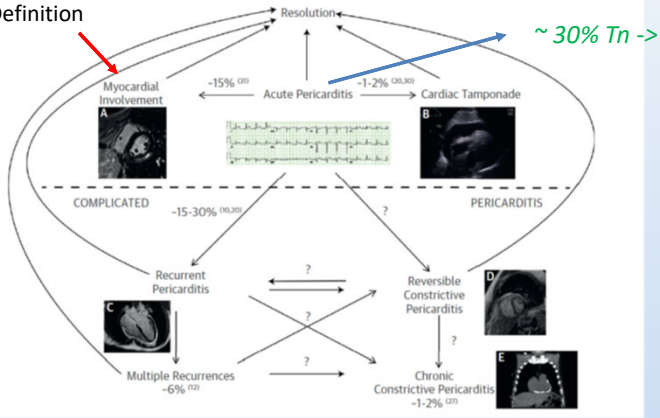
Definition

~ 30% Tn -> CMR



Cremer et al, JACC. 2016;68(21):2311-28

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Treatment

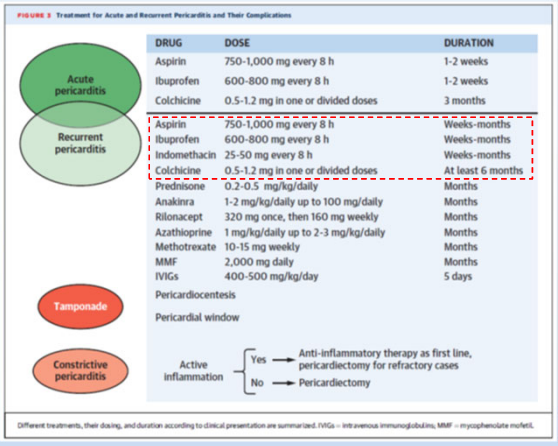

Table 7 Tapering of corticosteroids[15] (dosage information is provided for prednisone)

Starting dose 0.25–0.50 mg/kg/day[a]	Tapering[b]
>50 mg	10 mg/day every 1–2 weeks
50–25 mg	5–10 mg/day every 1–2 weeks
25–15 mg	2.5 mg/day every 2–4 weeks
<15 mg	1.25–2.5 mg/day every 2–6 weeks

2015 ESC Guidelines for the diagnosis and management of pericardial diseases
Management of Acute and Recurrent Pericarditis, Chiabrando et al, *JACC*; 75:1,2020, 76-92

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Management

- NSAIDS:
  - GI (ulcers)
  - Bleeding
  - HTN
  - Renal failure
  - Rarely hepatitis
- Colchicine:
  - GI (diarrhea). Rarely hepatitis.
  - Myelosuppression is rare
- Corticosteroids:
  - *Higher risk of recurrence (>4 fold increase), especially when use unopposed or with brisk tapering*
  - Prolonged taper (months)
  - Weight gain, elevated glucose, cushingnoid… etc

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Recurrent pericarditis

- Associated with a high burden of disease
  - Debilitating chest pain that limits ADL, physical activity, and leading to ER visits
  - Significant fear of recurrence and productivity loss
  - Significant side effects of conventional treatment options

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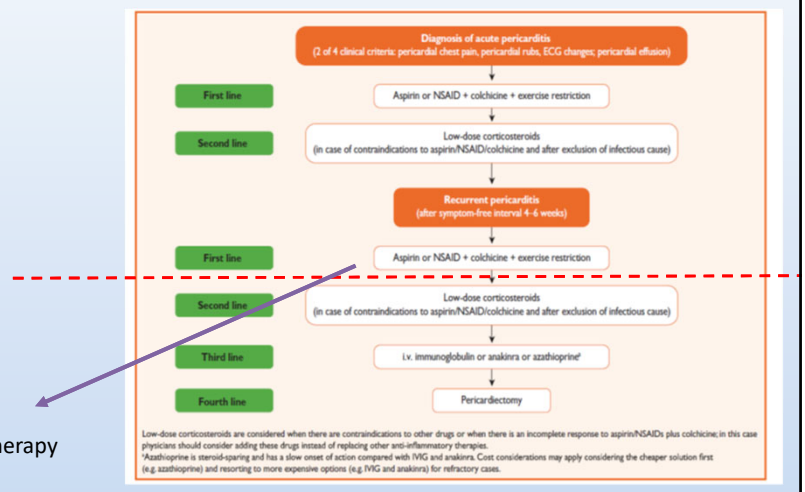
Treatment



Alternative therapy

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

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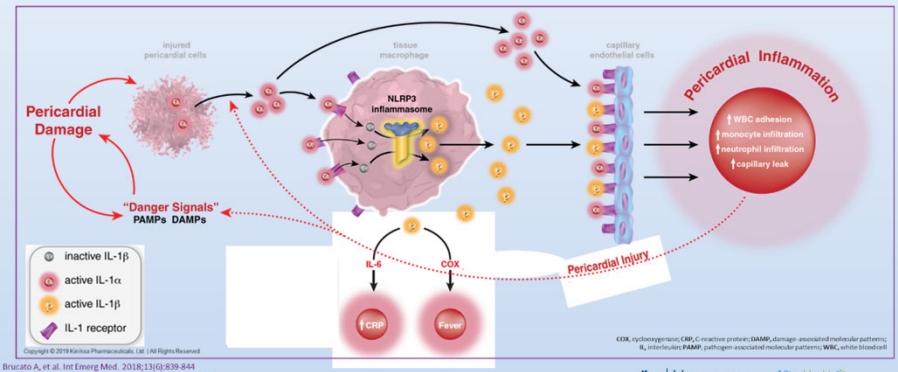
Background: Role of IL-1 in Recurrent Pericarditis (RP)

- Interleukin-1 (IL-1) is a family of cytokines which mediates the pathophysiology of RP
  - Tissue damage caused by IL-1α and IL-1β in the pericardium stimulates additional IL-1α and IL-1β, thereby creating a self-perpetuating cycle of pericardial inflammation[1-2]



1. Brucato A, et al. Int Emerg Med. 2018;13(6):839-844
2. Dinarello CA, et al. Nat Rev Drug Discov. 2012;11:633-652

Efficacy and Safety of Rilonacept in Recurrent Pericarditis: A Multicenter Phase 2 Clinical Trial, AHA abstract/poster 2019, Klein, Lin, et al

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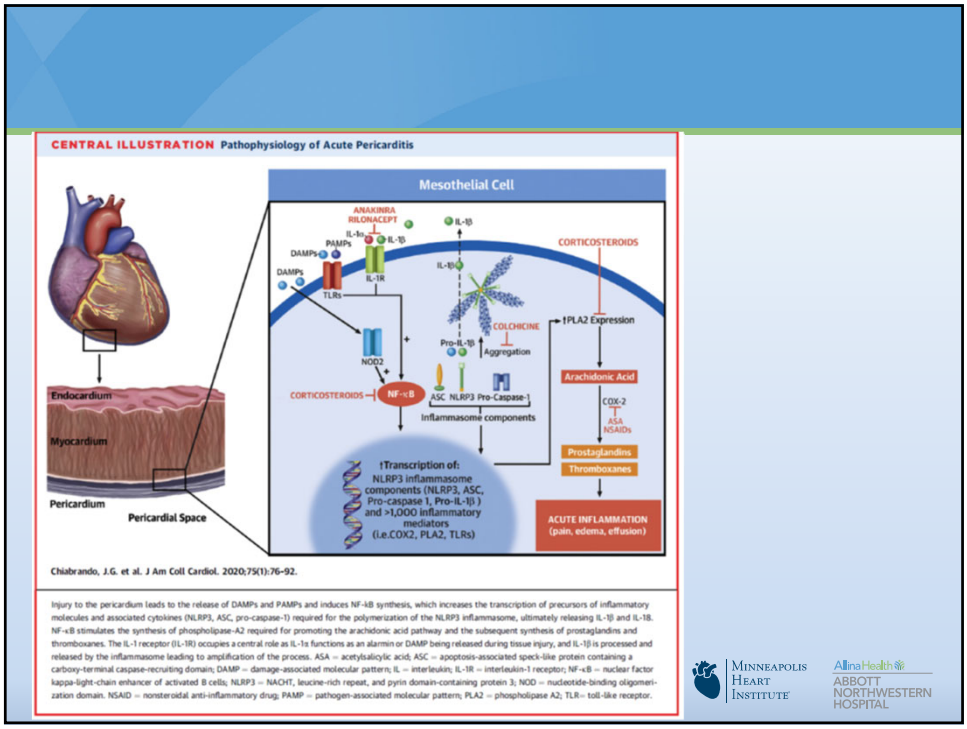
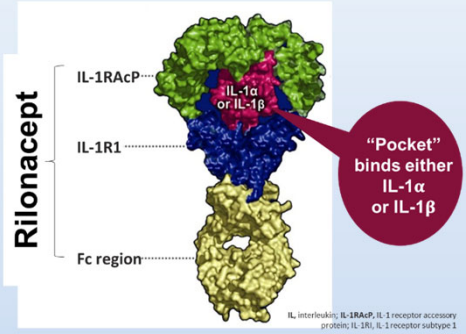


Rilonacept



Efficacy and Safety of Rilonacept in Recurrent Pericarditis: A Multicenter Phase 2 Clinical Trial, AHA abstract/poster 2019, Klein, Lin et al

- Dimeric fusion protein consist of ligand-binding domains of the extracellular portion of human IL-1 receptor component (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked inline to the Fc portion of the human IgG1
- Inhibits signaling by acting as a soluble decoy receptor that binds IL-1 α and β, preventing interaction with IL-1 cell surface receptors.
- CAPS (cryopyrin associated periodic syndrome).

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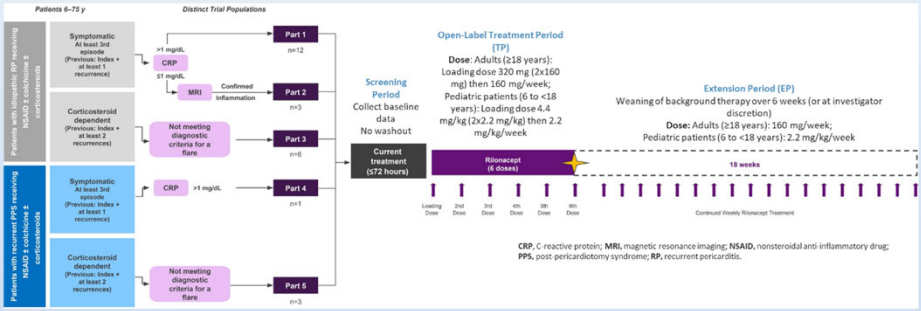
Rilonacept Phase 2 Study: Study Design

Figure 3. Study Design



Klein, Lin et al, Efficacy and Safety of rilonacept in recurrent pericarditis: A multicenter phase 2 clinical trial, AHA poster 2019

Christine Majeski, RN
Scott Sharkey, MD

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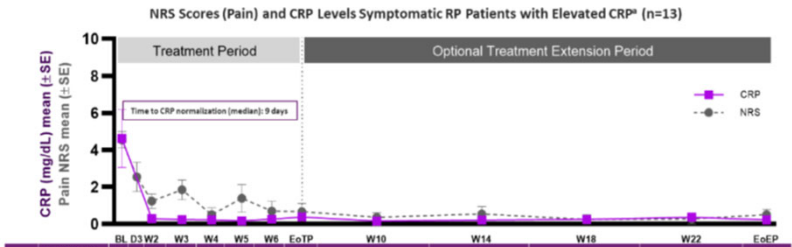
- Rapid, sustained, and meaningful reduction in patient's pericarditis pain and CRP in symptomatic RP with CRP > 1mg/dl (Part 1 and 4)
  - After first dose and sustained thru the EP



Klein, Lin et al, Efficacy and Safety of rilonacept in recurrent pericarditis: A multicenter phase 2 clinical trial, AHA poster 2019

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Rilonacept Phase 2 Study Results:
Corticosteroid (CS) Use in All Patients (Parts 1-5)

- Of 13 patients on CS at baseline who completed EP, 11 discontinued CS, and the remaining 2 successfully reduced the dose
  - None of the patients in EP required initiation of prednisone for pericarditis
  - There were no pericarditis recurrences based on Investigator's judgement after prednisone taper or discontinuation in EP

Corticosteroid Use in All Patients

	Idiopathic			PPS		Idiopathic or PPS
	Part 1	Part 2	Part 3	Part 4	Part 5	
Disease Status:	Active	Active	CS-dep	Active	CS-dep	All[a]
CRP requirement (mg/dL):	>1	≤1	N/A	>1	N/A	N/A
N:	12	3	6	1	3	25
Baseline						
Pts on prednisone[b], n	4	2	6	0	3	15
Mean dose (mg/day)	8.4	40.0	8.9	0	7.7	12.7
Min	1.0	30.0	2.5	0	3.0	1.0
Max	12.5	50.0	30	0	15.0	50.0
Corticosteroid Changed During TP and EP Combined						
Prednisone dose decreased[c, d]	**0/3**	**1/2 (50.0)**	**1/5 (20.0)**	**0/0**	**0/3**	**2/13 (15.4)**
Prednisone stopped[c, d]	**3/3 (100)**	**1/2 (50.0)**	**4/5 (80.0)**	**0/0**	**3/3 (100)**	**11/13 (84.6)**
Prednisone dose increased[c]	0/3	0/2	0/5	0/0	0/3	0/13
Prednisone initiated[e]	0/11	0/3	0/5	0/1	0/3	0/23

[a]Parts 1-5; [b]2 patients on prednisone at baseline did not enter EP (one in Part 1 and in Part 3)
[c]Subjects who entered the study on prednisone; [d]1 patient decreased prednisone dose in TP, and 1 stopped prednisone in TP (both in Part 2); [e]All subjects in EP

Klein, Lin et al, Efficacy and Safety of rilonacept in recurrent pericarditis: A multicenter phase 2 clinical trial, AHA poster 2019

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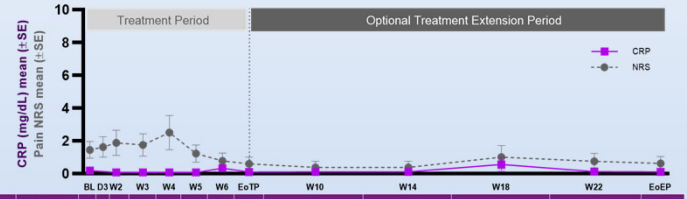
Rilonacept Phase 2 Study Results:
Pericarditis Pain Scores and CRP in Corticosteroid-dependent patients (Parts 3 and 5)

- Corticosteroid-dependent patients who entered the study without an active pericarditis episode maintained low average pain and CRP levels without disease recurrence despite tapering off the corticosteroids while rilonacept treatment continued (Parts 3 and 5)

NRS Scores (Pain) and CRP Levels Non-Active CS-dependent Patients[a] (n=9) During TP and Throughout EP (Parts 3 and 5)



		BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	9		8	9	5	9	5	9	7	8	4	8	8
	CRP Mean	0.19		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]Part 3 and Part 5 combined
CRP, C-reactive protein; **EoTP**, end of treatment period; **EoEP**, end of extension period; **CRP**, C-reactive protein; **NRS**, numeric rating scale

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PROMIS® Scale (v1.2)[a]: Global Health by Symptomatic Patients (Parts 1, 2, 4) and CS-Dependent (Parts 3, 5)

Disease Status:	Idiopathic or PPS	
	Parts 1,2,4 Active (n=16)	Parts 3,5 CS-dependent (n=9)
Global Physical Health, mean (SD)		
Baseline	39.94 (8.941)	43.3 (5.311)
End of TP	51.35 (7.962)	45.09 (4.057)
Final Visit	51.32 (6.564)	46.81 (9.266)
Global Mental Health, mean (SD)		
Baseline	44.5 (10.484)	46.49 (7.767)
End of TP	50.13 (11.325)	47.91 (5.509)
Final Visit	50.54 (10.995)	50.66 (6.299)

*PROMIS® - Patient Reported Outcomes Measurement Information System.
The higher the score, the better global health is. US national average score for Global Physical and Mental Health is 50 (SD 10; Hays RD, et al. Qual Life Res. 2009;18:873-80)

Klein, Lin et al, Efficacy and Safety of rilonacept in recurrent pericarditis: A multicenter phase 2 clinical trial, AHA poster 2019

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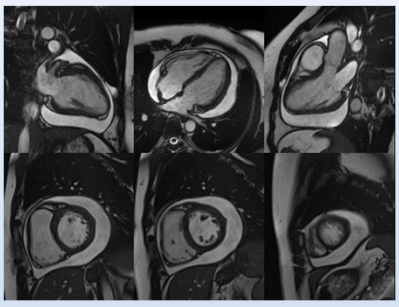
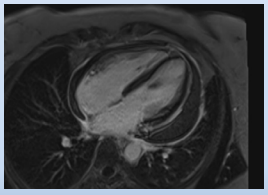
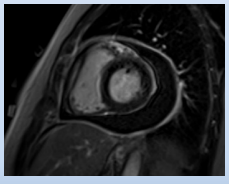
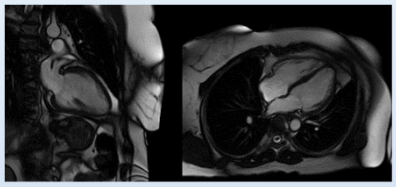
Before

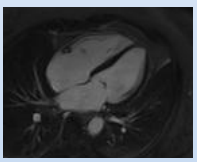


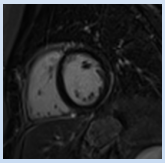




After







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- Rapid improvements in patient-reported outcomes (pain, QoL) and other clinical manifestations of pericarditis (CRP and CMR LGE) persisted throughout the 6-month study period.
  - In CS-dependent pts: low NRS and CRP levels maintained throughout the 6-month duration of the study
- Rilonacept allowed for discontinuation/tapering of corticosteroids without pericarditis recurrences, suggesting a potential corticosteroid-sparing effect.
- Possibly obviating corticosteroid use altogether, thus eliminating or reducing the risk of significant corticosteroid-associated morbidity.

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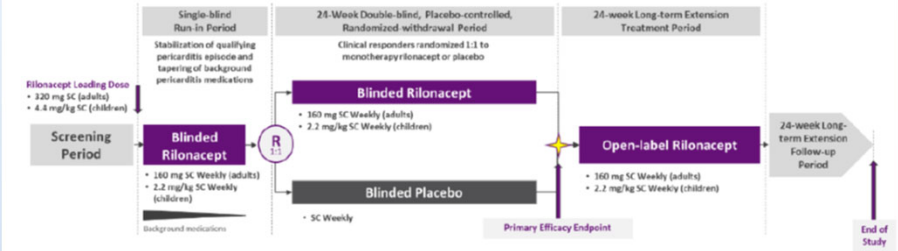
Phase 3 Pivotal Study of Rilonacept in Recurrent Pericarditis

Study Design + Schematic

Phase 3, global, multi-center, double-blind, placebo-controlled, randomized withdrawal study with open-label extension in ~56 patients at approximately 50 sites in 4 countries (US, Italy, Australia & Israel)



- **Screening Period:** Assessment of disease characteristics, baseline therapy and the pretreatment workup
- **Single-blind Run-In (RI) Period:** Blinded rilonacept is administered SC once weekly in all participants as they are weaned off background standard of care (SOC) therapy for their pericarditis disease. Duration of the run-in period undisclosed in order to maintain study Participants blinded to the start of the randomized-withdrawal period.
- **Double-blind placebo-controlled Randomized-Withdrawal (RW) Period** (pericarditis recurrence event-driven duration, minimum of 24 weeks): Participants who were able to stop background SOC pericarditis therapy and who achieve Clinical Response at the end of Run-In Period are randomized 1:1 in a double-blind manner to rilonacept or placebo
- **Long Term Extension Treatment Period (LTE-TP)** (24 weeks): All participants completing the RW period (including participants transitioned to open-label rilonacept upon pericarditis recurrence) will have an option to receive up to 24 weeks of open-label rilonacept 160 mg* SC injections weekly based on their clinical status and at the discretion of the investigator
- **Long Term Extension Follow-Up Period (LTE-FUP)** (24 weeks): All participants in the LTE-TP will be followed in the LTE-FUP for safety and potential pericarditis recurrences

RHAPSODY

SC, subcutaneous; * 2.2 mg/kg in pediatric participants
Rilonacept in recurrent pericarditis (RP) is for investigational use only.
Imazio M, et al. Eur Heart J 2019; 40 (Suppl 1): P3349 | Clinicaltrials.gov; NCT03737110

> 70 patients enrolled.

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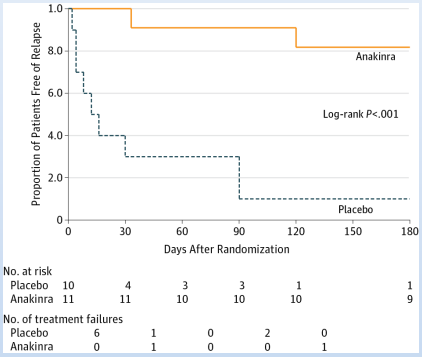
- Anakinra, IL1β recombinant receptor antagonist.
- Agent initially used to treat rheumatoid arthritis.



JAMA. 2016;316(18):1906-1912.

Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence: The *AIRTRIP* Randomized Clinical Trial

- **Optimal duration unknown**
- **Daily dosing**
- **Recurrence is common after discontinuation of the medication**

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Treatment for refractory pericarditis

- Other immunosuppressives:
  - Azathioprine
  - Methotrexate
  - Mycophenolate
  - IVIG
- Pericardiectomy

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Pericardial constriction

- Relatively uncommon, < 1%.
- Incidence more related to *etiology* of pericarditis and *NOT* the number of episodes of pericarditis (TB, post cardiac injury, radiation, malignancy, rheumatologic diseases).
- Presentation:
  - Signs and symptoms of right heart failure -> cardiac cachexia
  - Fatigue
  - SOB
  - LE edema, abdominal fullness
  - Can occur without increased pericardial thickness (~ 20%)

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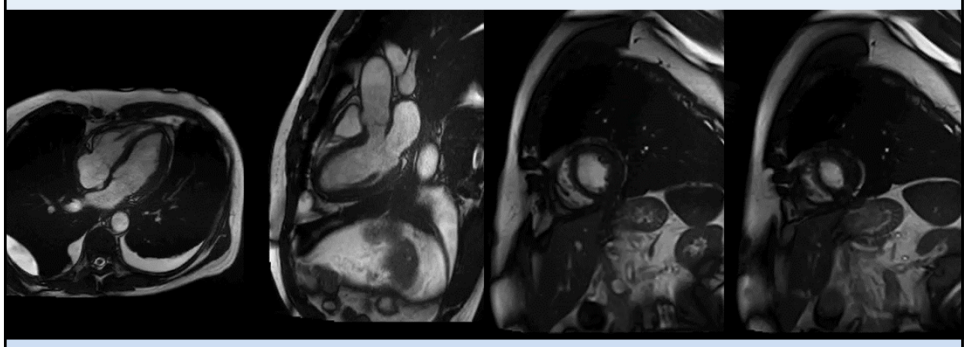

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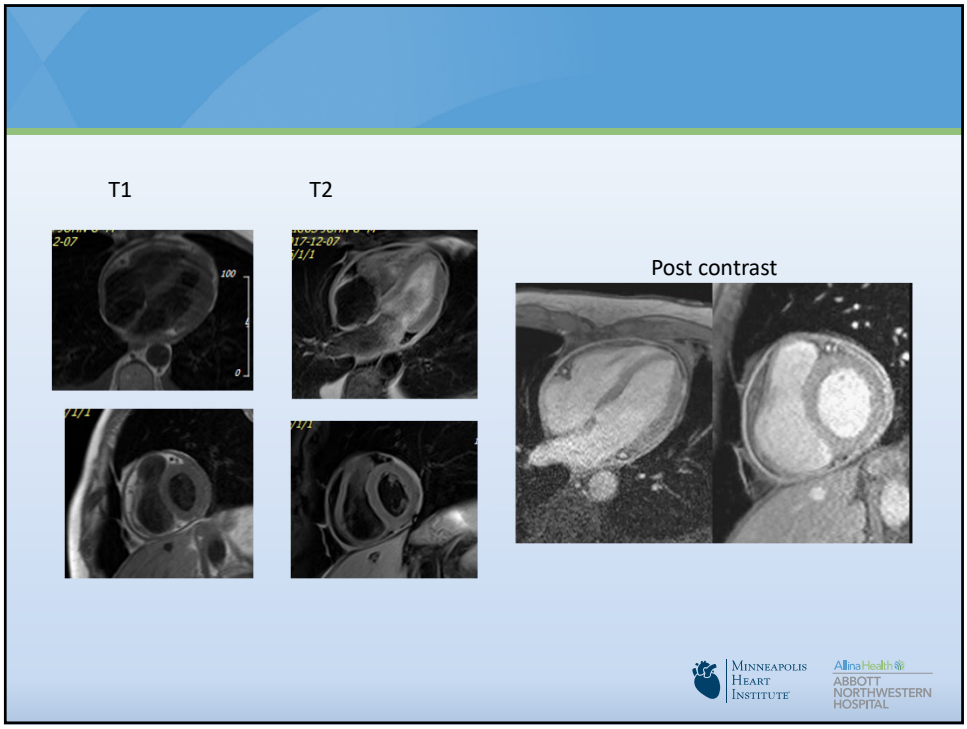
T1
T2
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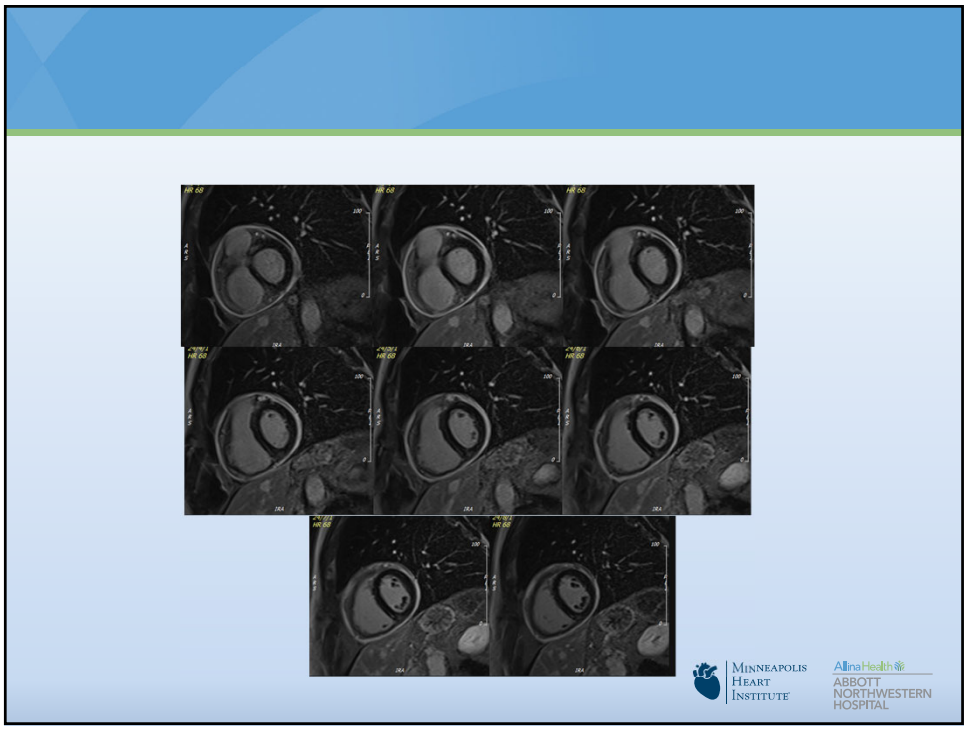
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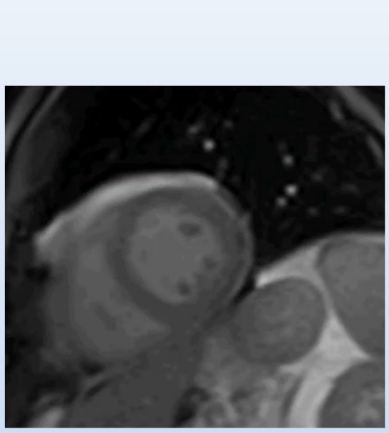

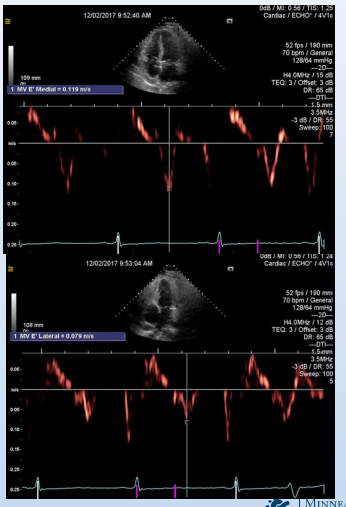

Medial

Lateral

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Pericardial constriction

- Can occur even with normal pericardial thickness, ~ 20%.
- Can be transient
  - New onset within 6 months
  - Especially in presence of pericardial LGE or edema with elevated CRP
  - Trial of anti-inflammatories
- Can persist despite pericardiocentesis (effusive constrictive)
- Permanent cases: surgical pericardiectomy (CT to identify calcification)

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Summary

- Acute pericarditis is usually self limited, mostly viral in etiology.
- Recurrent pericarditis, however, is common with significant morbidity.
- Troponin elevation is *NOT* associated with worse outcome in viral pericarditis.
- Troponin should be obtained in all pericarditis patients and CMR should be performed when elevated.
- NSAIDs + colchicine is the first line therapy.
- Steroid is a risk factor for recurrence and should be avoided. When used, low dose weight based. Gradual taper is vital.

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Summary

- Rilonacept, an IL1α and β receptor decoy, has shown promising result. Phase 3 trial ongoing.
- Pericardial constriction can be transient and warrant trial with medical therapy first.
- Constriction can occur without increased pericardial thickness.
- CMR is an excellent tool in the diagnosis of pericarditis and constriction.

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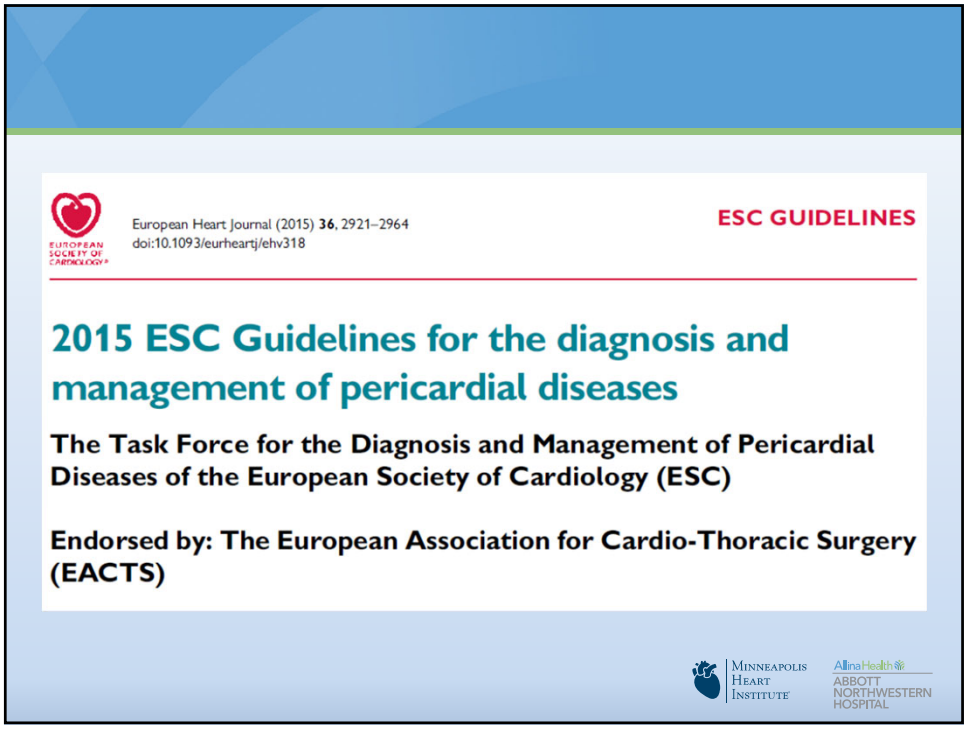
European Heart Journal (2015) 36, 2921–2964
doi:10.1093/eurheartj/ehv318
ESC GUIDELINES
2015 ESC Guidelines for the diagnosis and management of pericardial diseases
The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)
Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS)
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