MHIF FEATURED STUDY: Exact Trial

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%

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

SPONSOR: Xylocor
    Therapeutics, Inc

OPEN AND ENROLLING:
EPIC message to Research MHIF Patient Referral
Spotlight on the Rhapsody Team!

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

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.
Diagnosis and Management of Pericarditis

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

• Disclosures:
  — none
Objectives

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

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

• 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
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.

Epidemiology

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

• 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.
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

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
Diagnosis

- 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*

Diagnosis

• No specific biomarkers

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

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

Diagnosis

• Routine identification of the putative virus is NOT recommended.
  • Enteroviruses (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.
### Diagnosis

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st level (all cases)</td>
<td>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 Xray.</td>
</tr>
<tr>
<td>2nd level (if 1st level not sufficient for diagnostic purposes)</td>
<td>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 modena due to effusions not responding to conventional anti-inflammatory therapy. Additional testing should be directed to specific etiologies according to clinical presentation (presence of high risk clinical criteria).</td>
</tr>
</tbody>
</table>

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

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### LGE

**T1**  
**T2**  
**SSFP**  
**NO LGE**
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.
**Treatment**

**Acute pericarditis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dosage</th>
<th>Tx duration</th>
<th>Tapering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>750-1000 mg every 8h</td>
<td>1-2 weeks</td>
<td>Decrease doses by 250-500 mg every 1-2 weeks</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>600 mg every 8h</td>
<td>1-2 weeks</td>
<td>Decrease doses by 200-400 mg every 1-2 weeks</td>
</tr>
<tr>
<td>Colchicine</td>
<td>0.5 mg once (&lt;70 kg) or 0.5 mg b.i.d. (≥70 kg)</td>
<td>3 months</td>
<td>Not mandatory alternately 0.5 mg every other day (&lt;70 kg) or 0.5 mg once (≥70 kg) in the last week</td>
</tr>
</tbody>
</table>

* 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

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

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

<table>
<thead>
<tr>
<th>CMR criteria</th>
<th>Se</th>
<th>Spe</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Pericardial thickening</td>
<td>38.9</td>
<td>99.4</td>
<td>94.9</td>
<td>95.4</td>
<td>18.5</td>
<td>1.0</td>
</tr>
<tr>
<td>(2) Pericardial effusion (T2w)</td>
<td>68</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>75.7</td>
<td>N.A. *</td>
</tr>
<tr>
<td>(3) Pericardial LGE</td>
<td>64.8</td>
<td>99.2</td>
<td>98.8</td>
<td>98.4</td>
<td>73.8</td>
<td>1.0</td>
</tr>
<tr>
<td>(4) Pericardial effusion and LGE</td>
<td>52.3</td>
<td>89.8</td>
<td>83.8</td>
<td>85.3</td>
<td>5.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>RP patients (N = 512)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrences within 4 years of the initial AP diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥2 recurrences</td>
<td>184 (35.9)</td>
</tr>
<tr>
<td>≥3 recurrences</td>
<td>93 (18.2)</td>
</tr>
<tr>
<td>≥4 recurrences</td>
<td>50 (9.8)</td>
</tr>
</tbody>
</table>

![Graph showing recurrence rates over time](chart.png)
Definition

\[ \sim 30\% \text{Tn} \rightarrow \text{CMR} \]

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

Treatment

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
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, cushingoid... etc

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
Treatment

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

Alternative therapy

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 inflammation1-2
Rilonacept

- 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).

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

- 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

NRS Scores (Pain) and CRP Levels Symptomatic RP Patients with Elevated CRP (n=13)

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

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>CS requirement (mg/day)</th>
<th>Part 1</th>
<th>Part 2</th>
<th>Part 3</th>
<th>Part 4</th>
<th>Part 5</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>4-12</td>
<td>12-3</td>
<td>6</td>
<td>4-12</td>
<td>12-3</td>
<td>31-75</td>
</tr>
<tr>
<td>Mean dose</td>
<td></td>
<td>4.8</td>
<td>4.0</td>
<td>8.9</td>
<td>0</td>
<td>7.7</td>
<td>12.7</td>
</tr>
<tr>
<td>Min</td>
<td></td>
<td>1.0</td>
<td>3.0</td>
<td>2.5</td>
<td>0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td>12.9</td>
<td>30.0</td>
<td>30.0</td>
<td>0</td>
<td>12.6</td>
<td>39.0</td>
</tr>
</tbody>
</table>

**Corticosteroid Changed During TP and EP Combined**

| Prednisone dose decreased $^1$ | 0/3 | 1/3 (33%) | 1/3 (33%) | 0/3 | 0/3 (0%) | 2/3 (67%) |
| Prednisone stopped $^1$ | 0/3 | 1/3 (33%) | 1/3 (33%) | 0/3 | 0/3 (0%) | 2/3 (67%) |
| Prednisone increased $^1$ | 0/3 | 0/3 (0%) | 0/3 (0%) | 0/3 | 0/3 (0%) | 0/3 (0%) |

$^1$ Only patients who achieved a stable low prednisone dose (≤5 mg/day) and remained on it for at least 6 months and 6 months after EP.

Klein, Lin et al., Efficacy and Safety of Rilonacept in Recurrent Pericarditis: A Multi-Center Phase 2 Clinical Trial, AHA poster 2019.

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

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

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Idiopathic or PPS</th>
<th>CS-Dependent (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parts 1, 2, 4</td>
<td>Active (n=16)</td>
<td>39.9 (8.941)</td>
</tr>
<tr>
<td></td>
<td>Final Visit</td>
<td>51.85 (7.962)</td>
</tr>
<tr>
<td>Parts 3, 5</td>
<td>Active (n=18)</td>
<td>51.12 (6.564)</td>
</tr>
</tbody>
</table>

Global Physical Health, mean (SD)

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Idiopathic or PPS</th>
<th>CS-Dependent (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>44.5 (10.484)</td>
<td>46.49 (7.767)</td>
</tr>
<tr>
<td>End of TP</td>
<td>50.13 (11.325)</td>
<td>47.91 (5.509)</td>
</tr>
<tr>
<td>Final Visit</td>
<td>50.54 (10.995)</td>
<td>50.66 (6.239)</td>
</tr>
</tbody>
</table>

Global Mental Health, mean (SD)

**PROMIS®** - Patient-Reported Outcomes Measurement Information System.
For higher the score, better the global health. *CS* = cumulative change score for Global Physical and Mental Health is 0-50. N=16, mean (SD). doi: 10.1161/CIRCOUTCOMES.119.003948.
• 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.
• Anakinra, IL1β recombinant receptor antagonist.
• Agent initially used to treat rheumatoid arthritis.

**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

<table>
<thead>
<tr>
<th>No. of treatment failures</th>
<th>Fluoro</th>
<th>Anakinra</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Treatment for refractory pericarditis**

• Other immunosuppressives:
  – Azathioprine
  – Methotrexate
  – Mycophenolate
  – IVIG
• Pericardiectomy
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%)
T1  T2  Post contrast
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)
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.

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.