Title: Treatment of Acute Pericarditis With Anakinra

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TREATMENT OF ACUTE PERICARDITIS WITH ANAKINRA: A PILOT STUDY

Acute pericarditis is a clinical syndrome characterized by an inflammation of the pericardial layers[1-2]. It can be caused by a variety of infectious and non-infectious agents, but it most commonly either follows a viral infection of the upper respiratory tract (when the virus is gone) or has no apparent cause, in which case it is referred to as idiopathic[1-2]. Acute pericarditis occurs rather abruptly in previously healthy individual, generally a child or young adult. While the prognosis of acute pericarditis is favorable, with most cases resolving within few days, it is associated with chest pain and discomfort, often severe and requiring an escalation of therapy, and it is occasionally associated with life-threatening complications, such as pericardial tamponade – hypotension and shock due to impaired cardiac filling secondary to large pericardial effusion[1].

Acute pericarditis is diagnosed in 1 in 20 (5%) ED visits for chest pain, 1 in 1,000 (0.1%) hospital admissions, and in 1 in 10,000 (0.01%) healthy individuals[1], reflecting ***a significant clinical burden*** worldwide.

The ***pathophysiology*** of acute pericarditis is a stereotypical response to an acute injury to the mesothelial cells constituting the pericardial layers around the heart. The inflammation is initiated by an 'irritant' which can be the virus itself or the release of cellular debris[3-5]. The response is however sustained by an amplification of the injury through the activation of the Nod-like receptor 3 (NLRP3) inflammasome, an intracellular macromolecular structure responsible for sensing danger or injury and intensifying the inflammatory response through the release of mature Interleukin-1β (IL-1β)[3-5]. IL-1β is indeed an apical pro-inflammatory cytokine that stimulates the synthesis of inflammatory mediators such as cyclo-oxygenase-2 (COX-2), prostaglandins and subsequent hyperemia, edema, and hyperesthesia characteristic of the acute pericarditis syndrome (Figure 1)[6]. In most instances, by the time the subject presents with chest pain, the initial insult can no longer be identified, and all that is seen in the inflammatory response.

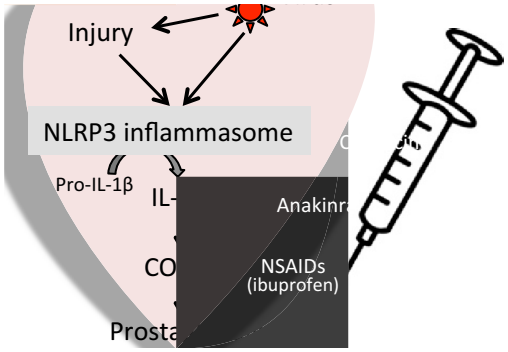

Figure 1. Pathophysiology of acute pericarditis: an injury due to an infectious or non-infectious pathogen triggers the formation of the NLRP3 inflammasome initiating a local and systemic inflammatory response.

Anti-inflammatory therapy has been the mainstay of the treatment for acute pericarditis, yet there are no drugs indicated and/or approved by the Food & Drug Administration specifically for the treatment of acute pericarditis, and the treatments conventionally used are associated with rate limiting side effects or high rate of recurrences[1-2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first line treatment. The anti-inflammatory activity of NSAIDs is related to the inhibition of COX-2 and reduction in prostaglandins synthesis, resulting in local control of pain (Figure 1). NSAIDs (such as indomethacin, diclofenac, ibuprofen) are generally effective in controlling symptoms but these drugs significantly increase risk of gastro-intestinal bleeding, hypertension and renal failure, and are associated with a significant recurrence rate after discontinuation of treatment. Colchicine is used as a second line drug, and is also highly effective by inhibiting tubulin aggregation and NLRP3 inflammasome formation. Colchicine however is associated with a 15-20% discontinuation due to diarrhea and other gastrointestinal discomforts[7], and, although rarely, also with bone marrow suppression (Table 1). Glucocorticoids (such prednisone) are rarely used acute pericarditis because althou very effective in controlling acu pericarditis by inhibiting NF- signaling, these drugs increase r of gastro-intestinal bleedi hypertension, and are a associated with a higher recurrer rate. In some rare cases, acu pericarditis is secondary to anothe disease such as bacterial pneumonia, cancer invading the pericardium, tuberculosis, connective tissue diseases – in such cases treatment is aimed at the underlying disease. While anti-inflammatory drugs relieve pain in all types of pericarditis, elimination of the offending agent is essential for healing.

Treatment	Advantage(s)	Disadvantage(s)
Non-steroidal anti-inflammatory drugs (NSAIDs)[i.e. ibuprofen]	Highly efficacious in relieving pain	Increased blood pressure, sodium/ water retention, risk of bleeding
Colchicine	Greater response rate when added to NSAIDs, prevents recurrences when added to NSAIDs	Gastrointestinal intolerance (15-25%); bone marrow suppression (rare)
Glucocorticoids [i.e. prednisone]	Preferred in cases of connective tissue diseases	Impaired glucose control, increased blood pressure, sodium/water

There is ***a clear need to develop novel therapies for acute pericarditis***.

INNOVATION:

As represented in Figure 1, NLRP3 and IL-1β occupy a central role of in the pathogenesis of acute pericarditis: activation of the NLRP3 inflammasome leads to release of mature IL-1β, synthesis of COX-2 and prostaglandins and subsequent hyperemia and pain. Subjects with specific mutations in the *Nlrp3* (also known as *cryopyrin),* rendering it constitutively active, experience spontaneous bouts of systemic inflammation – cryopyrin-associated periodic syndromes [CAPS][8-9]- which are exquisitely responsive to IL-1β blockers. The clinical manifestations of CAPS vary from mild to severe systemic inflammation, with acute pericarditis being one of the more severe clinical presentations[10-11]. These rare cases of genetically mutated *Nlrp3* highlight the importance of NLRP3 in acute pericarditis. Another relatively uncommon syndrome with familiar transmission is recurrent idiopathic pericarditis – a syndrome of isolated recurrent acute pericarditis on an auto-inflammatory basis, and although the gene(s) involved are unknown, idiopathic pericarditis is also responsive to IL-1β blockers[12]. Most cases of pericarditis are however acquired and, generally, related to recent viral infections. Either the transient infection of the pericardial cells by the virus(es) or the injury related to the infection leads to activation of the NLRP3 inflammasome and the NF-kB and COX2-dependent inflammation, which leads to a full blown acute inflammatory response that is at that point 'sterile' – free of virus(s). The clinical syndrome of pain and discomfort is related to the sterile inflammatory response. The beneficial effects of NSAIDs are mediated through inhibition of COX-2 and reduction in prostaglandin production[1-2]. More recently colchicine has been shown to be effective in acute pericarditis[13]. The renewed interest in colchicine as anti-inflammatory therapy in acute inflammatory disease derives from its use as a treatment of gouty arthritis. This has led to a better understanding of the mechanism of action[14-15]. In vitro studies now link it to the NLRP3 inflammasome, colchicine inhibits microtubule formation and interfering with the formation of the macromolecular structure composed of ASC (apoptosis-associated speck-like protein containing a caspase recruiting domain), NLRP3, pro-capase-1 and pro-IL-1β, and hence preventing activation of the NLRP3 inflammasome and the release of active IL-1β[14-15]. While effective in many cases, colchicine is limited by dose-dependent side effects, mainly gastrointestinal[7]. IL-1β blockers are highly effective in treating acute and chronic pericarditis, including those severe cases that are refractory to NSAIDs and to colchicine[2,16-25]. There are several drugs approved by the FDA as IL-1β blockers including anakinra (Kineret®), canakinumab (Ilaris®), and rilonacept (Arcalyst®) but none are approved for acute pericarditis[26-27].

Developing a an **IL-1 blocker as preferred treatment for acute pericarditis** *without the side effects of the currently available treatments*, would be of great clinical, and commercial, impact.

In conclusion, the current treatment for acute pericarditis is based on NSAIDs and/or colchicine. While it is considered standard of care, this strategy is not based on large clinical trials, and failure of this strategy is known to occur in the following terms: 1) Failure to achieve resolution of symptoms; 2) occurrence of side-effects limiting use; 3) early recurrence of symptoms after discontinuation of treatment. Anakinra (kineret) has been shown to treat and cure refractory and recurrent pericarditis. This study is aimed at determining whether anakinra is also effective as first line treatment in acute pericarditis.

Anakinra is likely to have a more favorable risk profile and be more effective than standard of care for acute pericarditis. The risk of anakinra use are limited to injection site reaction (approximately 10% if treatment is continued for 2 weeks or more, less if treatment is given for less than 1 week), a reduction of symptoms and signs of systemic infection which may lead to a more widespread infection at time of diagnosis (this risk is low, <5% per year with continuous treatment, and is reduced by clinical awareness and monitoring for changes in clinical status). The potential benefit is for a rapid and sustained resolution of acute pericarditis without effects on renal function (i.e. non-steroidal anti-inflammatory drugs), gastrointestinal side effects (i.e. colchicine) and increased risk of bleeding (i.e. non-steroidal anti-inflammatory drugs).

SPECIFIC AIMS:

To determine the **efficacy and tolerability** profile of **anakinra in acute pericarditis**

- ***Step I*** – Assessment of **acute pain relief** with anakinra at **6 hours**
  (additional treatments allowed only as rescue strategy [>9 pain], NSAIDs discouraged)
- ***Step II*** – Assessment of **subacute pain relief** with anakinra at **24-hour**
  (additional treatments allowed, NSAIDs discouraged)

- ***Step III*** – **Comparison of 3-day vs 7-day anakinra treatment** with assessment at **7 and 30 days**
  Randomized doubled-blinded assignment *(additional treatments allowed)*

Milestones for Step I [Open label anakinra]:

- Relief of chest pain within 6 hours of treatment
  - Comprehensive pain assessment scale and Visual Analog Pain (0-10) scale
- Effects on ECG (ST elevation score)
- Need for rescue pain treatment (opioids) for severe intractable pain
- Interval change in IL-6 levels from baseline to 6 hours
- Side effects profile

Milestones for Step II [Open label anakinra]:

- Relief of chest pain at 24 hours with Visual Analog Pain (0-10) scale
- Effects on ECG (ST elevation score)
- Use of additional analgesic or NSAIDs
- Side effects profile
- Interval change in IL-6 levels from baseline at 24 hours

Milestones for Step III [Duration of Anakinra treatment]:

- Relief and/or recurrence of chest pain on day 7 and 30
  - Comprehensive pain assessment scale and Visual Analog Pain (0-10) scale
- Changes in pericardial effusion at echocardiography on day 7 and 30 vs day 1
- Side effects profile on day 7 and 30
- Recurrence rate leading to urgent office visit, emergency department visit, hospitalization, or other
- Comprehensive metabolic profile and complete cell count with differential on day 7 and 30
- Interval change in CRP andIL-6 levels from baseline to day 7 and 30

Inclusion criteria:

- Age ≥12 years in presence of a parent able to provide consent or age >18 years
- First or recurrent episode of acute pericarditis, defined as the presence of at least 2 of the following:
  - Chest pain (suggestive of pericarditis and not explained by other condition)
  - Pericardial friction rub on physical exam
  - ST-segment elevation and/or PR depression on ECG
  - New or worsening pericardial effusion
- Pain of moderate-to-severe intensity (pain score ≥6 on a scale of 0-10 where 0 is no pain at all and 10 is the worst pain ever experienced) at time on enrollment
- Ability to provide written informed consent if 18 years or older or to provide assent in presence of parental consent if 12-17 years of age

Exclusion criteria:

- Pericarditis due to bacterial or fungal infection
- Pericarditis due to malignancy
- Pericarditis after cardiac surgery
- Tamponade or need for pericardiocentesis for diagnostic/therapeutic purposes
- Pregnancy or breastfeeding
- Hypersensitivity to anakinra, latex or products derived from *Escherichia coli*
- Chronic pain syndromes or chronic use of analgesic drugs

Monitoring for use of pain medications

The use of pain medications will be closely monitored during the study.

- During the first 6 hours (Step I)- the use of additional pain medications will be discouraged unless considered a necessary rescue strategy for pain exceeding 9 in 0-10 pain scale.
- During the time between 6-24 hours (Step II)- the use of additional pain medication will be allowed, but the

use of non-steroidal anti-inflammatory drugs will be discouraged. Additional pain medications (i.e. acetaminophen, tramadol, oxycodone, morphine, or other) will be considered.

- Between day 2 and day 30 (Step III), there will be no restriction on the use of pain medications, but the subjects will be asked to record the use of all pain medications on a dedicated diary.

Sample size for Steps I and II:

Visual Analogue Scale Score	Standard deviation	Absolute change at 6 and 24 hours	Sample Size (Power=80%)	Sample Size (Power=90%)
8	3	-3	10	13
		-4	7	8
	2	-2	8	11
		-3	4	5

Proposed sample size:

- 14 subjects

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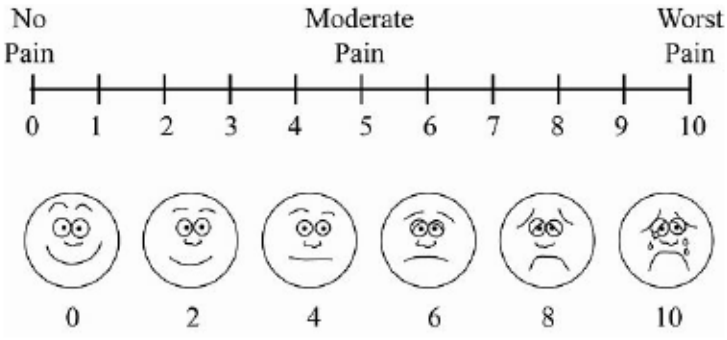
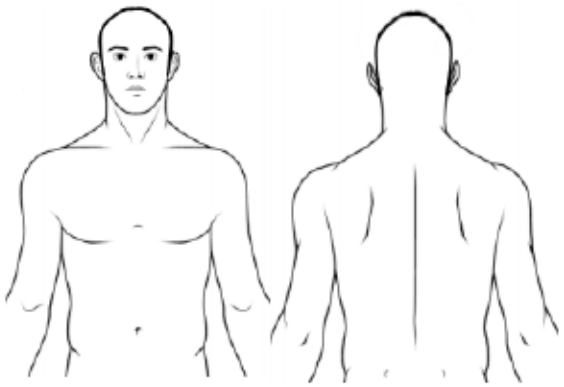
Subject Identifier: Date:

Please rate the intensity of your pain below: Mark the areas where you currently feel pain.





Frequency of pain:

___ Constant
___ Frequent
___ Infrequent
___ Unknown

Description of pain:

___ Aching
___ Burning
___ Cramping
___ Crushing
___ Dull
___ Numbness
___ Pins and needles
___ Sharp
___ Shooting
___ Throbbing

Change in pattern of pain:

Has the pain changed in intensity in the last 24 hours?

___ Yes (if yes, describe below) ___ No ___ Unknown

Causes of pain or worsening of pain:

___ Movement
___ Coughing
___ Cold
___ Heat
___ Fatigue
___ Anxiety
___ Other (describe below):

What relieves the pain?

___ Cold
___ Heat
___ Exercise
___ Eating
___ Medications
___ Herbals
___ Adjuvants
___ Massage
___ Relaxation
___ Rest
___ Repositioning
___ Distraction

Rate how the pain has had an effect in each area in the past 24 hours:

___ 0 or no effect
___ 2 or mild effect
___ 5 or moderate effect
___ 10 severe effect

In the past 24 hours, how much have the medications or treatments eased your pain?

___ 0 or no relief
___ 2 or mild relief
___ 8 or relief
___ 10 or complete relief