The ARAMIS trial

Anakinra versus Placebo, a Double Blind Randomized Controlled Trial for the Treatment of Acute Myocarditis

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on behalf of the ARAMIS investigators
Declaration of interest

Dr Mathieu Kerneis reports:

- consulting/lectures fees from Kiniksa, Eligo, Sanofi, Bayer.
- Research grants from Federation Francaise de Cardiologie and French Health Ministry
- Patent for the use of Abatacept in ICI induced myocarditis

All Disclosures are available on [www.action-group.org](http://www.action-group.org)
Study Organization

ARAMIS = Independent Academic Trial

- **Academic coordinating center**: Institute of Cardiology – ACTION Group – Pitié Salpêtrière Hospital
- **Academic Sponsor**: Assistance Publique-Hopitaux de Paris
- **Academic Global Trial Operations**: URC Lariboisiere, ACTION Group, Paris
- **Academic Funding**: French Ministry of Health (PHRC)
- **Investigation Sites**: 6 academic centers in France
- All analyses were performed by an independent academic statistician
Background
Acute Myocarditis

Acute myocarditis (AM) is an inflammation of the myocardium that can cause life-threatening events.

Ammirati et al. Circ 2018
Treatment of Acute Myocarditis

There is no evidence that a treatment targeting inflammation can improve outcome in « virus-negative » myocarditis patients\(^1\).

A strategy of immunomodulation has not been evaluated in acute myocarditis patients with unknown viral replication (without EMB)\(^2\).

Experimental studies and case reports suggest that blockade of the IL1-β pathway could be effective in AM \(^3,4\).

Anakinra, an IL1-R antagonist, used in inflammatory diseases, has an acceptable safety profile\(^5\).

\(^1\) Frustaci, et al. EHJ 2009 - TIMIC Trial  
\(^2\) Tschöpe, et al. Nat Rev Cardiol 2021  
\(^5\) Brucato A et al., JAMA, 2016
Goal

To perform a pragmatic trial evaluating the inhibition of the IL-1β immune innate pathway with anakinra, to reduce the risk of clinical events in acute myocarditis patients.
Study design
Study Design of the ARAMIS Trial

Randomized, Double Blind, Multicenter, Phase IIb trial

AM patients

Diagnosis

Within 72 hours

Treatment

Placebo + Standard Therapy

Anakinra 100mg sc o.d. + Standard Therapy

Follow-up

Number of days alive free of any myocarditis complications

Number of days considered for the Primary Endpoint

Admission
For a Suspected AM

Confirmation of diagnosis and randomization

Hospital Discharge

Primary Endpoint

Kerneis et al. ACVD 2023

28 days
### Inclusion/Exclusion Criteria

**Inclusion**

Myocarditis was defined as follows:

- Chest Pain
- **AND** modification of the ECG *or* elevated Troponin (at least 1.5 X ULN)
- **AND** CMR Lake Louise Criteria
- **AND** Normal Coronary angiography or CTA in > 40 y/o *or* with CV risk factors

**Exclusion**

- < 18 y/o or > 65 y/o
- LV assistance
- Mechanical Ventilation
- **Any clinical suspicion of autoimmune, giant cell, eosinophilic, or sarcoidosis related myocarditis**
- Renal Failure
- Anti-TNF, CTC/NSAID use
- Malignancy
Endpoints

Primary Efficacy endpoint: 
Number of days alive free of any myocarditis complications

- HF requiring hospitalization
- Chest Pain requiring medication
- LVEF < 50% in TTE
- Ventricular arrhythmia, VT or VF

within 28 days post hospitalization

Primary Safety endpoint: 
Number of SAEs, including those potentially related to the drug:

- Severe infection
- ALT/AST > 10x ULN
- Neutropenia < 1. 109/L
- Renal failure (↑ 50% creat),
- Thrombopenia < 50 000 mm3,
- BARC> 3, Anaphylactic reaction
- 100% ↑ of LDL Cholesterol
Sample Size

Superiority trial
anakinra at the approved dosage of 100mg o.d + SOC (betablocker + ACE inhibitor)
vs placebo + SOC

↑ of the number of days free of myocarditis complications
> 1.5 day = clinically meaningful

SD of the 1°EP = 2.3
based on the AMPHIBIA registry (NCT04844151)

60 patients in each group
⇒ 80% power to demonstrate a 1.5 day difference
⇒ 5% two-sided significance level
120 subjects were randomized between 2017 and 2021

59 were assigned to anakinra
57 subjects in the ITT population
58 subjects in the safety population
1 randomized in the placebo arm have received anakinra

61 were assigned to placebo
60 subjects in the ITT population
59 subjects in the safety population
1 randomized in the placebo arm have received anakinra

1 study discontinuation (no ttt)
1 consent withdrawal
1 administrative reason
Patient characteristics
<table>
<thead>
<tr>
<th>Clinical Presentation (1/2)</th>
<th>Anakinra N=57</th>
<th>Placebo N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age, (Q1;Q3), yrs</strong></td>
<td>28.0 (22.8 ; 38.1)</td>
<td>29.0 (23.2 ; 34.0)</td>
</tr>
<tr>
<td><strong>Male — no of patients (%)</strong></td>
<td>52 (91.2%)</td>
<td>50 (83.3%)</td>
</tr>
<tr>
<td><strong>Current smoker — no. (%)</strong></td>
<td>30 (52.6%)</td>
<td>30 (50.0%)</td>
</tr>
<tr>
<td><strong>Past Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocarditis — no. (%)</td>
<td>1 (1.8%)</td>
<td>3 (5.0%)</td>
</tr>
<tr>
<td>Recent Bacterial infection— no. (%)</td>
<td>9 (15.8%)</td>
<td>6 (10.0%)</td>
</tr>
<tr>
<td>Recent Viral infection — no. (%)</td>
<td>25 (43.9%)</td>
<td>27 (45.0%)</td>
</tr>
<tr>
<td>Chest Pain — no. (%)</td>
<td>57 (100%)</td>
<td>60 (100%)</td>
</tr>
<tr>
<td>Dyspnea — no. (%)</td>
<td>4 (7.0%)</td>
<td>9 (15.0%)</td>
</tr>
<tr>
<td>Cardiogenic shock — no. (%)</td>
<td>1 (1.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Ventricular fibrillation — no. (%)</td>
<td>1 (1.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Conduction disorders — no. (%)</td>
<td>0 (0.0%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Clinical infectious syndrome — no. (%)</td>
<td>16 (28.1%)</td>
<td>18 (30.0%)</td>
</tr>
</tbody>
</table>
## Clinical Presentation (2/2)

<table>
<thead>
<tr>
<th></th>
<th>Anakinra N=57</th>
<th>Placebo N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin in fold increase of the ULN - Median (Q1;Q3)</td>
<td>98 (33;194)</td>
<td>75 (22;217)</td>
</tr>
<tr>
<td>CRP, mg/L - Median (Q1;Q3)</td>
<td>37 (16;68)</td>
<td>23 (14;52)</td>
</tr>
<tr>
<td>(NTpro)BNP, in fold increase of the ULN - Median (Q1;Q3)</td>
<td>0.9 (0.4;1.9)</td>
<td>0.5 (0.3;1.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Anakinra N=57</th>
<th>Placebo N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right or Left BB block — no. (%)</td>
<td>5 (8.8%)</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>ST-segment elevation — no. (%)</td>
<td>37 (64.9%)</td>
<td>39 (65.0%)</td>
</tr>
<tr>
<td>ST segment depression — no. (%)</td>
<td>5 (8.8%)</td>
<td>7 (11.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Anakinra N=57</th>
<th>Placebo N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Imaging — no. (%)</td>
<td>48 (84.2%)</td>
<td>47 (78.3%)</td>
</tr>
</tbody>
</table>

0 patient with EMB
## Non Invasive Imaging

<table>
<thead>
<tr>
<th></th>
<th>Anakinra N=57</th>
<th>Placebo N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular ejection fraction (TTE), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1;Q3)</td>
<td>60 (50;61)</td>
<td>60 (50;60)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>40,73</td>
<td>35,66</td>
</tr>
<tr>
<td><strong>Ventricular dysfunction with TTE (LVEF&lt;50%) — no. (%)</strong></td>
<td>7 (12.3%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td><strong>Regional wall motion abnormalities (TTE) — no. (%)</strong></td>
<td>18 (31.6%)</td>
<td>16 (26.7%)</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction (MRI), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1;Q3)</td>
<td>54 (50;60)</td>
<td>55 (52;60)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>36,72</td>
<td>38,70</td>
</tr>
<tr>
<td><strong>Ventricular dysfunction with MRI (LVEF&lt;50%) — no. (%)</strong></td>
<td>13 (22.8%)</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td><strong>Absence of pericardial effusion — no. (%)</strong></td>
<td>48 (85.7%)</td>
<td>47 (78.3%)</td>
</tr>
</tbody>
</table>
Results
Study course

AM patients

Diagnosis

2 days (1;3)
Min – Max = 0 - 4

Confirmation of diagnosis and randomization

Treatment

2 days (1;3)
Min – Max = 1 - 6

Hospital Discharge

Follow-up

28 days

Primary Endpoint

CCU Admission
For a Suspected AM

Composite Outcome
13.7%

Number of days considered for the Primary Endpoint
Primary Endpoint: Number of days free of complications

95% CI 0.0 (-1.0;0.0)*

p-value = 0.168*

Mean ± sd

Placebo: 29.72 ± 5.66

Anakinra: 29.75 ± 4.18

Red Line = Median
Box = Min-Max

* Hodges-Lehmans's median difference
* Wilcoxon-Mann Whitney test
Non parametric Ancova p-value = 0.192
## Components of the Primary endpoint

<table>
<thead>
<tr>
<th>Component</th>
<th>Anakinra N=57</th>
<th>Placebo N=60</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome* — no. (%)</td>
<td>6 (10.5%)</td>
<td>10 (16.7%)</td>
<td>0.59 (0.19; 1.78)</td>
</tr>
<tr>
<td>Ventricular arrhythmia at 28 days post discharge — no. (%)</td>
<td>1 (1.8%)</td>
<td>1 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Chest pain requiring medication at 28 days post discharge — no. (%)</td>
<td>2 (3.5%)</td>
<td>6 (10.0%)</td>
<td>0.33 (0.06; 1.76)</td>
</tr>
<tr>
<td>Ventricular dysfunction (LVEF&lt;50%) at 28 days post discharge — no. (%)</td>
<td>4 (8.5%)</td>
<td>4 (7.4%)</td>
<td>1.16 (0.27; 5.09)</td>
</tr>
</tbody>
</table>

*ventricular arrhythmia, HF, chest pain requiring medication or LVEF<50% at 28 days post discharge — no. (%)*
## Safety Endpoints

<table>
<thead>
<tr>
<th>Serious Adverse Event — no. of patients (%)</th>
<th>Anakinra (N=58)</th>
<th>Placebo (N=59)</th>
<th>Odds Ratio* (95% CI)</th>
<th>Odds Ratio** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Event — no. of patients (%)</td>
<td>7 (12.1%)</td>
<td>6 (10.2%)</td>
<td>1.21 (0.37; 3.94)</td>
<td>1.20 (0.35; 4.07)</td>
</tr>
</tbody>
</table>

### Serious Adverse Event — no. of events

<table>
<thead>
<tr>
<th>Serious Adverse Event* — no. of events</th>
<th>Anakinra</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>One patient can present several events</td>
<td>10/10</td>
<td>6/6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious Adverse Event potentially related to the drug. (Hepatic cytolysis, n=1)</th>
<th>Anakinra</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe Infection</th>
<th>Anakinra</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Unadjusted Odds Ratio. **Adjusted Odds Ratio for Age and baseline LVEF
Conclusions

ARAMIS, the largest RCT in acute myocarditis, enrolled for the first time an all-comer acute myocarditis population diagnosed on CMR, mostly at low risk of events.

A short administration of anakinra did not increase the number of days free of myocarditis complications.

There was no safety issue with anakinra administered during the acute phase of myocarditis diagnosed without EMB (no proof of absence of viral replication).

Further RCT studies are needed to explore the potential benefit of the anti-inflammatory strategy in acute myocarditis patients at higher risk of events.

Larger studies are needed to evaluate prolonged anti inflammatory strategies in acute myocarditis patients at « low-to-moderate risk » (16% of events at M1).
Thank You to the ARAMIS Team

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