Myocarditis: The heart team approach

The immunologist: Immunosuppressive therapy. When, How and for how long?

By M. Wafaie Aboleineen, MD, FACC

Myocarditis: Is a diverse group of heart-specific immune processes classified by clinical and histopathological manifestations.

Up to 40% of DCM is associated with inflammation or viral infection.

Global deaths for women (orange) and men (blue) due to cardiomyopathy and myocarditis.

Stephane Heymans et al. JACC 2016

CENTRAL ILLUSTRATION: Multiphase Model of Myocarditis

Quiescent regulatory immune elements (myocytes and dendritic cells)

Infectious or Noninfectious Inflammatory Trigger (frequently viruses)

Acute myocarditis

Inflammation of heart muscle

Symptoms:
- Chest pain
- Heart failure
- Tachyarrhythmias
- Acute cardiomyopathy

Pathogenesis:
- Effector immune response
- Antigen bearing cells
- Auto-antigen specific T cells, macrophages and antibodies

Regulatory elements restore tolerance:
- Asymptomatic or mildly decreased cardiac reserve function
- Possible myocyte hypertrophy or mild scarring

Effector immune elements dominate:
- Chronic recurrent chest pain
- Progression to cardiomyopathy
- Persistent cardiac inflammation with or without viral presence

EMB remains the gold standard diagnostic technique for myocarditis.

After acute myocarditis, the inflammatory process is spontaneously resolved after 1 to 4 months.

If immune response fails to eliminate inflammatory process, causing damage to the myocardium.

Specific treatments can be initiated if myocardial injury is still not irreversible.

Proposed mechanism of how infection of cardiac endothelial cells or cardiac myocytes by virus leads to direct cellular damage.


**(NSAIDs) and colchicine**

In viral myocarditis: NSAIDs increased inflammation. Therefore, the lowest required dose are reserved for patients with perimyocarditis
(c) Immunosuppressive therapy

Most data on safety and efficacy obtained using:

- Steroids alone,
- Azathioprine and steroids, or
- Cyclosporine A, azathioprine and steroids.

Mainly in:

- Chronic virus-negative forms.
- Giant cell myocarditis.
- Autoimmune (virus-negative & autoantibody +ve).
- Drugs hypersensitivity hypereosinophilia.

Table 6 Controlled immunosuppression trials in myocarditis and dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Type</th>
<th>Pts (n)</th>
<th>Diagnosis</th>
<th>Primary endpoint</th>
<th>Results</th>
<th>Author**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone trial for DCM</td>
<td>1989</td>
<td>Randomized controlled</td>
<td>102</td>
<td>&quot;Reactive&quot; DCM (n = 60)</td>
<td>Either higher LV ejection fraction (LVF) at 3 months</td>
<td>Favourable</td>
<td>Pamplin</td>
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<tr>
<td></td>
<td></td>
<td>(RCT); prednisone (PON)</td>
<td></td>
<td>&quot;Nonreactive DCM&quot; (n = 42)</td>
<td>or lower LV end-diastolic dimension and better exercise tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTT</td>
<td>1995</td>
<td>RCT: PON and cyclosporine</td>
<td>111</td>
<td>Acute biopsy-proven myocarditis</td>
<td>LVEF at 6 months</td>
<td>Neutral</td>
<td>Macce</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and ciclosporine or</td>
<td></td>
<td>(unknown aetiology)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell myocarditis</td>
<td>2008</td>
<td>Prospective: PON and</td>
<td>11</td>
<td>Giant cell myocarditis</td>
<td>Survival at 1 year</td>
<td>Favourable</td>
<td>Cooper</td>
</tr>
<tr>
<td>treatment trial</td>
<td></td>
<td>ciclosporine and</td>
<td></td>
<td>(autoimmune)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Prospective: PON and</td>
<td>41</td>
<td>Active myocarditis and chronic heart failure</td>
<td>LVEF at 1 year</td>
<td>Favourable in virus-negative salo-positive autoimmune forms</td>
<td>Frustaci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ciclosporine and</td>
<td></td>
<td>(unknown aetiology)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>RCT: PON and azathioprine</td>
<td>84</td>
<td>Inflammatory DCM</td>
<td>LVEF at 3 months, sustained at 2 years</td>
<td>Favourable</td>
<td>Wojnice</td>
</tr>
<tr>
<td>TIMIC</td>
<td>2009</td>
<td>RCT: PON and azathioprine</td>
<td>85</td>
<td>Inflammatory virus-negative DCM</td>
<td>LVEF at 6 months</td>
<td>Favourable</td>
<td>Frustaci</td>
</tr>
</tbody>
</table>

A.L.P. Caforioet al, EHJ, 2013

Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study

Improvement with immunosuppression. After 6 months, marked reduction in LV. volumes and increase in LVEF (from 24 to 50%) were associated with disappearance of activated T lymphocytes and myocyte necrosis present at baseline,

Andrea et al., TIMIC study, Eur Heart J. 2009
Comparison between baseline and 6 months follow-up. Variation in LVEF (A), LVEDV (B), and LVEDD
Andrea et al, TIMIC study, Eur Heart J. 2009

Recommendations

21. Immunosuppression should be started only after ruling out active infection on EMB by PCR.

22. Consideration of immunosuppression in:
- autoimmune myocarditis, including giant cell myocarditis,
- cardiac sarcoidosis, and
- myocarditis associated with known extracardiac autoimmune disease (SLE).

**Recommendations**

23. Steroid therapy in
- sarcoidosis.
- infection-negative eosinophilic or toxic myocarditis.

24. Immunosuppression, in infection-negative lymphocytic myocarditis.

25. Follow-up EMB may be required to guide the intensity and the length of immunosuppression.


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**AHA SCIENTIFIC STATEMENT**

**Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies**

A Scientific Statement From the American Heart Association

Current Therapeutic Options:

**Giant cell myocarditis:**

- **Antithymoglobulin** 275 mg in 500 mL 0.9% saline solution for 12 h/24 h Days 1 to 5 Under cardiac monitoring
- **Ciclosporine**
  - Start dose 200 mg/24 h (100 mg/12 h) Targeted trough level: 100-120 mg/mL 1 year
- **Methylprednisolone**: 1 mg/kg After 4 weeks: decrease by 10 mg, and then another 10 mg every 2 weeks until 5-10 mg maintenance dose 1 year
Current Therapeutic Options:

**Cardiac sarcoidosis**

**Methylprednisolone**: 1 mg/kg After 4 weeks: decrease by 10 mg, and then another 10 mg every 2 weeks until 5-10 mg maintenance dose 6 months


**Recommendations With Strong Level of Consensus for Cardiac Sarcoidosis**

1. An echocardiogram should be performed in patients with HF (Level of Evidence C).
3. Corticosteroids are recommended to treat patients with cardiac sarcoidosis (Level of Evidence B).

**Recommendations With Moderate Level of Consensus for Cardiac Sarcoidosis**

3. Other immunosuppressive therapies (e.g., methotrexate, **azathioprine**, **mycophenolate mofetil**, **cyclophosphamide**, **pentoxifylline**, and **thalidomide**) are reasonable in patients who cannot tolerate corticosteroids and in patients who continue to worsen clinically despite treatment with corticosteroids (Level of Evidence C).
**Current Therapeutic Options:**

**Chronic/autoimmune myocarditis (inflammatory cardiomyopathy), eosinophilic myocarditis**

**Azathioprine**

50 mg/12 h for 6 months

Weekly laboratory control with blood count/liver enzymes during the first Month.

**Methylprednisolone**

1 mg/kg After 4 weeks: decrease by 10 mg, and then another 10 mg every 3 weeks until 5-10 mg maintenance dose 6 months

**In all cases PPI’s  20 mg/24 h, calcium 1 g/24 h**


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**Table 1. Responsiveness of myocarditis to immunosuppressive therapy**

<table>
<thead>
<tr>
<th>Type of myocarditis</th>
<th>Response</th>
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<tbody>
<tr>
<td>Myocarditis associated with hypereosinophilic syndrome</td>
<td>+++</td>
</tr>
<tr>
<td>Myocarditis associated with connective tissue disorders</td>
<td>++</td>
</tr>
<tr>
<td>Rejection of transplanted heart</td>
<td>++</td>
</tr>
<tr>
<td>Giant-cell myocarditis</td>
<td>+/-</td>
</tr>
<tr>
<td>Viral/idiopathic myocarditis</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Conclusions

Immunomodulating and immunosuppressive therapy have been effective, in:
- Chronic, virus negative inflammatory cardiomyopathy.
- Acute giant cell myocarditis.
- Sarcoidosis.
- Acute myocarditis associated with autoimmune diseases (SLE).
Lack of identification of viral agents remains a major limit, explaining the non-responders.

FRUSTACI A et al., circulation, 2015