Myocarditis: The heart team approach

# The immunologist:

# Immunosuppressive therapy. When, How and for how long?

By

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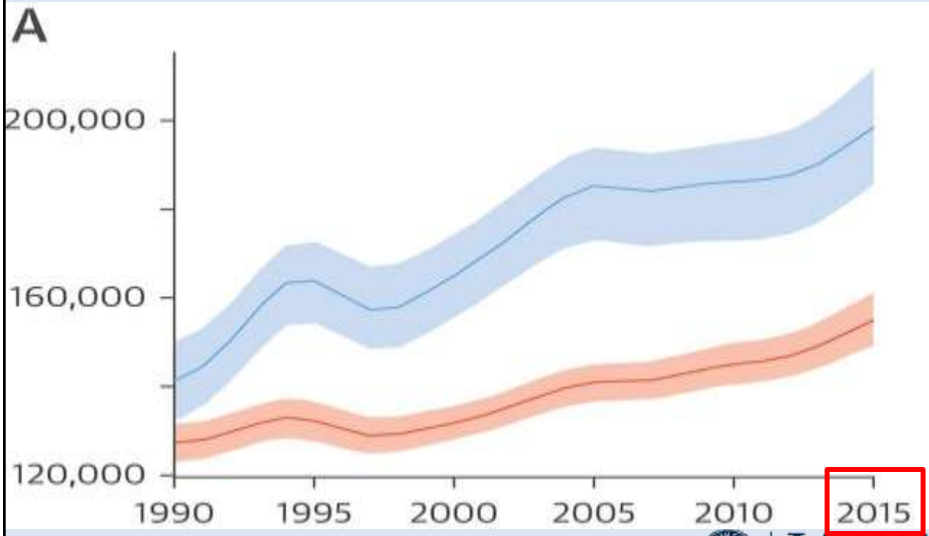
## Myocarditis :

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

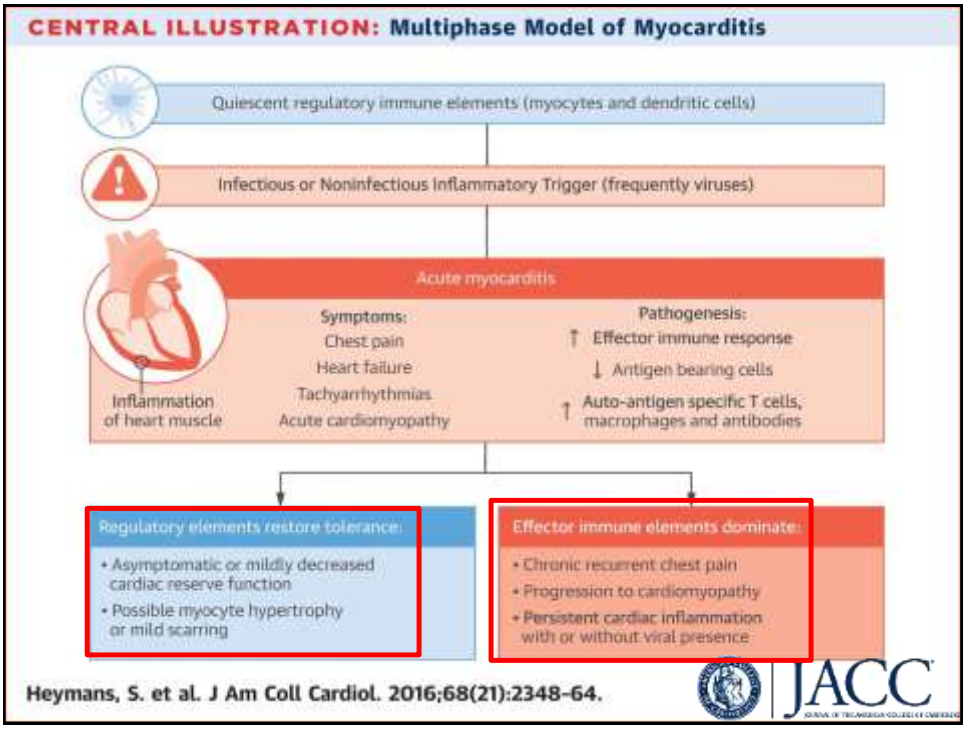
*Up to 40% of DCM.is associated with inflammation or viral infection.*

*Stephane Heymans, MD, et al ,JACC ,2016*

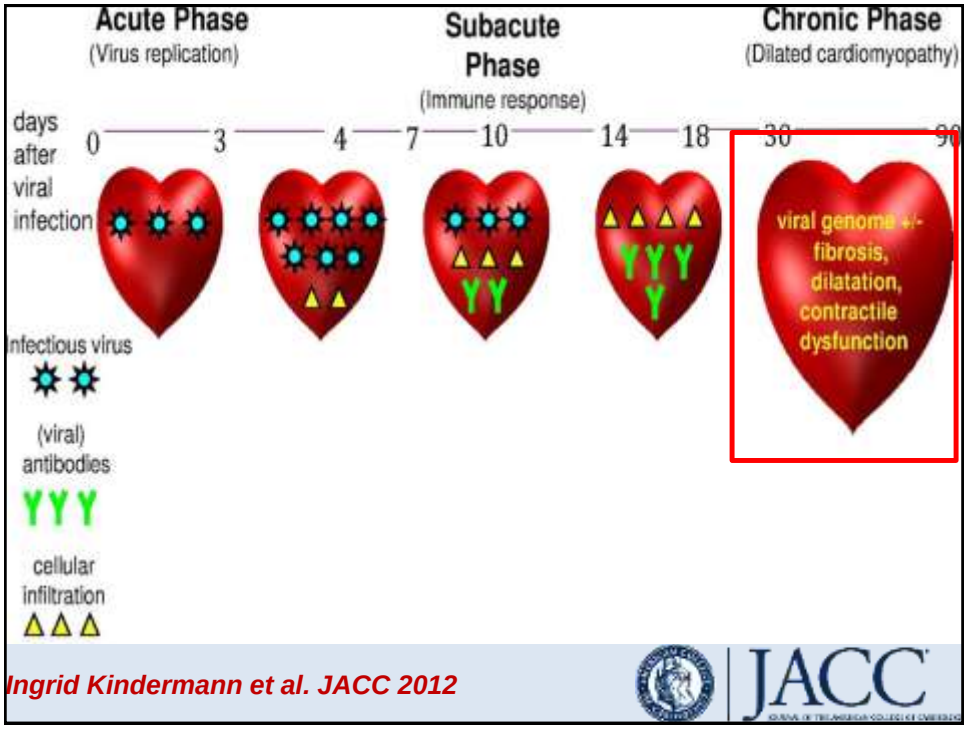
## *Global deaths for women (orange) and men (blue) due to cardiomyopathy and myocarditis .*




*Stephane Heymans et al. JACC 2016*




**Heymans, S. et al. J Am Coll Cardiol. 2016;68(21):2348-64.**




## *EMB remains the gold standard diagnostic technique for myocarditis .*

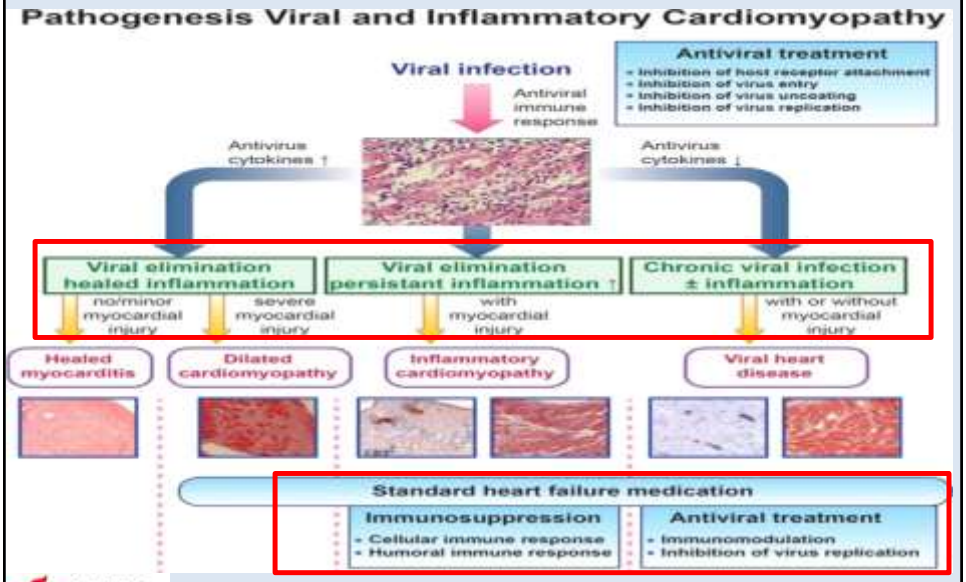
*After acute myocarditis, the inflammatory process is spontaneously resolved after 1 to 4 months.*

*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.*

*F. Dominguez et al. / Rev Esp Cardiol. 2016*

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




***Charles E. ,et al, Circulation. 2014***

## *(NSAIDs) and colchicine*

*In viral myocarditis:*
*NSAIDs increased inflammation.*
*Therefore, the lowest required dose are reserved for patients with perimyocarditis*

European Heart Journal (2013) 34, 2636–2648
doi:10.1093/eurheartj/eht210

ESC REPORT

# Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4],

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

## *(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 .*

*Alida L. P. Caforio , et al ,ESC,2013*

**Table 6** Controlled immusuppression trials in myocarditis and dilated cardiomyopathy

| Trial | Year | Type | Pts (n) | Diagnosis | Primary endpoint | Results | Author[ref] |
|---|---|---|---|---|---|---|---|
| Prednisone trial for DCM | 1989 | Randomized controlled trial (RCT): prednisone (PDN) | 102 | 'Reactive' DCM ($n = 60$) 'Nonreactive DCM)' ($n = 42$) | Either higher LV ejection fraction (LVEF) at 3 months or lower LV end-diastolic dimension and better exercise tolerance | Favourable | Parrillo[176] |
| MTT | 1995 | RCT: PDN and cyclosporine or azathioprine | 111 | Acute biopsy-proven myocarditis (unknown aetiology) | LVEF at 6 months | Neutral | Mason[6] |
| Giant cell myocarditis treatment trial | 2008 | Prospective: PDN and cyclosporine | 11 | Giant cell myocarditis (autoimmune) | Survival at 1 year | Favourable | Cooper[99] |
| | 2003 | Prospective: PDN and azathioprine | 41 | Active myocarditis and chronic heart failure (aetiology known in retrospect) | LVEF at 1 year | Favourable in virus-negative aabs-positive autoimmune forms | Frustaci[100] |
| | 2001 | RCT: PDN and azathioprine | 84 | Inflammatory DCM (unknown aetiology, increased HLA espression on EMB) | LVEF at 3 months, sustained at 2 years | Favourable | Wojnicz[103] |
| TIMIC | 2009 | RCT: PDN and azathioprine | 85 | Inflammatory virus-negative DCM | LVEF at 6 months | Favourable | Frustaci[101] |

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

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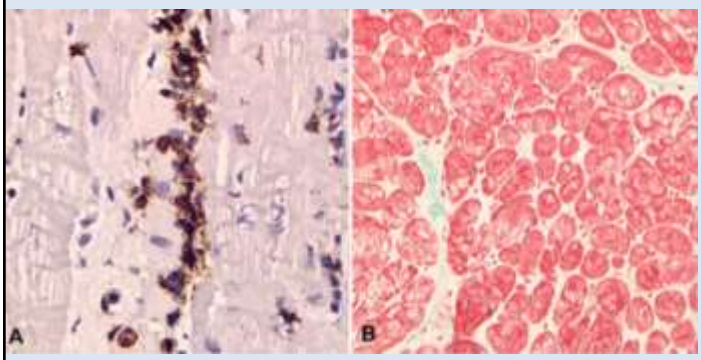
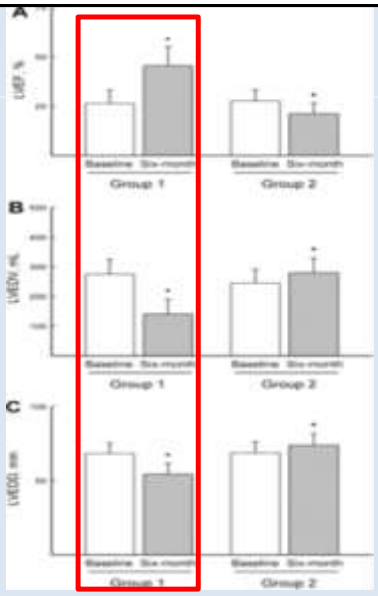
***Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study***




***Improvement with immunosuppression. after 6 month 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***

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*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 extra-cardiac autoimmune disease (SLE) .*

*Alida L. P. Caforio , et al ,EHJ,2013*

# 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.*

*Alida L. P. Caforio , et al ,EHJ,2013*

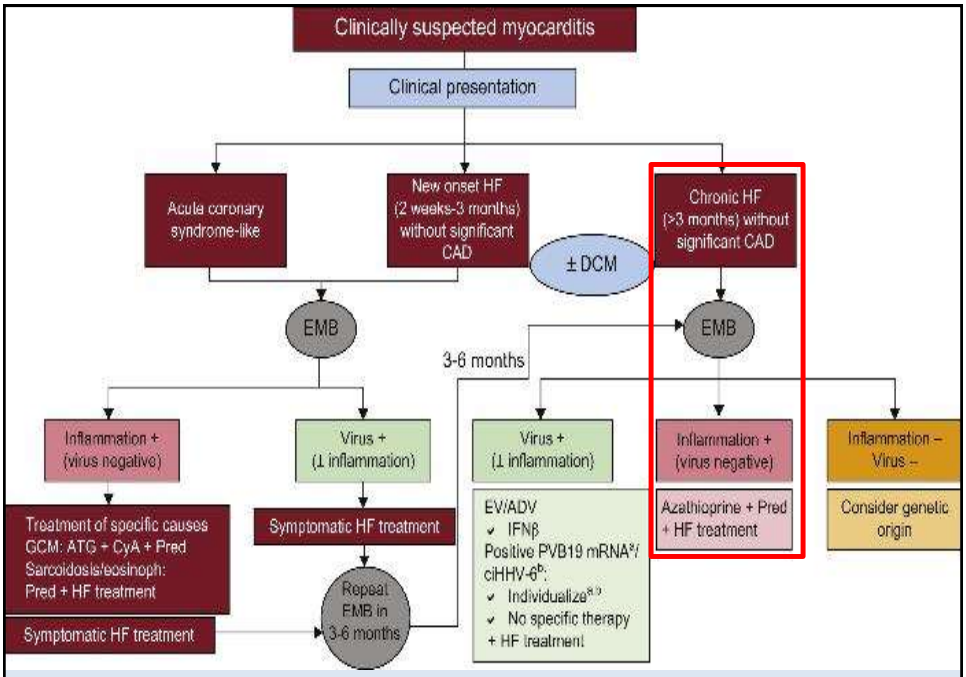
AHA SCIENTIFIC STATEMENT

## Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies

A Scientific Statement From the American Heart Association

*Biykem Bozkurt, MD et al ,Circulation. 2016.*

American Heart Association




*F. Dominguez et al. / Rev Esp Cardiol. 2016*

# *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***

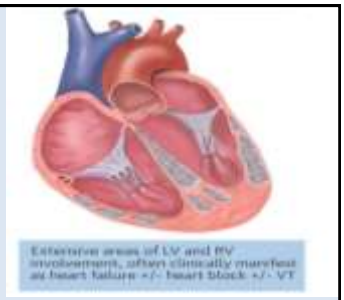
*Start dose 200 mg/24 h (100 mg/12 h) Targeted trough level: 100-120 mg/mL 1 year*

***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*

*F. Dominguez et al. / Rev Esp Cardiol. 2016*

*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*

*F. Dominguez et al. / Rev Esp Cardiol. 2016*

***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 (eg, 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).*

American Heart Association.

## *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***

*F. Dominguez et al./ Rev Esp Cardiol. 2016*

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

| Type of myocarditis | Response |
|---|---|
| Myocarditis associated with hypereosinophilic syndrome | +++ |
| Myocarditis associated with connective tissue disorders | ++ |
| Rejection of transplanted heart | ++ |
| Giant-cell myocarditis | +/− |
| Viral/idiopathic myocarditis | +/− |

*A. Frustaci et al,Circulation 2015.*

# 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*