Review Article

Int Jou Hea Bio Sci, 5(3), 2024, 6-11

International Journal of Health care and Biological Sciences

Content available at www.saap.org.in Online ISSN: 2582-7499

Open Access

AN OVERVIEW OF NOVEL DRUG THERAPIES FOR VIRAL MYOCARDITIS

Shaik Ghan Saida*, Dudekula Khasim vali, Chandu Babu Rao and Chembeti Vijayalakshmi.

Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur-522017.Andhra Pradesh, India.

Article History

Received on: 15-06-2024
Revised on: 11-07-2024
Accepted on: 28-07-2024

Abstract

Sudden cardiac death usually follows a cardiotropic viral infection, which is followed by aggressive inflammatory destruction of the myocardium. Myocarditis is a common cause of dilated cardiomyopathy. This disease's variable clinical manifestations and range of aetiologies have made it difficult to characterize. Viral infections are the primary cause of inflammatory cardiomyopathy. Developments in cardiac MRI and molecular viral identification using endomyocardial biopsies have enhanced our capacity to identify and comprehend the pathophysiological underpinnings of this enigmatic illness. For both the acute and chronic stages of myocarditis, there are currently few treatment options available. Immunosuppressive and immunomodulatory treatments have shown promise in a number of randomized, controlled trials; nonetheless, more research is necessary. This Review delves into the pathogenesis, natural history, diagnosis methods, and evidence-based therapy approaches for myocarditis. The field of myocarditis treatments is set to advance with the development of new imaging modalities and human in vitro disease models.

Keywords: Myocarditis, Endomyocardial biopsy, Cardiac MRI, Immunotherapy.

***Corresponding Author**
Shaik Ghan Saida

DOI: https://doi.org/10.46795/ijhcbs.v5i3.617

Introduction

Myocarditis is a Condition Characterized by Inflammation of the Heart Muscle or Myocardium. It can weaken the Heart's Ability to Pump Blood, Leading to Symptoms Such as Chest Pain, Shortness of Breath, and Rapid or Irregular Heart Rhythms. Myocarditis can be caused by Viral, Bacteria, Fungal, or Parasitic Infections, as well as certain medications, Chemical or Autoimmune Disorders. A novel cause of myocarditis is immune checkpoint inhibitor (ICI)-induced myocarditis, a rare but severe complication in this evolving field of therapy in oncology. Viral myocarditis is caused by a variety of more than 10 genera, such as coxsackievirus, adenovirus, parvovirus, hepatitis c virus, influenza virus, HIV, etc[1]. The most Frequently reported and extensively studied one is coxsackievirus B3 (CVB3), Which causes- 30% of all viral myocarditis cases. This virus can infect multiple organs of humans such as the heart, pancreas, brain, liver, spleen, etc., and cause myocarditis, particularly in children and young people[2]. Viral myocarditis is characterized by inflammatory infiltration of immune cells in the heart muscle after viral infection. This viral infection can cause direct damage to cardiomyocytes as well as immune-mediated destructions of the myocardium, leading to cardio dysfunction. In addition, viral myocarditis often progresses into dilated cardiomyopathy (DCM), an end-stage heart dysfunction [3]. Viral myocarditis is one of the major life- threatening diseases in children. It is the cause of 20% of sudden unexpected death in young people [4]. To date, there is no specific treatment for this viral infection. CVB3 is a positive signal-stranded, non-enveloped RNA virus of the enterovirus genus of Thepicornaviridae family. Its genome is 7.4 kb long, containing a single open reading frame flanked by the 5' and3' untranslated regions (UTRs). The 5' UTR is 741 nucleotides long and harbors several cis-acting translational elements, such as the internal ribosomal entry site (IRES) and the cloverleaf sequences crucial structures for viral translation and transcription.

Epidemiology

The exact incidence of viral myocarditis is challenging to determine due to the wide range of symptoms and the difficulty in diagnosing the condition. Moreover, not all cases of viral myocarditis are reported or diagnosed accurately. Studies suggest that the incidence varies between different regions and populations, ranging from 1 to 10 cases per 100,000 individuals per year. Similarly,

determining the prevalence of viral myocarditis is complicated due to underdiagnosis or misdiagnosis. The prevalence of the disease is estimated to be around 1-5% in patients with unexplained dilated cardiomyopathy.

It is more commonly observed in younger individuals, particularly children and young adults. Viral myocarditis can affect individuals of all age groups. However, it is more frequently observed in children under the age of 16 and young adults between the ages of 20 and 40. In children, viral myocarditis exhibits a bimodal age distribution, with peaks occurring in infancy and adolescence. Males tend to be more frequently affected by viral myocarditis than females, with a male-to-female ratio of 2:1. Viral myocarditis shows some geographical variation, with different viruses being more prevalent in specific regions. For example, Coxsackievirus B is prevalent worldwide, while HHV-6 is more commonly associated with viral myocarditis in Japan. Geographical variation might also reflect differences in healthcare infrastructure, reporting systems, or virus prevalence in specific regions.

Risk Factors of Viral Myocarditis

The risk factors for viral myocarditis, which is inflammation of the heart muscle caused by viral infections, can include:

1. Viral infections: Exposure to certain viruses, such as coxsackievirus B, adenovirus, human herpesvirus 6(HHV-6), and parvovirus B19, increases the risk of developing viral myocarditis.
2. AGE: Young children and young adults are more susceptible to viral myocarditis than older individuals. Children under 5 years old and adults between 20-40 years old have a higher risk.
3. Immunocompromised state: Individuals who have weakened immune systems, such as those with HIV/AIDS, undergoing immunosuppressive therapy, or organ transplant recipients, have an increased risk of viral myocarditis.
4. Genetic factors: Certain genetic factors may predispose individuals to develop viral myocarditis. Mutations or variations in genes that play a role in the immune response can impact an individual's susceptibility to the disease.
5. Environmental factors: Exposure to certain environmental factors, including toxins or pollutants, may increase the risk of developing viral myocarditis. For example, exposure to heavy metals like lead or mercury, or certain chemicals, can contribute to myocardial damage.

It is important to note that while these factors increase the susceptibility to viral myocarditis, not everyone with these risk factors will develop the disease. Additionally, viral myocarditis can also occur in individuals without any risk factors [5].

Pathophysiology

Infectious and non-infectious agents cause myocarditis and the ensuing cardiomyopathy that might occur. Over the past 4 decades, viral infection has increasingly been recognized as the most common etiology. Using PCR technology and in situ hybridization techniques, viral RNA and DNA have been identified within the myocardium of affected patients.

``Common causes of myocarditis. Viral infections are the most common etiology, but several other aetiologies of myocarditis have also been implicated.

Infectious Aetiologies		Non-Infectious Aetiologies	
Viral agents	Bacterial Agents	Toxins	ImmunologicalSyndromes
Adenoviruses	Borella Species	Anthracyclines	Churg-Strauss Syndrome
Enteroviruses	Mycobacterium Species	Cocaine	Diabetes Mellitus
Herpesviruses	Mycoplasma pneumonia	Interleukins-2	Inflammatory
Hepatic c virus	Streptococcal Species	Hypersensitivity	Giant cell myocarditis
HIV	Treponema Pallidum	Cephalosporins	Wegener granulomatosis
Influenza A	Fungal agents	Digoxin	Systemic lupus
Parvovirus B19	Aspergillus Species	Diuretics	Takayasu arteritis
Parasitic agents	Candida Species	Dobutamine	Thyrotoxicosis
Larva Migrans	coccidiosis Species	Sulphonamides	
Schistosomiasis	Cryptococcus Species	Tricyclic	
Protozoal agents	Histoplasma Species	Antidepressants	
Trypanosoma cruzi			

Table: - 1 Enteroviruses (most commonly coxsackie B viruses) are responsible for up to 25% of viral myocarditis cases and, of all the major pathogens, their mode of cardiac infectivity is the best characterized in animal models. Enteroviruses gain access to human hosts via the gastrointestinal or respiratory tracts; the heart is targeted secondarily.

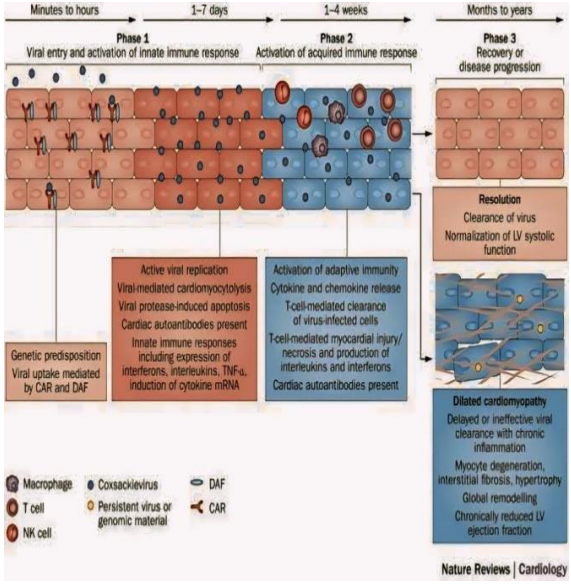

Figure: 1 temporal phases of coxsackievirus-mediated myocarditis. Phase 1 commences with viral entry into the host and transit to the myocardium. In predisposed individuals, coxsackievirus binds to DAF on the cell surface, which shuttles the virus towards the CAR, localized at cell-cell junctions. The complex is internalized by the cell, triggering numerous cellular responses and activation of the host's innate immunity. Virus replication within the cardiomyocyte causes cell lysis, which prompts a set of cascades leading to the release of cytokines. In phase 2, both cellular and humoral responses contribute to autoimmune- mediated injury. The first immune cells recruited to the injured myocardium are NK cells, followed by macrophages [6].

Signs & Symptoms

The signs and symptoms of viral myocarditis can vary in severity and may include:

- Heart palpitations
- Weakness
- Chest pain
- Fever
- Shortness of breath
- Irregular heartbeat
- Light-headedness
- Fatigue
- Signs of infection, such as fever, muscle aches, sore throat, and headache

Diagnosis:

The diagnosis of viral myocarditis often involves a combination of clinical evaluation, non- invasive tools, and, in some cases, invasive procedures. Some of the key methods used for diagnosis include:

1. Clinical Evaluation: This involves assessing the patient's symptoms, and medical history, and conducting a physical examination. Symptoms of myocarditis can be diverse, including fatigue, chest pain, shortness of breath, and heart palpitations.
2. Cardiac Magnetic Resonance Imaging (MRI): Cardiac MRI is a non-invasive imaging technique that can be useful for diagnosing myocarditis. It can provide detailed images of the heart, allowing for the detection of inflammation and damage to the heart muscle. under its capacity to detect inflammation, edema, necrosis, and fibrosis within myocardial tissue.41 Several imaging sequences exist that can be used to differentiate and identify various characteristics associated with both acute and chronic myocarditis.

   Endomyocardial Biopsy (EMB): In some cases, EMB may be used for confirming the diagnosis, especially in patients with acute dilated cardiomyopathy, life-threatening arrhythmias, or those who do not respond to conventional supportive therapy. However, it is an invasive procedure and not always performed routinely [7].
3. Biomarkers: Blood tests to measure biomarkers such as cardiac troponins and B-type natriuretic peptide (BNP) can help in the diagnosis and assessment of the severity of myocarditis [8].

According to the results from my web search, some of the potential blood biomarkers for viral myocarditis are:

- sST2**:** This is a protein that is released by the heart when it is inflamed.
- cMet-expressing T cells**:** These are immune cells that are involved in the development of myocarditis and dilated cardiomyopathy.

These biomarkers may offer a way to diagnose viral myocarditis with a simple blood test, which could lead to earlier treatment and better outcomes for patients. However, further research is needed to confirm their validity, reliability, and clinical utility [9].

4. Polymerase Chain Reaction (PCR) and Situ Hybridization: These molecular techniques can be used to detect viral RNA and DNA within the myocardium, providing evidence of viral infection.

The diagnosis of viral myocarditis is a complex process that may involve multiple diagnostic tools to confirm the presence of the disease and its underlying cause. The specific diagnostic approach used for each patient will depend on their clinical presentation and the available resources [10].

Treatment

Over the past several years, animal studies and clinical trials have focused on a variety of therapeutic options, including immunosuppressants, immunomodulators, antivirals, nonsteroidal anti-inflammatory agents (NSAIDs), and immunoglobulin.

Bed rest and conventional therapy

The one treatment strategy universally advocated for myocarditis is bed rest. In guinea pigs infected with myocarditis, higher mortality, and more extensive histologic disease were observed in animals that were exercised when compared with unexercised controls [11]

Thus, all patients suspected of having acute myocarditis should be admitted to a hospital for observation and a regimen of modified bed rest designed to decrease myocardial damage and promote healing. Additionally, patients should avoid alcohol and cigarettes. A passive physical activity program with a very low level of caloric expenditure is appropriate and will help prevent venous stasis and skeletal muscle atrophy. A ventricular assist device or extracorporeal membrane oxygenation may rarely be required to sustain patients with refractory cardiogenic shock [12].

If patients show no improvement or reveal evidence of decompensation, a positive inotrope (eg, intravenous dobutamine) can be used intermittently.

Immunosuppressive Treatment

Techniques designed to distinguish autoimmune from viral myocarditis (eg, viral hybridization) vary greatly between institutions. Even the Dallas criteria, created to standardize the histopathologic diagnosis of myocarditis, allow considerable inter-observer variability [13]. This difficulty with histopathologic classification partially explains the inconclusive results of immunosuppressive trials in myocarditis/DC. The results were inconclusive: there appeared to be no hemodynamic.

There are several other clinical trials controlled and uncontrolled that have looked at the effect of prednisone, azathioprine, and/or cyclosporine treatment in myocarditis [14].

– Lymphocyte infiltrate

– Increased high-density lipoprotein class I and II expression

– Increased expression of adhesion molecules on the endothelium and in the interstitial

– Increased finding of IgA, IgG, and IgM.

Non-steroidal anti-inflammatory Drugs (NSAIDs)

Although no prospective controlled studies have been conducted, NSAIDs have been studied in animal models of viral and autoimmune myocarditis. Several studies have shown that salicylates, indomethacin, and ibuprofen, given early in the course of myocarditis, lead to exacerbation of the disease, with more severe histologic damage.

Immunoglobulins Treatment

Recently, an increasing amount of clinical trial data has revealed a beneficial role for immunoglobulins in treating viral myocarditis and DC. The efficacy of high-dose

Immunoglobulins in the treatment of respiratory syncytial virus, idiopathic thrombocytopenic purpura, Kawasaki disease.

Cytokines and immunomodulation

As previously mentioned, the process by which viral myocarditis progresses to DC has two stages. Initially, a protective immune response is induced by infiltrating macrophages,

natural killer cells, and antiviral antibodies. A growing body of evidence suggests thatcytokines play an important role in this process. Furthermore, studies have proven that patients with acute myocarditis have elevations of interleukin (IL)-1α, IL-1β, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor. Most of this work has focused on the modulation of IL-2, TNF, IFN-α, and IFN-β, IFN-γ [15].

Interleukins

IFN-α

Produced primarily by leukocytes, IFN-α appears 4 to 6 hours after viral stimulation and is believed to reduce viral replication. In 1988, Kishimoto et al [16]. demonstrated that IFN-α wascapable of inhibiting viral replication and reducing myocardial inflammation when given to

mice before infection with coxsackievirus B3. When coxsackievirus B3–infected mice were treated with M-CSF from days 0 to 14 of infection, cardiac disease was noted to be significantly reduced.

IFN-β

IFN-β has also been shown to have antiviral activity against coxsackievirus and shows promisein treating viral-induced myocarditis. In a series of 22 patients with persistent LV dysfunction, symptomatic HF, and enteroviral or adenoviral persistence in the myocardium by PCR, IFN-βwas given simultaneously for 24 weeks. After 6 months of IFN-β treatment, the LV end- diastolic dimension and LV end-systolic dimension had decreased significantly, with an associated increase in LVEF. Adverse effects of IFN-β, such as deterioration of LV function, or induction of arrhythmias, did not ensue in any of the patients during or after the 6 months oftreatment.

IFN-γ

IFN-γ is secreted by natural killer cells during innate immune responses and by antigen- activated T lymphocytes during adaptive immune responses. Recently, IFN-γ has been proposed to decrease viral replication in myocarditis by activating natural killer cells and macrophages. In this study, DBA/2 mice inoculated with encephalomyocarditis virus were given recombinant murine IFN-γ or IFN-α/β either preceding viral infection or after infection. This protection was a direct consequence of reduced viral replication in the pancreas and reduced spread of coxsackievirus B3 to the heart.

Antivirals

Antiviral therapy has been shown to benefit murine models of viral myocarditis provided that treatment is started early in the course of infection. In 1985, Matsumori et al. [17] first showed that mice treated with ribavirin from the first inoculation with encephalomyocarditis revealed prolonged survival and less myocardial damage than controls. When ribavirin administration was begun on day 1 of infection, viral replication, and myocardial damage were reduced and survival increased. When treatment was started on day 4 of illness, no difference was seen between the experimental and control mice. A new class of antiviral compounds (isoxazoles) has been synthesized. These drugs have a broad anti-picornavirus activity and function by inhibiting viral uncoating.

Vaccines

An alternative approach to the treatment of viral myocarditis has been the development of virus-specific vaccines. Attenuated vaccines have successfully prevented myocarditis after viral challenges in mice, pigs, and elephants Because both vaccinated and control pigs failedto develop clinical disease, apparently because of the low virulence of the strains in this species, protection in pigs could not be evaluated.

Conclusion

A cardiotropic viral infection usually causes myocarditis, which is characterized by the myocardium's aggressive inflammatory deterioration. Myocarditis's many aetiologies and inconsistent clinical manifestations have made it difficult to characterize as a disease entity. While EMB is still the gold standard, CMR is a useful auxiliary in making the diagnosis. More advanced biopsy specimen analysis, including the identification of viral genomes and immunohistochemical assessment, along with targeted sample collection directed by CMR, may result in broader indications for pursuing EMB.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

Reference

1. Abbasi J. Potential New Blood Biomarker for Myocarditis Detection. JAMA. 2021 Jul 13;326(2):124-. https://copilot.microsoft.com/sl/bS0e1sP9hzU
2. Abdel-Aty H, Boyé P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, Bock P, Dietz R, Friedrich MG, Schulz-Menger J. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. Journal of the American College of Cardiology. 2005 Jun 7;45(11):1815-22. https://pubmed.ncbi.nlm.nih.gov/15936612/
3. Andréoletti L, Lévêque N, Boulagnon C, Brasselet C, Fornes P. Viral causes of human myocarditis. Archives of cardiovascular diseases. 2009 Jun 1;102(6-7):559-68. https://pubmed.ncbi.nlm.nih.gov/19664576/
4. Farinha IT, Miranda JO. Myocarditis in paediatric patients: unveiling the progression to dilated cardiomyopathy and heart failure. Journal of cardiovascular development and disease. 2016 Nov 8;3(4):31. https://pubmed.ncbi.nlm.nih.gov/20109598/
5. Gowri SP, Lakshmi HV, Bhanu VN, Brahmaiah B, Nama S, Rao CB. Proniosome: a novel approach to vesicular drug delivery system. The Pharma Innovation. 2013 May 1;2(3, Part A):166. 11.pdf (thepharmajournal.com)
6. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K. 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. European heart journal. 2013 Sep 1;34(33):2636-48. https://pubmed.ncbi.nlm.nih.gov/23824828/
7. Dey B, Hwisa NT, Khalf AM, Mitra A, Katakam P, Rao CB. Pharmaco-epidemiological Studies on Self Medication and Drug Utilization Pattern in Chronic Diseases via Prescription Auditing. International Journal of Scientific Research in Knowledge. 2013 Nov 1;1(11):464. (PDF) Pharmaco-epidemiological Studies on Self Medication and Drug Utilization Pattern in Chronic Diseases via Prescription Auditing (researchgate.net)
8. Chapman NM, Ragland A, Leser JS, Höfling K, Willian S, Semler BL, Tracy S. A group B coxsackievirus/poliovirus 5′ nontranslated region chimera can act as an attenuated vaccine strain in mice. Journal of virology. 2000 May 1;74(9):4047-56. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC111918/
9. Costanzo-Nordin MR, Reap EA, O'connell JB, Robinson JA, Scanlon PJ. A nonsteroid anti-inflammatory drug exacerbates Coxsackie B3 murine myocarditis. Journal of the American College of Cardiology. 1985 Nov 1;6(5):1078-82. https://pubmed.ncbi.nlm.nih.gov/2995470/
10. Drory Y, Turetz Y, Hiss Y, Lev B, Fisman EZ, Pines A, Kramer MR. Sudden unexpected death in persons< 40 years of age. The American journal of cardiology. 1991 Nov 15;68(13):1388-92. https://pubmed.ncbi.nlm.nih.gov/1951130/
11. Fairley CK, Ryan M, Wall PG, Weinberg J. The organisms reported to cause myocarditis and pericarditis in England and Wales. Journal of Infection. 1996 May 1;32(3):223-5. https://pubmed.ncbi.nlm.nih.gov/8793712/
12. Fohlman J, Pauksen K, Hyypia T, Eggertsen G, Ehrnst A, Ilba¨ ck NG, Friman G. Antiviral treatment with WIN 54 954 reduces mortality in murine coxsackievirus B3 myocarditis. Circulation. 1996 Nov 1;94(9):2254-9. https://pubmed.ncbi.nlm.nih.gov/12079640/
13. Fohlman J, Pauksen K, Hyypia T, Eggertsen G, Ehrnst A, Ilba¨ ck NG, Friman G. Antiviral treatment with WIN 54 954 reduces mortality in murine coxsackievirus B3 myocarditis. Circulation. 1996 Nov 1;94(9):2254-9. https://pubmed.ncbi.nlm.nih.gov/19389557/
14. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. The Lancet. 2006 Aug 19;368(9536):687-93.

https://pubmed.ncbi.nlm.nih.gov/16371764/

15. Gullestad L, Aass H, Fjeld JG, Wikeby L, Andreassen AK, Ihlen H, Simonsen S, Kjekshus J, Nitter-Hauge S, Ueland T, Lien E. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation. 2001 Jan 16;103(2):220-5. https://pubmed.ncbi.nlm.nih.gov/11208680/
16. Horwitz MS, Knudsen M, Ilic A, Fine C, Sarvetnick N. Transforming growth factor-β inhibits coxsackievirus-mediated autoimmune myocarditis. Viral immunology. 2006 Dec 1;19(4):722-33. https://pubmed.ncbi.nlm.nih.gov/17201667/
17. Horwitz MS, Knudsen M, Ilic A, Fine C, Sarvetnick N. Transforming growth factor-β inhibits coxsackievirus-mediated autoimmune myocarditis. Viral immunology. 2006 Dec 1;19(4):722-33. https://pubmed.ncbi.nlm.nih.gov/24667923/