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COVID-19 MRNA VACCINE ASSOCIATED MYOCARDITIS-A REVIEW OF ITS CLINICAL ASPECTS, MECHANISMS, TREATMENT, AND PREVENTIVE STRATEGIES

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ABSTRACT

The most frequent cause of myocarditis, or inflammation of the heart muscle, is a viral infection. This unusual cardiac disorder makes it challenging for the heart to pump blood because it weakens the heart muscle. Myocarditis, an underdiagnosed illness, is a common cause of acute heart failure, abrupt death, and persistent dilated cardiac myopathy. Myocarditis is a clinical and histological term for a variety of pathological immune processes in the heart. In patients with acute and chronic myocarditis, changes in the number and function of lymphocyte subsets and macrophages, as well as antibody-mediated injury, are common. Vaccines that have shown protection against the morbidity and mortality of covid-19 associated with the uncommon side effect of acute myocarditis have confounded immunization efforts. The incidence, diagnostic measures, and treatment for myocarditis with the Covid-19 vaccine have been discussed. The incidence is about 20-30 per million cases mainly affecting male patients in the age group of under 30 years. Although the mechanisms are mostly theoretical, molecular mimicry and innate immune responses have been proposed. Individual and population-level benefits of vaccination outweigh the risks of this rare and mild form of myocarditis, according to risk-benefit analyses. Myocarditis following covid-19

mRNA vaccination is relatively rare and usually resolves within a few days or weeks especially in children and young adolescents mainly males. So, alternative Covid-19 vaccination like covishield, covaxin, and sputnik v can be recommended for adolescents and adults.

KEYWORDS: myocarditis, dilated cardiac myopathy, antibody-mediated injury, mRNA vaccine, risk-benefit analysis.

INTRODUCTION

SARS-lung-damaging cov-2's coronavirus has a wide range of clinical manifestations, including asymptomatic infection and moderate upper respiratory disease to severe viral pneumonia, respiratory failure, shock, and, in rare cases, death. A single-stranded enclosed positive sense RNA virus known as a coronavirus belongs to the family Coronaviridae's order Nidovireles.[1] some of the widely approved vaccines for covid 19 infection are sputnik(Gam-COVID-vac), covaxin(BBV152), covishield(AZD1222), Pfizer/BioNTech and moderna (BNT 162b2 and MRNA-1273). Infection with Covid-19 represents a new class of vaccine products-They are made up of messenger ribonucleic acid (mRNA) strands in lipid nanoparticles. These mRNA vaccines designed by biotech/Pfizer and Moderna had an effectiveness of around 95% and they were the first mRNA vaccines to acquire 'Emergency Use Authorisation' (by Food and Drug Administration-FDA) and 'Conditional Approval' (by European Medical Agency-EMA).[2] The viral spike (s) glycoprotein of sars-cov-2 is encoded by these mRNA covid-19 vaccinations, which has two proline polymorphisms (k986p and v987p mutations) to maintain the glycoprotein's prefusion conformation (wrap *et al*.,).[3] Moderna and biotech/current Pfizer's mRNA covid-19 vaccines must be stored between 15 and 25◦c and 60 and 90◦c respectively (EMA) to prevent degradation.[4] Most mRNA vaccinations are now delivered intramuscularly.[5] The EMA assessment report describes the mechanism of action of mRNA vaccines at the injection site as follows: When LNP- RNA formulated vaccine is administered intramuscularly (IM), a brief local inflammatory response occurs that encourages the migration of neutrophils and antigen-presenting cells (APCS) to the site of injection.[4]

Joseph Freidrich Sobernheim originated the word myocarditis in 1837; however, its use covered previously unreported cardiomyopathies such as ischemic heart disease and hypertensive heart disease. The world health organization and the international society

federation of cardiology did not make attempts to differentiate between myocarditis and other cardiomyopathies until the 1980s.[6]

In general, myocarditis is defined as an inflammatory illness of the heart muscle cells and is pathologically diagnosed as an infiltration of mononuclear cells to the myocardium by conventional histology and immunohistochemistry methods. Myocarditis can be acute, sub-acute, or chronic, and it can affect either localized or widespread regions of the myocardium.[7] Patients with fulminant myocarditis (multiple foci of active myocarditis) have class IV symptoms listed by the New York heart association, including flu-like symptoms associated with cardiogenic shock and left ventricular systolic failure.[8] Additional features include leucocytosis, eosinophilia (including rare instances of eosinophilic myocarditis), increased erythrocyte sedimentation rate, and increased levels of cardiac troponin or the Creatine kinase biomarker.[9]

CLINICAL ASPECTS OF MYOCARDITIS

Myocarditis is estimated to affect 22 out of every 100,000 people worldwide each year. Furthermore, according to recent research from the American Heart Association and the American College of Cardiology, myocarditis is the third largest cause of sudden cardiac mortality in elite athletes. Acute viral infection(s) may cause myocarditis in 1% to 5% of individuals.[10,11] Myocarditis can be caused by a variety of infectious agents, including viruses, bacteria, Chlamydia, rickettsia, fungus, and protozoa, as well as non-infectious factors, such as toxins and hypersensitivity responses. The most frequent cause of myocarditis among these triggers, particularly in children, is a viral infection.[8] Myocarditis With Non-Specific Symptoms Including Chest Pain, Dyspnoea, And Palpitations. Asymptomatic patients have an increase in troponin concentration, electrocardiography changes, and abnormal cardiac functions on echocardiogram or cardiac MRI.[12]

CLINICAL ASPECTS OF COVID 19 INDUCED MYOCARDITIS

The novel mRNA vaccine has been linked to several rare adverse events, including acute myocarditis, despite several clinical trials showing it to be generally safe and well tolerated. The center for disease control and prevention reported a link between the covid-19 vaccination and acute myocarditis through analysis of the vaccine adverse events reporting system (VAERS), a network that promotes voluntary reporting of side effects associated with vaccination administration. The general population had a covid-19 vaccination-induced myocarditis rate of 0.48 per one lakh and recipients aged 18 to 29 at a rate of 1.2 per one

lakh. The analysis discovered that the adolescent male population is the most affected subpopulation, typically exhibiting symptoms of chest pain, shortness of breath, and palpitations around one week after the second vaccination dose. J r power *et al*., study shows 54 cases of myocarditis among 2.5 million vaccinated recipients, resulting in an incidence of 2.13 cases per 1 lakh person-years with a median age of 27.[13]

EPIDEMIOLOGY OF VACCINATION

During the study period, there were 1991 reports of myocarditis to VAERS from 192405448 people who received a total of 354100, 845 mRNA-based covid19 vaccines 1626 of these reports corresponded to the myocarditis case definition. The median age was 21 years, and the median symptom onset time was 2 days. Males accounted for 82% of myocarditis cases following mRNA vaccination. After sequential doses, including a booster dose of the bnt162b2 mRNA vaccine, the covid19 vaccination remains modest However, younger men are more at risk for myocarditis after immunization, particularly with the second dose of the mrna1273 vaccine.[14]

COVID 19 VACCINE INSTANCES

Pfizer and Moderna's approved vaccines use mRNA technology and lipid nanoparticle (LNP) delivery systems, whereas AstraZeneca, Johnson and Johnson, and Gam-COVID-vac (Sputnik V) use DNA delivered within non-replicating recombinant adenovirus (AdV) vector systems. India's indigenous solution to the SARS-CoV-2 pandemic is Bharat Biotech's Whole Virion Inactivated Corona Virus Antigen BBV152 (Covaxin). Chimpanzee adenovirus-vectored vaccination ChAdOx1 nCoV-19 from Oxford-AstraZeneca (AZD1222) (COVISHIELD) are the most effective top 5 vaccines for covid-19. In the case of sputnik v vaccine, our immune system responds to the vaccine by producing antibodies against the SARS-CoV-2 virus and inducing T-cell responses. In the event of future infection, our bodies can produce these antibodies quickly to bind to the virus and prevent it from entering our cells. T-cells are capable of destroying contaminated cells. In this way, both the viral vector and the SARS-CoV-2 spike protein help to build immunity.[15,16]

Frequent COVID-19 mRNA booster injections may have a deleterious effect on immunological response and may not be practical, according to European Medicines Agency guidelines. Several factors can contribute to the decrease in immunity, including N1-methyl pseudouridine, the spike protein, lipid nanoparticles, antibody-dependent enhancement, and the original antigenic stimulus. The delivery system of Pfizer and moderna mRNA vaccines

are by lipid nanoparticles(LNP) which will in turn lead to a decrease in the immune response. LNP-encapsulated mRNA causes severe inflammation. Further booster vaccinations should be avoided as a precaution. Several practical measures to prevent immunity reduction have been reported. These include limiting the use of non-steroidal anti-inflammatory drugs, such as acetaminophen, to maintain deep body temperature, using antibiotics appropriately, quit smoking, managing stress, and limiting the use of lipid emulsions, such as propofol, which may cause perioperative immunosuppression. Patients become immunocompromised to certain infections like myocarditis.[17]

VARIATION BETWEEN VACCINATION TYPES

The majority of large population studies have focused on the incidence associated with the BNT 162b2 and MRNA-1273 mRNA vaccines, in part because these were the first vaccinations to gain broad approval and availability. Early data from the CDC VAERS research revealed that the MRNA-1273 vaccination was related to greater rates of myocarditis than the BNT 162b2 vaccine, with around 2.8-fold and 2.5-fold higher rates of myocarditis after the first and second doses, respectively.[13]

MECHANISM OF COVID-19 mRNA VACCINE INDUCED MYOCARDITIS

In contrast, to live viruses or DNA, SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA that encodes the virus' spike glycoprotein. Some RNA molecules have the potential to trigger the mammalian innate immune system and be immunogenic, which will kill the mRNA before it reaches the target cells, stop the spike protein from forming, and prevent the creation of antibodies. The creation of mRNA vaccines has been made possible by ground-breaking research on the nucleoside alterations of mRNA that have been demonstrated to decrease innate immunogenicity and lessen cytokine activation. Although it has been demonstrated that nucleoside modifications of mRNA diminish their innate immunogenicity, in some people with a genetic predisposition, the immune response to mRNA may not be dialed down and may trigger an abnormal innate and acquired immune response. Hence, the immune system may mistake the vaccine's mRNA for an antigen, activating immunologic pathways and pro-inflammatory cascades that may contribute to the systemic response that, in some people, includes the development of myocarditis. This mRNA is subsequently sufficiently translated into SARS-CoV-2 spike protein in the host cytoplasm for CD8+ and Th1-type CD4+ T-cells to develop an adaptive immunological response.[18]

When the Covid-19 virus is exposed, vaccine-induced antibodies bind to the viral envelope spike protein, which inhibits the viruses ability to bind to the host cell surface protein angiotensin-converting enzyme 2 (ACE2), which is necessary for cell entry and infection and also marks the virus for eradication. This distinct method of vaccine-induced immunity has led to the theory that excessive innate immune activation brought on by both the lipid nanoparticle and RNA components of the Covid-19 vaccines can result in vaccine-associated myocarditis.[19]

Another possible mechanism is molecular mimicry between the spike protein of SARS-CoV-2 and cardiac self-antigens. Cross-reactivity of pathogen-directed antibodies with human proteins through molecular mimicry is the prevailing hypothesis for autoimmune disorder's infrequent but statistically significant correlation. Considering the absence of evidence for a long-lasting autoimmune response following Covid-19 vaccination. Investigations would imply that it is conceivable for cardiac antigens to react with antibodies produced by Covid-19 immunization. Nevertheless, the clinical consequences of this remain unknown.[20]

CLINICAL EXAMINATION

The diagnosis of mild myocarditis is based on compatible clinical findings and is confirmed by elevated levels of blood markers or an electrocardiogram indicative of cardiac injury, as well as the discovery of new abnormalities on cardiac MRI or echocardiography. In patients with severe myocarditis, a heart biopsy is frequently used to confirm the diagnosis.[18]

In a study given by Kozkurt *et al*., people presented with symptoms of chest pain, fever, and myalgia, immediately after 2-3 days of mRNA Covid-19 vaccination but polymerase chain reaction, a Covid-19 diagnostic test, was negative. The greatest amount of cardiac troponin was present in the subjects, and it typically peaked three days after immunization. In most cases, the ECG was abnormal, with ST elevations. Only 40% of the patients had an abnormal echocardiogram, with only a small percentage having a <50% left ventricular ejection fraction on presentation.

Cardiac MRI was abnormal in all of the patients tested, with findings consistent with myocarditis, such as late gadolinium enhancement and myocardial Oedema. When b-type natriuretic peptide or n-terminal pro-b-type natriuretic peptide levels were measured, they were mildly elevated in roughly two-thirds of the patients. Most patients had increased C -

reactive protein levels, which gradually reduced along with troponin during their hospitalization.

With or without treatment, almost all patients had resolution of signs and symptoms, as well as improvements in diagnostic markers and imaging.[21]

RISK VERSUS BENEFIT

Despite the rare cases of myocarditis, the benefit-risk-benefit analysis for Covid-19 vaccination shows a favorable balance for all age and gender groups.

According to a CDC analysis released in June 2021, 11,000 Covid-19 cases, 560 hospital admissions, 138 ICU admissions, and six Covid-19-related deaths could be avoided for every million males aged 12-29 who received a 2-dose regimen of the mRNA Covid-19 vaccine, as opposed to the 39–47 myocarditis cases that were anticipated following Covid-19 vaccination. The CDC's (Center for Disease Control and Prevention) recommendations to immunize children between the ages of 12 and 15 were based on this analysis of Covid-19 prevalence, morbidity, and mortality rates from May 2021.[21]

Gurdasani *et al.*, estimated that in children aged 12 to 17, the number of avoided Covid-19-related hospitalizations exceeds the incidence of mRNA vaccine-associated myocarditis, provided that the incidence of Covid-19 is greater than 30/per 100,000 teenagers per week. These models are useful for health officials, but they conceal the fact that, while more than 95% of vaccine-associated myocarditis cases result in an inpatient admission, more than 80% of Covid-19 cases are never admitted, even though these infections can have long-term consequences.[13]

The risk ratio of myocarditis associated with Covid-19, on the other hand, was estimated to be 18.28. Furthermore, Covid-19 vaccination reduces the risk of myocardial injury and myocarditis 1,000-fold in the general population, with a minor 1-5-fold increased risk of mild myocarditis in young adults.[22]

PREVENTION STRATEGIES

Although uncommon, the risk of myocarditis should be taken into consideration in patients who complain of chest discomfort within a week following immunization, especially in younger patients.[21] While the data on vaccine-associated myocarditis strongly favors

vaccination in terms of both patient and population-level benefits, more research is required to reduce this adverse event.

Some people have hypothesized that mRNA vaccine dose reduction, a method used to provide vaccinations to children under 12, may lower the risk of myocarditis in susceptible individuals without losing immune response.[13]

A dose-reduction strategy is further supported by recent VAERS (vaccine adverse event reporting system) surveillance data showing fewer reports of myocarditis in children aged 5 to 11 than in teenagers. To minimize myocarditis with mRNA vaccines, a greater investigation into the mechanisms of vaccine-associated myocarditis is ultimately required.[23]

TREATMENT FOR VACCINE-ASSOCIATED MYOCARDITIS

The patient's age, clinical presentation, potential other causes and comorbidities, hemodynamic and rhythm stability, and clinical course all influence evaluation and management. Patients who experience chest pain, evidence of myocardial injury, ECG changes, cardiac imaging abnormalities, arrhythmia, or hemodynamic instability following Covid-19 vaccination will almost certainly require hospitalization and close monitoring. Non-steroidal anti-inflammatory drugs, steroids, and colchicine were used to treat some of the patients with myocarditis after Covid-19 vaccination, in addition to supportive care.[21] Corticosteroids are proposed as a preferred treatment for vaccine-associated myocarditis.[23]

Colchicine, non-steroidal anti-inflammatory drugs, and steroids may be considered in patients with persistent mild symptoms but no hemodynamic instability, arrhythmia, significant left ventricular dysfunction, or heart failure. Intravenous steroids and intravenous immunoglobulin, along with other cardiac or circulatory supportive measures, can be considered in patients with left ventricular dysfunction, heart failure, new-onset arrhythmia, or hemodynamic instability. Guideline-directed therapy, including β-blockers and angiotensin-converting enzyme inhibitors, should be initiated in patients with left ventricular systolic dysfunction.[24]

Inotropic therapy and mechanical support may be considered in rare cases of fulminant myocarditis.[25]

RECOVERY FROM COVID 19 VACCINE-INDUCED MYOCARDITIS

Other types of AM have been shown to cause persistent cardiomyopathy; the largest registry of children with AM found that 48% had persistent systolic dysfunction, 7% died, and 19% required transplant over 3 years. Adult results are quite different; an analysis of the Lombardy registry shows that among 429 patients with AM who survived their hospitalization, only 2.8% had MACE at the 5-year follow-up, and 4.5% had residual LV dysfunction at a median follow-up of 200 days.[26]

Guideline-directed medical therapy should be initiated in patients with persistent cardiac dysfunction. Because little is known about the long-term outcomes of vaccine-associated myocarditis, it is reasonable to use these surveillance measures for the time being. It is also known that limiting exercise for 3-6 months after vaccine-associated myocarditis allows for recovery and the prevention of sudden cardiac death, just as it does in general myocarditis. Until vaccine-associated myocarditis is better understood, this is the most secure strategy, possibly with a shorter 3-month exercise restriction.[27]

CONCLUSION

Covid-19 vaccine-associated myocarditis is rare but a serious condition and has a low severity compared to myocarditis. Despite rare cases of self-limited myocarditis, the benefit-risk assessment for Covid-19 vaccination shows a favorable balance for all age and gender groups; thus, Covid-19 vaccination is currently recommended for everyone over the age of 12. Molecular mimicry has long been implicated as a cause of vaccine-associated autoimmune phenomena, and it may play a role in myocarditis in these patients. While 95% of vaccine-associated myocarditis cases are reported from inpatient hospitalizations, a significant number of cases likely go unnoticed in the outpatient population. myocarditis is mainly affecting young children below 30 years because of mRNA vaccine leads to a decrease in the immune response. Further study should be done regarding the effects of the Covid-19 vaccine on myocarditis.

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