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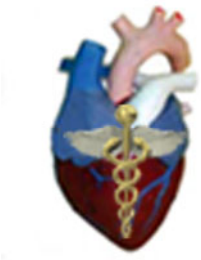

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EDITORIAL

Cardiovascular Complications of COVID-19 Vaccination

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Abstract

Currently available COVID-19 vaccines may confer several side-effects, including cardiovascular (CV) adverse effects. Among them, perimyocarditis, acute myocardial infarction, arrhythmias and vaccine-induced immune thrombotic thrombocytopenia (VITT) with multiple vascular beds involved causing cerebral venous sinus thrombosis, splanchnic vein thrombosis, deep vein thrombosis and pulmonary embolism, as well as arterial thrombosis, constitute the most worrisome CV complications. ***Rhythmos 2021;16(4): 73-78***.

Key Words: COVID-19; SARS-CoV-2; COVID vaccines; cardiovascular complications; myocarditis; pericarditis; myocardial infarction; arrhythmias; vascular thrombosis

Abbreviations: COVID-19 = corona virus disease 2019; CV = cardiovascular; LGE = late gadolinium enhancement; MI = myocardial infarction; STEMI = ST-elevation myocardial infarction; VITT = vaccine-induced immune thrombotic thrombocytopenia

Introduction

Currently available vaccines for corona-virus disease-19 (COVID-19) infection have been shown to have several adverse effects in recipients; however, the general consensus is that the advantages of vaccination outweigh any potential risks conferred by vaccines in view of the serious and life-threatening complications of the COVID-19 infection.[1-5] Thus, vaccination is encouraged in all people, including patients with cardiovascular (CV) disease. Nevertheless, one needs to be aware of certain vaccine-related side-effects, including relevant CV adverse effects, which should be taken into consideration by vaccinees and care-takers (Table 1).[1]

From the outset, it should be noted that there are several reports on vaccine-associated myocarditis, after mRNA vaccination for both Pfizer and Moderna.[6-11] The association between myocardial infarction (MI) and COVID-19 vaccination is unclear; however, MIs have been reported occurring post-vaccination in some individuals without CV risk factors.[12-14] Vasospastic

allergic MI in response to vaccine (Kounis syndrome) has been implicated as one possible mechanism; [14] vaccine-induced immune thrombosis with thrombocytopenia (VITT) has been reported as the cause in an another instance.[15] In this context, for acute CV diseases, such as acute MI, acute heart failure or exacerbation of chronic heart failure, vaccination should be postponed until the patient is in a stable condition.

In addition to myocarditis and possible MI, post-vaccination pericarditis, vasculitis, and cardiac arrhythmia in patients with good general past health after mRNA vaccination have also been reported for both Pfizer and Moderna vaccines. [10, 16]

According to a recent report, among 4863 adverse CV events reported from BNT162b2 Pfizer, 1222 AstraZeneca, Moderna, and other COVID-19 vaccines, the list included tachycardia (16.41%), flushing (12.17%), hypertension (5.82%), hypotension (3.60%) and peripheral coldness (2.41%).[17] Acute MI, cardiac arrest, and circulatory collapse were linked to the vaccines in the age group >75 years. Hypertension, severe hypertension, supraventricular tachycardia, sinus tachycardia, and palpitations were associated across all age groups and either gender. Temporal association of these CV events with COVID-19 vaccination is apparent; however, the causality is yet to be established.

Table 1. Cardiovascular Complications of COVID-19 Vaccines

Myocarditis / Pericarditis
Acute myocardial infarction
Vaccine-induced immune thrombotic thrombocytopenia (VITT)
Arrhythmias
Takotsubo syndrome

Myocarditis / Pericarditis

As mentioned, several cases of myopericarditis following the receipt of mRNA-based (Pfizer-BioNTech and Moderna) COVID-19 vaccines have been reported.[18-24]

A case of acute perimyocarditis and pericardial effusion emerging at 10 days following the second dose of Moderna COVID-19 vaccination was reported.[25] Hospital course was complicated initially by circulatory collapse necessitating aggressive fluid resuscitation, and later by cardiac arrest, acute kidney injury, disseminated intravascular coagulation (DIC) and hemodynamic instability. The patient finally recovered after a three-week hospital stay and was discharged on a non-steroidal anti-inflammatory drug.

Data from the largest health care organization in Israel evaluating the safety of the BNT162b2 mRNA vaccine among vaccinated persons, individually matched to unvaccinated persons (control group), each group including a mean of 884,828 persons, indicated that the vaccine was associated with an excess risk of *myocarditis* (1 to 5 events per 100,000 persons) (risk ratio, 3.24; risk difference, 2.7 events per 100,000 persons).[26] On the other hand, SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis (risk ratio, 18.28; risk difference, 11 events per 100,000 persons) and of additional serious adverse events, including pericarditis, arrhythmia, deep-vein thrombosis, pulmonary embolism, MI, intracranial hemorrhage, and thrombocytopenia.

According to the US Centers for Disease Control and Prevention, myopericarditis rates are ≈12.6 cases per million doses of second-dose mRNA vaccine among individuals 12-39 years of age.[27] Patients with myocarditis present with chest pain, usually 2 to 3 days after a second dose of mRNA vaccination, in association with ST elevation on ECG, increased cardiac troponin levels, and cardiac MRI suggestive of myocarditis (subepicardial distribution). Although the mechanisms of this complication have not been elucidated, molecular mimicry between the spike protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and self-antigens, trigger of preexisting dysregulated immune pathways in certain individuals, immune response to mRNA, and activation of immunologic pathways, and dysregulated cytokine expression have been proposed. There is male predominance in myocarditis cases for unclear reasons. In almost all patients, symptoms and signs resolve and diagnostic markers and imaging improve with or without treatment. Nevertheless, patients diagnosed with mRNA vaccine-associated myocarditis should be followed-up for possible chronic sequelae and potential compromise of LV function.

Early diagnosis and management of suspected myocarditis following mRNA COVID vaccination may avert serious subsequent problems.[28] When suspected, the initial investigation should include a comprehensive history and physical examination, a 12-lead electrocardiogram and serological biomarkers that include high-sensitivity cardiac troponin, natriuretic peptides and markers of inflammation. Further evaluation includes echocardiography and cardiovascular magnetic resonance imaging (MRI).

Interestingly, a recent case report of “myocarditis” in a 37-year-old man admitted with acute chest pain 19 days after his first dose of mRNA-1273 SARS-CoV-2 vaccination (Moderna) indicated that myocardial

microthrombi without inflammatory cell infiltration may be a possible mechanism in some cases.[29] Right ventricular endomyocardial biopsy revealed that erythrocyte-rich microthrombi occluded capillary vessels accompanied by extravasation of erythrocytes without inflammatory cell infiltration in the myocardium, thereby precluding the pathological diagnosis of myocarditis. The levels of D-dimer and haptoglobin were within the normal range. Serological testing excluded systemic virus infections.

Biventricular systolic dysfunction in acute myocarditis after mRNA-1273 vaccination was reported in a 20-year-old woman with a history of Kawasaki disease who developed fever, chest pain and dyspnea 2 weeks after her second dose of mRNA-1273 SARS-CoV-2 vaccination (Moderna).[30] She had sinus tachycardia with ST-segment elevation in leads II and V1–4 on ECG; echocardiography showed global biventricular hypokinesis with a very small pericardial effusion; cardiac troponin I was elevated at 8801.8 ng/L. She had a normal coronary angiography. Late gadolinium-enhanced imaging was consistent with acute perimyocarditis; myocarditis was confirmed by endomyocardial biopsy demonstrating lymphocytic infiltration in the myocardium. She responded to conservative management.

However, in some cases of histologically confirmed myocarditis developing within 2 weeks after Covid-19 mRNA vaccination, the course may be fulminant and fatal.[11]

COVID-19 vaccination-associated myocarditis has also been reported in adolescents.[9, 31] According with a retrospective multicenter study, 63 patients with a mean age of 15.6 years (92% male) who had received an mRNA vaccine, all, but one, developed myocarditis after the second dose.[31] Arrhythmias developed in 4 patients; 14% had mild reversible left ventricular dysfunction. Myocardial injury as evidenced by LGE on CMR was more prevalent in comparison with multisystem inflammatory syndrome in children. All patients had a favorable course with resolution of symptoms, arrhythmias and restoration of LV dysfunction in the majority (86%) of patients at a mean of 35 days. Similarly, in another series of 7 cases of acute myocarditis or myopericarditis in healthy male adolescents who presented with chest pain all within 4 days after the second dose of Pfizer-BioNTech COVID-19 vaccination, symptoms resolved rapidly in all patients.[9] Three patients were treated with nonsteroidal anti-inflammatory drugs only, and 4 received intravenous immunoglobulin and corticosteroids.

The incidence rate of myocarditis or pericarditis is reported to be 12.6 cases per million doses of second-dose mRNA vaccine among individuals 12-39 years of age without a history of COVID-19 infections or comorbidities. These typically occur 2-3 days after the second dose of mRNA vaccination.[16, 27] The median duration of admission for diagnosed myocarditis is 2 days, with no readmissions or deaths reported.[16] The course of post-vaccination myopericarditis is generally mild and responsive to conservative management such as rest and treatment with anti-inflammatory drugs.

Importantly, the vaccine-associated risk ratio of myocarditis is 3.24, whereas the risk ratio of COVID-19 infection-associated myocarditis is 18.28.[26] In view of the emerging evidence, the Advisory Committee on Immunization Practices (ACIP) of the US determined that the benefits of using mRNA COVID-19 vaccines clearly outweigh the risks in all populations, including adolescents and young adults. [32]

A recent review reported that among 2,000,287 persons receiving at least 1 COVID-19 vaccination (BNT162b2 vaccine of Pfizer/BioNTech, mRNA-1273 vaccine of Moderna, and Ad26.COV2.S vaccine of Janssen/Johnson & Johnson), 20 individuals (15 males, median age 36 years) had vaccine-related *myocarditis* (1 per 100,000) and 37 (27 males, median age 59 years) had *pericarditis* (1.8 per 100 000). [16] Myocarditis occurred a median of 3.5 days after vaccination. Four persons (20%) developed symptoms after the first vaccination and 16 (80%) developed symptoms after the second dose. Nineteen patients (95%) were admitted to the hospital. All were discharged after a median of 2 days. *Pericarditis* occurred after the first immunization in15 cases (40.5%) and after the second immunization in 22 cases (59.5%). Median onset was 20 days after the most recent vaccination. Thirteen (35%) were admitted to the hospital, none to intensive care. Median stay was 1 day.

As of 11 June 2021, a total of 1226 reports of probable myocarditis/pericarditis cases were reported in the Vaccine Adverse Event Reporting System (VAERS) after ~300 million COVID-19 mRNA vaccine doses (approximate prevalence of ~4.8 cases per 1 million doses (www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html).[33] These were mainly young men developing myocarditis/pericarditis after the second dose of the vaccine. The most common symptoms and signs were chest pain (>85%), ST or T-wave changes and elevated cardiac enzymes (>60%, both). Almost all patients (>95%) were hospitalized but the majority fully recovered.

Guidance. Some guidance for health providers on approaching suspected and confirmed cases of myopericarditis related to COVID-19 mRNA vaccination has been suggested.[34] It starts with standardized workup that includes serum troponin measurement and polymerase

chain reaction testing for COVID-19 infection, routine additional laboratory work, and a 12-lead electrocardiogram. Echocardiography is the imaging modality of choice. Hospitalization should be considered based on the results of standard investigations. Treatment is largely supportive. COVID-19 vaccination is recommended for all individuals in accordance with immunization guidelines. In patients with suspected myocarditis/pericarditis after the first dose of an mRNA vaccine, deferral of a second dose is recommended until additional reports become available.

Thrombosis/ Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

In addition to patients with COVID-19 infection, thrombosis associated with thrombocytopenia may also occur in individuals vaccinated against SARS-CoV-2; this rare effect occurs at a very low incidence (1/100 000) and more prevalently in young women; it is independent from known risk factors of thrombosis, is caused by antibodies against platelet PF4 and is managed with immunoglobulin and glucocorticoids.[35] This vaccine-induced immune thrombotic thrombocytopenia (VITT) could be fatal.[36] VITT most commonly presents with cerebral venous sinus thrombosis; however, splanchnic vein thrombosis, deep vein thrombosis and pulmonary embolism (VTE) and arterial thrombosis are also common, while multiple vascular beds may be involved. [37]

In the spring of 2021, reports emerged of unusual cerebral venous sinus thrombosis in combination with thrombocytopenia noted within 4 to 28 days of vaccination with the ChAdOx1 nCov-19 (AstraZeneca/Oxford) and Ad.26.COV2.S (Janssen/Johnson & Johnson) adenovirus-based COVID-19 vaccines.[38] These reports of vaccine-induced immune thrombotic thrombocytopenia led to a brief suspension of the use of these vaccines by several countries.[39] Thromboses in the cerebral and splanchnic veins among patients vaccinated in the preceding 4 weeks were described in 17 patients out of 7.98 million recipients of the Ad26.COV2.S vaccine (with 3 fatalities related to cerebral vein thrombosis) and 169 cases of cerebral vein thrombosis among 35 million ChAdOx1 recipients. Events were associated with thrombocytopenia and anti-PF4 (antibodies directed against platelet factor 4). Unlike the related heparin-induced thrombotic thrombocytopenia, with an estimated incidence of <1:1000 patients treated with heparin, and a mortality rate of 25%, vaccine-induced immune thrombotic thrombocytopenia has been reported in 1:150 000 ChAdOx1 recipients and 1:470 000 Ad26.COV.2 recipients, with a reported mortality rate of 20% to 30%.

The features of this condition resemble heparin-induced thrombocytopenia, despite the absence of heparin exposure.[40] It is best to avoid heparin in these patients. Management with intravenous immunoglobulin (1 g/kg for 2 days) and corticosteroids is recommended, as well as consideration of plasma exchange, and non-heparin anticoagulation (argatroban, fondaparinux). Due to the relatively low risk of severe COVID-19 in young women (<50 years), an alternative vaccine should be considered.

The World Health Organization (WHO) has produced a document guiding diagnosis and management of VITT (https://apps.who.int/iris/bitstream/handle/10665/342999/WHO-2019-nCoV-TTS-2021.1-eng.pdf), advising against the use of heparin and recommending against the use of platelet infusion in all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe (platelets <50,000 /μL) and platelet transfusion is required to be able to proceed with surgery.[37] WHO recommends the use of IV immunoglobulins (IVIG) and/or non-heparin-based anticoagulants; WHO does not provide any recommendation for steroid treatment, but notes the general use of steroids and the likelihood that steroids will usually be given in combination with other treatments.

Acute Myocardial Infarction

As mentioned, MIs have been reported that are temporally associated with COVID-19 vaccination.[12-14] Vasospastic allergic MI in response to vaccine (Kounis syndrome) or VITT have been implicated as possible mechanisms. [14,15]

A study evaluating cardiac complications associated with COVID-19 vaccination identified 30 patients admitted with acute myocardial infarction (MI) (n=29) (14 ST-segment elevation – STEMI and 15 non-ST-segment elevation MI - NSTEMI) or myocarditis (n=1) developing within 2 weeks of vaccination.[41 Aye] Of these patients, 5 developed heart failure, 2 had cardiogenic shock, 3 were intubated, and 1 succumbed. In a systematic review of 16 studies, 41 myocarditis and 6 MI cases were identified. In the pooled analysis of these studies and the study cohort, 77 patients were identified, 35 patients with MI and 42 with myocarditis. Majority were men, and myocarditis patients were younger than MI patients. Patients with myocarditis developed symptoms after a median of 3 days postvaccination, with MI patients after a median of 1 day. Thirty-five (83%) myocarditis and 6 (33%) MI patients developed symptoms after their second dose. Majority of the myocarditis (83%) and MI patients (86%) had the Pfizer BioNTech; the remaining patients with myocarditis had received the Moderna vaccine (14%) and Janssen

vaccine (2%), while the other MI patients received the Oxford-AstraZeneca vaccine (11%) and Moderna vaccine (3%). Left ventricular ejection fraction was lower than normal for all patients. Thirty-two (76%) myocarditis patients had late gadolinium enhancements (LGE) on cardiac magnetic resonance imaging (MRI), with the majority having subepicardial LGE followed by midmyocardial LGE. Among MI patients who underwent coronary angiogram, percutaneous coronary intervention (PCI) was performed in 60% of patients, with the left anterior descending artery (LAD) being the most common culprit vessel.

Arrhythmias

Fever-related ventricular fibrillation as a potential adverse effect of COVID-19 vaccination was recently reported in a patient with Brugada syndrome who was vaccinated with the Comirnaty (BioNTech/Pfizer) vaccine after the second-dose.[42]

Takotsubo Syndrome

Even the development of stress cardiomyopathy (Takotsubo syndrome - TTS) has been described after administration of the COVID-19 vaccine.[43] A 73-year-old woman with recently diagnosed MI with no obstructive coronary atherosclerosis (MINOCA) presented with typical chest pain starting less than a day after receiving the Moderna vaccine. ECG and echocardiography findings were consistent with mid-ventricular TTS. The authors indicate that risk factors including gender, age, anxiety about the vaccine, and possibly the vaccine itself might have all contributed to the TTS presentation.

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