بسم الله الرحمن الرحيم

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Myocardial Safety Following COVID-19 Vaccination

Thesis

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List of Abbreviations

Abb.	Full term
2D	Two-dimensional
AM	Acute myocarditis
BSA	Body surface area
CA	Cardiac amyloidosis
CDC	Centers for Disease Control and Prevention
CMR	Cardiovascular magnetic resonance
COVID-19	Coronavirus disease 2019
CRT	Cardiac resynchronisation therapy
CRTCD	Cancer therapy–related cardiac dysfunction
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
EF	Ejection fraction
FDA	Food and Drug Administration
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFrEF	HF and reduced EF
ICD	Implantable cardioverter defibrillator
IVS	Interventricular septum
LGE	Late gadolinium enhancement
LNP	Lipid nanoparticle
LS	Longitudinal strain
LV	Left ventricular
LVAD	Left ventricular assist device

List of Abbreviations Cont...

Abb.	Full term
LVEDD	Left ventricular diameter in end diastole
LVESD	LV end systolic diameter
NIAID	National Institute of Allergy and Infectious Diseases
NYHA	New York Heart Association
PH	Pulmonary hypertension
PWD	Pulsed-wave Doppler echocardiography
ROI	Region of interest
RV	Right ventricle
SARS	Severe acute respiratory syndrome
SCD	Sudden cardiac death
STE	Speckle tracking echocardiography
TAPSE	Tricuspid annular plane systolic excursion
WHO	World Health Organization

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INTRODUCTION

Viral infection has been described as one of the most common causes of myocarditis, especially associated with influenza and parvovirus B-19 infection. Myocarditis has been reported following many different vaccines, with the smallpox vaccine having the strongest association ***(Keinath et al., 2018).***

Due to the few cases of myocarditis reported post COVID-19 vaccine, little is known about this process.

The Israeli Ministry of Health reported 62 cases of myocarditis in patients vaccinated for COVID-19 out of 5 million vaccinated individuals. Most cases occurred after the second dose of mRNA vaccines, with only 6 cases diagnosed after the first dose. The prevalence was higher in men under 30 years of age, increasing from 1/100 000 for the general population, to 1/20 000 for the 16-30 years old group. Two of the 62 patients died.

The U.S. Department of Defense reported 14 military personnel diagnosed with myocarditis following COVID vaccination, 13 of them after their second dose of COVID-19 mRNA vaccines. Three of the personnel received Pfizer/BioNTech vaccine, and 11 had received the Moderna vaccine, with an occurrence of 0.52/100 000 among the 2.7 million military personnel vaccinated ***(Lee, 2021; Staff, 2021).***

At time of writing, neither the FDA nor CDC have reported any safety signals for myocarditis following the administration of the approved COVID-19 vaccines . At present time, there are no reports in the scientific literature reporting notion of myocarditis related to COVID-19 vaccination ***(Wilner, 2021).***

Aim of the Work

The aim of this study is to detect any evidence of myocardial damage after COVID-19 vaccination.

REVIEW OF THE LITERATURE

Introduction to COVID-19 virus and its effect on the heart

The global pandemic of coronavirus disease 2019 (COVID-19) continues to cause considerable morbidity and mortality worldwide ***(Shi et al., 2020).*** The main focus of the research communication has been on acute respiratory complications, especially in critically ill patients. A number of case reports and small series suggested that COVID-19 prominently affects the cardiovascular system by exacerbating heart failure in patients with pre-existing cardiac conditions ***(Shi et al., 2020, Guo et al., 2020 and Inciardi et al., 2020)*** and troponin elevation in critically ill patients ***(Li et al., 2020).***

Fulminant myocarditis was suspected in 7% of patients with lethal outcome ***(Ruan et al., 2020).*** The proposed pathophysiological mechanisms of cardiac injury include inflammatory plaque rupture, stent thrombosis, cardiac stress due to high cardiac output, and infection via the angiotensin-converting enzyme 2 receptors causing systemic endothelitis ***(Chen et al., 2020 and Varga et al., 2020).*** A small number of autopsy cases suggest infiltration by interstitial mononuclear inflammatory cells ***(Xu et al., 2020),*** suggesting myocardial inflammation as the underlying mechanism, and some severe cases of myocarditis have been reported ***(Inciardi et al., 2020***

and Wei et al., 2020). In a small study of recovered patients with ongoing cardiac symptoms, cardiovascular magnetic resonance (CMR) imaging revealed cardiac involvement in 58% of patients consisting of myocardial oedema and scar by late gadolinium enhancement (LGE) ***(Huang et al., 2020).***

Overt fulminant myocarditis has been reported in isolated patients with COVID-19 infection. However, the current data indicate that the presence of SARS-CoV-2 in cardiac tissue does not necessarily cause an inflammatory reaction consistent with clinical myocarditis. The long-term consequences of this cardiac infection requires further investigation ***(Lindner et al., 2020).***

Chapter 1

Different Types of COVID-19 Vaccines

COVID-19 is caused by a new positive-strand RNA coronavirus (SARS-CoV-2), which belongs to the *Coronaviridae* family, along with the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronavirus ***(Ortiz-Prado et al., 2020 and Padron-Regalado, 2020).*** Their genome encodes several non-structural and structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins ***(Du et al., 2009).*** The majority of the candidate vaccines for COVID-19 that employ administration of viral antigens or viral gene sequences aim to induce neutralising antibodies against the viral spike protein (S), preventing uptake through the human ACE2 receptor and, therefore, blocking infection ***(InvivoGen, 2020).***

However, a growing body of literature highlighting the importance of cellular responses on the recovery of COVID-19 patients ***(Cox and Brokstad, 2020 and Peng et al., 2020)*** has promoted not only the use of vaccine strategies that favour the induction of T cell mediated responses, but also the screening of their production in clinical trial participants.

Current vaccine candidates against SARS-CoV-2 in Phase 3 clinical evaluation:

1. **Nucleic acid vaccines**
2. **Replication-defective viral vector vaccines**
3. **Inactivated pathogen vaccines**

1. Nucleic acid vaccines (mRNA vaccines)

a. mRNA-1273 (Moderna/US NIAID)

Boston based Moderna Therapeutics partnered up with the National Institute of Allergy and Infectious Diseases (NIAID) to produce the first vaccine candidate that entered clinical trials in 63 days after the genome sequencing of SARS-CoV2. The vaccine is based on an mRNA molecule that contains the information for the synthesis of the stabilised pre-fusion form of the SARS-CoV-2 Spike (S) protein encapsulated in a lipid nanoparticle (LNP) vector that enhances uptake by host immune cells. The administered mRNA uses the host cell transcription and translation machinery to produce the viral antigen that is afterward presented in T lymphocytes and is also directly recognised by B lymphocytes of the host, thereby initiating an adaptive immune response directed against the S protein of the virus ***(Kyriakidis et al., 2021).***