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REVIEW

COVID-19 mRNA vaccines and myopericarditis

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Abstract

Globally, vaccination against COVID-19 has prevented countless infections, hospitalisations and death and represents the most successful intervention in combating the pandemic caused by SARS-CoV-2 infection. Utilisation of existing mRNA vaccine technology has allowed for rapid development of highly immunogenic and effective vaccines. Myopericarditis can occur as an adverse effect of COVID-19 mRNA vaccination, albeit at significantly lower rates than those that occur during SARS-CoV-2 infection. Higher rates are seen in adolescent males, usually within 1–5 days of receiving the second vaccine dose. Although most cases are self-limited and respond to first-line treatment, refractory cases can occur, with a limited evidence base on which to guide management. Here, we present a brief review of COVID-19 mRNA vaccines and associated myopericarditis including risk factors, proposed mechanism, and treatment including management strategies for refractory disease.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third novel member of the coronavirus family that has caused significant disease in a number of countries in the past two decades. Currently, at more than 250 million infections globally, COVID-19 has overwhelmed healthcare systems across the world. Use of established vaccine technology has facilitated the rapid development and testing of highly effective vaccines that have thus far become the most successful interventions in combating the pandemic. Approved COVID-19 vaccines employ a variety of platforms, including for the first time in a large-scale vaccination programme, *in vitro* transcribed messenger ribonucleic acid (mRNA).

mRNA vaccine technology

The promise of mRNA therapeutics as a novel approach to vaccination emerged in the 1990s, with successful *in vivo* induction of a virus-specific T cell response in mice injected with liposome-covered mRNA encoding an influenza nucleoprotein.[1] In principle, mRNA vaccination relies on cellular uptake of mRNA that then uses host cell machinery for translation and production of the encoded protein. Peptides from the translated foreign protein are presented on class I major histocompatibility complex (MHC) molecules to T cells, generating an antigen-specific immune response. The introduced mRNA does not integrate into the host genome and provides a transient platform prior to its degradation.[2] Obstacles to the development of successful mRNA vaccines to date have been the inherent immunogenicity and fragility of the RNA molecule.[2] Foreign RNA is recognised by innate immune sensors, leading to activation of pro-inflammatory cascades and an immune response against the RNA itself rather than the encoded protein. Nucleoside modification reduces this immunogenicity and has been a crucial advance in the field.[2,3] Additionally, naked mRNA is rapidly degraded by extracellular RNAses and cannot penetrate cell membranes; encapsulation of target mRNA in lipid nanoparticles increases stability and facilitates intracellular transport.[3]

mRNA COVID-19 vaccines

Two mRNA vaccines targeting SARS-CoV-2 are currently available for use in Australia, BNT162b2 (Comirnaty, Pfizer, Inc., Philadelphia, PA, USA) and mRNA-

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1273 (Spikevax, ModernaTX, Inc., Cambridge, MA, USA). Both contain nucleoside-modified mRNA encoding the spike glycoprotein of SARS-CoV-2, encapsulated in lipid nanoparticles.[4] Following intracellular transport, viral mRNA is translated into spike protein, stimulating an adaptive immunological response and the generation of IgG anti-spike protein antibodies. These antibodies neutralise SARS-CoV-2 by preventing attachment of viral spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor expressed on host cells.

Both COVID-19 mRNA vaccines were shown to have clinical efficacy and excellent safety profiles in large-scale phase 3 clinical trials in adults.[5,6] Identified adverse events included lymphadenopathy[5,6] and facial palsy[5] as well as mild systemic reactions that occurred at increased frequency in younger adults and following the second dose.[5,6]

Myopericarditis as a complication of mRNA vaccines

Myopericarditis following vaccination is documented as early as 1957 following smallpox vaccination, and case reports describe rare occurrence after inactivated influenza, diphtheria, tetanus and polio as well as quadrivalent human papillomavirus vaccination.[7] Prior to COVID-19, surveillance data through the US Vaccine Adverse Event Reporting System reported a 0.1% incidence of post-vaccination myopericarditis, with the majority of cases occurring in males within 2 weeks of vaccination.[7] Although myopericarditis was not observed in phase 3 trials of mRNA COVID-19 vaccines,[5,6] post-vaccination surveillance and published case reports identified this as a complication in early/mid-2021. Based on evident risk and published case reports, the US Food and Drug Administration added a warning of the risk of myocarditis and pericarditis with both mRNA vaccines in June 2021.[8]

Proposed mechanism

The exact processes underlying mRNA vaccine-induced myopericarditis have not been elucidated, but a number of hypotheses are proposed.[4,9] These include a hyper-immune response similar to the multi-system inflammatory response seen in children with COVID-19 (MIS-C), although this is not supported by measurement of vaccine-induced antibody levels in affected patients.[9] Other possibilities include molecular mimicry between antibodies generated against SARS-CoV-2 spike protein and a self-antigen, or aberrant induction of apoptosis with subsequent inflammation.[9] Presentation after 2–3 days is earlier than would be expected for delayed-type hypersensitivity, and patients do not demonstrate eosinophilia, nor features of thrombosis or mast cell activation syndrome. Alternatively, RNA is itself a potent immunogen and may elicit a bystander effect by activation of pre-existing autoreactive cells in young patients previously exposed to COVID-19.[9] Further studies are required to investigate these possibilities and also to elucidate whether vaccine-induced myocarditis is related to the delivery of spike protein or to the mRNA platform itself.

Incidence and risk factors

The incidence of COVID-19 mRNA vaccine-associated myopericarditis is low, with estimates ranging from 4 to 29.8 cases per million doses of mRNA vaccine.[10–13] A population analysis of >800 000 vaccinated individuals with matched controls in Israel revealed an excess risk of myocarditis (risk ratio (RR), 3.24; 95% confidence interval (CI), 1.55–12.44) and pericarditis (RR 1.27; 95% CI 0.68–2.31), translating to approximately three excess myocarditis events and one excess pericarditis event per 100 000 persons compared to the general population.[14] A further nationwide analysis of >5 million adult BNT162b2 vaccine recipients identified 136 cases of definitive/probable myocarditis, with an increased risk after the second dose in young, male recipients.[15] Early evidence in the United Kingdom suggests the risk of myocarditis may be higher with Spikevax (29.8 per million doses) compared with Comirnaty (7.6 reports per million doses).[13] This trend has also been observed in US and Canadian data, and is accompanied by higher rates of pericarditis following Spikevax compared with Comirnaty.[16]

mRNA vaccine myopericarditis occurs more commonly in males aged ≤40 years following the second dose.[12,14,15,16] Median age at presentation is 25 years[12,14] with the highest risk in male recipients aged 16–19.[15] Young men account for approximately 80–90% of cases, with an incidence rate 5–25 times the expected rate for myocarditis.[11] There is no current evidence that individuals with pre-existing cardiovascular disease or even prior myopericarditis are at increased risk. The rate of myocarditis following Comirnaty vaccination in Australia is presented in Table 1.[17]

Clinical manifestations

COVID-19 mRNA vaccine-associated myopericarditis can range in severity. Median time to symptom onset is 3 days, with the vast majority occurring by day 7 post-vaccination.[10,16] A small number of cases have been reported at 2–3 weeks post-vaccination.[18] Acute chest

Table 1 Rates of myocarditis cases (levels 1–3) following Comirnaty (Pfizer) vaccination in Australia

Age (years)	All doses		Second dose	
	Rate† per 100 000 doses		Rate† per 100 000 doses	
	Male	Female	Male	Female
12–17	6.8	1.4	10.6	2.4
18–29	3.5	1.2	5.7	1.8
30–39	1.4	0.6	1.4	0.5
40–49	0.7	0.6	1.0	0.9
50–59	0.4	0.3	0.1	0.4
60–69	0	0.3	0	0
70+	0	0.2	0	0
All ages†	2.1	0.8	3.0	1.0

†The rate includes cases of myocarditis that occurred after vaccination but may not be vaccine related. The number of younger people vaccinated is still relatively low in Australia, so estimated reporting rates are based on limited data.

pain is the most common presenting symptom (86–93%),[9,12] often pleuritic, and exacerbated in the supine position if there is associated pericardial involvement. Other common symptoms include fever, malaise, dyspnoea, palpitations and syncope.[9,10,12] Most cases are mild and resolve within 7–14 days;[4,9,12] however, fulminant myocarditis leading to heart failure, ventricular fibrillation induced cardiac arrest and sudden death have also been reported as temporally associated with COVID-19 mRNA vaccination.[19] Whether cases that develop after the first vaccine dose are more severe than those that develop following the second dose is unclear, although interestingly, in one case series, all three patients who experienced myocarditis after dose 1, had confirmed COVID-19 infection more than 2 months prior.[20]

Diagnosis

The diagnostic evaluation of suspected vaccine-induce myopericarditis includes a full blood count and inflammatory markers, N-terminal pro-B-type type natriuretic peptide (NT-proBNP), cardiac troponin, electrocardiography (ECG), echocardiography and/or cardiac magnetic resonance imaging (MRI).[4,9] A chest X-ray is recommended as detection of an enlarged cardiac silhouette suggests accompanying pericardial effusion.[16] A simultaneous diagnostic work-up to exclude acute COVID-19 infection by polymerase chain reaction (PCR) as well as other infectious and non-infectious causes of myopericarditis should also be undertaken. Most importantly, acute myocardial ischaemia can also occur post COVID-19 vaccination[21] and urgent appropriate investigation and management of an acute coronary syndrome is essential, particularly in at-risk patients. Coronary artery disease and acute ischaemia remains the most likely cause of acute chest pain in the context of an abnormal ECG and cardiac investigations in older patients. A pooled analysis of adverse cardiac events following COVID-19 vaccination demonstrated that patients with acute myocardial ischaemia post-vaccination are more likely to be older, male and present 24 h after the first dose.[21]

Probable myocarditis is defined as the presence of clinical symptoms (≥1 of chest pain, dyspnoea, palpitations or syncope) and at least one of the following: consistent changes on ECG, echocardiography, raised troponin and/or cardiac MRI.[10] Probable pericarditis is defined as the presence of clinical symptoms (≥2 of chest pain, pericardial rub, characteristic ECG changes, palpitations or syncope) and at least one of the following: consistent changes on ECG, troponin, new or worsening pericardial effusion on echocardiography/MRI.[10]

Between 61−100% of patients with mRNA vaccine myopericarditis have an abnormal ECG; findings can include ST segment elevation, PR depression and T-wave changes.[9,10,18] Echocardiography may demonstrate pericardial thickening or effusion in pericarditis, and global or regional left ventricular (LV) dysfunction in myocarditis, although sensitivity is low in mild disease and findings are often normal.[4] White cell count and C-reactive protein are elevated in 71–100% of hospitalised patients,[22] with NT-proBNP elevated in approximately two-thirds.[4] A review of published case series demonstrates elevation of troponin in all cases; similarly, MRI abnormalities were evident in 100% of patients across six separate case series.[4] Typical MRI findings include pericardial enhancement, myocardial oedema and late gadolinium enhancement characteristically distributed in the basal inferolateral and anterolateral LV wall.[9,10,18] Histological confirmation of myocarditis through endomyocardial biopsy is not required for diagnosis, but if performed, may demonstrate no abnormality,[23] or endointerstitial oedema, together with infiltration of T-cells and macrophages.[15]

Management

Management of suspected mRNA vaccine myopericarditis should occur under the guidance of a cardiologist, with input from infectious diseases and/or immunology colleagues. All symptomatic patients with a high index of suspicion for myopericarditis as evident by ECG changes and abnormal cardiac imaging should be admitted to hospital for monitoring; patients with benign investigations may be discharged if deemed appropriate following cardiologist review.

There are currently no randomised controlled trials to guide treatment decisions, and cases are managed as per conventional myopericarditis guidelines. This is supported by published case reports, in which non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and steroids in standard doses have been used with good effect.[4,9,18,22] In our experience, first-line therapy with colchicine and NSAIDs/aspirin is beneficial, with corticosteroids reserved for refractory cases. As corticosteroids can reduce the immune response to the vaccine, avoidance for the first 1–2 weeks post-vaccination and minimisation of duration is prudent if tolerated.[9] In patients with heart failure, new-onset arrhythmia, or haemodynamic instability, intravenous (IV) steroids and IV immunoglobulin (IVIg) together with cardiac or circulatory supportive measures can be considered.[4,9,22] A guide to doses is available in Marshall *et al.*,[22] who report use of IV methlyprednisone (10 mg/kg × 3 doses), oral prednisone (30 mg twice daily) and IVIg (1.5 g/kg) with success. β-blocker and ACE inhibitor therapy are indicated in the presence of LV systolic dysfunction, although the optimal duration of these agents is uncertain. Restriction of strenuous physical activity and competitive sports is recommended in all patients until after resolution of symptoms and ECG changes.[16] A proposed treatment algorithm is presented in Figure 1.

Prognosis

The outcome of vaccine-associated myopericarditis appears favourable, with or without treatment.[4,12] Although reports indicate that symptoms usually resolve within 7 days, in our experience, clinical features can persist for several weeks. Most patients requiring hospitalisation are discharged within 1 week,[4,9,12] and repeat ECG/echocardiography and blood tests demonstrate resolution of abnormalities.[10] There is little evidence to date regarding long-term outcomes, and Australian guidelines recommend specialist follow up for at least 12 months.[16] For patients with persistent arrhythmia, LV dysfunction or persisting cardiac MRI abnormalities, ongoing monitoring is indicated as per the treating cardiologist.

Cardiac complications of COVID-19 infection

SARS-CoV-2 can directly infect the heart and vasculature due to their expression of the ACE2 receptor.[24] Although myocarditis was not seen in previous coronavirus respiratory syndromes,[4] cardiac involvement is common in COVID-19,[4] and can be asymptomatic.[18] Ischaemic and non-ischaemic processes such as hypoxia, sepsis, thromboembolism and hyperinflammation play a

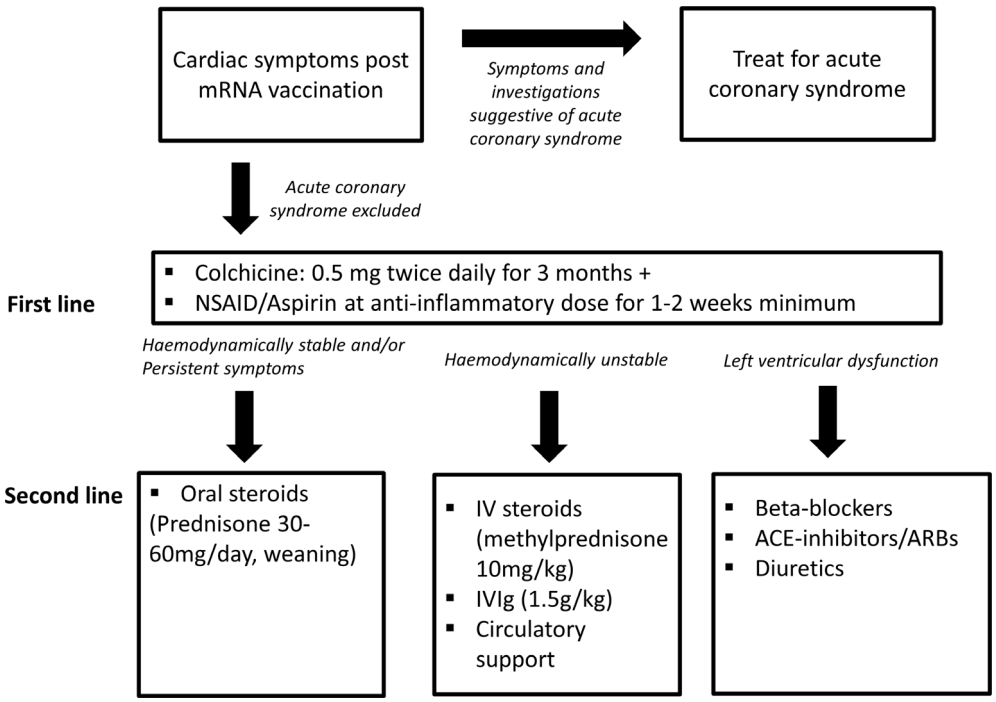

Figure 1 Proposed treatment algorithm for mRNA vaccine-associated myopericarditis. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IV, intravenous; IVIg, intravenous immunoglobulin; mRNA, messenger ribonucleic acid; NSAID, non-steroidal anti-inflammatory drug.

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causative role,[25] with myocardial injury evident in 28–60% of COVID-19 cases.[20,26] Clinical manifestations include myocardial infarction, heart failure, cardiogenic shock, pericardial disease, arrhythmia or death.[24] Both fulminant and non-fulminant myocarditis can occur[25]; overall the RR of myocarditis and pericarditis in COVID-19 is 18.3 and 5.4 respectively.[14] Additionally, survivors of COVID-19 may experience long-term cardiac abnormalities.[25] The frequency and severity of cardiac complications in COVID-19 must be considered when evaluating the low frequency of myopericarditis seen following mRNA vaccination.

Vaccine recommendations as per the Australian Technical Advisory Group on Immunisation[16]

Pre-existing cardiac disease is not a contraindication to mRNA vaccination. Patients with a history of myopericarditis within the preceding 3 months, acute rheumatic fever or decompensated heart failure can receive an mRNA vaccine but medical or specialist consultation should be sought regarding additional precautions. If myocarditis is confirmed after the first dose of an mRNA vaccine, the second dose should be delayed and a non-mRNA vaccine administered after recovery. In the setting of isolated pericarditis with normal investigations, a second mRNA dose can be administered following a minimum 6-week interval after resolution of symptoms. If pericarditis is accompanied by abnormal cardiac investigations, then decision-making is dependent on age and sex, with males aged 12–24 years advised to receive a non-mRNA vaccine as dose 2. A decision regarding a third or 'booster' dose is not informed specifically by current guidelines, and advice as per the above is recommended.

Conclusion

Although myopericarditis can rarely occur following COVID-19 mRNA vaccination, the observed incidence is low and most cases respond favourably and rapidly to treatment. Risk factors include male gender and age 16–25 years, with an increased incidence following the second dose. Vigilance is recommended, particularly in high-risk patients who experience chest pain within a few days of vaccination. Coronary artery disease and acute coronary syndromes must be considered in all patients presenting with chest pain and abnormal cardiac investigations. When balanced against cardiovascular and other risks of COVID-19, a benefit–risk assessment overwhelmingly recommends vaccination for all age and sex groups.[4,16] At the current time, evidence-based guidance is limited and may well evolve, given the need for booster doses and emergence of COVID-19 variants.

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