ACADEMIC

Association between mRNA COVID-19 vaccination and myocarditis

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Abstract

In early December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan City, China, causing the first cases of coronavirus disease (COVID-19). It rapidly spread globally, and by 11 March 2020, a pandemic was declared by the World Health Organisation (WHO). The unprecedented global disruption to the spheres of society, the economy, and personal health placed increasing pressure on the development of safe and efficacious vaccines against COVID-19. Of those developed, the Pfizer (BioNTech/Comirnaty BNT162b2) and Moderna (mRNA-1273) vaccines both utilise messenger RNA (mRNA) technology to provide immunisation against COVID-19. Clinical trials have demonstrated high efficacy of these mRNA vaccines in providing protection against COVID-19.[1] However, reports from the Centres for Disease Control and Prevention (CDC) have described an association between the mRNA COVID-19 vaccines and the development of myocarditis. International literature has identified myocarditis developing in young males following mRNA COVID-19 vaccination. Preliminary results reported by the Centre for Adverse Reactions Monitoring (CARM) suggest that this adverse effect has also occurred in the New Zealand (NZ) population. The true incidence of post-vaccination myocarditis remains uncertain, as recorded cases rely on passive reporting systems; hence, there may be under-reporting of cases. Therefore, continued evaluation of case reports, retrospective studies, and ultimately an active reporting system, will be required to determine the rate of myocarditis following COVID-19 mRNA vaccination. In the interim, it has been determined that the benefits of the COVID-19 vaccination in reducing the risk of developing COVID-19 outweigh the potential adverse effects of the vaccine.

Discussion

DEVELOPMENT OF MRNA COVID-19 VACCINES

mRNA vaccines have been rapidly developed for the prevention of COVID-19. In December 2020, the United States (US) Food and Drug Administration (FDA) granted emergency authorisation to two mRNA vaccines: the Pfizer vaccine and the Moderna vaccine.[1] Both of these vaccines are recommended as an initial two-dose schedule to ensure an adequate immune response.[1]

Multinational, placebo-controlled, observer-blinded trials have been conducted to assess the efficacy of the mRNA COVID-19 vaccines. It was concluded that the Pfizer vaccine was 95.0% effective (95% CI, 90.3–97.6) in preventing infection with COVID-19, and the Moderna vaccine, 94.1% (95% CI, 89.3–96.8) effective.[2,3] In regard to local reactogenicity, pain at the injection site was the most common adverse vaccine reaction reported by trial recipients who received either the Pfizer or Moderna vaccine.[2,3] In the Pfizer clinical trial, pain was reported more frequently among the younger participants (83% after first dose; 78% after the second dose) compared to participants older than 55 years (71% after the first dose; 66% after the second dose).[2] After the first and second doses of the Moderna vaccine, 84.2% and 88.6% of participants in the younger and older age groups, respectively, reported pain at the injection site.[3] This local reactogenicity resolved within one to two days and was graded as mild-to-moderate in severity.[2,3] The most frequent systemic adverse drug reactions reported by participants receiving either of the vaccines included fatigue, headache, fever, myalgia, arthralgia, nausea, vomiting, and chills, and were more common among the younger participants.[2,3] These minor adverse reactions following both vaccines were transient and self-limiting, resolving within a few days post-vaccination.[2,3] In these clinical trials, myocarditis was not listed as an adverse drug reaction.

ASSOCIATION BETWEEN MRNA COVID-19 VACCINATION AND MYOCARDITIS

Myocarditis is an inflammatory disease of the heart muscle, which may manifest following infection from a wide spectrum of pathogens, including viruses (the most common cause), bacteria, and fungi.[5] Myocarditis may also be induced by cardiotoxins and hypersensitivity reactions.[5] Epidemiological studies show that myocarditis occurs more commonly in men than women, with a median age of 33 years.[6] Male patients with myocarditis are, on average, significantly younger than females, with prevalence highest in the 16–20-year-old age group.[6] Clinical manifestations of myocarditis include chest pain, dyspnoea, palpitations, and fever, with subsequent diagnostic investigations revealing elevated troponin levels and/or abnormal findings on electrocardiogram, echocardiogram, or cardiac MRI.[7] Globally, the background rate of myocarditis is estimated to be 22 cases per 100,000 person-years.[7]

INTERNATIONAL DATA

Vaccine-associated myocarditis is a rare adverse reaction that has previously been associated with the smallpox vaccine, with less frequent informal reports following other vaccines.[9] Myocarditis was not reported as a potential adverse event in clinical trials of COVID-19 vaccines, and adverse cardiac events of any kind occurred in <0.1% of trial participants, with rates comparable in recipients of the vaccine and recipients of the placebo.[8]

Initial reports of myocarditis following COVID-19 mRNA vaccination emerged from Israel at the end of April 2021. After distributing 5 million vaccinations, the Israeli Ministry of Health reported 62 cases of myocarditis developing in vaccinated people.[10,11] Of these, the majority of cases followed the second vaccination. There was a strong male predominance, and a particularly high incidence in men under 30 years of age (1 in 20,000 men).[10,11] There were two reported deaths in 62 cases of post-vaccination myocarditis.[10,11] Following these initial reports, on 9 July 2021, the WHO Global Advisory Committee on Vaccine Safety issued an official statement regarding the risks of myocarditis following mRNA COVID-19 vaccination.[14]

The Vaccine Adverse Event Reporting System (VAERS) is the US reporting system for vaccine safety. This is a passive reporting system which relies on individuals to report their adverse treatment reactions to the CDC and FDA. At the time of the CDC COVID-19 Vaccine Safety Update delivered in 23 June 2021, approximately 296 million doses of COVID-19 vaccinations had been administered across the US, 52 million of which had been administered to people 12–29 years of age.[7] Of these, 30 million were first and 22 million were second mRNA vaccine doses.[7] The CDC reported that as of 11 June 2021 there had been a total of 1226 reports of myocarditis to VAERS following mRNA COVID-19 vaccination, combining cases from both the Pfizer and Moderna vaccines.[12]

Of the VAERS-reported myocarditis cases, the majority followed the second mRNA vaccine dose of either the Pfizer or the Moderna vaccine.[12] Of the two mRNA vaccines, the Pfizer vaccine was associated with the majority of myocarditis cases.[12] VAERS data shows that those developing myocarditis following vaccination had an average age of 30 years for the first vaccination dose and 24 years for the second vaccination dose. The average time of symptom onset was four days following the first vaccination dose and three days following the second vaccination dose. The data from VAERS shows that the majority of people who experienced myocarditis as an adverse reaction from either dose were male: first dose 66%, second dose 79%.[12] The group with the highest incidence of reported myocarditis following COVID-19 vaccination for both doses was males in the 12–39 year age bracket. As of 28 June 2021, 780 of the 1226 reports of myocarditis to VAERS were regarding those under the age of 30 years.[13] VAERS data showed that after 4,337,287 second doses administered to men aged 18–24 years, there were 233 reports of myocarditis in a 21-day window following administration of the vaccine, when 2–25 would have been expected based on background rates and prediction models.[12] After 5,237,262 doses administered to women in this age group, 27 cases were seen in a 21-day window following administration of vaccine, against a prediction of 2–18.[12] The overall data from VAERS as of 11 June 2021 found in the 12–29 year age group who received an mRNA COVID vaccine there were approximately 40.6 cases of myocarditis per million second doses among males, and 4.2 cases per million second doses among females. For persons over 30 years of age, the reported rates were 2.4 and 1.0 per million second doses for males and females, respectively.[14]

Given the apparent skewed prevalence of myocarditis developing in the younger population following COVID-19 vaccination, the CDC prioritised a review of myocarditis in those under 30 years. Of the 323 cases identified in this age group, the median age was 19 years. 291 were male, and 32 were female.[7] 92% of these patients experienced onset of symptoms within seven days of vaccination, the median interval being two days between vaccine administration and symptom onset.[7] Patients tended to present with chest pain, associated with ST or T-wave changes on electrocardiogram (ECG) and elevated cardiac markers, with fewer reports of abnormal cardiac imaging.[7] Supportive therapy was the mainstay of treatment, with targeted cardiac medications and interventions adopted when appropriate.[7] Although treatment data reported to VAERS is largely preliminary and incomplete, many patients have experienced resolution of symptoms with conservative treatment such as non-steroidal anti-inflammatory medications.[7] 309 of the 323 patients were hospitalised, but the acute clinical course was generally mild.[7] Of these hospitalised patients, 295 were discharged, and 79% of these patients had fully recovered and returned to their normal daily activities by the time of review.[12] There were no reported deaths in this data set.[7,12] Follow-up of these patient outcomes will be essential in order to ascertain the long-term outcomes after myocarditis occurring after COVID-19 vaccination.

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) has implemented the Yellow Card scheme, a passive reporting system to flag potential side effects and adverse reactions to the COVID-19 vaccine. As of 7 July 2021, an estimated 19.7 million first doses of the Pfizer vaccine and 1.1 million doses of the Moderna vaccine have been administrated in the UK. Within this, 87,789 Yellow Cards had been reported for the Pfizer vaccine and 8,953 for the Moderna vaccine.[4] Of these Yellow Cards, there were 81 reports of myocarditis following the administration of the Pfizer vaccine and 9 reports of myocarditis following the Moderna vaccine.[4] These reports corroborate international findings that there is a consistent pattern of cases occurring more frequently in males, more commonly after the second vaccine dose, and that cases are usually associated with mild and self-limiting symptoms.[12]

NEW ZEALAND DATA

As of January 2022 in New Zealand, everyone aged five years and over is eligible for COVID-19 vaccination. CARM is a Dunedin-based national monitoring centre for adverse reactions to treatments. This is a passive reporting system which relies on health professionals to report suspected adverse reactions to CARM. CARM collaborates with other international monitoring centres, including the database of WHO's International Drug Monitoring Programme.

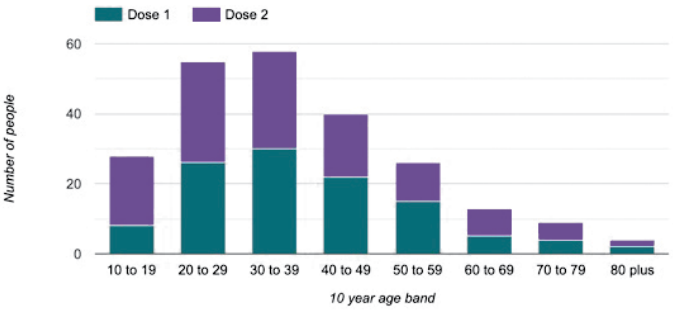

Figure 1 - Graph depicting the cases of post coronavirus disease (COVID-19) vaccine myocarditis in New Zealand reported to the Centre for Adverse Reactions Monitoring (CARM) (data up to December 1 2021).[18]

An initial communication from CARM on 21 June 2021 officially reported that Medsafe has concluded that myocarditis is a rare side effect of immunisation with the Pfizer vaccine.[15] This was further corroborated with an alert issued by CARM on 20 December 2021 containing updated statistics since the inclusion of reports for children aged 12–16 years.[18] CARM's most recent report concurs with the international findings that myocarditis typically occurs in younger men, shortly after the second dose of the vaccine, and cases are typically mild with a short recovery period.[15,18] The latest issue reports that CARM has received 233 reports of spontaneous myocarditis, 58% of which were males, and 52% of cases occurred after the second dose.[18] CARM emphasises that the reports of myocarditis do not necessarily have a causal relationship with the administration of the vaccine and may represent coincidental events.[18] As the rate of myocarditis following COVID-19 infection is a higher rate than after vaccination, CARM concludes that the benefits of the Pfizer vaccination outweigh the risk of adverse events, including myocarditis, for people of all age groups.[15,18]

LIMITATIONS

One of the most significant limitations of the data on the association between myocarditis and mRNA COVID-19 vaccination is the voluntary reporting systems upon which this data relies.[16] Passive surveillance is a reporting system which relies on patients seeking healthcare and then healthcare professionals recognising the connection as a vaccine-associated adverse event. Active surveillance is when officials actively search for information by contacting healthcare providers.

The US VAERS, UK Yellow Card Scheme, and NZ CARM are all passive reporting systems, collating data which is voluntarily supplied from healthcare professionals and members of the public. These passive monitoring systems are a suboptimal method of surveillance with potential for under-reporting and incomplete data. Due to the nature of passive reporting, adverse events, including myocarditis, may have

a coincidental relationship to the timing of vaccine administration and not necessarily be confirmed side effects from the vaccine.

Active surveillance monitoring has the capacity to provide more accurate and complete data; however, it is more resource- and expense-intensive. Databases involved in active monitoring contain millions of enrolled patients; thus, have high potential to identify rare adverse events. The Global Vaccine Data Network (GVDN) is a multinational research network involving six continents, 17 countries, and 21 population sites, representing over 290 million people. The GVND is an example of an active monitoring system which has the capacity to investigate vaccine safety and effectiveness. The University of Auckland group UniServices has been awarded nearly NZ$8 million by the CDC to coordinate a COVID-19 vaccine monitoring study with the GVDN database.[17] Until the publication of the data from this study, adverse vaccine reactions will continue to be collated through passive monitoring systems.

RISK-BENEFIT ANALYSIS

Although cases of myocarditis following COVID-19 vaccination are rare, given the large number of doses administered, it is an important safety consideration, particularly in the young male cohort where cases of myocarditis are more prevalent.

Rapidly emerging international data has demonstrated a plausible correlation between the development of myocarditis and the mRNA COVID-19 vaccination. Given the strong correlation of myocarditis following COVID-19 vaccination in the young male cohort, there is particular concern for the risks of the vaccine in this population group. The Advisory Committee on Immunisation Practices (ACIP) in the US has assessed the benefit-risk balance of mRNA vaccines in adolescents and young adults, comparing the benefits (prevention of COVID-19 disease and associated hospitalisation, ICU admission, and death) to the risk of myocarditis following vaccination.[7] It was concluded that the benefit outweighed the risk in all populations. However, the balance of the benefits against the risks varied by age and sex due to the higher prevalence of myocarditis in young males and the higher risk of poor outcomes related to COVID-19 related illness with increasing age.[7] Per 1 million second-dose mRNA COVID-19 vaccinations in males aged 12–29, there are estimated to be 39–47 cases of myocarditis after COVID-19 vaccination versus 11,000 cases of COVID-19 and subsequently 560 hospitalisations, 138 intensive care unit admissions, and 6 deaths.[7] Per 1 million second-dose COVID vaccinations for persons ≥30 years, there are estimated to be three to four myocarditis cases after COVID-19 vaccination versus 15,300 COVID-19 cases, 4,598 hospitalizations, 1,242 ICU admissions, and 700 deaths.[7] Therefore, at the CDC ACIP meeting, it was concluded that, based on international data, the benefits of the COVID-19 vaccination to the individual and population outweighed the potential adverse event of myocarditis.

A population health lens must also be applied when weighing up the benefits and risks of the COVID-19 vaccination. The ACIP has predicted that in the foreseeable future there will be no alternatives to mRNA vaccines that provide the same level of protection against infection, hospitalisation, and death from COVID-19 for the adolescent age group, who have a higher prevalence of myocarditis adverse vaccine reactions.[7] Additionally, the benefit of protection against COVID-19 illness that the vaccine offers is important in this cohort in ensuring continued education and social activities. Ethnic considerations are also essential. Stemming from colonisation, systemic racism and structural inequities embedded in the healthcare system mean that Māori face a much greater health burden from COVID-19. It is estimated that COVID-19 hospitalisation and fatality rates are 2.5 times greater for Māori than non-Māori.[19] Achieving equitable vaccination rates for Māori is thus crucial in reducing their healthcare burden. However, analysis of vaccine uptake per rate ratio of Māori compared with non-Māori reveals that in the majority of age groups, the rate is <1.0, meaning Māori are vaccinated at lower rates than non-Maori.[20] The Māori population is younger overall than the non-Māori population in New Zealand; thus, any changes in vaccine policy for the young male cohort have the potential to disproportionately affect young Māori who already have lower vaccination rates.[7,21] This has the potential to exacerbate poorer health outcomes from COVID-19 related illness in an already vulnerable community.[7,19]

Conclusion

Current national and international data has demonstrated an association between myocarditis and mRNA COVID-19 vaccination. Passive international reporting systems demonstrate a higher incidence of post-vaccination myocarditis in young males, although this has not been replicated yet in New Zealand. Continued surveillance is required to determine the causal relationship between the development of myocarditis and COVID-19 mRNA vaccination, ideally with future analysis through an active reporting system. COVID-19 vaccine administration continues to be recommended for everyone aged 12 years and older, given the risk-to-benefit ratio. Serious complications related to COVID-19 pose greater risk than the potential adverse events following vaccination, including the risk of myocarditis post-vaccination in the young male cohort.

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