Radiology

Postvaccine Myocarditis: A Risk Worth the Reward?

Betty Raman, MBBS, DPhil • *Stefan Neubauer, MD*

Dr Betty Raman is an academic cardiologist, British Heart Foundation Transition Intermediate Clinical Research Fellow, and principal investigator at the Radcliffe Department of Medicine, University of Oxford. She serves on the executive committee of three urgent public health UK COVID-19 follow-up studies and leads the imaging arm (multiorgan MRI) of two of them. She is devoted to understanding the long-term effects of COVID-19 on multiorgan health and improving risk stratification for patients with hypertrophic cardiomyopathy.

Professor Stefan Neubauer is head of the Division of Cardiovascular Medicine and director of the Oxford Centre for Clinical Magnetic Resonance Research, University of Oxford, John Radcliffe Hospital, United Kingdom. His research interests include cardiovascular MR, multiorgan MRI, and novel coronary CT. He has published more than 450 manuscripts, was president of the Society for Cardiovascular Magnetic Resonance (SCMR) (2006–2007), chairman of the British SCMR (2008–2010), and international associate editor of *European Heart Journal* (2010–2020). Awards and honors include an American Heart Association Paul Dudley White Award (2005), British Cardiovascular Society Thomas Lewis Lecture (2008), European Magnetic Resonance Award (2010), SCMR Gold Medal (2013), and RT Hall Lecture (2017).

The benefits of a mass rollout of the COVID-19 vaccine are undeniable. Millions of deaths, hospitalizations, and intensive care admissions have been averted across all age groups due to the success of national vaccine programs. The link between cases and fatal outcomes may finally be severed in some countries. Economic growth is expected to reach prepandemic levels as normality returns to many lives. Declining mental health is predicted to improve and vital hospital resources may be diverted back to other patients in need of medical attention. The finish line is finally visible as nations seek to build herd immunity through vaccine mandates. But will there be barriers in this final phase of the pandemic? The answer is complex and multifactorial, with vaccine hesitancy expected to play a critical role.

Of available vaccines, the messenger RNA (mRNA) vaccine, a relatively new mode of inducing immunity, has been remarkably resilient in protecting against new versions of COVID-19. The superiority of mRNA vaccines has been particularly visible in the context of the Omicron SARS-CoV-2 variant, a highly contagious variant shown to efficiently evade both natural and induced immunity in individuals (particularly in non-mRNA vaccine recipients). The trouble with mRNA vaccines, however, is the risk of myocarditis, which is an emerging focus of public concern that generates arguments in favor of vaccine refusal and hesitancy.

Reassuringly, numerous epidemiologic studies have confirmed that myocarditis following mRNA vaccination is rare. In a recent Danish study by Husby et al (1), the incidence of myopericarditis following the BNT162b2 vaccine in 3.5 million people was 1.4 per 100 000 individuals and following the mRNA-1273 vaccine was 4.2 per 100 000. An Israeli study of 9.2 million residents noted an overall rate of myocarditis of 2.35 per 100 000 in individuals vaccinated with BNT162b2 after the second dose. By contrast, the risk of myocarditis secondary to COVID-19 has been shown to be at least four- to fivefold higher in two studies (2,3). Furthermore, risks of other complications such as pericarditis, arrhythmia, deep vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia were also substantially higher after acute COVID-19 when compared with vaccine-related adverse events.

While the prevalence of mRNA vaccine–associated myocarditis is now reasonably well characterized, the pattern and extent of myocardial injury compared with other forms of myocarditis remain poorly understood. To address these gaps, in this issue of *Radiology*, Fronza and colleagues (4) evaluated the extent of myocardial injury with vaccine-associated myocarditis compared with that of COVID-19 illness and other myocarditis not associated with COVID-19. Cardiac MRI findings from 92 consecutive patients with suspected myocarditis were retrospectively assessed as part of this study. Of all the myocarditis cases, 66% were not related to COVID-19 illness or vaccination (including postinfectious, autoimmune, drug-induced, hypereosinophilic, and idiopathic cases), 23% were mRNA vaccine–related and 11% were COVID-19 illness–related. Just over half of the patients who had vaccine-linked myocarditis received the mRNA-1273 vaccine and 43% received the BNT162b2 vaccine. Previous studies (5–7) have reported clinical and MRI findings from postvaccine myocarditis in selected cohorts of hospitalized patients, although none of them had a control group.

In line with prior studies, patients with vaccine-associated myocarditis were predominantly male (81%) and younger (mean age, 31 years ± 14 [SD]) (4). Chest pain or myocarditis symptoms were reported at a median of 3

From the Oxford Centre for Clinical Magnetic Resonance Research, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, National Institute for Health Research (NIHR), Oxford Biomedical Research Centre (BRC), Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Headley Way, Level 0, Oxford OX3 9DU, United Kingdom. Received February 1, 2022; revision requested, revision received, and accepted February 3. **Address correspondence to** B.R. (email: *betty.raman@cardiov.ox.ac.uk*).

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See also the article by Fronza et al in this issue.

days from the second dose in 81% of patients. Cardiac MRI performed in both hospitalized and nonhospitalized patients with vaccine-associated myocarditis was also uniquely assessed in this study. The authors observed that nonhospitalized patients with myocarditis had MRI abnormalities comparable with those needing hospital admission for vaccine-associated myocarditis. Patients with vaccine-associated myocarditis frequently had subepicardial fibrosis, a pattern similar to that of myocarditis secondary to COVID-19 and other etiologies. However, midwall fibrosis was notably less frequent and left ventricular impairment less common in vaccine-associated myocarditis. Even the extent of late gadolinium enhancement (focal fibrosis) in the vaccine group was lower and abnormalities on tissue characterization (T1 and T2 mapping), although common (affecting 67%–79% of patients), were less severe in magnitude relative to the other groups. At short-term follow-up (22 days [IQR, 7–48 days]), the outcome of patients with vaccine-associated myocarditis showed no major adverse events. In contrast, patients with COVID-19 illness–associated myocarditis had three major adverse cardiovascular events (MACE) and those with myocarditis of other etiologies had five MACE at a median of 211 days and 195 days, respectively.

The main findings highlighted by Fronza et al (4) are as follows. First, COVID-19 vaccine–associated myocarditis tended to be mild both in the clinical presentation and extent of injury. This is in keeping with other case series and cohort descriptions of vaccine-associated myocarditis (5–7). Second, postvaccine myocarditis fibrosis was predominantly subepicardial in distribution, a pattern linked to better outcomes in a prior study of myocarditis (8). Third, while previous publications focused on more severe cases of myocarditis (such as those needing hospital admission), in this study, even patients with mild forms of myocarditis had abnormalities at detailed cardiac evaluation. This finding highlights the need for surveillance of patients with suspected myocardial involvement after receiving an mRNA vaccine. Finally, the short-term follow-up of a small group of patients with vaccine-related myocarditis was relatively uneventful. This hints toward a possible benign prognosis, although the follow-up duration of the comparator groups (post-COVID-19 illness and other myocarditis) were much longer, limiting the validity of this conclusion.

While the study by Fronza et al (4) had some novel findings, there were several limitations, some of which were acknowledged by the authors. This includes its limited sample size, retrospective nature (making it susceptible to reporting bias), short follow-up of the vaccine group, and heterogeneity of patient populations. Inconsistent imaging protocols (eg, use of 1.5-T and 3-T scans) and varying intervals from symptom onset to imaging across groups can also be problematic, as native T1 and T2 mapping are highly sensitive to field strength, effects of comorbidities, and timing from acute insult to imaging. Although the authors attempted to adjust for some of these differences statistically, and by using *z* scores, imperfections in covariates and normal ranges may still result in residual confounding. Therefore, prospective cohort studies with larger sample sizes, consistent imaging protocols, and longer follow-ups are needed to validate these findings in the future.

Despite the numerous reports of mRNA vaccine–associated myocarditis, underlying pathophysiologic mechanisms that may contribute to presentations are still unknown and represent an important area of research. Three possible explanations for myocarditis have been put forward by experts, yet these are lacking consistent confirmatory evidence. These include an mRNA vaccine immunogenic response, cross-reactivity of spike antibodies with myocardial contractile proteins, and hormonal differences in immune response. Foreign RNA molecules are typically highly immunogenic and have been shown to activate the innate immune system, leading to the early destruction of RNA molecules before they enter the cells. Nucleoside modifications of mRNA are a revolutionary approach shown to considerably reduce this immunogenicity (9), making it possible to safely and effectively administer mRNA vaccines to millions of people and protect them against serious illness secondary to COVID-19. However, in certain genetically predisposed individuals, inappropriate activation of the innate and acquired immune response can still occur, leading to the release of proinflammatory cytokines and immunologic activation, and subsequent myocardial injury.

Another mechanism considered plausible is the cross-reactivity of SARS-CoV-2 spike glycoprotein antibodies and cardiac self-antigens (10). Molecular mimicry between the spike glycoprotein and structurally identical protein sequences, including myosin heavy chain, may trigger an autoimmune response to cardiac antigens and potentially induce myocardial inflammation. Finally, the strong predisposition for males to develop mRNA-induced myocarditis implies that hormonal differences in immune response may be a driver for myocardial inflammation. Indeed, the helper T-cell response is favorably promoted by testosterone, which also inhibits other anti-inflammatory cells. By contrast, estrogen has many anti-inflammatory properties and, therefore, protects against numerous inflammatory diseases before the onset of menopause.

The risk of myocarditis linked to mRNA vaccination has been a major source of public anxiety, although several studies have confirmed the rarity of this complication. In this work by Fronza et al (4), we are once again reassured that myocarditis secondary to mRNA vaccination is most likely mild and self-limiting and may have minimal short-term consequences, albeit larger studies with longer-term follow-up are needed. In comparison, COVID-19 illness–associated myocardial injury, hospitalization, and death continue to pose a real threat to the unvaccinated population and vital lifeline of hospital resources. Global efforts to promote vaccine equity and education will be necessary to bridge the gaps in population immunity against COVID-19.

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