New Details of Myocarditis Linked to COVID Vaccines

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Further details from multiple cases of myocarditis linked to the Pfizer and Moderna mRNA COVID vaccines have been described in recent papers in the medical literature.

The cases appear to occur almost exclusively in males and most often in younger age groups. While symptoms and signs of myocarditis mostly resolved with a few days of supportive care, long-term effects are unknown at present.

The authors of all the reports and of two accompanying editorials in *JAMA Cardiology* are unanimous in their opinion that the benefits of vaccination still outweigh the risks.

The Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices met last week to discuss this issue. At that meeting, it was reported that 323 cases of myocarditis or pericarditis in individuals aged 29 years and younger have been confirmed, but committee members delivered a strong endorsement for continuing to vaccinate young people with the mRNA vaccines.

The current case reports are published in two papers in *JAMA Cardiology* and in three in *Circulation*.

US Military Reports 23 Cases

In one report in *JAMA Cardiology*, authors led by Jay Montgomery, MD, from Walter Reed National Military Medical Center in Bethesda, Maryland, describe 23 cases from the US Military Health System of individuals with acute myocarditis who presented within 4 days after mRNA-based COVID-19 vaccination (7 Pfizer and 16 Moderna).

All patients were male, 22 of 23 were on active duty, and the median age was 25 (range 20-51) years; 20 of the 23 cases occurred after receipt of a second dose of an mRNA COVID-19 vaccine.

The patients all presented with acute onset of marked chest pain. All patients had significantly elevated cardiac troponin levels. Among eight patients who underwent cardiac magnetic resonance imaging (cMRI), all had findings consistent with the clinical diagnosis of myocarditis.

Additional testing did not identify other possible causes of myocarditis. All patients received brief supportive care and were recovered or recovering.

The authors report that the military administered more than 2.8 million doses of mRNA COVID-19 vaccine in this period, and while the observed number of myocarditis cases was small, the number was "substantially higher" than expected among male military members after a second vaccine dose.

They note that, based on historical data, among the 544,000 second doses to military members there may have been 0 to 10 expected myocarditis cases, but they observed 19 cases.

"All patients in this series reflect substantial similarities in demographic characteristics, proximate vaccine dose, onset interval, and character of vaccine-associated myocarditis. The consistent pattern of clinical presentation, rapid recovery, and absence of evidence of other causes support the diagnosis of hypersensitivity myocarditis," they state.

They add that presentation after a second vaccine dose or, in three patients, when vaccination followed SARS-CoV-2 infection, suggests that prior exposure was relevant in the hypersensitivity response.

"The spectrum of clinical presentation and reliance on patients seeking health care and on health care professionals recognizing a rare vaccine-associated adverse event limits determination of the true incidence of this

condition," the authors write.

They stress that recognition of vaccine-associated myocarditis is clinically important because diagnosis impacts management, recommendations for exercise, and monitoring for cardiomyopathy.

But the authors also acknowledge that it is important to frame concerns about potential vaccine-associated myocarditis within the context of the current pandemic.

"Infection with SARS-CoV-2 is a clear cause of serious cardiac injury in many patients…. Prevalence of cardiac injury may be as high as 60% in seriously ill patients. Notably, nearly 1% of highly fit athletes with mild COVID-19 infection have evidence of myocarditis on cMRI," they write.

"Given that COVID-19 vaccines are remarkably effective at preventing infection, any risk of rare adverse events following immunization must be carefully weighed against the very substantial benefit of vaccination," they conclude.

Four Cases at Duke

In the second paper in *JAMA Cardiology*, a group led by Han W. Kim, MD,

report four patients with acute myocarditis occurring within days of mRNA COVID-19 vaccination (2 Pfizer and 2 Moderna) in patients treated at Duke University Medical Center. The hospital courses of the four patients with myocarditis following COVID-19 vaccination were uneventful, and they were discharged within 2 to 4 days.

The authors say that, although a causal relationship cannot be established, none of the patients had a viral prodrome or had coincident testing that revealed an alternative explanation.

They state that these four patients represent the majority of patients with acute myocarditis identified in the past 3 months at their institution, and this led to the highest total number of patients with acute myocarditis compared with the same 3-month period for the past 5 years.

"Additionally, we identified only those patients with severe unremitting chest pain who sought medical attention. Those with mild or moderate chest pain might not seek medical attention, and it is possible that subclinical myocarditis may occur and could be detected by active surveillance, as has been described with smallpox vaccination," they write.

Further Case Reports

In one of the papers in *Circulation*, a group led by Kathryn F. Larson, MD, from the Mayo Clinic in Rochester, Minnesota, describe eight patients hospitalized with chest pain who were diagnosed with myocarditis within 2 to 4 days of receiving either the Pfizer or Moderna vaccine.

Two of the patients had previously been infected by SARS-CoV-2 without need for hospitalization. All individuals were otherwise healthy males between the ages of 21 and 56. All but one patient developed symptoms after their second dose, and the one patient who developed myocarditis after the first vaccine dose had previously been infected with SARS-COV-2.

Systemic symptoms began within 24 hours after vaccine administration in five of eight patients, with chest pain presenting between 48 and 96 hours later. Troponin values were elevated in all individuals and appeared to peak the day after admission, whereas none had eosinophilia.

Cardiac MRI revealed findings consistent with myocarditis in all patients. All patients had resolution of their chest pain and were discharged from the hospital in stable condition.

"The patients presented here demonstrated typical signs, symptoms, and diagnostic features of acute myocarditis. The temporal association between receiving an mRNA-based COVID-19 vaccine and the development of myocarditis is notable," the authors say.

They add that they would consider the use of corticosteroids in these patients but caution that this could reduce the specific immune response against SARS-COV-2 triggered by the vaccine. "Thus, the duration of corticosteroid administration should be limited to the resolution of the symptoms or ventricular arrhythmias or the recovery of the left ventricular ejection fraction."

Pending publication of long-term outcome data after SARS-CoV-2 vaccine-related myocarditis, they suggest adherence to the current consensus recommendation to abstain from competitive sports for a period of 3 to 6 months with reevaluation prior to sports participation.

In another of the *Circulation* papers, a group led by Carolyn M. Rosner, MSN, present a case series of seven patients hospitalized for acute myocarditis-like illness following COVID-19 vaccination, from two US medical centers, in Falls Church, Virginia, and Dallas, Texas.

All patients were males below the age of 40 years and of white or Hispanic race/ethnicity. Only one patient reported prior history of COVID-19 infection. Six patients received mRNA (Moderna or Pfizer) and one received the adenovirus (Johnson & Johnson) vaccine. All patients presented 3 to 7 days postvaccination with acute onset chest pain and biochemical evidence of myocardial injury.

Hospital length of stay was 3 days, and all patients' symptoms resolved by hospital discharge.

And finally, the third paper in *Circulation* reports a detailed description of one patient — a 52-year-old, previously healthy male who presented with acute myocarditis 3 days after the administration of the second dose of Moderna's COVID-19 vaccine. The symptoms resolved, and there was a gradual improvement in cMRI findings. Ischemic injury and other potential causes of acute myocardial injury were excluded, as were other potential infectious causes of myocarditis, and there was no evidence of systemic autoimmune disease.

"Clinicians should be aware that myocarditis may be present in patients exhibiting cardiac signs and symptoms 2-4 days after COVID-19 vaccination," the authors say.

They add that additional surveillance of such adverse events post-COVID-19 vaccination will help identify subgroups at higher risk for this vaccine-related effect, and whether additional precautions are necessary.

"Benefits Outweigh Risk"

In an accompanying editorial in *JAMA Cardiology*, three doctors from the CDC cite several other reports of myocarditis after mRNA COVID vaccination. These include a case report published in *Pediatrics* of seven male adolescents aged 14 to 19 years who presented with myocarditis or myopericarditis within 4 days after receipt of a second dose of the Pfizer vaccine.

But the editorialists note that the most comprehensive data about the risk for myocarditis following immunization with mRNA vaccines comes from Israel.

The Israeli Ministry of Health recently posted data describing 121 myocarditis cases occurring within 30 days of a second dose of mRNA vaccine among 5,049,424 persons, suggesting a crude incidence rate of approximately 24 cases per million.

On the current case reports, the CDC doctors write: "The striking clinical similarities in the presentations of these patients, their recent vaccination with an mRNA-based COVID-19 vaccine, and the lack of any alternative etiologies for acute myocarditis suggest an association with immunization."

They say that acute onset of chest pain 3 to 5 days after vaccine administration, usually after a second dose, is a typical feature of reported cases and suggests an immune mediated mechanism.

But SARS-CoV-2 infection also causes cardiac injury which may result in severe outcomes, and based on currently available data, myocarditis following immunization with current mRNA-based vaccines is rare.

"At present, the benefits of immunization in preventing severe morbidity favors continued COVID-19 vaccination, particularly considering the increasing COVID-19 hospitalization rates among adolescents reported during spring 2021," the editorialists state.

But they add that many questions remain. These include whether modifications are needed to the vaccine schedule among persons with a history of possible or confirmed myocarditis after COVID-vaccine; how should postvaccine myocarditis be managed; how often should follow-up assessments be performed; how might follow-up assessments affect recommendations to avoid vigorous physical activity following the diagnosis of myocarditis; and do all likely cases of acute myocarditis that appear to be uncomplicated require cardiac MRI for more definitive diagnosis?

"While the data needed to answer such questions are being collected, there is an opportunity for researchers with

expertise in myocarditis to develop a comprehensive, national assessment of the natural history, pathogenesis, and treatment of acute myocarditis associated with receipt of mRNA-based COVID-19 vaccines," they conclude.

In a second editorial in *JAMA Cardiology*, a group of editors from the journal acknowledge that they recognize that publication of the current case reports may contribute to additional public concern regarding immunization. But they add that clinicians discussing immunization with patients should recognize that these case series suggest that the symptomatic events consistent with myocarditis are still very rare and appear to be self-limiting.

"Given the risks of COVID-19, including the risk of myocarditis from COVID-19 infection, the editors do not believe these case reports are sufficient to interrupt the march toward maximal vaccination against SARS-CoV-2 as expeditiously as possible," they say.

JAMA Cardiology. Published online June 29. Montgomery et al. Full text, Kim et al. Full text, CDC Editorial, JAMA editors' editorial

Circulation. Published online June 16. Larson et al. Full text, Rosner et al. Full text

Muthukumar et al. Full text

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