

## Receipt of mRNA Vaccine against Covid-19 and Myocarditis

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After mass vaccination with messenger RNA (mRNA) vaccines against coronavirus disease 2019 (Covid-19), myocarditis in male teenagers emerged as a possible rare side effect, which led to great concern in the public and potentially fostered vaccine hesitancy or refusal. Myocarditis in general practice, independent of vaccination, is most common in young men and resolves spontaneously in at least half of patients. However, the condition may lead to dilated cardiomyopathy, heart transplantation, or death in up to a quarter of cases.<sup>1-4</sup>

The diagnosis of myocarditis is challenging. Presentations range from incidental diagnosis with mild or no cardiac symptoms to acute, chronic, or fulminant heart failure, life-threatening arrhythmia, and troponin release in the context of normal coronary arteries.<sup>1-4</sup> The diagnosis is typically based on clinical, electrocardiographic, and echocardiographic findings, elevated troponin levels, and a typical pattern on cardiovascular magnetic resonance imaging (MRI). But the diagnosis of this condition and a determination of its cause often remain uncertain and cannot be definitive without endomyocardial biopsy or autopsy.<sup>1,2</sup>

According to the World Health Organization<sup>5</sup> and cardiology societies,<sup>1,3,4,6</sup> myocarditis is defined as an inflammatory disorder of the heart muscle that is characterized by lymphocytic and monocytic infiltrates within the myocardium, myocyte degeneration, and nonischemic necrosis (the so-called Dallas criteria).<sup>7</sup> A definitive diagnosis depends on these and other established histologic, immunohistochemical, immunologic, and molecular criteria, including the results of polymerase-chain-reaction assay or in situ hybridization for the identification of cardiotropic viruses.<sup>1-6</sup> Biopsy-proven myocarditis may be caused by infectious (mainly viral) or noninfectious sources, including toxic and immune causes.<sup>1,5</sup> It follows that for a truly definitive diagnosis of myocarditis occurring after vaccination, endomyocardial biopsy would need to be performed and viral myocarditis (including from Covid-19 infection) would need to be ruled

out to exclude a chance occurrence of myocarditis temporally associated with the vaccine.<sup>1-6</sup>

In this issue of the *Journal*, two groups of investigators report retrospective data on cases of presumed myocarditis that were detected after receipt of the BNT162b2 mRNA vaccine (Pfizer–BioNTech) in Israel. In the report by Mevorach and associates,<sup>8</sup> the investigators reviewed data from medical records obtained from the Israeli Ministry of Health regarding hospitalized patients with suspected myocarditis among vaccinated persons, as compared with unvaccinated controls, during the 6-month period from December 2020 through May 2021. The diagnosis of myocarditis was based on the Brighton Collaboration definition. The result was that there were 136 definite or probable cases of suspected postvaccinal myocarditis reported during the surveillance of more than 5 million vaccinated persons. Among these presumed cases, 95% of the patients had a benign, self-resolving course, but one patient died. The rate ratio for myocarditis among fully vaccinated persons as compared with unvaccinated persons was 2.35, and the highest rate was among male recipients between the ages of 16 and 19 years.<sup>8</sup> In the second Israeli report, Witberg and colleagues identified 54 cases that fulfilled the definition of myocarditis used by the Centers for Disease Control and Prevention (CDC) among more than 2.5 million vaccinated persons listed in the database of Clalit Health Services, the largest health care organization in Israel. All the patients had a favorable outcome, including one who initially had cardiogenic shock.<sup>9</sup> The estimated incidence of myocarditis up to 42 days after at least one dose of vaccine was 2.13 cases per 100,000 persons. As in the report by Mevorach et al., the highest incidence was among young men (between the ages of 16 and 29 years in the study by Witberg et al.).

The two studies have similar limitations. In both analyses, the Brighton Collaboration and CDC definitions do not require a biopsy for the diagnosis of myocarditis, so both groups are reporting clinically suspected myocarditis of unspecified cause. Only two patients who were

described by Mevorach and one by Witberg underwent endomyocardial biopsy, none fulfilled the Dallas histopathological criteria for myocarditis,<sup>7</sup> and none underwent a viral search on endomyocardial biopsy. This form of aggressive workup was not practical in the survey studies reported in this issue. Nevertheless, because biopsies were not routinely performed, we cannot judge whether the cases would have fulfilled the more stringent Dallas criteria. MRI was performed in a modest percentage of the patients in the two studies (35% and 28%, respectively), which provided noninvasive characterization of myocardial tissue that at least ruled out ischemic myocardial damage,<sup>1,2</sup> a point that is relevant, since most of the patients had an elevated troponin level as a criterion for diagnosis. It is worth noting that the occurrence of myocarditis in vaccinated persons in these studies does not necessarily imply that the vaccine alone was the cause but may reflect an effect of an adjuvant that promoted, reactivated, or accelerated naturally occurring myocarditis due to viral or immune-mediated causes.<sup>10</sup>

Most of the reported cases that occurred after vaccination had an uneventful course. The take-home messages from the two studies may be that clinically suspected myocarditis is temporally associated with the BNT162b2 mRNA vaccine but is rare, is more common in young male patients, and (with a few exceptions) is self-limiting. As acknowledged by the authors, temporal association does not imply causation, and the risk of vaccinal myocarditis is very low. The results of these two studies are valuable for doctors, patients, and the public to reduce the fear of myocarditis as a reason for excluding young people from vaccination, especially since myocarditis has also been temporally associated with Covid-19.<sup>10</sup> Meanwhile, active surveillance for myocarditis should continue, and endomyocardial

biopsy could be performed in severe cases to affirm the diagnosis and possibly to guide therapy, such as the use of antiviral drugs or immunosuppressive and immunomodulatory agents.<sup>1-4,10</sup>

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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