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Commentary

The Novel Platform of mRNA COVID-19 Vaccines and Myocarditis: Clues into the Potential Underlying Mechanism

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Acute myocarditis is the second most common inflammatory heart disease after pericarditis, with an estimated annual incidence of 22 cases per 100,000 subjects [1]. The absence of specific pathognomonic features in conjunction with the wide spectrum of clinical manifestations that range from subclinical cases to sudden cardiac death, render myocarditis particularly challenging. Myocarditis is most often the result of viral infections. The currently pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as an additional causal agent of myocarditis.

Several highly effective vaccines that avert COVID-19 hospitalizations and deaths were available just over a year after the emergence of SARS-CoV-2. This record in the history of vaccinology has allowed for the re-opening of societies and the return to a new normalcy after strict lockdowns. Two of the leading vaccines that were granted emergency use authorization, Pfizer-BioNTech's Tozinameran (Comirnaty, BNT162b2) and Moderna's CX-024414 (mRNA-1273), are based on the novel platform of messenger RNA (mRNA). As mass vaccination efforts intensify, the meticulous safety monitoring of COVID-19 vaccines continues. Recent reports on the potential link between mRNA vaccination and myocarditis raised concerns among healthcare workers, the public and social media.

In more detail, Israel, that is leading the vaccination race, reported in late April that it is examining cases of myocarditis that occurred days after receipt of the Pfizer-BioNTech vaccine. A total of 62 cases (updated on June 2 to 275 cases between December 2020 and May 2021) were recorded (56 after the second- and 6 after the first dose) out of 5 million vaccinated, or 1 in 100,000 who received a second dose (0.001%); notably, however, this percentage was five times higher in the 16–30 years age group (1/20,000 or 0.005%). Of the 62 cases, 60 were hospitalized but recovered and were discharged, while two young, previously healthy people died (a 22-year-old female and a 35-year-old male). Abu Mouch *et al.* just presented in detail six cases of myocarditis, with a mild clinical course, in young males shortly after BNT162b2 vaccination [2]. Additional myocarditis cases post mRNA COVID-19 vaccination were recorded in European countries (e.g., in France), but with no further details disclosed. In the United States, myocarditis after vaccination was reported in military personnel [7]. The 23 recorded cases (16 Moderna/ 7 Pfizer-BioNTech recipients) in 2.8 million vaccinated (0.000821%) confirmed the rarity of event. Of the 23 cases, 20 occurred after the second dose and three after the first vaccine dose.

Side effects officially filed for COVID-19 vaccines were released by the European Medicines Agency (EMA) on May 29, 2021. Available data on acute myocarditis cases post mRNA vaccination are summarized in Table 1. Such a link was not observed after receipt of vector-based vaccines (Johnson & Johnson and AstraZeneca). Reported associations are indeed rare, predominantly found among males, and corresponding to 1.60 cases/million doses for Pfizer-BioNTech and 3.04 cases/million doses for Moderna. Most cases were in the working age population (18–64 years), some among older individuals (65–85 years) who were prioritized for vaccination, and a few were among adolescents 12–17 years whose vaccination has just been approved (as of May 10). Although rare, the identified association can be serious as shown by the finding that a large proportion of cases did not recover and by the (albeit few) fatalities. The association of myocarditis with male sex and younger age could be attributed to sex hormones which may account for a more intense inflammatory response. As suggested by experimental studies on myocarditis in mice, testosterone may be implicated in the inhibition of anti-inflammatory cells and the stimulation of immune responses mediated by Th1-lymphocytes [3]. But what could be triggering the inflammatory response that perhaps for some prone individuals is localized in the cardiac muscle tissue in the first place?

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