Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Internal Medicine 92 (2021) 28–30

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Ideas and Opinions

Exploring the possible link between myocarditis and mRNA COVID-19 vaccines

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Myocarditis is an inflammatory cardiomyopathy, most frequently caused by viral agents, affecting 10-20 individuals per 100.000 each year in the general population [1]. Myocarditis (sometimes associated with pericarditis) following vaccine administration has been traditionally reported as a rare event, accounting for 0.1% of > 620.000 reports recorded at the Vaccine Adverse Event Reporting System (VAERS) over a period of 18 years [2]. Of note, most of the events occurred after administration of live-attenuated smallpox vaccine and less commonly after other vaccines, such as diphtheria, tetanus, and polio, influenza or hepatitis B [2].k

Nowadays, the coronavirus disease 2019 (COVID-19) outbreak is a major challenge for healthcare systems, also considering its potential to cause cardiovascular complications [3]. Great efforts have been made worldwide to promptly develop effective vaccines and reduce morbidity and mortality rates from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Available vaccines have proven highly effective at preventing symptomatic disease in clinical trials [4–6] and real-world reports [7] and are playing an essential role in flattening the epidemiology curve and, mostly, in reducing COVID-19 hospitalisations [7]. Some concerns have been raised after very rare cases of myocarditis and pericarditis recently reported by the Center for Disease Control and Prevention (CDC) as potentially associated with COVID-19 mRNA vaccinations [8], namely the Pfizer-BioNTech mRNA vaccine (BNT162b2) and the Moderna mRNA vaccine (mRNA-1273).

As of 11 June 2021, a total of 1226 reports of probable myocarditis/pericarditis cases were filed in the VAERS after ~300 million COVID-19 mRNA vaccine doses administered resulting in a rough prevalence of about 4.8 cases per 1 million doses administered (https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html). Subjects were most commonly young men, after receiving the second dose of the vaccine and experiencing symptoms at a median time of 3 days after vaccination. In detail, 484 reports (i.e. 39%) were related to individuals < 30 years of age. Of them, 323 were analysed by the CDC and fulfilled the criteria for the diagnosis of myocarditis/pericarditis (https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html). The estimated rate of myocarditis/pericarditis in subjects younger than 30 years after receiving the second dose of the vaccine was approximately of 40 cases per million among males and 4.2 cases per million among females. Conversely, these rates declined to 2.4 and 1.0 per million, respectively, for males and females older than 30 years (https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html). Further dedicated studies are required to understand the causes underlying such a significant gender difference in post-vaccination myocarditis in younger individuals. The most common clinical presentations were chest pain (> 85%), ST or T-wave changes and elevated cardiac enzymes (> 60%, both). Almost all patients (> 95%) were admitted to the hospital, but the vast majority recovered completely and was discharged without any residual cardiovascular damage at short term follow-up.

In landmark studies on COVID-19 mRNA vaccine [4,6], no safety issues concerning post-vaccine myocarditis was reported. In detail, in the phase 3 trial, BNT162b2 vaccination showed an efficacy of 52% at 12 days after the first dose and of 95% after the second dose administered 3–4 weeks apart in healthy subjects without previous SARS-CoV-2 infection [4]. Of note, the incidence of serious adverse events was comparable in the vaccine and placebo groups (0.6% and 0.5%, respectively) [4]. Furthermore, a recent, large, prospective observational study conducted in the United Kingdom investigated the rate of short-term adverse effects from the two BNT162b2 and ChAdOx1 nCoV-19 vaccines [7]. In this real-world setting, side effects (predominantly mild in severity and self-limiting) were found in fewer than one in four people, being less common than that reported in phase 3 trials. Younger individuals (≤ 55 years), women, those with previous SARS-CoV-2 infection and subjects receiving the second dose of the vaccine had a higher frequency of systemic adverse effects, such as headache and fatigue, but no episode of myocarditis [7]. Outside of the United Kingdom, the Israeli Ministry of Health and the United States

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https://doi.org/10.1016/j.ejim.2021.08.018
Received 16 August 2021; Accepted 20 August 2021
Available online 28 August 2021

Department of Defense reported 148 myocarditis among 10.4 million vaccinated individuals and 23 male military personnel after 2.8 million vaccine doses. These reports detected a higher incidence of myocarditis in fully vaccinated (both doses) male adolescents and young adults aged 16–30, especially in the age range 16–19 [8]. Although having criteria for myocarditis at cardiac magnetic resonance, only two reported patients with myocarditis following COVID-19 vaccination underwent cardiac biopsy and neither of them had histological findings consistent with myocarditis (i.e. inflammatory infiltrates) [9,10]. Of note, cardiac biopsy was rarely performed as most patients had low-risk syndromes resolving completely within a short time [11].

Although these findings deserve attention and raise potential concerns for vaccination in younger adults, some points should be taken into account and caution in interpretation is required.

At first, it should be considered that these vaccines are safer than those used in the past as they contain nucleoside-modified mRNA, encoding the viral spike glycoprotein of SARS-CoV-2, and no trace of the live virus [4,6]. Recent studies report a reduction in the incidence of asymptomatic SARS-CoV-2 infection and the associated infectivity among patients receiving the BNT162b2 mRNA vaccine [12]. The impact of vaccination on breakthrough infections among fully vaccinated health care workers has been recently investigated by Bergwerk et al [12]. In this study, the rate of breakthrough infections in the 4 months following the second dose of the BNT162b2 mRNA COVID-19 vaccine was extremely low, accounting for 0.4% of all cases. These patients were asymptomatic or had very mild symptoms and were less contagious than unvaccinated individuals were. Further studies are needed to confirm these results after the spreading of novel virus variants (e.g., delta variant).

Secondly, VAERS suffers from some limitations: (a) accepts all reports regardless of the quality and completeness of information, (b) it cannot be used to determine cause-effect relationship, and, c) it is subject to reporting biases [13]. Therefore, future studies enrolling unbiased and larger populations are needed.

Thirdly, no major safety issues emerged from clinical trials on mRNA vaccines [4,6].

Finally, although one might speculate that a possible relationship exists between vaccination and myocarditis, temporal association does not prove causation and only future dedicated studies can address this question.

The COVID-19 pandemic is an ongoing rapidly evolving scenario with a growing number of unmet needs and grey areas to be addressed. According to one of the most promising hypotheses for the possible link between vaccination ad myocarditis, a hyperimmune response to the second dose of the vaccine is plausible in younger adults, also considering that adolescents have a more robust immune response to SARS-CoV-2 infection than adults (i.e. multisystem inflammatory syndrome in children) [14]. In case this theory will find confirmation, possible measures need to be explored to reduce the risk of myocarditis in people younger than 30 years; these may include the adoption of a longer interval between the first and second doses than in adults, and dosage reduction of the second dose [14].

European Medicines Agency (EMA) and other authorities will continue to monitor the vaccines' safety and efficacy as more adolescents and young adults are fully vaccinated with the second dose. Meanwhile, "healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. They should tell people receiving these vaccines to seek immediate medical attention if symptoms indicative of myocarditis or pericarditis occur. These include breathlessness, a forceful heartbeat that may be irregular and chest pain", as recommended by the EMA in an official note published on 09 July 2021 (https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis). Further studies are required to estimate the real incidence of myocarditis following COVID-19 vaccination worldwide.

At this point in time, very rare cases of myocarditis in younger adult men can occur following COVID-19 vaccination, but they are clinically mild and with benign evolution. To date, the benefit-risk assessment for COVID-19 vaccination shows a favourable balance in light of the potential of short- and long-term major cardiovascular and non-cardiovascular complications associated with this disease [3] and the long life-expectancy of this population.

Therefore, COVID-19 vaccination is strongly recommended to prevent major complications and death.

Some scenarios deserve specific considerations: a possible "vulnerable" population posing a clinical dilemma is represented by patients who had a previous or a recent episode of myocarditis. We suggest taking an attitude of prudence in this population and discourage patients from receiving COVID-19 vaccination in the first 6 months following disease onset or in presence of persistent or relapsing troponin release. Similarly, subjects are discouraged from receiving the second dose of the vaccine in case they develop myocarditis following the first dose, especially young patients. Finally, caution is recommended for vaccine administration in young patients with immune-mediated diseases or under chronic immunosuppression [15] as the cost-effectiveness analysis of vaccination in these settings requires careful evaluation in the nearest future.

Sources of funding

None.

Declarations of Competing Interest

The authors declare they have no conflict of interest.

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