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Myocarditis Following SARS-CoV2 mRNA Vaccination Against COVID-19

Facts and Open Questions

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Acute myocarditis most commonly results from a viral infection, with an age-standardized incidence of 40 per 100,000 subjects.[1] Common upper respiratory viruses, enteroviruses, human herpesvirus 4 and 6, parvovirus B19, and others can induce exaggerated inflammation in the heart, mainly in young men with a certain immune and genetic susceptibility.[1] Myocarditis as well as pericarditis may also rarely occur after vaccination, as observed with the large vaccination programs against influenza, hepatitis B, or smallpox, and more recently with the worldwide vaccination program against SARS-CoV-2.[2-5] In particular, messenger RNA (mRNA)-based technology vaccines (Moderna mRNA-1273 and less so Pfizer-BioNTech BNT162b2) may trigger self-limited and mild myocarditis in 1 to 5 in 100,000 vaccinated individuals. Still, the benefit-risk assessment for COVID-19 (mRNA) vaccination against COVID-19-related hospitalizations, intensive care unit admission, and death underscores a very strong favorable balance of vaccination for all age and sex groups—starting from adolescence—despite this minor risk.[6,7] COVID-19 vaccination also reduces the danger of myocardial injury (and myocarditis) or arrhythmias (reviewed in Rosano et al[8]).

Important questions about COVID-19 mRNA vaccination-related myocarditis remain. What is the real incidence of COVID-19 vaccination-related myocarditis? What are the immune mechanisms, in particular with mRNA vaccinations? Are specific vaccination schemes more predisposing? Why are mainly young men affected? Is it wise to give a (booster) vaccination in subjects with a history of myocarditis or vaccination-related myocarditis?

What is the real incidence of acute myocarditis following vaccination? The rapid reporting of myocarditis cases has instigated the preemptive medical surveillance. The control population may influence the relative increase of myocarditis. Studies using control historical data pre-COVID report a 5× increase of myocarditis in COVID-19-vaccinated individuals.[2,3] In contrast, studies in which common myocarditis is assessed in nonvaccinated individuals during the vaccination period report a 1.5× increase compared with nonvaccinated individuals.[5] Still, for patients receiving mRNA-1273, the adjusted HR among 12- to 39-year-olds was 5.24 (95% CI:

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ABBREVIATIONS AND ACRONYMS

mRNA = messenger RNA

2.47-11.12) and the absolute rate was 5.7 (95% CI: 3.3-9.3) per 100.000 vaccinated individuals within 28 days of vaccination.[4]

Finally, the minimal diagnostic criteria for myocarditis—a combination of symptoms, electrocardiographic changes, and cardiac "injury" biomarkers—might have resulted in an overestimation, whereas the lack of cardiac magnetic resonance in patients with troponin increase—performed in only 30%—may have resulted in a relative underestimation of myocarditis cases. Similarly, endomyocardial biopsies were performed in <5%, making the diagnosis of myocarditis in patients with myocardial injury less certain. Case reports of myocarditis more than 1 or 2 weeks after the booster vaccination are also less certain, as the vast majority of both viral and vaccination associated myocarditis occurs within the first week after viral infection or vaccination.

What are the mechanisms of COVID-19 (mRNA) vaccination-related myocarditis in young men? Until now, all studies only established a temporal relationship between vaccination and (peri)myocarditis, without a definite causality. Still, the increased risk of myocarditis after mRNA compared with non-RNA vaccines is a distinct observation. An mRNA immune reactivity may be underlying. Next, the antibodies against the SARS-CoV-2 spike glycoproteins encoded in the mRNA vaccines might cross-react with myocardial contractile proteins,[8] but a higher incidence of myocarditis would be expected with this. A multisystem inflammatory syndrome has been reported with the mRNA vaccines, indicating that this immune reaction involves a broader multiorgan involvement than only the heart. Last, but not least, mRNA vaccines—in particular mRNA-1273—cause a stronger—and more long-lasting—immune response, which may act as the final catalyst in immune and genetically susceptible young men. In line, the Moderna mRNA-1273 vaccine has at least 3× the mRNA contents as the Pfizer preparation, and is associated with at least 3× the risk of myocarditis.[5] The young male predominance both in viral and vaccination-related myocarditis suggests that hormonal factors may also be involved. Testosterone can inhibit anti-inflammatory immune cells and promote a more aggressive T helper 1 cell-type immune response. In contrast, estrogen has inhibitory effects on proinflammatory T cells, resulting in a decrease in cell-mediated immune responses.

Why mainly after the second vaccination? Why are only 20% of myocarditis cases observed after the first vaccination, with the remainder after the second? The predominance in the young age after the second vaccination may suggest that a stronger or distinct T (memory) cell-mediated immune response may be involved. What should we expect after the third and fourth boosters? Numbers do not report a further increase after the third vaccine booster. As viral or COVID-19 vaccination-related myocarditis only occurs in 40 of 100,000 individuals, with a reported 1.5× increase after mRNA vaccination, thousands of previous common myocarditis patients (or billions of vaccinated individuals) would be required to study the risk of recurrent (vaccination-related) myocarditis after COVID-19 booster vaccination. As recurrent viral myocarditis is rare, and most cases of recurrent (peri) myocarditis have an underlying (auto)immune mechanism different from the COVID-19 mRNA vaccination-related myocarditis, a significantly increased risk of myocarditis after the booster vaccination in previous myocarditis patients is not to be expected. While low incidence of booster-associated myocarditis to date is encouraging, until more data are available, no firm conclusions can be made at this time. Also, fewer people have received a third vaccine booster (29%), compared with the 65% of people in the United States who have received 2 vaccines.[9] Furthermore, the proportion receiving boosters was less likely to include younger adults, the most predisposed cohort subset to vaccine-associated myocarditis. Finally, as the risk of myocarditis is the highest with the mRNA COVID-19 vaccination, mRNA-1273 in particular, one might consider administration of non-mRNA vaccines as a booster in these patients with previous COVID-19 mRNA vaccine-related myocarditis. Real-life evidence for this suggestion for sure first requires prospective evaluation. Given the superior efficacy of mRNA—compared with non-mRNA—vaccines, one may consider a comparative trial with surrogate endpoints such as peak neutralizing antibodies.

What about mixing different vaccines, and the time interval between different doses? An interdose interval of <30 days has the highest rate of myocarditis in those individuals who received NBT162b2 followed by mRNA-1273, as revealed by the Ontario study in Canada (>19 million doses of mRNA vaccines).[4] A short interdose interval and a heterologous vaccine schedule with mRNA-1273 as the second vaccine, in addition to young age and male sex, therefore results in the highest absolute rate of myocarditis. The reported rate of myocarditis with mRNA-1273 given >2 months after the first dose is 3× lower compared with the short interdose interval (<30 days), indicating that booster vaccination given with a longer interval results in in a much lower risk of myocarditis. Elucidating the immune alterations at the cellular level that underlie these differences with varying

intervals between doses may help further understand how the mRNA vaccination may trigger myocarditis in susceptible young men. Besides considering non-mRNA vaccines in patients with previous mRNA vaccination-related myocarditis, one may also advise a longer interdose interval to decrease the risk of myocarditis. This approach should be subjected to rigorous replication, validation, and prospective clinical evaluation, as this opinion is now solely based on retrospective observations. Of importance, a longer interdose interval might also result in a higher protection against COVID-19 itself.[10,11]

Possible facts:

- The relative increased risk of mRNA-vaccination related myocarditis may be 1.5× higher than in nonvaccinated individuals.
- The absolute risk is 1 to 5 per 100,000 vaccinated individuals, making myocarditis a rare event.
- Vaccination-related myocarditis has a milder presentation, a higher recovery rate, and lower mortality compared with common pre-COVID myocarditis.
- As in common (pre-COVID) myocarditis, mainly young men are affected, suggesting that there are distinct hormonal and immune mechanisms involved.
- A dose interval of >2 months might blunt the increased risk of myocarditis with the mRNA vaccination, and might even reduce COVID-19 severity.

Call for additional evidence:

- What are the best diagnostic criteria for vaccine-related myocarditis?
- What are the reasons for the Moderna mRNA-1273 vaccine to have a higher risk of myocarditis compared with the Pfizer preparation? The mRNA content?
- What is the incidence of booster (third and fourth) associated myocarditis? In the young?
- A dose interval of >2 months might blunt the increased risk of myocarditis with the mRNA-1273 vaccination.
- Are non-mRNA vaccines as a booster in patients with previous mRNA vaccination-related myocarditis the best option?

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