Clinical Infectious Diseases

EDITORIAL COMMENTARY

Insights From a Murine Model of Coronavirus Disease 2019 (COVID-19) mRNA Vaccination-Induced Myopericarditis: Could Accidental Intravenous Vaccine Injection Induce Myopericarditis?

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(See the Major Article by Li et al on pages 1933–50.)

Keywords. myocarditis; pericarditis; SARS-CoV-2; COVID-19; vaccine.

According to the Johns Hopkins Coronavirus Resource Center, almost 212 million people have tested positive for coronavirus disease 2019 (COVID-19) worldwide. This has been associated with 4.4 million deaths as of August 2021. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is often accompanied by relatively high rates of myocarditis or pericarditis. Fortunately, almost 5 billion vaccine doses have been administered, but large percentages of the population have not been partially or fully vaccinated. Certain geographic areas, such as Africa, have low vaccine penetration. Since vaccination is the key to controlling COVID-19, it is crucial to understand potential complications of COVID-19 vaccination and the mechanisms by which they may occur.

As COVID-19 vaccinations have been administered to large populations, myocarditis and pericarditis have been identified as rare complications of mRNA vaccines produced by Pfizer and Moderna. The Vaccine Adverse Event Reporting System (VAERS) reported a rate of 0.41 cases per 100 000 vaccinations based on voluntary reporting of events [1]. The rate reported among active military was 1.9 cases per 100 000 vaccines [2]. A recent report from a large healthcare system used diagnosis codes to estimate a rate of 1.0 myocarditis cases and 1.9 pericarditis cases per 100 000 vaccinations [3]. A common finding among all reports is that the clinical course of vaccine-associated myocarditis and pericarditis generally resolves within days with treatment in most cases. It is rarely, if ever, associated with death. While rare and self-limited, many patients require hospitalization for management and to ensure no other cause for the clinical presentation. Furthermore, the presence of any, albeit rare, complication contributes to hesitancy toward vaccination in some populations. Therefore, identifying a model system that clarifies mechanisms that contribute to vaccine-associated myocarditis and pericarditis could improve vaccination rates and avoid these rare clinical presentations. For example, in a preprint, Nicolai et al [4] describe a murine model of an adenoviral vector vaccine for COVID-19 using the ChAdOx1 nCov-19 vaccine that has been linked to a rare thrombosis with thrombocytopenia syndrome. They demonstrate that intravenous injection of this vaccine leads to low platelet counts, clot formation, and platelet activating PF4-polyanion antibodies similar to thrombotic thrombocytopenia.

In this issue of *Clinical Infectious Diseases*, Can et al [5] have described an important and novel murine model of COVID-19 mRNA vaccination with features of myocarditis and pericarditis—that is, myopericarditis. This murine model has the potential to provide significant insights into the pathogenesis of myopericarditis after COVID-19 vaccination via intramuscular and intravenous routes. For example, the authors demonstrate in their paper that the inflammation in the myocardium after intravenous injection of the vaccine consists primarily of CD68+ macrophages or histiocytes, but not CD3+ T lymphocytes. In comparison, evaluation of tissue from 2 patients suspected to have post–COVID-19 mRNA vaccination–related myocarditis demonstrated T cells and macrophages, admixed with eosinophils, B cells, and plasma cells However, the myocarditis in those cases was only temporally associated with the vaccine [6]. Since it is not common to obtain tissue in post-vaccine myopericarditis and since causality can be

Received 23 August 2021; editorial decision 25 August 2021; published online 28 August 2021.

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Clinical Infectious Diseases® 2022;74(11):1951–2

https://doi.org/10.1093/cid/ciab741

challenging in isolated clinical cases, the histological information from the mouse model gives valuable insight into the mechanisms of post–vaccine-mediated inflammation. Notably, COVID-19–induced murine myocarditis is also associated with macrophage infiltration instead of the T-cell infiltration typically associated with viral myocarditis. Furthermore, the data presented document the patterns of cytokine induction that occur with COVID-19 vaccination in the mouse and the differences that occur over time with intramuscular compared with intravenous injection. This murine model will allow activation and inhibition of specific proteins in the inflammatory cascade using novel therapies or disruption of relevant genes through knockout strategies to determine the effect on myopericarditis.

It is important to note that future applications of the murine model system will likely require further investigation into how well this model represents the rare complication of myopericarditis following COVID-19 mRNA vaccination in humans. For example, it is often challenging to correlate the dose of a drug when adjusted to body weight between a small mouse and a much larger human. In this case, the mouse received 0.25 μg per gram weight. The Pfizer mRNA vaccine dose in humans is 0.4×10^{-3} μg per gram for a 70-kg person. Additional investigation will also be needed to determine the effect of murine strain in the model system of myopericarditis. This is particularly true since Balb/c mice, used in the study by Can et al, have a propensity to develop cardiac calcinosis [7]. Epicardial calcification was one of the outcomes observed in the vaccinated mice. Calcification of the pericardium is a finding typically observed in chronic, constrictive pericardial disease in humans.

One of the major conclusions by Can et al relates to differences in the severity of myopericarditis with intravenous injection compared with intramuscular injection of the vaccine. They demonstrated that intravenous injection of the COVID-19 mRNA vaccine increased the severity of vaccine-induced myopericarditis compared with intramuscular injection. Given the increased severity of myopericarditis following intravenous injection of the vaccine, the authors extend these observations to propose that the rare injection of a vaccine into a vein during planned intramuscular injection could contribute to the onset of myopericarditis. This is a relevant question since it is generally not recommended that a person administering the COVID-19 mRNA vaccine aspirate before injecting it into the deltoid muscle.

The concern about accidental intravenous injection during an intended intramuscular injection has been extensively studied [8]. Aspiration for a few seconds before injecting the intended drug is a way to avoid accidental intravenous injection. Most healthcare organizations conclude that the risk of any complication associated with the accidental intravenous injection is low since there have not been significant complications when the injection occurs without aspiration. Furthermore, it is often pointed out that there are not a plethora of vascular structures in the area of injection in the deltoid muscle. Most organizations, such as the Centers for Disease Control and Prevention and the World Health Organization, do not recommend aspiration before injection, citing increased pain as a primary reason.

Finally, the data described in the murine model of myopericarditis reinforce the safety of COVID-19 mRNA vaccination. Despite a small difference in weight after vaccination, they report that the mice maintained their healthy appearance and activity with intramuscular or intravenous injection. In addition, even with intravenous injection and the identification of inflammatory heart disease, there was no report of increased death in the mice during the study. Furthermore, with intramuscular and intravenous administration of the vaccine, the amount of the mRNA by reverse transcription–polymerase chain reaction in tissue falls precipitously within days of the injection. It is near baseline by 14 days. These findings support the concept that the severe risks of COVID-19, including the complications of myocarditis and pericarditis, are far greater than the small risk of myopericarditis after the COVID-19 vaccination.

Does accidental intravenous injection of the COVID-19 mRNA contribute to the rare incidence of myopericarditis? The data presented suggest that it is plausible and that it would be appropriate to consider further. However, the rare incidence of myopericarditis after vaccination will make it challenging to design a definitive study in humans.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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