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Mechanisms Are Emerging for COVID-19 Vaccine–Associated Myocarditis

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More than 5 years after the first shots pierced arms, researchers are discovering mechanisms that could help to explain the rare but well-known adverse effect of COVID-19 vaccine–associated myocarditis, a noninfectious form of heart muscle inflammation. A recent study describes immune factors elevated in the uncommon condition and offers a potential pathway to prevent or treat it.

Why This Matters

For every million doses of COVID-19 mRNA vaccine administered, about 30 people will develop myocarditis after the first or, more commonly, second dose, according to the authors whose findings were published in *Science Translational Medicine* in December. For reasons that aren't fully understood, the incidence is higher in males, particularly those younger than 30 years, in whom about 60 cases per million doses occur. Although the condition usually resolves with time, it can on occasion be more serious. And beyond COVID-19, understanding the drivers of mRNA vaccine–associated myocarditis will be increasingly important as mRNA technology expands to other infectious diseases and cancer treatment.

Multimedia

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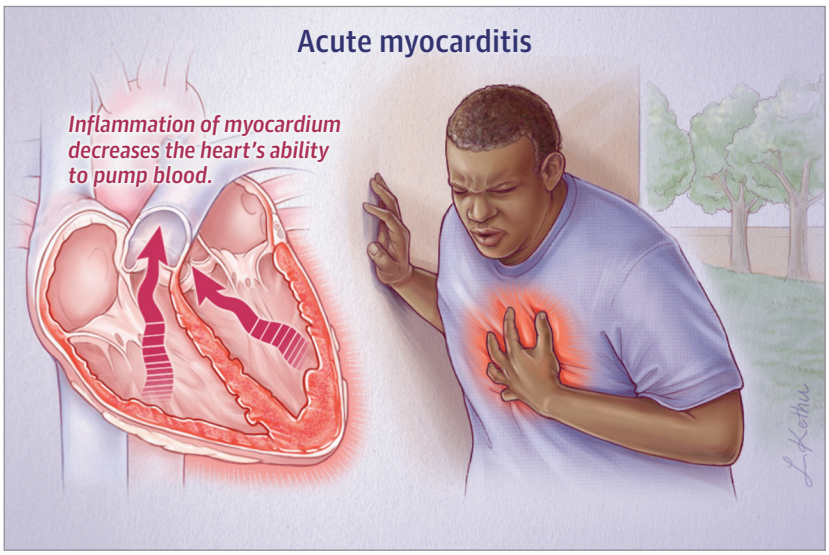
The Background

Physician-scientist Joseph C. Wu, MD, PhD, the study's senior author and director of the Stanford Cardiovascular Institute, said he decided to investigate the complication after noticing how frequently his patients with cardiac conditions asked him if the COVID-19 vaccine was safe. He realized that he could do more than just discuss with them the rarity of the adverse effect and the benefits of vaccination. His laboratory was well poised to study the phenomenon: his team had the platforms and the technical expertise to generate heart muscle cells and tiny beating cell clusters called cardiac spheroids, both of which they could use to model the organ's response to vaccination.



The Methods

The researchers focused their investigation on the role of cytokines, proteins produced in the body that affect the immune system and are elevated in blood samples of patients with COVID-19 mRNA vaccine–associated myocarditis. First, they reanalyzed human plasma from 2 studies: a time-course study that measured cytokine levels in healthy people after they had received a COVID-19 vaccine and a comparative study of cytokines in people with vaccine-associated myocarditis and a group of vaccinated control subjects. For their experiments, they established a mouse model of mRNA vaccination using a vaccine dose higher than the human equivalent in order to reliably produce cardiac injury. And they used human-induced pluripotent stem cells (iPSCs) to generate 3 types of cells—endothelial cells, white blood cells called macrophages, and heart muscle cells called cardiomyocytes—and 3-dimensional cardiac spheroids made up of them.

"iPSC-derived cardiomyocytes are powerful tools to model disease in humans and quite mature as a technology," Melanie Ott, MD, PhD, director of the Gladstone Infectious Disease Institute, who was not involved with the study, explained in an email.

Based on the greater incidence of vaccine-associated myocarditis in males, as well as estrogen's established cardioprotective properties, the researchers also evaluated whether estradiol or a weak plant-based estrogen called genistein could lessen cytokine-induced myocardial injury.

The Findings

Of the 27 cytokines detected in both of the human plasma analyses, the researchers winnowed their investigations to a particular pair: CXCL10 and IFN-γ. These were the 2 cytokines most elevated in the days immediately after vaccination in the time-course study, and levels of both were higher in the myocarditis group than the control group in the comparative study. In in vitro experiments, exposing macrophages to the vaccines increased levels of these cytokines.

When the researchers treated cardiomyocytes to a cocktail of the cytokines at a concentration representing peak amounts in patients with myocarditis, they observed impaired contractility, an increase in arrhythmia-like events, and an upregulation of inflammatory genes. Conversely, neutralizing the cytokines lessened vaccine-induced cardiac injury in mice and markers of cardiac stress in spheroids.

Finally, oral genistein given a week before the second shot of the vaccine blunted the surge of these cytokines and

the resulting myocardial injury in young male mice, without reducing titers of vaccine-induced antibodies.

The authors concluded that their work "implicates the CXCL10–IFN-γ axis as a key mediator of myocardial injury in multiple preclinical models of mRNA vaccination and proposes a potential strategy to mitigate this adverse effect."

The Limitations

Vassilios Vassiliou, MBBS, PhD, MA, a clinical professor of cardiac medicine and consultant cardiologist at the University of East Anglia in Norwich, UK, who also was not involved with the project, called the report "a strong, thoughtfully constructed mechanistic paper that tackles a clinically important but difficult problem."

The researchers acknowledged several limitations, however, including an imperfect mouse model and a focus on cytokines that could have missed other mechanisms.

Vassiliou said that although the experimental models "do not fully recapitulate" clinical myocarditis in humans, "the authors show convincing evidence for the involvement, at least partially, of CXCL10 and IFN-γ."

"These are familiar suspects in different disease settings that include inflammation and are therefore plausible," added Ott, who is a professor of medicine at the University of California, San Francisco. "The question remains what is the causative agent that sets this amplification loop into motion and why are only certain people susceptible."

Ott also said she would have liked the inclusion of a non–mRNA COVID-19 vaccine as a control group or a non–COVID-19 mRNA vaccine "to see what mediates the inflammatory phenotype: spike, the vector, the dosage of the antigen…."

The Estrogen Factor

Estrogen can be protective against cardiovascular events, Vassiliou noted, so it's natural to speculate that the female hormone could influence why fewer women than men experience vaccine-induced myocarditis. The study wasn't designed to test this idea directly, but the genistein findings do suggest it, Wu said.

Ott called this aspect of the study "tantalizing" and said it provides a clue to the sex difference in vaccine-associated myocarditis, as well as a path to possible prevention or treatment. "A more formal investigation of female hormones over other causes of sex differences including X chromosome–encoded cytokines should follow," she said.

The Clinical and Research Implications

Vassiliou coauthored a recent European Society of Cardiology clinical consensus statement on cardiovascular disease and COVID-19, including vaccination. He said the new study offers proof-of-concept evidence that therapeutics like genistein could modulate the pathway underlying vaccine-associated myocardial injury. A critical next step, he noted, will be prospective human studies that systematically characterize cytokines around the time of vaccination and assess whether genistein can calm these inflammatory responses and protect against vaccine-associated myocarditis without immunological tradeoffs.

Wu cautioned that the incidence of myocarditis after vaccination is too low to widely recommend genistein for prevention: "We're not advocating giving genistein to everybody," he said. He does, however, think the plant compound could have broad applications for inflammatory conditions if its potency can be increased, something his laboratory is working on.

Wu also said he thinks vaccine-makers could test next-generation COVID-19 mRNA vaccines in human iPSC-derived platforms to find the safest formulation. But for now, he emphasized that his study should not be interpreted to mean that COVID-19 vaccination is unsafe. "That's the wrong message," he said. "It very, very rarely causes myocarditis." ■

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Conflict of Interest Disclosures: Dr Ott reported being a cofounder of DirectBio Inc and serving on the scientific advisory board for InvisiShield Technologies Ltd. Dr Vassiliou reported receiving speaker fees from Daiichi-Sankyo and Novartis and a grant for investigator-initiated research from B Braun Ltd. Dr Wu reported being cofounder of Greenstone Biosciences and receiving funding support from the National Institutes of Health, the Department of Energy, the American Heart Association, and the California Institute for Regenerative Medicine.

Note: Source references are available through embedded hyperlinks in the article text online.