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Invited Commentary

COVID-19, COVID-19 Vaccinations, and Subsequent Abnormalities in the Retina: Causation or Coincidence?

Lee M. Jampol, MD; Robert Tauscher, MD; Hans Peter Schwarz, MD

Pichi and colleagues¹ in this issue of *JAMA Ophthalmology* describe ocular adverse events after Sinopharm COVID-19 vaccination, including 4 retinal events. Little is known about this vaccine.² Despite the large number of doses of vaccine having been administered worldwide, its adverse systemic events remain uncertain. We will review the evidence regarding associations of COVID-19 infection or COVID-19 vaccination with subsequent ocular adverse events, in particular retinal problems, to consider whether these abnormalities are causally associated or just coincidental. COVID-19 infection causes widespread damage to multiple organs. Proinflammatory cytokines are released and are strong inducers of a procoagulant/prothrombotic reaction,³ resulting in intravascular coagulopathies and endothelial injury. In regard to the retina, COVID-19 infection can be associated with anemia, hypertension or hypotension, hypoxia, and other systemic morbidities, which can contribute to retinal findings such as nerve fiber layer infarcts, hemorrhages, or microaneurysms. Vasculitis and thromboembolism also can contribute to retinal ischemia. Thus, we are not surprised to see reports of retinal hemorrhages, dilated and tortuous retinal veins, central retinal vein occlusion, central retinal artery occlusion, acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy, acute retinal necrosis, endophthalmitis, optic neuritis, and others. These may not be due to the virus, but due to the systemic complications that this virus can cause. In the hundreds of millions of cases of COVID-19 infection seen worldwide, findings supporting direct retinal damage (other than vascular damage) from the virus have not been described. Retinal macro- and microvascular damage⁴ seen in patients with COVID-19 could be related to systemic thromboembolism, other systemic morbidities, or to the effect of the virus on retinal vessels. COVID-19 infection is also associated with a

massive dysregulation of the humoral immune system characterized by the appearance of potent autoantibodies reacting against a wide range of soluble and tissue-specific proteins, which also might contribute to ocular disease.

What about COVID-19 vaccination and the retina? There have been anecdotal cases of adverse retinal ischemic events presented at conferences and undoubtedly awaiting publication. For example, we recently saw a middle-aged woman with diabetes and hypertension with a remote branch retinal artery occlusion in the left eye. Optical coherence tomography on the right showed AMN. Two weeks prior, she had received a Johnson & Johnson COVID-19 vaccination. Is the AMN from the vaccination or related to her systemic vasculopathy? When rare retinal findings (eg, AMN) are noted in association with a more common event (in this case COVID-19 vaccination), the findings may be unrelated. However, there are situations where one can suspect the associations have a real cause-and-effect relationship. Post-adenovirus vector vaccination (Johnson & Johnson, AstraZeneca), patients can have potentially life-threatening cerebral venous sinus thrombosis (CVST).⁵ These patients often have thrombocytopenia, which is very rarely associated with thrombosis. While CVST and thrombocytopenia after COVID-19 vaccination are extremely rare, it is much more common than in the general population. In these patients with CVST, the presence of platelet-activating autoantibodies against platelet factor 4 causes multicellular activation of coagulation. It mimics autoimmune heparin-induced thrombocytopenia. This syndrome is now called vaccine-induced immune thrombotic thrombocytopenia. It usually occurs within the first 3 weeks following vaccination, mostly in younger women. Antiplatelet factor 4 antibodies are pathognomonic for vaccine-induced immune thrombotic thrombocytopenia. As of April 4, 2021, 169 cases of CVST were reported in 34 million individuals vaccinated with AstraZeneca in the European Union and UK, corresponding to a reporting rate of 5 cases per million vac-



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nated adults.⁶ As of April 12, 2021, 6 cases of CVST with thrombocytopenia were reported after 6.86 million Johnson & Johnson doses, corresponding to a reporting rate of 0.87 cases per million doses.⁷ A causal relationship with vector-based vaccination thus is considered plausible by regulatory agencies. In contrast to vector-based vaccines, CVST with thrombocytopenia has not occurred after 183 million messenger RNA (mRNA) COVID-19 vaccine doses administered.

As reviewers for journals and participants in conferences, we are seeing patients presenting who have had COVID-19 vaccination with possible secondary retinal findings (eg, AMN or paracentral acute middle maculopathy). Vaccines have different mechanisms of inducing immunity and different adverse event profiles. COVID-19 vaccines differ in terms of genetic construct (mRNA vs DNA) or vector virus (human replication-incompetent adenovirus [Ad26.COV2S] for Johnson & Johnson vs chimpanzee replication incompetent adenovirus [ChAdOx1] for AstraZeneca). With the adenovirus vector vaccines, DNA encoding the spike protein is delivered and the immune system generates antibodies to this protein. With the Pfizer and Moderna vaccines, the mRNA for the spike protein is encapsulated in liposomes and endocytosed into the muscle cell. The mRNA is translated into S protein in the host cell cytosol. This protein is then expressed on the cell surface where it induces an immune response. In contrast to all other vaccines, the coding sequence SARS-CoV-2 S immunogen in the AstraZeneca vaccine has not been modified to stabilize and to mitigate shedding of the expressed S protein.⁸ Thus, it is possible that expressed S protein in the circulation after AstraZeneca vaccination can induce a proinflammatory/procoagulant response or direct disturbance of endothelial cell integrity.

More than 1.5 billion doses of COVID-19 vaccinations have been administered worldwide and likely will save hundreds

of thousands if not millions of lives. How does one determine if retinal abnormalities are related to the vaccination when they appear soon after inoculation? These various events (eg, AMN) are seen occasionally in unvaccinated patients; is the vaccine causative or coincidental? If these cases are submitted to a journal, should such articles be published? Should a reader accept that the findings are causally related to COVID-19 vaccination? The establishment of a causal relationship between the vaccine and an observed pathology will remain challenging and should be guided by the scientific/medical principles of assessing whether the observation is definitely, probably, possibly, unlikely, or not related.

Since vaccinations do not involve intact virus, the mechanism of ocular disease would be immunologic response to the spike antigen, other viral antigens, or to components of chimpanzee or human adenovirus. Molecular mimicry (the structural similarities of SARS-CoV-2 or human or chimpanzee adenovirus components) and self-antigens could contribute to the pathogenesis of any retinal pathologies.

Surveillance for adverse events following vaccinations is required in clinical trials and common adverse events are detected. When a much larger number of vaccinations are done it is very difficult to rule out coincidence for rare events. If unique aspects (eg, age, sex, systemic findings, eye findings, and other morbidities) of the adverse events are noted, then causation should be suspected. If the pathophysiology of the vaccine response fits with the pathology, causation can be suspected. Could the adenovirus vaccines, which can cause thrombosis, vasculitis, and morbidities, cause ocular adverse events or are the events coincidental? Are the events described by Pichi et al¹ with an inactivated viral vaccine coincidental or associated with the vaccine? They are one piece of evidence that now should await confirmation or refutation.

ARTICLE INFORMATION

Author Affiliations: Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Jampol, Tauscher); Department of Medicine, University of Vienna, Vienna, Austria (Schwarz).

Corresponding Author: Lee M. Jampol, MD, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, 645 N Michigan Ave, Ste 440, Chicago, IL 60611 (l-jampol@northwestern.edu).

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