Ischemic and Inflammatory Ocular Adverse Events Following Different Types of Vaccination for COVID-19, and Their Incidence Analysis

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ABSTRACT

Background: To evaluate the ocular adverse event (OAE) and the incidence rate that can occur after coronavirus disease-2019 (COVID-19) vaccination.

Methods: Patients who visited with an ophthalmologic diagnosis within a month of COVID-19 vaccination were retrospectively analyzed. OAEs were categorized as ischemia and inflammation by their presumed pathogenesis, and were compared by types of vaccine: messenger ribonucleic acid (mRNA) and viral vector vaccine. The crude incidence rate was calculated using data from the Korea Disease Control and Prevention Agency.

Results: Twenty-four patients with OAEs after COVID-19 vaccination were reviewed: 10 patients after mRNA and 14 after viral vector vaccine. Retinal vein occlusion (9 patients) and paralytic strabismus (4 patients) were the leading diagnoses. Ischemic OAE was likely to occur after viral vector vaccines, while inflammatory OAE was closely related to mRNA vaccine (p=0.017). The overall incidence rate of OAE was 5.8 cases per million doses: 11.5 per million doses in viral vector vaccine and 3.4 per million doses in mRNA vaccine.

Conclusion: OAEs can be observed shortly after the COVID-19 vaccination, and their category was different based on the types of vaccine. The information and incidence of OAE based on the type of vaccine can help monitor patients who were administered the COVID-19 vaccine.

Keywords: Coronavirus; Messenger ribonucleic acid vaccine; Ocular adverse event; Viral vector vaccine

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has led to huge changes for humanity, not only medically, but also economically, socially, and politically. To overcome this catastrophe, vaccines for the disease have been developed and used globally in enormous amounts. Currently, there are four types of COVID-19 vaccine: messenger ribonucleic acid (mRNA) vaccines (BNT162b2, Pfizer-BioNTech [1] ; mRNA-1273, Moderna [2]), protein subunit vaccines (NVXCoV2373, Novavax [3]), viral vector vaccines (Ad26.COV2, Janssen Johnson & Johnson [4] ; ChAdOx1 nCoV-19/AZD1222, Oxford-AstraZeneca [5]), and whole virus vaccines (PiCoVacc, Sinovac19 [6] ; BBIBP-CorV, Sinopharm [7]). Among these, mRNA and viral vector vaccines are predominantly utilized globally.

The typical vaccine development timeline lasts 5 to 10 years, and sometimes longer, to assess whether the vaccine is safe and efficacious in clinical trials. Vaccines for COVID-19, however, were developed and distributed in 1–2 years under emergency use authorization, considering the global threat of the disease. Therefore, concerns about the safety of the vaccine have always been an issue. The occurrence of myocarditis or thrombosis with thrombocytopenia syndrome in relation to COVID-19 vaccine has been reported [8, 9]. Questions about the possibility of ocular adverse event (OAE) with COVID-19 vaccination were also raised. Facial nerve palsy/Bell's palsy, abducens nerve palsy, acute macular neuroretinopathy, superior ophthalmic vein thrombosis, corneal graft rejection, uveitis, central serous chorioretinopathy, Vogt–Koyanagi–Harada reactivation, and onset of Graves' disease were reported to be related to COVID-19 vaccination [10]. Although these events can occur temporally related to the COVID-19 vaccination, neither the causality nor the types of OAE based on the category of vaccination were not elucidated yet.

(blinded) province is one of the eight provinces of South Korea, with a population of approximately 1,600,000 people. There is a single tertiary medical center within the province. Analyzing patients who presented with ocular discomfort at the sole tertiary medical center of the province, possible OAE following COVID-19 vaccination, and their crude occurrence rate after COVID-19 vaccination could be estimated.

MATERIALS AND METHODS

In this retrospective observational study, we reviewed patients who visited the Ophthalmology Department of University Hospital due to the development of any ocular symptoms after COVID-19 vaccination from March 2021 to May 2022. The present study protocol was reviewed and approved by the Institutional Review Board

Institutional Review Board of University Hospital (approval No. 2021-11-008) and adhered to the tenets of the Declaration of Helsinki. The need to obtain informed consent from the participants was waived because of the retrospective nature of this study.

The participants visited the hospital via the emergency room or outpatient clinic after referral by a local ophthalmology clinic with ocular symptoms after COVID-19 vaccination. We only included participants complaining of ocular symptoms with onset less than one month after vaccination. Demographic features of the included participants, such as age, sex, and medical history including hypertension (HTN) or diabetes mellitus (DM), were collected. The type, dose of vaccine, and symptom onset were assessed and documented. If there were systemic symptoms including headache, fever and/or general weakness were present, the information was also collected. Based on their manufacturing, vaccines were categorized into mRNA vaccine and viral vector vaccine.

The participants underwent thorough ophthalmologic examinations, including extraocular muscle movement examination, manifest refraction, slit lamp examination, fundus photography, and visual field testing. The prism alternate cover test was performed when the patient had double vision. If there was an overt ophthalmologic disorder, a diagnosis was made, and the participant was classified as having OAE. OAEs were classified into two categories based on their pathogenesis: ischemia and inflammation. Retinal vein occlusion, anterior ischemic optic neuropathy and paralytic strabismus were considered as ischemia, while uveitis, scleritis, keratitis, optic neuritis and uveal effusion were considered as inflammation. The patients were then treated based on their ocular diagnoses.

Data on the total cumulative dose of each vaccine in (blinded) Province were acquired from the Korea Disease Control and Prevention Agency (KDCPA). The crude incidence rate (event per dose) of ocular symptom occurrence and ocular adverse event occurrence after COVID-19 vaccination was estimated, assuming that the population of (blinded) province adhered to the healthcare delivery system.

All statistical analyses were performed using Statistical package for the social sciences (SPSS) version 21.0 (SPSS Inc, Chicago, IL, USA) was used. Chi-square analysis was used to compare the sex, presence of medical history, systemic symptom, and type of OAE between mRNA and viral vector vaccines. Student t-test was used to compare age, dose, and symptom onset. The weighted t-test was used to compare the crude incidence rate between the viral vector vaccines and the mRNA vaccines. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 24 patients were reviewed for OAE after COVID-19 vaccination (Table 1). The mean age was 57.4 ±

17.2 years and 10 patients (41.7%) had medical history of conditions such as DM or HTN. Specifically, within our study participants, 2 patients were identified with DM, 6 with HTN, and 2 with both DM and HTN. Among these, one individual with DM was undergoing hemodialysis due to end-stage renal failure. None of the patients had a prior diagnosis of malignancy or hematologic disorders. There was a case of anterior uveitis in a patient previously diagnosed with Behçet's disease, though this patient had never before experienced any form of uveitis. No other patients in our study exhibited signs of autoimmune disorders.

Patients reported ocular symptoms an average of 6.8 ± 4.9 days post-vaccination. All of 24 OAE cases represented their first diagnosis; there were no recurrent cases, including uveitis, uveal effusion, and RVO. Ocular symptoms mostly occurred after the first vaccine dose (58.3%), followed by the second (33.3%) and the third doses (8.4%). The most frequent OAE was retinal vein occlusion (RVO), followed by paralytic strabismus. Anterior uveitis, scleritis, keratitis, and optic neuritis were also noted after vaccination. Half of the patients reported experiencing systemic symptoms, including general weakness, fever, myalgia, and headache, before the occurrence of OAE.

During the study period, a total of 4,151,640 doses of COVID-19 vaccines were administered in (blinded) province, Korea, consisting of 2,931,793 mRNA vaccine doses and 1,219,847 viral vector vaccine doses. During this time, 24 cases of OAEs were identified. Therefore, under the assumption that the population of (blinded) province adheres to the healthcare delivery system, it is estimated that OAEs might occur at a rate of approximately 5.8 cases per million vaccine doses.

The study participants were further analyzed based on the type of vaccine they received. No significant differences were found between the vaccine groups (mRNA and viral vector) regarding factors such as sex, age, underlying conditions, symptom onset, vaccine dose, and presence of systemic symptoms (Table 2). However, it was observed that OAEs associated with inflammation predominantly occurred with mRNA vaccines, whereas OAEs related to ischemia were primarily seen after administration of viral vector vaccines (Table 2 and Fig. 1) (p=0.017). Moreover, OAEs were more frequently observed after viral vector vaccines (11.5 per million doses) than after mRNA vaccines (3.4 per million doses) (p = 0.013).

DISCUSSION

In this study, we revealed that OAEs including RVO, uveitis and paralytic strabismus can occur within a week after the COVID-19 vaccination. Viral vector vaccines were associated with ischemic events, whereas mRNA

vaccines were frequently linked to inflammatory events. Nevertheless, the causative role of the COVID-19 vaccine in triggering OAEs cannot be confirmed through this study. Hence, there is no definitive evidence to recommend avoiding COVID-19 vaccination due to potential ophthalmologic complications. Since the observed ocular diagnoses were not conclusively associated with the COVID-19 vaccine, we chose to use the term "adverse event" instead of "complication" throughout this manuscript. Reports about the occurrence of ocular adverse event after COVID-19 vaccination, albeit rare, are present [10, 11]. However, despite its possible relationship, there is currently no substantive evidence to counterweigh the overwhelming benefits of COVID-19 immunization [12].

The association between COVID-19 vaccines and thrombotic side-effects, including vaccine induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) were suggested after global mass vaccination began [13-15]. Such potentially fatal conditions have been prominently associated with the viral vector vaccine [16]. Retinal hemorrhages and retinal vascular occlusions, as ocular adverse events, have also been reported in the aftermath of COVID-19 vaccination [17-19]. Parul et al. postulated that retinal hemorrhages, vascular occlusions, and angle-closure glaucoma were most frequently reported with the AZD 1222 vaccine, as deduced from their review of 48 literatures on ocular adverse events associated with COVID-19 vaccination [17]. Consistent with these findings, our study has also revealed a significant association between ischemic OAEs and viral vector vaccines.

Regarding the pathogenesis of thromboembolic events, the proposed mechanism involves the formation of reactive anti-Platelet Factor 4 (PF4) antibodies, leading to excessive platelet activation, aggregation, and consumption [14]. This process resembles heparin-induced thrombocytopenia, albeit without exposure to heparin itself [14]. The formation of antibodies that recognize the multimolecular complex between PF4 and heparin can induce monocyte and platelet activation, thereby heightening thrombogenicity through the release of selectin P and E, von Willebrand factor, interleukin 6, and thrombin [20-22]. This results in thrombocytopenia due to platelet consumption and increased thrombogenicity. The detection of anti-PF4 antibodies in 67% of individuals vaccinated with the first dose of the AstraZeneca/Oxford vaccine supports the possibility that thromboembolic events may occur following the administration of viral vector vaccines [23]. Furthermore, the adenoviral epitopes utilized in vaccines exhibit a strong affinity for PF4, mimicking the effect of heparin [24]. This allows PF4 tetramers to cluster and form immune complexes through electrostatic interaction, resulting in massive FcγRIIa (also known as CD32a) dependent platelet activation [24]. This evidence may explain why viral vector vaccines could be associated with ischemic events following COVID-19 vaccination.

Meanwhile, an inflammatory adverse event following COVID-19 vaccination was also suggested. Occurrence

of myocarditis characterized by mixed inflammatory infiltrate of macrophage, lymphocytes and eosinophils [25, 26], and hyper inflammatory syndrome [27] was observed after administrating mRNA vaccines. Possible temporal association between noninfectious uveitis and COVID-19 vaccination, especially mRNA vaccines, were reported as ocular adverse events [28-30]. The attributable risk of BNT195b2 for uveitis were 11.2 cases per million doses in the first dose, and 8.6 cases per million doses in the second dose [29]. We also found that the inflammatory OAEs are significantly related to the mRNA vaccines in the current study.

It is assumed that the causative factor resulting uveitis after COVID-19 vaccination is a viral mNRA-induced immune response [31]. A single-strand mRNA of mRNA vaccines can activate endosomal toll-like receptors (TLR), including TLR3 and TLR7 upon entry into a cell [32]. Subsequently activated inflammasome in the cytosol, an inflammatory response is triggered by generation of type 1 interferons [33]. This surge in type 1 interferons could potentially drive an autoimmune manifestation in individuals with a pre-existing history of autoimmunity, or those with an as-yet-undiscovered susceptibility to developing one.

It may not be feasible to consider the pathogenesis of inflammatory and ischemic events as entirely independent, given that immune complex formation can result in vascular obstruction and subsequent ischemic conditions [34, 35]. The double-stranded DNA inside the viral vector, as well as the single-stranded RNA within mRNA vaccine, also encodes the spike protein antigen and induces the production of type 1 interferons via activation through TLR9 [32]. This can explain why the both inflammatory and ischemic OAEs can be associated after the COVID-19 vaccination, regardless of the types of vaccine. Nevertheless, concerns about an increased risk of thrombosis seem to be more connected with viral vector vaccines, while inflammatory events have been reported more frequently with mRNA vaccines [36, 37]. It is notable that this study revealed that 41.7% with OAEs had a medical history of hypertension or diabetes mellitus. Patients with hypertension or diabetes mellitus had damaged retinal endothelium and pericytes, as proven by experimental research [38]. This damage could potentially facilitate the accumulation of immune complex-associated cytokines around microvessels, thereby enhancing vasculitis. Furthermore, vascular obstruction and ischemia may also be more readily manifested in damaged endothelium.

In this study, we estimated the incidence of OAEs, assuming that the population of (blinded) province uniformly engages with the healthcare delivery system. The overall incidence rate was found to be 5.8 cases per million doses, which was comparable to the other studies using a large database with reporting system (8.9 cases and 11.2 cases per million doses) [29, 30]. However, our incidence result appears lower than these reports, possibly due to the presence of individuals who are not captured within the healthcare delivery system [29, 30]. The incidence rate of uveitis in our study was 0.40 cases per million doses, which is similar to previous reports showing 0.57, 0.44, and

0.35 cases per million doses for BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines respectively [28].

The primary concern in investigating OAE following vaccination is determining whether these ocular abnormalities are attributable to the vaccination. Due to the lack of control group data in our study, we cannot conclusively state whether COVID-19 vaccination increases the incidence of OAEs compared to the general population. A particular issue arises with diabetic and/or hypertensive patients, who are inherently at risk for conditions such as paralytic strabismus or RVO, thus complicating the direct linkage of such OAEs to vaccination. The incidence rates of paralytic strabismus and RVO in our study were significantly lower than those reported in studies of the general population [39, 40], because our research exclusively included patients with a recent history of COVID-19 vaccination. Consequently, our focus shifted towards the different pathogenesis categories of developed OAEs, in light of various reports suggesting a potential relationship between mRNA vaccines and unexpected inflammatory responses [25-27, 41].

Considering the difference in incidence between vaccine types, it is not prudent to assert that viral vector vaccines are more associated with OAEs than mRNA vaccines based solely on the current data. The total number of mRNA vaccine doses administered was over twice that of viral vector vaccines; hence, a small difference in cases could be disproportionately amplified. There are reports suggesting that viral vector vaccines are associated with systemic side effects, such as lymphadenopathy, fever, and chills, while mRNA vaccines are often linked with local side effects like injection site redness and pain [42]. However, the observed difference in incidence between mRNA vaccines and viral vector vaccines warrants further investigation.

Recent evidence showing no significant increase in corneal graft rejection and RVO post-COVID-19 vaccination strengthens the argument for the continued use of COVID-19 vaccines, highlighting their benefits against the minimal risk of OAEs [43, 44]. The risk profile of COVID-19 vaccines is not considered significantly different from that of other well-established vaccines, reinforcing their safety in the context of ocular health [43]. Nevertheless, our study, alongside these findings, introduces important considerations concerning the detection of suspicious OAEs post-vaccination, as reported in our study and earlier publications [10-12, 19, 30]. This indicates a need for ongoing vigilance and research to understand the mechanisms behind these rare events and identify potentially at-risk populations. Furthermore, the reliance on electronic health record data and population-based studies may overlook granular clinical details and individual patient experiences, which are crucial for a comprehensive understanding of OAEs. This gap underscores the importance of case reports and smaller, detailed studies alongside large-scale analyses to capture the full spectrum of vaccine-related adverse effects.

This study has several important limitations. Foremost, it is not possible to definitively establish a causal

relationship between COVID-19 vaccination and the observed ocular adverse events. Adverse effects can occur sporadically due to a variety of risk factors unrelated to the vaccine. Although we only included patients who reported symptoms within a month of vaccination to exclude temporally unrelated adverse events, a direct link to the vaccine could not be proven. Supportive laboratory data, such as serum anti-PF4 antibody or type 1 interferon levels, could strengthen the suggestion of vaccination-associated pathogenesis. Second, our study only included subjects who experienced ocular discomfort severe enough to prompt a clinic visit. Consequently, other ocular events that did not cause significant visual symptoms may have been overlooked. Third, we calculated the incidence rate of OAE based on the assumption that patients in the province follow the healthcare delivery system. In South Korea, all citizens are covered by mandatory national public health insurance, increasing the likelihood that patients experiencing OAE would be referred to the single tertiary hospital in the province. The estimated incidence rate in our study is comparable to previous investigations utilizing large databases drawn from national health records reporting systems [29, 30]. Nevertheless, some individuals may choose to bypass the local system and seek treatment in a different province. Thus, a population-based study using national health insurance records could provide a more accurate assessment of the nationwide incidence rate.

In conclusion, ocular adverse events, including retinal vein occlusion and paralytic strabismus, may be observed following COVID-19 vaccination, with an incidence of 5.8 cases per million doses. Among these events, the development of ischemic OAEs such as retinal vein occlusion or paralytic strabismus appears to be closely associated with viral vector vaccines, while the development of inflammatory OAEs such as uveitis, scleritis, and optic neuritis seems to be more likely with mRNA vaccines. Our study suggests that viral vector vaccines may result in more OAEs than mRNA vaccines, though further investigations involving larger cohorts are necessary to substantiate this observation.

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Conflicts of interest:

The authors report there are no competing interests to declare.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603-15.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403-16.
3. Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med* 2021;385:1172-83.
4. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021;384:2187-201.
5. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99-111.
6. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science* 2020;369:77-81.
7. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis* 2021;21:39-51.
8. Salah HM, Mehta JL. COVID-19 Vaccine and myocarditis. *Am J Cardiol* 2021;157:146-8.
9. Hafeez MU, Ikram M, Shafiq Z, et al. COVID-19 Vaccine-associated thrombosis with thrombocytopenia syndrome (TTS): A systematic review and post hoc analysis. *Clin Appl Thromb Hemost* 2021;27:10760296211048815.
10. Ng XL, Betzler BK, Testi I, et al. Ocular adverse events after COVID-19 vaccination. *Ocul Immunol Inflamm* 2021;1-9.
11. Eleiwa TK, Gaier ED, Haseeb A, et al. Adverse ocular events following COVID-19 vaccination. *Inflamm Res* 2021;70:1005-9.
12. Wang MTM, Niederer RL, McGhee CNJ, Danesh-Meyer HV. COVID-19 vaccination and the eye. *Am J Ophthalmol* 2022;240:79-98.
13. Suresh P, Petchey W. ChAdOx1 nCOV-19 vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis (CVST). *BMJ Case Rep* 2021;428:117607.
14. Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J*

Med 2021;384:2254-6.

15. Palaiodimou L, Stefanou MI, Katsanos AH, et al. Cerebral venous sinus thrombosis and thrombotic events after vector-based COVID-19 Vaccines: A systematic review and meta-analysis. *Neurology* 2021;97:2136-47.
16. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, et al. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. *J Neurol Sci* 2021;428:117607.
17. Ichhpujani P, Parmar UPS, Duggal S, Kumar S. COVID-19 vaccine-associated ocular adverse effects: An overview. *Vaccines (Basel)* 2022;10:1879.
18. Choi M, Seo MH, Choi KE, et al. Vision-threatening ocular adverse events after vaccination against coronavirus disease 2019. *J Clin Med* 2022;11:3318.
19. Park HS, Byun Y, Byeon SH, et al. Retinal hemorrhage after SARS-CoV-2 vaccination. *J Clin Med* 2021;10:5705.
20. von Hundelshausen P, Lorenz R, Siess W, Weber C. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Targeting pathomechanisms with bruton tyrosine kinase inhibitors. *Thromb Haemost* 2021;121:1395-9.
21. Althaus K, Marini I, Zlamal J, et al. Antibody-induced procoagulant platelets in severe COVID-19 infection. *Blood* 2021;137:1061-71.
22. Datta P, Zhang F, Dordick JS, Linhardt RJ. Platelet factor 4 polyanion immune complexes: Heparin induced thrombocytopenia and vaccine-induced immune thrombotic thrombocytopenia. *Thromb J* 2021;19:66.
23. Terpos E, Politou M, Ntanasis-Stathopoulos I, et al. High prevalence of Anti-PF4 antibodies following ChAdOx1 nCov-19 (AZD1222) vaccination even in the absence of thrombotic events. *Vaccines (Basel)* 2021;9:712.
24. Huynh A, Kelton JG, Arnold DM, et al. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature* 2021;596:565-9.
25. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation* 2021;144:471-84.
26. Choi S, Lee S, Seo JW, et al. Myocarditis-induced sudden death after BNT162b2 mRNA COVID-19 vaccination in korea: case report focusing on histopathological findings. *J Korean Med Sci* 2021;36:e286.

27. Ouldali N, Bagheri H, Salvo F, et al. Hyper inflammatory syndrome following COVID-19 mRNA vaccine in children: A national post-authorization pharmacovigilance study. *Lancet Reg Health Eur* 2022;17:100393.

28. Singh RB, Parmar UPS, Kahale F, et al. Vaccine-associated uveitis after COVID-19 vaccination: Vaccine adverse event reporting system database analysis. *Ophthalmology* 2023;130:179-86.

29. Tomkins-Netzer O, Sar S, Barnett-Griness O, et al. Association between vaccination with the BNT162b2 mRNA coronavirus disease 2019 vaccine and noninfectious uveitis: A population-based Study. *Ophthalmology* 2022;129:1087-95.

30. Hashimoto Y, Yamana H, Iwagami M, et al. Ocular adverse events after coronavirus disease 2019 mRNA vaccination: Matched cohort and self-controlled case series studies using a large database. *Ophthalmology* 2023;130:256-64.

31. Rabinovitch T, Ben-Arie-Weintrob Y, Hareuveni-Blum T, et al. Uveitis after the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: A possible association. *Retina* 2021;41:2462-71.

32. Teijaro JR, Farber DL COVID-19 vaccines: modes of immune activation and future challenges. *Nat Rev Immunol* 2021;21:195-7.

33. Pardi N, Hogan MJ, Porter FW, Weissman D mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov* 2018;17:261-79.

34. Mücke VT, Knop V, Mücke MM, et al. First description of immune complex vasculitis after COVID-19 vaccination with BNT162b2: a case report. *BMC Infect Dis* 2021;21:958.

35. Hakroush S, Tampe B Case Report: ANCA-associated vasculitis presenting with rhabdomyolysis and pauci-immune crescentic glomerulonephritis after Pfizer-BioNTech COVID-19 mRNA vaccination. *Front Immunol* 2021;12:762006.

36. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384:2092-101.

37. Wack S, Patton T, Ferris LK COVID-19 vaccine safety and efficacy in patients with immune-mediated inflammatory disease: Review of available evidence. *J Am Acad Dermatol* 2021;85:1274-84.

38. Hillman N, Cox S, Noble AR, Gallagher PJ. Increased numbers of caveolae in retinal endothelium and pericytes in hypertensive diabetic rats. *Eye (Lond)* 2001;15:319-25.

39. Martinez-Thompson JM, Diehl NN, Holmes JM, Mohney BG. Incidence, types, and lifetime risk of adult-onset strabismus. *Ophthalmology* 2014;121:877-82.

40. Song P, Xu Y, Zha M, et al. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health* 2019;9:010427.

41. Abu Mouch S, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. *Vaccine* 2021;39:3790-3.

42. Klugar M, Riad A, Mekhemar M, et al. Side effects of mRNA-based and viral vector-based COVID-19 vaccines among German healthcare workers. *Biology (Basel)* 2021;10:752.

43. Dorney I, Shaia J, Kaelber DC, et al. Risk of new retinal vascular occlusion after mRNA COVID-19 vaccination within aggregated electronic health record data. *JAMA Ophthalmol* 2023;141:441-7.

44. Roberts HW, Wilkins MR, Malik M, et al. A lack of an association between COVID-19 vaccination and corneal graft rejection: results of a large multi-country population based study. *Eye (Lond)* 2023;37:2316-9.

Figure legends

Fig 1. Occurrence of ischemic and inflammatory ocular adverse events (OAE) with different type of vaccine. Ischemic OAE includes retinal vein occlusion, paralytic strabismus, anterior ischemic optic neuropathy, while inflammatory OAE includes anterior uveitis, scleritis, optic neuritis, keratitis, and uveal effusion. Viral vector vaccines were closely related to ischemic OAE, whereas messenger ribonucleic acid vaccines were associated with inflammatory OAE ($p=0.017$).

Table 1. Characteristics of the study subjects, who have ocular adverse events after COVID-19 vaccination.

	study subjects (n=24)
Sex (Male / Female)	9 / 15
Age (years)	57.4 ± 17.2
Medical history (HTN or DM)	10 (41.7%)
Symptom onset after vaccination (days)	6.8 ± 4.9
Type of the vaccine (number of eyes)	
mRNA vaccine	10 (38.5%)
Viral vector vaccine	14 (61.5%)
Dose (number of eyes)	
1st	14 (58.3%)
2nd	8 (33.3%)
3rd	2 (8.4%)
Ocular diagnosis (number of eyes)	
Retinal vein occlusion	9
Paralytic strabismus	4
Anterior uveitis	2
Keratitis	2
Optic neuritis	2
Scleritis	2
Uveal effusion	2
Anterior ischemic optic neuropathy	1
Prior systemic symptoms (number of patients)	12 (50.0%)
General weakness	5
Headache	3
Fever, myalgia	2
Facial flushing	1
Numbness of hands/feet	1
Cumulative OAE incidence rate (per million doses)	5.8

COVID-19, coronavirus disease 2019; mRNA, messenger ribonucleic acid

Table 2. Comparison of demographic data and the type of ocular adverse events between mRNA and viral vector vaccines

	mRNA	Viral vector	P value
Number of patients	10	14	
Sex (Male/Female)	3/7	6/8	0.521
Age (year)	53.0 ± 19.2	61.6 ± 14.8	0.282
DM or HTN (number of patients)	4 (40.0%)	6 (42.9%)	0.889
Symptom onset (days)	5.6 ± 3.7	7.6 ± 5.8	0.348
Dose (number)	1.7 ± 0.8	1.4 ± 0.5	0.500
1st dose (eyes)	5	9	
2nd dose (eyes)	3	5	
3rd dose (eyes)	2	0	
Systemic symptoms (number of patients)	5 (50.0%)	7 (50.0%)	1.000
	General weakness (2) *Headache (1)* *Facial flushing (1)* *Numbness of hands/feet (1)*	*General weakness (3)* *Fever (2)* *Headache (2)*	
Ocular adverse event (number of patients)	Ischemia 3 (30%) Inflammation 7 (70%)	Ischemia 11 (79%) Inflammation 3 (21%)	0.017
Ischemia	*Retinal vein occlusion (2)* *AION (1)*	*Paralytic strabismus (4)* *Retinal vein occlusion (7)*	
Inflammation	*Anterior uveitis (2)* *Scleritis (1)* *Optic neuritis (2)* *Uveal effusion (2)*	*Scleritis (1)* *Keratitis (2)*	
Incidence (per million doses)	3.4	11.5	0.013

DM, diabetes mellitus; HTN, hypertension; mRNA, messenger ribonucleic acid; AION, anterior ischemic optic neuropathy