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COMMENTARY

Ophthalmological Considerations for COVID-19 Vaccination in Patients with Inflammatory Eye Diseases and Autoimmune Disorders

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ABSTRACT

The global impact imposed by the coronavirus disease 2019 (COVID-19) pandemic may be soon alleviated by the introduction and worldwide dissemination of safe and effective vaccines. This expedited timetable for development and approval of COVID-19 vaccines is an unprecedented extraordinary, concerted achievement by the scientific community. With the pending global rollout of vaccines, each with different mechanisms of action, physicians of various specialties will need to identify vulnerable patient groups for special considerations or advice. In this commentary, we analyse the important considerations for COVID-19 vaccines in patients with inflammatory eye diseases. Scrutiny of immunogenicity and adverse effects, particularly antibody-dependent enhancement, would better help in counselling these patients undergoing vaccination. More research on pharmacovigilance would allow for tailored guidelines and personalised management strategies.

Keywords: Autoimmune disorders; COVID-19; Inflammatory eye disease; Ophthalmic considerations; Pandemic; Vaccination

Key Summary Points

As production and distribution of the COVID-19 vaccines gathers momentum, physicians will need to be aware of special considerations for vulnerable patients, such as those with inflammatory eye diseases.

There is also potential for lower vaccine efficacy in pharmacologically immunosuppressed patients.

Furthermore, physicians and ophthalmologists may need to be aware of the possibility of vaccine-induced antibody-dependent enhancement of pre-existing inflammatory eye diseases.

Above all, it is important to emphasize the need to maintain preventive measures in protecting oneself against COVID-19 infection while the pandemic continues, even after vaccination.

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INTRODUCTION

The worldwide emergence of the severe acute coronavirus syndrome coronavirus 2 (SARS-CoV-2) has, to date, affected more than 86 million people globally since the World Health Organization (WHO)'s pandemic declaration on 11 March 2020 [1, 2]. The deleterious health consequences and socioeconomic reverberations of the coronavirus disease 2019 (COVID-19) have made accelerated development of therapeutics and vaccines exigent. Expedited development of vaccines was availed by the Access to COVID-19 Tools Accelerator (ACT-A)—a global collaboration amongst organisations such as the WHO, GAVI, and the Coalition for Epidemic Preparedness Innovations (CEPI). As of December 2020, there are 71 vaccine candidates (23 in phase I, 32 in phase II, 18 in phase III) in the clinical development process [3]. Currently, nine vaccines—BNT162b2 (BioNTech/Pfizer), Sputnik V (Gamelaya), mRNA-1273 (Moderna), ChAdOx1 (University of Oxford), BBIBP-CorV (Sinopharm), Covishield (Serum Institute of India), Covaxin (Bharat Biotech), CoronaVac (Sinovaac), and Ad5-nCoV (Cansino Biologics)—have been approved for use [3, 4]. The last four are approved for early or limited use in a few countries.

There is limited data to guide the use of COVID-19 vaccines for patients with underlying ophthalmological diseases. This may be attributable to the unprecedented time frame of vaccine development and approval. Vaccine development typically spans across 10–15 years from initial scientific discovery, preclinical and clinical studies, to licensure [5]. The sped-up timeline may be attributable to the rapid deployment of flexible vaccine platforms, generous funding, innovative trial designs and multinational cooperation. Timely legislative changes by pharmaceutical regulatory bodies have also contributed to the streamlined vaccine development process [6].

Traditionally, clinical trials consist of four successive phases:

(1) Phase I assesses the safety profile and immunogenicity of vaccine candidates by testing in a small group of healthy individuals (< 100).
(2) Phase II studies the safety and immunogenicity of the vaccine in a larger group of a few hundred individuals. These individuals would include at-risk populations. The optimal dose, vaccine regimen and method of delivery are also assessed.
(3) Phase III further evaluates the efficacy and safety of the vaccine in a larger population of people in different regions and countries (in thousands).
(4) Phase IV involves safety surveillance after the drug has been approved for use.

This pandemic necessitated a new trial design. Rather than implementing phases in succession, phases may overlap or be combined. Phase III trials are swiftly commenced upon interim analysis of phase I/II trials, whilst commercial production may begin while awaiting results from phase III [7]. The homogenous study populations in pre-marketing randomised clinical trials preclude the assessment of vaccine usage in patients with underlying ophthalmological pathologies. The lack of pharmacovigilance studies as of yet restricts vaccination guidelines for special subpopulations to only a hypothetical basis. Herein, we propose several key considerations for physicians when considering administration of COVID-19 vaccines to patients with ophthalmological diseases. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Immunogenicity of the Vaccine

The immunological basis of vaccines lies in the priming of the antiviral innate immune response followed by the activation of adaptive

immunity for long-term immunological memory. Briefly, microbial components contained within vaccines or expressed by vaccines in human cells are recognised by antigen-presenting cells (APCs), triggering downstream signalling cascades and production of cytokines and chemokines [8]. Migration of APCs to draining lymph nodes and the subsequent sensitisation of T cells activate antigen-specific cell-mediated and humoral responses to varying degrees depending on the type of vaccine [9]. A small subset of T and B cells that was clonally expanded during the course of primary immune response survives as memory cells, which allows for a secondary response that is of higher speed and magnitude upon re-encounter with the same pathogen [10]. The immunogenicity of the candidate vaccine, i.e. the ability to generate an immune response, constitutes an important endpoint for phase I and II clinical trials. For COVID-19 trials, the immunogenicity profile is evaluated on the basis of the titre of neutralising antibodies, although many studies have also evaluated T cell responses as an equally important correlate of protection [11]. Similar to other vaccines, the immune response shows high interpersonal heterogeneity, with immunosenescence or immunosuppression being important factors driving variation [12]. These demographics are commonly encountered in ophthalmology. For instance, the immunological underpinnings of various eye diseases may reflect a derangement in systemic immunity despite the eye being a prototypic immune-privileged organ [13]. Another example would be the ocular effects of autoimmune disorders; the altered immunological state may stem from the original disease or a consequence of immunosuppressive therapy use. Therefore, more data for efficacy and safety is key to inform the use of vaccines in these demographic populations [14].

Patients who are pharmacologically immunosuppressed constituted a significant group of vulnerable patients for ophthalmologists during the pandemic. Immunosuppressive therapy is increasingly used to manage ocular inflammation, which is a major cause of ocular morbidity. The dilemma over the use, timing, dosage and duration of immunosuppression in patients with COVID-19 persists [15]. The conundrum will likely extend to COVID-19 vaccine administration given the limited safety and efficacy data. A risk–benefit analysis may be challenging. First, the relationship between impaired immune status and disease outcomes is unclear. Immunosuppressed individuals are, by default, at increased risk of infections. Yet, anecdotal evidence points to an asymptomatic or mild course of disease in immunocompromised patients, such as organ transplant recipients and patients with HIV [16–18]. The immunosuppression is likely beneficial in dampening the hyperinflammation, which is the major driver of organ damage [19]. On the other hand, impairment of antimicrobial immunity may increase the viral load and drives inflammation, thus severity [20]. This could also be explained by the occurrence of locus minoris resistentiae with the eye being an immunologically privileged organ. Second, the weakened immune systems may undermine the immunogenicity of the vaccine. This has been demonstrated in other vaccines, with lower seroprotection and seroconversion rates observed when compared with healthy controls [21]. However, immunogenicity may not always correlate with clinical efficacy [22]. Nevertheless, it would be important to remind such patients, even after vaccination, to continue measures to protect themselves from COVID-19 infection during the pandemic. Third, the safety profile has not been assessed in this group of patients. Ocular inflammatory diseases can occur in isolation or as part of systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) and Sjögren's syndrome. The immunogenicity of COVID-19 vaccines could potentially induce or trigger autoimmune diseases. Autoimmunity may be stimulated antigen-specifically, i.e. via molecular mimicry between microbial antigen and that of the host, or non-antigen-specifically, i.e. secondary to heightened innate immune response or the release of sequestered self-antigens [23]. Associations between autoimmunity and vaccines, albeit rare, have been reported [24]. Maillefert et al. reported development, exacerbation or relapse of rheumatic disorders following hepatitis B vaccination, but a causal relationship

could not be established [25]. Contrastingly, a prospective study on 27 patients with SLE showed no statistically significant difference in flare rates between vaccinated and non-vaccinated subjects [26]. It is important to note that the presence of a flare is assessed by an index that considers organ manifestations, which may not take into consideration other parameters of flare such as hospitalisations and changes to medications [27]. Additional questions should also be addressed: (1) Should immunosuppressive or immunomodulatory treatments be altered? Reduced dosage or a bridging therapy with local and regional therapies have already been observed in patients with active uveitis since the pandemic [28, 29]. However, the risk of disease relapse may have grave consequences on visual function and quality of life. Whilst this approach was considered to minimise the susceptibility to severe respiratory infections, whether this should be considered in the context of immunisation against SARS-CoV2 requires further consideration. (2) What is the optimal timing of vaccination, in relation to disease activity and the timing of immunosuppressant usage? Most vaccination studies conducted in patients with autoimmune inflammatory rheumatic diseases include patients at the quiescent stage, with insufficient data for those with moderate to severe disease activity [22]. The recommendations from the European League Against Rheumatism (EULAR) favour vaccination during quiescent disease and preferably before initiating immunosuppression if without indications for urgent administration [22]. However, this should be considered on a case-by-case basis with shared decision-making, taking into account patients' preference, concerns, and risk of acquiring COVID-19.

Adverse Events of COVID-19 Vaccines

A meta-analysis of five randomised, double-blind, placebo-controlled trials of COVID-19 vaccine candidates noted that local and systemic adverse events reported were all transient, and mostly mild or moderate [30]. Common local adverse reactions include pain, itching, redness, swelling and induration. Systemic reactions, such as fatigue, headache, muscle pain, joint pain and malaise/anorexia are significantly more likely in vaccinated subjects compared to control [30]. However, the spectrum of adverse effects may not yet be fully demonstrated given the relatively small number of studies included and the exclusion of single-blind or placebo-free studies. Notably, some approved vaccine candidates such as the ChAdOx1 nCoV-19 were excluded from the analysis.

Antibody-dependent enhancement (ADE) is a concern for the development of COVID-19 vaccines. Whilst high-affinity antibodies against epitopes of viral particles may result in elimination of the virus, heterotypic (non-neutralising) antibodies or of suboptimal concentration will worsen disease severity. Two distinct mechanisms in which antibodies are exploited to enhance viral infection have been documented. Enhanced virus uptake occurs when the Fc region of the antibody–virus immunocomplex binds to Fcγ receptor (FcγR)-expressing phagocytic cells. This may lead to an increase in virus-infected cells (termed extrinsic ADE), or heightened viral replication with modulation of the antiviral signalling pathway (termed intrinsic ADE) [31]. ADE has been documented in preclinical studies of vaccine candidates against severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [32]. It is theorised that the risk of ADE is higher in inactivated vaccines. Inactivated vaccines are promising given their speed and ease of production, safety profile compared to live attenuated vaccines, and high potency [33, 34]. However, the presentation of multiple epitopes, particularly at immunodominant sites in close proximity to the receptor binding domain of the spike protein, may precipitate the production of sub- or non-neutralising antibodies [35, 36]. The subsequent virus internalisation will exacerbate pre-existing infection or induce harmful immunopathology. There is inconclusive evidence to suggest the occurrence of ADE in SARS-CoV2 infections. It is encouraging that ADE was not observed in preclinical studies of the approved inactivated vaccines, BBIBP-CorV and CoronaVac, in rhesus

macaques [37, 38]. CoronaVac's 100% efficacy against severe COVID-19 further suggests a low risk of ADE. Yet, larger-scale phase III trials will provide critical data regarding its safety profile. Human convalescent plasma trials have also not shown definite signals of ADE [39–41]. The impact of immunological memory to endemic coronaviruses on SARS-CoV2 acquisition and clinical outcomes remains unclear. The cross-reactive antibodies to endemic coronaviruses, which have extensive sequence homology to SARS-CoV2, may mediate ADE without viral neutralisation [42]. Substantial cross-reactivity to spike glycoproteins, which is essential for viral entry and fusion, has been observed in plasma in infected patients [43, 44]. Yet a retrospective study analysing the comprehensive respiratory panel PCR (CRP-PCR) data in 15,928 patients suggests that prior coronavirus exposure may be protective against severe COVID-19 [45]. It is important to note that the retrospective nature of the study, the small sample size and the differences in assays may introduce bias.

In the context of COVID-19, ADE may precipitate ocular or neuro-ophthalmological manifestations, with the former shown to have a positive correlation with increased disease severity [46].

Ocular Manifestations: Impacts on Anterior Segment

(1) Conjunctivitis. Unilateral and bilateral conjunctivitis have been reported [47–51]. Signs and symptoms may range from mild (e.g. tearing, conjunctival hyperaemia, foreign body sensation) to severe (e.g. photophobia, chemosis, follicular reaction) [46, 52]. The timing of presentation is variable; conjunctivitis may appear as the sole presenting sign, an initial symptom, synchronously with other well-known constitutional and respiratory symptoms, or in the late stage after serological clearance [50, 51, 53, 54]. Whilst mostly resolved within 1–2 weeks without complications, relapse has been reported in a case report [52, 55].

(2) Keratitis and episcleritis. Albeit rare, superficial punctate keratitis and keratoconjunctivitis have been described in case studies [48, 56]. Episcleral involvement has also been documented [57, 58].

Ocular Manifestations: Impacts on Posterior Segment

The effect of COVID-19 on the retina and the optic nerve is only reported in small case studies. The virus may affect ganglion cells and inner plexiform layers, optic discs and retina [59–61].

Neuro-Ophthalmological Manifestations

Ophthalmoplegia secondary to cranial nerve palsies has been reported [62, 63]. Possible postulated explanations include direct viral invasion, post-viral acute demyelinating inflammatory polyneuropathy, and ischaemia.

There remain several questions to be elucidated. The first pertains to the paradoxical nature of the protective effects versus ADE risk of vaccines. Granted the uncertainty over the relevance of ADE in patients with COVID-19, would the administration of vaccine imply the protection from SARS-CoV-2, thus in turn associated ocular and neuro-ophthalmological pathologies? Second, do chronic eye diseases confer additional risk to ADE-mediated ophthalmological complications? This has not been discussed in the extant literature. However, an analogous comparison may be the relationship between chronic eye diseases and neuro-ophthalmological presentation of SARS-CoV-2. The ocular manifestations of COVID-19 could be explained by the ocular tropism of respiratory viruses due to the anatomical and cellular similarities between ocular and respiratory systems [64]. Therefore, it may be inferred that eye diseases with altered anatomical or mucosal immune properties may affect susceptibility to virus-related ocular diseases [65]. Other pathogeneses may account for the ophthalmological symptoms, for instance immune-vascular inflammation and thrombotic complications [57, 60]. A prospective cohort study of ocular manifestations of COVID-19 did not demonstrate a statistically significant increase in the risk of conjunctival congestion in patients with chronic eye diseases (e.g. conjunctivitis,

keratitis, xerophthalmia) [54]. Third, the implications of ADE for ophthalmological patients may not be straightforward. The transient nature of ocular manifestations, such as conjunctivitis, may not warrant vaccines as a contraindication to patients with underlying anterior segment disorders. That said, the management approach needs to be considered should these ocular complications arise. Whilst dependent on the severity of the presentation, guidelines as to when a conservative approach or an escalated treatment strategy should be implemented would be ideal.

CONCLUSION

The global rollout of the COVID-19 vaccines is a crucial step in controlling the current pandemic. As proven in phase III clinical trials, the leading vaccines under production are safe and effective in protecting patients from symptoms and severe illness due to COVID-19. As production and distribution of the vaccines gathers momentum, medical professionals will need to be aware of special considerations for vulnerable patient groups under their care, such as patients with inflammatory eye diseases and autoimmune disorders. While long-term evidence from clinical trials is still lacking, this commentary highlights several key areas that should be of importance during counselling of patients with underlying inflammatory eye diseases, with or without immunosuppressive treatment. This includes the potential for lower vaccine efficacy in pharmacologically immunosuppressed patients and the potential risk of vaccine-induced ophthalmic ADEs. Above all, it is important to emphasize the need to maintain preventive measures in protecting oneself against COVID-19 infection while the pandemic continues, even after vaccination.

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Data Availability. The authors agree to make all materials, data and associated protocols promptly available to readers without undue qualifications in material transfer agreements.

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