Review of Ocular Manifestations and Drugs Used for the Treatment of Ocular Complaints in COVID-19

Arash Khorram1, Nafiseh Khosravi-Dehaghi2,3, Bahareh Hajikhani4, Masoud Dadashi1,5, Fatemeh Sameni6,7*

1Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
2Department of Pharmacognosy, School of Pharmacy, Alborz University of Medical Sciences, Karaj, Iran
3Evidence-Based Phytotherapy and Complementary Medicine Research Center, Alborz University of Medical Sciences, Karaj, Iran
4Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
6Department of Microbiology, Faculty of Medicine, Shahed University, Tehran, Iran
7Molecular Microbiology Research Center, Shahed University, Tehran, Iran

Received: May 6, 2023
Revised: May 15, 2023
epublished: May 28, 2023
*Corresponding Author:
Fatemeh Sameni,
Email: Sameni.f@yahoo.com

Abstract
SARS-CoV-2 has been infrequently isolated from conjunctival swabs; it is associated with ocular manifestations, including conjunctivitis, blurred vision, dry eye, and hyperemia in patients with confirmed COVID-19. In some cases, ocular manifestations may be the first and only symptoms of COVID-19 related to the greater severity of the systemic disease. According to the eye manifestations, physicians have prescribed different medications. For example, drugs such as azithromycin eye drops, dexamethasone, moxifloxacin, and ganciclovir ophthalmic gel have been used for the treatment of conjunctivitis. The role of ophthalmologists in the prevention and screening of COVID-19 is highlighted due to the ocular manifestations. The most common ocular symptoms associated with COVID-19 infection, treatment, and potential side effects of drugs utilized to combat these complications are reviewed in this article.

Keywords: COVID-19, Ophthalmology, Ocular manifestations, Conjunctivitis, Treatment, Side-effects

Background
The outbreak of novel coronavirus (2019-nCoV), the causative agent of COVID-19, originated in Wuhan, China, in December 2019 and quickly spread around the world.1-3 The causative organism of this pandemic has been named SARS-CoV-2, which has a single-stranded positive-sense RNA genome. The SARS-CoV-2 genome encodes 16 non-structural proteins; some of them, which are called accessory proteins, and 4 structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, are required for the assembly of new virions. The nucleocapsid is an essential protein that packages the RNA into helical RNP (ribonucleocapsid), and the spike protein is located on the virus surface and promotes virus attachment to the host cell.4,5 The most common clinical manifestations of COVID-19 include fever, myalgia, cough, fatigue, and a sore throat.5,6 The majority of the COVID-19 patients showed bilateral lung affection. Skin manifestation, loss of smell and taste, and gastrointestinal bleeding are also reported in these patients.5,6 COVID-19 is known to cause respiratory tract manifestations, but transmission from the ocular surface to the eye should not be ignored.9 Some publications reported that ocular symptoms occur when the disease progresses to systemic, while other reports indicated that ocular manifestations can be the first signs of infection and raise suspicion of COVID-19. The most frequent manifestations of ocular involvement among COVID-19 patients are dry eye, a foreign body sensation, redness, tearing, itching, eye pain, and discharge, respectively. Notably, the most prevalent ocular disease in COVID-19 patients was conjunctivitis.10-12 The current study aimed to discuss and determine several ocular involvements resulting from SARS-CoV-2 infection and the treatment of these complaints.

Evidence of Ocular Manifestations
Based on investigations, viruses can lead to several ophthalmic diseases.13-15 To control coronavirus transmission, the best strategy is to block its potential transmission routes. Scientists have found SARS-CoV-2 in different body fluids, such as blood and feces, and different secretions, such as respiratory secretion. Evidence indicates that eyes could be a potential route for SARS-CoV-2 infection and the treatment of these complaints.
the cornea, conjunctiva, and epithelium of the lacrimal ducts may collect the infected tears, or the nasolacrimal duct may drain the viruses to the nasopharynx.18, 19 The presence of microvilli in the epithelial covering the nasolacrimal duct allows the secretion and reabsorption of tear fluid components.20 The lacrimal duct accumulates tear fluid from the ocular surface and transports it to the inferior meatus of the nose, expediting the drainage of virus from ocular to respiratory tract tissues in a replication-independent manner, thus serving as a conduit for virus-containing fluid exchange between these sites.21 The method for investigating the presence of SARS-CoV-2 in ocular tissue is to collect the specimen from the eyes with sterilized swabs and then transfer them to authorized laboratories to run the reverse transcription-polymerase chain reaction (RT-PCR) analysis. According to some studies, scientists collected samples from eyelids using cotton swabs without topical anesthesia and then transferred them to a viral transport medium before performing the test.18,19 Based on a study conducted by Wu et al, among 38 clinically confirmed COVID-19 patients, 12 patients had ocular manifestations, and the RT-PCR result was positive for 2 of them.22 According to a study conducted by Kaya et al, 5 (16%) out of 32 examined patients who did not have any ocular manifestations possessed viral RNA in their eye secretion. They did not demonstrate any signs of conjunctivitis or other ophthalmologic conditions. At the time of the study, half of the cases were positive for COVID-19 nasopharyngeal RT-PCR samples; in those 5 positive tear specimens, the results were also positive for nasopharyngeal specimens.23 In another survey of 30 patients, SARS-CoV-2 was detected in only one tear sample.23 In a study by Karimi et al on 43 patients, 3 positive results (7%) were found for viral RNA in the eyes and nasopharyngeal specimens. There were ocular manifestations in only one of the patients.24 Another study by Li et al included 49 laboratory-confirmed cases of COVID-19. The absence of any ocular symptoms made these patients unique; overall, 158 conjunctival manifestations were observed among 123 patients (75.4%).25

Table 1. Summary of COVID-19 Ocular Manifestations

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Location</th>
<th>Total Number of Patients With COVID-19</th>
<th>Number of Patients With Ocular Manifestation</th>
<th>Ocular Diseases</th>
<th>Ocular Signs and Symptoms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al</td>
<td>Retrospective case series</td>
<td>China</td>
<td>535</td>
<td>27</td>
<td>Conjunctival congestion</td>
<td>Ocular pain, photophobia, tearing, and dry eye conjunctival secretion</td>
<td>27</td>
</tr>
<tr>
<td>Guan et al</td>
<td>Retrospective case series</td>
<td>China</td>
<td>1099</td>
<td>9</td>
<td>Conjunctival congestion</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>Xia et al</td>
<td>Retrospective case series</td>
<td>China</td>
<td>30</td>
<td>1</td>
<td>Conjunctivitis</td>
<td>-</td>
<td>29</td>
</tr>
<tr>
<td>Sindhuja et al</td>
<td>Retrospective cross-sectional</td>
<td>India</td>
<td>127</td>
<td>12</td>
<td>Conjunctival congestion and hordeolum</td>
<td>Burning sensation and watering eyes</td>
<td>30</td>
</tr>
<tr>
<td>Bostanci and Ozates</td>
<td>Cross-sectional</td>
<td>Turkey</td>
<td>99</td>
<td>20</td>
<td>Follicular conjunctivitis and episcleritis</td>
<td>Hyperemia, increased secretion, and epiphora chemosis</td>
<td>31</td>
</tr>
<tr>
<td>Otaif et al</td>
<td>Case report</td>
<td>Saudi Arabia</td>
<td>1</td>
<td>1</td>
<td>Episcleitis</td>
<td>Foreign body sensations, redness, photophobia, and pain</td>
<td>32</td>
</tr>
<tr>
<td>Cheema et al</td>
<td>Case report</td>
<td>Canada</td>
<td>1</td>
<td>1</td>
<td>Conjunctivitis and keratoconjunctivitis</td>
<td>Photophobia and watery discharge</td>
<td>33</td>
</tr>
<tr>
<td>Martinez Díaz et al</td>
<td>Case report</td>
<td>Spain</td>
<td>1</td>
<td>1</td>
<td>Conjunctival injection</td>
<td>Lid oedema, redness, eyelid swelling, blurred vision, discomfort, and chemosis</td>
<td>34</td>
</tr>
<tr>
<td>Navel et al</td>
<td>Case report</td>
<td>France</td>
<td>1</td>
<td>1</td>
<td>Conjunctivitis</td>
<td>Pseudomembranous hemorrhagic chemosis</td>
<td>35</td>
</tr>
<tr>
<td>Rho et al</td>
<td>Case report</td>
<td>USA</td>
<td>1</td>
<td>1</td>
<td>Non-arteritic ischemic optic neuropathy</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>Abrishami et al</td>
<td>Cross-sectional</td>
<td>Iran</td>
<td>142</td>
<td>92</td>
<td>Conjunctival keratitis and cataract</td>
<td>Red eye, itching, foreign body sensations, hyperemia, and chemosis</td>
<td>37</td>
</tr>
<tr>
<td>Wu et al</td>
<td>Retrospective case report</td>
<td>China</td>
<td>38</td>
<td>12</td>
<td>Conjunctivitis</td>
<td>Secretion and hyperemia</td>
<td>38</td>
</tr>
<tr>
<td>Míndez Mangana et al</td>
<td>Letter to the editor</td>
<td>Spain</td>
<td>1</td>
<td>1</td>
<td>Episcleitis</td>
<td>-</td>
<td>39</td>
</tr>
<tr>
<td>Mohammadzadeh and Mohammadzadeh</td>
<td>Case report</td>
<td>Iran</td>
<td>1</td>
<td>1</td>
<td>Bilateral acute anterior uveitis and optic disk edema</td>
<td>Prolonged fever, myalgia, cough, diarrhea, skin rashes, blurred vision, photophobia, and eye redness</td>
<td>40</td>
</tr>
<tr>
<td>Bettach et al</td>
<td>Letter to the editor</td>
<td>Italy</td>
<td>1</td>
<td>1</td>
<td>Bilateral acute anterior uveitis</td>
<td>Fever, septic shock, gastrointestinal syndrome, heart failure, and a skin rash</td>
<td>41</td>
</tr>
</tbody>
</table>
swabs were taken from 49 patients; the samples were taken approximately 6 days after the onset of symptoms, and four different patients had positive results in their RT-PCR test. In a similar study, among 102 possible COVID-19 patients, 2 patients had ocular manifestations, and one had SARS-CoV-2 in conjunctival specimen. As reported by Güemes-Villahoz et al, 36 confirmed COVID-19 patients were evaluated for the presence of viral RNA in their eyes. Swabs were collected from both eyes; only half of the examined patients had conjunctivitis, and only 2 of 18 patients with conjunctivitis had positive RT-PCR results.

Interestingly, in a study on deceased COVID-19 patients conducted by Casagrande et al, 3 out of 14 eye retina specimens were positive for viral RNA. Contrary to all the data shared, RT-PCR has some limitations; the detection of a viral RNA in ocular secretion is not as easy as a nasopharyngeal sample; small quantities of this RNA, as well as a shorter duration of viral shedding in ocular secretion, may lead to negative results.

**Ocular Diseases and Manifestations in COVID-19**

Until now, 7 types of coronaviruses have been known to infect humans, which mostly lead to infections in the respiratory system. The main concern in COVID-19 patients is respiratory failure; however, other organs may play a role in the transmission and infection of the virus. According to recent reports, various ocular findings, including epiphora, conjunctivitis, conjunctival congestion, and chemosis, are prevalent in COVID-19 patients. Some ocular manifestations related to COVID-19 are shown in Figure 1. It has been revealed that having ocular diseases is correlated with more severe diseases. Foreign body sensations, blurred vision, dry eye, itching, and keratoconjunctivitis have been observed in ocular involvements.

**Conjunctivitis**

Several studies have shown that SARS-CoV-2 can cause conjunctivitis as an initial sign or during hospitalization. Compared to Guan et al, Chen et al reported a higher frequency of conjunctival congestion (5.05% vs. 0.82%). Sindhuja et al conducted a study on 127 patients who tested positive for COVID-19 and found that 12 had ocular complaints. Eight (6.29%) out of 127 had conjunctival congestion. Further, 2 out of 8 patients with ocular symptoms developed conjunctival congestion without any COVID-19-related symptoms. The time that these patients had conjunctival congestion was different in each case. According to 6 separate studies performed in China about COVID-19 ocular diseases, the prevalence of conjunctival congestion was different (0.81%, 3.33%, 4.68%, 31.57%, 1.1%, and 3.57%). The difference might be because of the sample size and the disease severity of the cases. Based on a report by Wu et al, a child with SARS-CoV-2 was the first pediatric case with ophthalmic involvement. He was characterized by conjunctivitis and eyelid dermatitis. According to a study conducted by Karimi et al on 43 patients, two patients demonstrated ocular manifestations; one of them had conjunctivitis, and the other had foreign body sensations. Furthermore, patients’ tears were tested by RT-PCR to investigate SARS-CoV-2. The result was positive only in 3 cases. However, just one of the positive results was related to a patient with ocular findings. As reported by Valente et al, among 27 confirmed COVID-19 patients in a pediatric hospital, 4 patients had viral conjunctivitis, characterized by mild conjunctival hyperemia and secretion. Among these 4 patients, just one had a positive RT-PCR result for SARS-CoV-2 from the conjunctival swab. Two more patients had positive results in their conjunctival swabs and developed no ocular symptoms. In a study by Khavandi et al, a woman went to the hospital with eye discharge and burning eyes. She had viral conjunctivitis. The RT-PCR test was performed on her conjunctival secretion, and the result was positive for SARS-CoV-2. Navel et al reported the first case of pseudomembranous and hemorrhagic conjunctivitis in a man diagnosed with COVID-19; first, ocular manifestations (i.e., conjunctival hyperemia and clear secretions) occurred, which indicated viral conjunctivitis. Follicles, petechiae, tarsal hemorrhages, and chemosis appeared and worsened the status. The physicians identified pseudomembranous on the tarsal conjunctiva. Additionally, superficial keratitis was described; as pseudomembranous appeared on day 19, it was essential to be aware of late ocular manifestations (more than two weeks) in patients. Based on a study conducted by Daruich et al, a patient in Argentina had foreign body sensations and eye redness. Further examination revealed moderate conjunctival hyperemia with unilateral eyelid edema. Nasopharyngeal RT-PCR for SARS-CoV-2 was positive. In a cross-sectional study...
performed by Abrishami et al, a total of one hundred forty-two patients who have been diagnosed with COVID-19 (clinically or laboratory-confirmed patients) were involved in this study. In terms of manifestations, the conjunctival hyperemia, chemosis, tearing, red eyes, eye itching, foreign body sensation, photophobia, and blurred vision were 28.9%, 15.5%, 23.2%, 16.2%, 8.4%, 13.4%, 0.7%, and 0.7%, respectively. In addition, 31% had red eyes, and 15.5% experienced conjunctival swelling.37

Keratoconjunctivitis
Based on a study performed by Cheema et al, a woman reported right eye conjunctivitis, photophobia, and watery discharge; Her eyelids were swollen, and she had mucous discharge from her right eye. Anterior segment examination represented conjunctival congestion, follicles, and one small pseudodendrite in the inferior temporal cornea; moreover, 8 small subepithelial infiltrates were detected at the superior temporal limbus, which became up to 50 areas after 6 days. The first COVID-19 case showed keratoconjunctivitis as the main manifestation.31 Based on a study by Alnajjar et al, a COVID-19 case was presented with keratoconjunctivitis and had respiratory symptoms 4 days after the initial keratoconjunctivitis. After 4 days of treatment, improvements were observed in COVID-19 pneumonia and ocular disease.44 In another confirmed COVID-19 patient, 10 days after being infected, conjunctivitis was detected in his left eye. The result of his conjunctival secretion being tested for SARS-CoV-2 was positive. Within 6 days of treatment, the patient’s condition improved, and he was discharged from the hospital. Five days later, keratoconjunctivitis was diagnosed in both eyes when the first symptoms were almost relieved. The condition worsened with spot staining at the periphery of the corneal epithelium. SARS-CoV-2 was not detected in conjunctival secretion this time, but an increase in inflammatory factors was observed in both eyes.49

Episcleritis
According to a study by Méndez Mangana et al, a woman consulted a centre in Barcelona because of eye redness, foreign body sensation, epiphora, and photophobia. Her visual activity was not impaired, and she was diagnosed with nodular episcleritis. This patient condition was the first episcleritis case related to COVID-19; hence, episcleritis should be considered a potential ocular disease in the COVID-19 pandemic.38 In addition, episcleritis can be an initial disease in patients infected with nCoV, as described by Otaif et al in a case from Saudi Arabia. A man with no medical condition had foreign body sensations and redness without decreased vision, discharge, photophobia, or pain. Further, he had no ocular surgery and no complaints in his right eye. Episcleritis was diagnosed, and examination demonstrated a clear cornea along with conjunctival and episcleral injection. Three days later, he experienced headache, shortness of breath, cough, and fever, with a positive COVID-19 RT-PCR result.32

Dacryoadenitis
Acute dacryoadenitis is an inflammatory enlargement of the lacrimal gland often caused by infection or an autoimmune disease, the most common causes of which are viral agents such as Epstein-Barr virus, adenovirus, and mumps. COVID-19 orbital involvement is rare, and only two cases of orbital cellulitis and sinusitis have been reported so far. Based on a report by Martínez Díaz et al, a man suffering from right eye pain with redness, blurred vision, and eyelid swelling presented to a hospital. Further investigation showed an enlargement of the lacrimal gland in his right eye. He had right eye dacryoadenitis and had no COVID-19-related systematic symptoms. However, 4 weeks prior, his parents had COVID-19. He presented with lid oedema, ptosis, chemosis, and conjunctival injection. The PCR test result was negative, but SARS-CoV-2 immunoglobulins G (IgG) and M were positive.34

Non-arteritic Ischaemic Optic Neuropathy
NAION is a rare yet harmful complication in this pandemic that causes loss of blood flow to the optic nerve, leading to acute, unilateral, and painless vision loss. One of the causes is prone positioning, a therapeutic strategy to treat acutely hypoxemic COVID-19 patients with acute respiratory distress syndrome (ARDS). NAION is devastating as it can cause vision loss, especially in COVID-19 patients with ARDS. Clarke et al reported a case of NAION, including optic disc oedema with right eye hemorrhages, in a 55-year-old positive COVID-19 patient after being in a prone position for 9 weeks.50 Rho et al described a NAION in a man who had a COVID-19 infection. SARS-CoV-2 may lead to hypoxemia and thrombophilia, which may cause NAION. However, it is not proven whether the relationship between NAION and COVID-19 is casual or coincidental.55

Uveitis
Uveitis (inflammation of the iris) has different kinds, causes, and etiologies, including autoimmune diseases, drug-related infections, and ocular injuries. Reports have been published regarding uveitis as an ocular manifestation in COVID-19 patients. Previous research indicates that this disease is either the result of the COVID-19 infection or occurs secondary to the infection. According to a study in Iran, a child presented to a hospital with fever, myalgia, cough, and abdominal pain, symptoms that occurred 6 days earlier; she also suffered from blurred vision, photophobia, redness, and pain in her eyes. Her PCR test for SARS-CoV-2 showed a positive
result. After consulting an ophthalmologist, bilateral acute anterior uveitis and optic disk edema were detected, and based on the World Health Organization criteria, she was diagnosed with multisystem inflammatory syndrome in children that can cause uveitis.50 According to another report by Bettach et al, a woman in Italy was diagnosed with bilateral anterior uveitis; the patient was kept in the hospital with MIS secondary to the COVID-19 infection and was under treatment. The SARS-CoV-2 IgG was positive despite the PCR test being negative, indicating that she had a COVID-19 infection before developing uveitis.40 According to some studies, uveitis can occur after COVID-19 vaccination in different people regardless of gender and age, and it is reported more in patients with a history of autoimmune disease, uveitis, and COVID-19. Furthermore, further studies are needed to understand the mechanism of this disease after vaccination.51,52

COVID-19 Entry Mechanism for the Host and Eye Protection in a Pandemic

By binding to human angiotensin-enzyme II (ACE2), SARS-CoV-2 enters respiratory epithelial cells via the spike glycoprotein.53 However, the expression of ACE2 is also identified in the corneal limbus; hence, SARS-CoV-2 interacts with transmembrane protease serine 2 of the host cells that contribute to the virulence and pathogenesis of ARS-CoV-2.54

Therefore, physicians must wear goggles with proper adhesion, glasses, or disposable face shields to prevent exposure, which may seem a little bit uncomfortable for long-term use.55 The American Ophthalmology Academy has advised some instructions for protection against SARS-CoV-2 while attending ophthalmology clinics; the recommendations are based on using proper disinfection methods for equipment (including slit lamps) and clinics with the use of alcohol-based bleaching agents and disinfectants; these methods need to be conducted before and after each individual’s visiting.56 Regarding all studies and reports, some ophthalmological recommendations, such as hand washing and avoiding touching the nose or eyes for COVID-19 conjunctivitis, could be practical to diminish the transmission rate and possible complications.57,58

Side Effects of Drugs in the Treatment of Coronavirus Disease 19

In addition to drugs’ beneficial effects in controlling COVID-19, their side effects must be considered in treating patients. Different clinical trials are being conducted to treat SARS-CoV-2 infection; for example, combinations of drugs such as hydroxychloroquine (HCQ) and azithromycin are used in this respect.59 According to a study, the ocular side effects of medications were observed in other diseases. Based on a study by Olson et al, different medicines, including antiviral, antimarial, and antimicrobial medications, can cause ocular side effects such as retinopathy, uveitis, dry eye, and lots of other symptoms and diseases. For instance, according to two studies, ribavirin caused retinal vein thrombosis and dry eye. Moreover, azithromycin was utilized in many studies and led to some ocular side effects, including conjunctivitis and color-vision defect.60 Hence, there is a possibility of possessing varied complaints because of the different drugs used in COVID-19 infection treatment.60 Each drug may have various side effects in short- or long-term use. HCQ and Chloroquine (CQ), which are widely applied in this pandemic, have gastrointestinal and ocular side effects.61 QC was used as an anti-malarial drug in the 19th century; although effective, it had extreme toxicity; thus, the pharmacists had to develop its derivate (HQC) to utilize alongside chloroquine because it was more effective and less toxic.62 Physicians started prescribing these medications with SARS-CoV-2 emerging because of their potential ability to inhibit virus replication cycles.52,63 The US Food and Drug Administration has given the green light for using these two drugs to treat COVID-19 because they play a critical role against viruses.63 Nonetheless, the usage is limited as they have some side effects such as vomiting, abdominal pain, nausea, diarrhea, rash or itching, coughing, and dyspnea in short-term use, which disappear with decreasing the dose.64,65 In addition to those side effects, they may cause extremely threatening arrhythmias and hypoglycemia. They may be toxic and highly toxic, especially in overdose.66 There is a risk of retinopathy, vacuolar myopathy, keratopathy, and conjunctivitis, and the main concern is retinal toxicity in long-term use.63,64 Fourteen to twenty-one days after CQ and HCQ administration, the deposition of these drugs can be observed in the cornea, which resolves after drug reduction; they may also be rectified even without stopping the therapy. Keratopathy is found with CQ more than HCQ. They also cause damage to the retina, both the outer layer and the inner retina. Animal models demonstrate that pathologic changes happen in all retina layers, but the principal damage is to rods and cones. The essential things to avoid toxicity are dose and duration of use66; it is not yet proven if they can have the same effect at a high dose. However, in a short period, physicians should be aware of older patients with coexistent ocular problems because, in that case, CQ and HQC may lead to degeneration even over a short period. With regards to related research, CQ and HCQ can bind to melanin in the retinal pigment epithelium, which can be the primary mechanism of toxicity; these two drugs can cause “bull’s eye” maculopathy even in a low dose, which is challenging.64,65 The reason for bull’s eye maculopathy is a ring of parafoveal retinal depigmentation that spares a foveal island; bull’s eye is a late stage of damage. Exposure to CQ and HQC in a short time is reversible, but unfortunately, in an extended length of time, it is
permanent and may cause irreversible diminishment of central vision, scotoma formation, color vision deficits, and cataracts. Additionally, cataracts were detected in patients who had been treated with CQ.62,64

Treatment of Ocular Complaints in COVID-19 Patients

For treating ocular complications, there are some suggestions and experiences from different physicians, as well as case reports (Table 2). In a study by Navel et al, which was mentioned above to treat conjunctivitis, the physician prescribed eyelid hygiene, artificial tears, and eyewash with saline; some symptoms disappeared after 2 days. In addition, azithromycin eye drops were administered twice a day for 3 days, alongside dexamethasone on day 20. There was no viral RNA in conjunctival secretion and tears.35 As described by Chen et al, a man had a sore throat and diarrhea, and his PCR test result was positive. He had bilateral redness 13 days after the first symptoms, as well as red eyes, tearing, and a foreign body sensation; on day 14, to cure his ocular symptoms, ribavirin was prescribed QID (four times a day); on day 19, the patient claimed that all his ophthalmologic symptoms were cured. It seems that using ribavirin eye drops improved his ocular symptoms.67 According to a survey by Cheema et al, a woman developed right eye conjunctivitis. She visited the hospital with a 1-day history of conjunctivitis, herpetic keratoconjunctivitis, and fever without impaired visual activity. The diagnosis was nodular episcleritis; therefore, the physician prescribed artificial tears and fluorometholone 5 times a day for 3 days.38

As reported in a study conducted in Saudi Arabia by Otaif et al, a man with no previous complications presented to the hospital owing to redness and a foreign body sensation in his left eye. He had no history of photophobia or decreased vision discharge. Based on clinical grounds, he had episcleritis; as a result, fluorometholone 0.1% QID was administered for seven days alongside a topical preservative-free lubricant. His PCR test became positive 3 days later.39 Based on a report by Salducci and La Torre, a man was detected with COVID-19. The man’s PCR result was positive for SARS-CoV-2. His wife was asymptomatic, except for some ocular findings such as viral conjunctivitis, characterized by red, irritated, swollen eyes, secretion, and conjunctival chemosis. The doctors prescribed topical therapy, including applying a cold compress to the closed eyelids for 5–10 minutes, 3 or 4 times a day. In addition, a local antiviral gel based on ganciclovir was prescribed 5 times a day for one week.68

Conclusion

This review represented the ocular manifestations of COVID-19 with/without other symptoms, even as the initial or sole complaints in infected patients. These signs are valuable to reduce virus transmission and control the spread of COVID-19 to optimize the clinical management of patients. Therefore, it is valuable to improve our understanding of SARS-CoV-2 pathogenesis and determine the extrapulmonary signs and symptoms of the virus, including ocular manifestations, to immediately diagnose the patients. Moreover, since SARS-CoV-2 RNA has been found in conjunctival specimens in some cases, the role of ophthalmologists in this infectious disease in guiding the population and controlling the pandemic is highlighted. Appropriate and safe eye protection and proper hand hygiene could reduce the personal risk of COVID-19 transmission in societies.

Table 2. Summary of Medication and Treatment Suggestions for Ocular Manifestations of COVID-19

<table>
<thead>
<tr>
<th>Ocular Manifestations</th>
<th>Medications/Prescriptions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td>Eyelid hygiene, artificial tears, eyewash with saline, azithromycin eye drops, and dexamethasone</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin and artificial tears</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Ganciclovir ophthalmic gel</td>
<td>68</td>
</tr>
<tr>
<td>Red eyes, tearing, and foreign body sensation</td>
<td>Ribavirin</td>
<td>67</td>
</tr>
<tr>
<td>Keratoconjunctivitis</td>
<td>Valacyclovir and moxifloxacin eye drops</td>
<td>38</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>Artificial tears and fluorometholone</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Fluorometholone and topical preservative-free lubricant</td>
<td>32</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>Corticosteroids, betamethasone eye drops, cycloplic eye drop, and topical dexamethasone</td>
<td>39, 40</td>
</tr>
</tbody>
</table>
Authors’ Contribution
Conceptualization: Masoud Dadashi, Fatemeh Sameni.
Data curation: Masoud Dadashi, Bahareh Hajikhani.
Investigation: Fatemeh Sameni, Arash Khorramp
Methodology: Masoud Dadashi
Project administration: Masoud Dadashi, Fatemeh Sameni.
Supervision: Masoud Dadashi, Nafiseh Khosravi-Dehaghi.
Validation: Bahareh Hajikhani, Nafiseh Khosravi-Dehaghi.
Writing—original draft: Fatemeh Sameni, Arash Khorramp
Writing—review & editing: Bahareh Hajikhani.

Competing Interests
The authors declare that they have no competing interests.

Ethical Approval
Not applicable.

Funding
None declared.

References


