

The Role of the Ocular Tissue in SARS-CoV-2 Transmission

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Abstract: The current global pandemic of coronavirus disease 2019 (COVID-19) has affected over 21 million people and caused over half a million deaths within a few months. COVID-19 has become one of the most severe public health crises in recent years. Compared to other pathogenic coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly infectious. Due to the lack of specific and effective treatment or vaccines, disease prevention and early detection are essential for establishing guidelines to mitigate further spread. The potential role of the ocular system in COVID-19 is still not clear but it has gained increasing attention. Here, we reviewed both clinical and research evidence on the ocular manifestations associated with COVID-19, the presence of SARS-CoV-2 in ocular surface tissues and tears, and the potential role of the eye in contracting SARS-CoV-2.

Keywords: COVID-19, SARS-CoV-2, eye, transmission, ACE2

SARS-CoV-2 and COVID-19

The initial outbreak of the global pandemic of coronavirus disease 2019 (COVID-19) was found in Wuhan, China in December 2019, which was later discovered to be caused by the novel coronavirus SARS-CoV-2.

Until August 2020, about 21 million COVID-19 cases have been reported worldwide with about 0.7 million deaths (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>). COVID-19 is characterized by a range of symptoms, including influenza-like illness with fever, cough, dyspnea, headache and myalgia in most cases, as well as potentially lethal respiratory infections and acute respiratory distress syndrome in severe cases.¹ The incubation period of SARS-CoV-2 is about 3 to 7 days. Approximately 80% of the patients have mild symptoms or are asymptomatic, 15% are severe requiring oxygen, and 5% are in critical condition requiring ventilator support.²

Coronaviruses (CoVs) are a family of single-stranded, positive RNA viruses characterized by spike proteins projecting from their envelopes.³ The coronavirus family has four subgroups (α , β , γ , and δ), of which the β subgroup contains 3 highly infectious viruses: SARS-CoV, MERS-CoV, and SARS-CoV-2.⁴ These viruses bind to host cell surface receptors (e.g. ACE2) using these spike proteins, fuse their viral envelope with the host cell membrane, and then enter the cell.⁵ Viral RNA uses the host cell for RNA replication, protein synthesis, as well as assembly and release of new viral particles. CoVs cause a variety of diseases in non-human species including birds and livestock, as well as mild to lethal

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respiratory diseases in humans.⁶ SARS-CoV and MERS-CoV caused outbreaks in 2002/2003 and 2012/2013, and studies indicated that their transmission is primarily through respiratory droplets, aerosols, close contacts, fecal-oral spread, and possibly the eye.⁷ Similarly, SARS-CoV2 has been reliably detected using RT-PCR in nasopharyngeal and oropharyngeal secretions, and it is also detectable in blood and stool samples.⁸

Since an effective therapeutic agent or vaccine is not yet available for SARS-CoV-2, it is important to understand the potential risks of each transmission modality in order to establish proper preventative measures. Current CDC guidelines recommend protecting the nose, mouth, and eye because they contain susceptible mucous membranes, which is based on the experience from previous SARS/MERS epidemics (<https://www.cdc.gov/coronavirus/2019-ncov/index.html>). Here, we provided a narrative review of current evidence to summarize and speculate the role of the ocular system in SARS-CoV-2 transmission.

Methodology

A literature search was performed using 4 databases (PubMed, Web of Science, Scopus, and Google Scholar) which returned studies published up to July 31st, 2020. Keywords included “COVID-19”, “SARS-CoV-2”, “eye”, “ocular”, “ophthalmic”, “ACE2” and MeSH terms (“COVID-19”, “severe acute respiratory syndrome coronavirus 2” and “Eye”). For this review, relevant studies that emphasized ocular manifestations of COVID-19 or SARS-CoV-2, viral detection of SARS-CoV-2 in ocular surface secretions or tears, and ACE2 presence in ocular tissues were included. Letters, editorials, case reports, case series, observational studies, reviews, meta-analyses, and systematic reviews were included in the literature search.

Ocular Manifestations of COVID-19

The prevalence of ocular manifestations of COVID-19 varies. According to our literature survey, it ranged from 0% to 32% (Table 1). However, several studies suggested that the prevalence of ocular signs and symptoms in COVID-19 patients is relatively low.⁹ Two separate meta-analyses on ocular manifestations estimated a pooled prevalence of 5.5% and <4%.^{10,11} Another meta-analysis showed that the prevalence of conjunctivitis in 1167 COVID-19 patients was about 1%.¹² Interestingly, the prevalence of conjunctivitis correlated with disease

severity: 3% of conjunctivitis in severe patients in contrast to 0.7% in non-severe patients.¹²

Overall, the most common ocular manifestation of SARS-CoV-2 infection is conjunctivitis or conjunctivitis-like signs and symptoms, which is similar to SARS-CoV and HCoV-NL63.^{13–16} Conjunctivitis may be unilateral or bilateral.⁹ Two case reports describe the presence of pseudomembranes among severe cases of conjunctivitis. Salducci et al reported one COVID-19 patient with pseudomembranes of fibrin, inflammatory cells, and enlarged preauricular and submaxillary lymph nodes.¹⁷ Navel et al reported one case with conjunctival pseudomembranes associated with petechial and tarsal hemorrhages.¹⁸ Cheema et al reported a case of keratoconjunctivitis with corneal subepithelial infiltrates and overlying epithelial defects.¹⁹

Other ocular manifestations include photophobia,²⁰ redness, ocular secretions, chemosis, itching, foreign body sensation, dry eyes, follicular conjunctivitis, and episcleritis²¹ (summarized in Table 1). Importantly, none of the studies reported any associated changes in visual acuity of COVID-19 patients with ocular manifestations.^{9,21–23}

There has been only one study showing retinal changes in COVID-19 patients.²³ Marinho et al examined 12 COVID-19 patients and found that all of them displayed hyper-reflective changes in retinal ganglion cell and inner plexiform layers binocularly using OCT. Four patients had cotton wool spots and microhemorrhages but no signs of intraocular inflammation. Despite OCT changes in the retina, no visual acuity nor pupillary reflex changes was found.

The timing and duration of ocular manifestations of COVID-19 also vary. In several cases, conjunctivitis-related discomfort was part of the initial chief complaint.^{19,22,24,25} One patient self-reported having 4 days of conjunctivitis and 3 days of fever prior to admission.²² Another case report described a man who presented with unilateral eyelid edema and moderate conjunctival hyperemia but then developed headache, fever, cough, and dyspnea hours after ocular discomfort.²⁴ Hong et al studied 64 COVID-19 patients, and found that 6 of 15 conjunctivitis patients showed ocular signs and symptoms prior to COVID-19 related fever or respiratory symptoms.²⁵ In a case report, Cheema et al found that a patient presented with keratoconjunctivitis 5 days prior to testing positive for COVID-19 via nasopharyngeal swab.¹⁹

In contrast, a few studies showed that some COVID-19 patients developed ocular manifestations several days after the onset of respiratory illness.^{9,26} Among a group of 18

Table 1 Summary of Ocular Manifestations and Detection of SARS-CoV-2 RNA on Ocular Surface

Authors	Study	Ocular Manifestations	SARS-CoV-2 Ocular Surface RNA	Ocular Signs and Symptoms
Salducci et al ¹⁷	Case report	Positive	NR	Photophobia, redness, serous secretions, chemosis, pseudomembranes of fibrin, inflammatory cells, preauricular and submaxillary LAD
Mendez Mangana et al ²¹	Case report	Positive	NR	Nodular episcleritis
Navel et al ¹⁸	Case report	Positive	NR	Tarsal pseudomembranes, petechial/tarsal hemorrhages
Hu et al ³³	Case report	Positive	Positive	Left lacrimal duct obstruction and mild tearing
Cheema et al ¹⁹	Case report	Positive	Positive	Keratoconjunctivitis
Chen et al ³⁷	Case report	Positive	Positive	Bilateral acute follicular conjunctivitis
Daruich et al ²⁴	Case report	Positive	NR	Unilateral eyelid edema, conjunctival hyperemia
Loon et al ²⁷	Case series	0 of 36 (0%)	3 of 36 (8%)	NR
Marinho et al ²³	Cross sectional	NR	NR	Retinal findings (hyper-reflective lesions at the level of ganglion cell and inner plexiform layers more prominent than at the papillomacular bundle, cotton wool spots, microhemorrhages)
Chen et al ²⁶	Cross sectional	27 of 535 (5%)	NR	Conjunctival congestion
Guemes-Villahoz et al ⁹	Cross sectional	18 of 689 (3%)	1 of 689* (6%)	Unilateral and bilateral conjunctivitis, redness, ocular secretions
Zhang et al ²²	Cross sectional	2 of 72 (3%)	1 of 72* (0.1%)	Conjunctivitis with conjunctival congestion and watery discharge
Zhou et al ³⁰	Cross sectional	8 of 121 (7%)	3 of 121 (2%)	Itching, redness, tearing, discharge, foreign body sensation
Ceran et al ²⁰	Cross sectional	20 of 93 (22%)	NR	Hyperemia, epiphora, ocular secretions, chemosis, follicular conjunctivitis, episcleritis, photophobia
Xie et al ³⁵	Cross sectional	NR	2 of 33 (6%)	NR
Wu et al ²⁹	Cross sectional	12 of 38 (32%)	2 of 38 (5%)	Conjunctivitis, conjunctival hyperemia, chemosis, epiphora, and increased secretions
Seah et al ³⁴	Prospective	0 of 17 (0%)	0 of 17** (0%)	NR
Xia et al ²⁸	Prospective	1 of 30 (3%)	1 of 30* (3%)	Conjunctivitis, conjunctival congestion, ocular secretions
Zhou et al ³⁰	Prospective	1 of 67 (1%)	3 of 67 (4%)	Conjunctivitis
Hong et al ²⁵	Retrospective	15 of 56 (27%)	1 of 56 (2%)	Sore eyes, itching, foreign body sensation, tearing, redness, dry eyes, ocular secretions, floaters, conjunctivitis
Guan et al ¹	Retrospective	9 of 1099 (0.8%)	NR	Conjunctival congestion
Loffredo et al ¹²	Meta-analysis	1%	NR	Conjunctivitis
Lawrenson et al ¹¹	Meta-analysis	<4%	3%	Conjunctivitis
Ulhaq et al ¹⁰	Meta-analysis	42 of 735 (5.5%)	NR	Conjunctivitis

Notes: *Sampled only symptomatic patients. **Schirmer test strips.

Abbreviation: NR, not reported.

COVID-19 patients with conjunctivitis, the mean onset of ocular manifestations was 8 days (ranging from 1–24 days) after the onset of COVID-19 symptoms.⁹ Another study of 27 patients reported that only 4 of the COVID-19 patients presented ocular conjunctival congestion as the initial symptom while the other 23 patients developed conjunctival congestion between 0–28 days after non-ocular COVID-19 symptom onset.²⁶

The Role of the Eye in SARS-CoV-2 Transmission

The ocular system may play three roles in viral transmission. First, the virus may be shed from ocular surface secretions and/or tears which facilitates viral spreading. Second, the initial viral infection may occur at ocular surface tissues. Third, the virus may spread to the respiratory system of the same individual with the ocular system acting as a conduit.

The Potential of Viral Shedding from Ocular Surface

It is postulated that ocular surface secretions and/or tears are the potential sources of SARS-CoV-2 transmission. Viral RNA was detected in tear samples from 2003 SARS outbreak patients using RT-PCR.²⁷ In Singapore, SARS-CoV was detected in tears from 3 of 8 probable SARS-CoV infected patients.²⁷ Similarly, many studies also showed SARS-CoV-2 RNA in ocular samples as described previously. However, the SARS-CoV-2 viral detection rate of conjunctival swabs is overall low. In one meta-analysis, the pooled rate of viral RNA detection was estimated to be 3%.¹¹ In another meta-analysis, Ulhaq and Soraya found that the specificity of SARS-CoV-2 viral detection using conjunctival swabs was 100% but the sensitivity was only 0.6% compared to nasopharyngeal swabs.¹⁰ Similarly, our literature review showed that ocular viral detection rate ranged from 0% to 8% among confirmed COVID-19 patients (Table 1).

Surprisingly, detection of SARS-CoV2 RNA is not always associated with ocular manifestations.^{22,28–31} Xia et al collected conjunctival swabs from 30 confirmed COVID-19 patients, among whom only 1 patient was SARS-CoV-2 viral RNA positive and that patient was the only individual with conjunctivitis.²⁸ In contrast, Wu et al reviewed 12 COVID-19 patients with conjunctivitis, and only 2 patients were viral positive for their conjunctival swabs.²⁹ Zhang et al also reported that one of the two

COVID-19 patients with conjunctivitis was SARS-CoV-2 RNA positive in the tear sample.²² Zhou et al studied conjunctival swabs from 121 COVID-19 patients, among whom there were 8 patients with ocular symptoms.³⁰ However, SARS-CoV-2 RNA was detected in the conjunctival swab in only 1 of the 8 patients, and that patient was a severe/critical case.³⁰ However, among the other 113 patients without any ocular symptoms, 2 were viral RNA positive in their conjunctival swabs.³⁰ In another study with 67 COVID-19 patients, Zhou et al found positive SARS-CoV-2 RNA test results in 1 patient and probable positive results in 2 patients, but none of the 3 patients had ocular complaints.³¹ There was only 1 patient with ocular manifestations in the same study but her conjunctival swab test result was negative.

It is not yet clear why there is an inconsistency between viral detection and ocular manifestations. Some studies suggested that the possibility of viral shedding in COVID-19 patients is relatively low compared to the respiratory system.^{26,32} One potential explanation is that the virus may be washed out or significantly diluted by the tear film, which could lead to low detection rates.²⁵ Interestingly, Hu et al reported one COVID-19 patient who showed persistently positive RNA results in conjunctival swabs for an additional 2 weeks despite the convalescence of symptoms and negative nasopharyngeal swabs.³³ This patient had lacrimal duct obstruction, suggesting less drainage through the nasolacrimal duct which could allow the virus to accumulate in his conjunctival sample.

Pre-existing ocular surface diseases may also affect viral detection.²⁵ Hong et al studied 56 COVID-19 patients and 15 of them had obvious ocular symptoms.²⁵ Among all 56 patients, only 1 patient showed positive SARS-CoV-2 in conjunctival swab. This patient had conjunctivitis as well as a history of prior pterygium surgery. The authors suggested that the patient's pre-existing ocular surface disease might have compromised the ocular defense mechanism which could predispose him to viral retention and detection.

Although these clinical studies provided insight into SARS-CoV-2 shedding, they have some limitations:

1) The majority of studies included only hospitalized patients, which is likely to introduce selection bias. Severe COVID-19 cases are more likely to have ocular manifestations or be evaluated for their ocular complaints.¹² For example, COVID-19 patients or suspects with only mild respiratory or ocular symptoms might not seek medical assistance, especially if their visual function was not impaired.

2) Another limitation is the heterogeneity in sample collection methods. Not all the studies utilized conjunctival swabs, which might produce different results for viral detection. For example, one study utilized Schirmer's test strips,³⁴ which collected mainly tears as opposed to both exfoliated cells and tears in conjunctival swabs.³⁵ Viral loads may differ between tears and ocular surface tissues, which could affect the ability for the conventional RT-PCR assay to detect SARS-CoV-2 RNA. In addition, appropriate swab materials should be used to facilitate viral RNA detection. For nasopharyngeal swabbing, the World Health Organization (WHO) recommends using synthetic fiber swabs with plastic shafts but not calcium alginate swabs or those with wooden shafts because they may contain substances that could inactivate the virus or interfere with the PCR test (<https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>).

Additionally, not all studies tested ocular samples for all subjects (Table 1). Since we now know that there is a significant proportion of RNA positive individuals without ocular manifestations, the detection rate might have been different. Other differences in sample collection techniques included the decision to use topical anesthetics during sampling as well as the sampling of one or both eyes.

3) The timing of sample collection may also affect results. Recent SARS-CoV-2 studies focusing on the upper respiratory tract showed that 1) viral loads in nasopharyngeal specimens peaked at 2–3 days after the onset of symptoms, and 2) viral loads between symptomatic and asymptomatic patients are equivalent.^{32,36} However, whether these findings apply to tear samples is unknown. Some studies suggest that earlier sampling may yield more positive results.^{27,35,37} For example, during the 2003 SARS outbreak, one study conducted in Singapore sampled 8 patients and detected 3 positive cases of SARS-CoV via conjunctival swab.²⁷ The 3 positive cases had a mean sampling time of 4.0 days since symptom onset, whereas the 5 negative had a mean sampling time of 19.4 days. Similarly, in a cross sectional study of 33 COVID-19 patients, most of the ocular samples were collected more than 7 days of symptom onset, and Xie et al found only 2 cases with positive ocular SARS-CoV-2 RNA results.³⁵ However, one case report described an individual who demonstrated positive conjunctival viral RNA at 13, 14, and 17 days after symptom onset, and his conjunctival viral RNA turned negative on day 19.³⁷ At this time, it is still difficult to determine the optimal time window to detect SARS-CoV-2 on the ocular surface. There are multiple factors to

consider such as self-reporting of symptoms, duration of symptoms, and fluctuation in viral load in ocular tissues.

The Potential of Contracting SARS-CoV-2 via the Eye

A major concern for public health as well as ophthalmologists is whether ocular exposure to SARS-CoV-2 may be a route of infection. There are a few reports suggesting this possibility.^{19,22} Lu et al reported that a respiratory specialist who was inspecting clinics within the Wuhan region, had complaints of redness in his left eye several days prior to developing respiratory symptoms and later he was tested positive for SARS-CoV-2.³⁸ He might have contracted SARS-CoV-2 via the eye since he wore N95 masks but did not wear protective eyewear. Zhang et al reported that an emergency department nurse in Wuhan China with inadequate eye protection while working with COVID-19 suspects had red and teary eyes from days 1–4 of disease onset.²² Although her conjunctival and nasopharyngeal swabs were both negative at day 10, she later developed fever and pneumonia and was later confirmed to have COVID-19.

The mechanism of SARS-CoV-2 infection of the ocular tissue, however, is still unclear. The membrane-associated angiotensin-converting enzyme 2 (ACE2) is believed to be the primary receptor/entry protein for coronaviruses including SARS-CoV and SARS-CoV-2,³⁹ while MERS relies on the DPP4 receptor.^{40,41} SARS-CoV-2 binds to ACE2 using its spike transmembrane protein, is processed by serine protease TMPRSS2, and enters host cells during early infection.^{5,39}

It is well-established that ACE2 is highly expressed in the lung and therefore SARS-CoV and SARS-CoV-2 are primarily associated with respiratory system diseases. Our current knowledge of SARS-CoV-2 infection mainly is based on research of the respiratory system, but recent literature suggested that the ocular system shares the same infection mechanism.^{42,43} Jiang et al developed human ACE2 receptor transgenic mice and infected them with SARS-CoV-2.⁴² They found that while most viruses were found in the lungs, low levels of viruses were also detected in the heart, brain, and eye, suggesting a tropism of SARS-CoV-2 for ocular tissues. In addition, Hui et al found that locally isolated SARS-CoV-2 viruses were able to infect human conjunctiva explants.⁴³ These studies support the possibility of entry of SARS-CoV-2 via the eye.

Since ACE2 is the key receptor for SARS-CoV-2 infection, its ocular expression is of particular importance. Previous studies showed the expression of RAS system components

and ACE2 in the posterior segment such as the retina and choroid.⁴⁴ Recent studies have attempted to determine ACE2 in ocular surface tissues, such as the conjunctiva and cornea, which are exposed to the external environment and are potential entry points for SARS-CoV-2 infection. Sungnak et al compared the expression of ACE2 among multiple tissues and organs and found that ACE2 is expressed in corneal epithelial cells.⁴⁵ Zhou et al had similar findings using post-mortem eyes and surgical specimens to study ACE2.⁴⁶ They found that both ACE2 and TMPRSS2 are significantly expressed and localized in corneal epithelial and endothelial tissues.

In contrast to the cornea, current studies showed that the expression of ACE2 in the conjunctiva is low.^{47–49} Lange et al used RNA sequencing (RNAseq) to determine ACE2 in 38 conjunctival samples from 38 patients.⁴⁷ The authors found no substantial expression of ACE2 or other co-receptors (TMPRSS2, ANPEP, DPP4, and ENPEP) at mRNA levels in conjunctival samples. Immunohistochemistry staining showed similar results. Ma et al studied human conjunctival and pterygium cell lines, and the authors found that a) ACE2 was expressed in only 2 of 3 conjunctival and pterygium cell lines, and b) TMPRSS2 was expressed in 1 of 3 pterygium cell lines but none of the 3 conjunctival cell lines.⁴⁸ Leonardi et al used RNAseq and microarray to study 18 healthy conjunctival samples and 6 ex vivo healthy cornea samples.⁴⁹ They found weak ACE2 expression and intermediate TMPRSS2 expression in the conjunctiva and cornea.

There are several potential protective factors that may inhibit ocular infection by SARS-CoV-2. We believe that low ACE2 expression level in the conjunctiva as well as constant flushing of ocular secretions and tears may play a role. Also, lactoferrin and secretory IgA in tears may inhibit SARS-CoV-2 infection. Notably, Lang et al found that lactoferrin inhibits SARS-CoV binding in a dose-dependent manner by interfering with viral attachment to heparan sulfate proteoglycans, an important anchoring site that assists in the initial stage of the virus binding the cell surface.⁵⁰ Although similar studies on SARS-CoV-2 have not been done, lactoferrin is very likely to inhibit SARS-CoV-2 since SARS-CoV-2 shares similar infection mechanisms with SARS-CoV.

The Potential Role of Ocular Tissues in Respiratory Tract Infection

Another potential role of the eye in viral transmission of SARS-CoV-2 could be as a transport conduit to respiratory tract tissues. When ocular secretions and tears are drained

through the nasolacrimal duct to the inferior meatus of the nose, viral particles may be transported from the ocular surface to the airway tissue causing respiratory infection and diseases.⁵¹ Recent studies have indicated that there is strong ACE2 expression specifically in nasal epithelial cells⁴⁵ which would be in direct contact with draining ocular secretions and tears. However, further studies are needed to evaluate this possibility as a route of infection.

Conclusions and Future Studies

The development of effective therapies and vaccines against the COVID-19 pandemic is still rapidly evolving. Therefore, understanding the possible transmission routes and mechanisms of SARS-CoV-2 infection is of utmost importance. Current studies suggested that the eye is a potential route for SARS-CoV-2 transmission and infection. However, the risk of viral spreading via ocular secretions and tears or contracting an infection via the eye is likely low comparing to other routes of infection such as respiratory tissues. This is supported by both clinical studies and research findings including low rates of viral RNA detected in conjunctival swabs and epidemiologic studies showing a relatively low likelihood of developing ocular manifestations or infection. Fortunately, there is no evidence showing that SARS-CoV-2 affects visual acuity or other visual functions. However, appropriate precautions and use of personal protective equipment for the eyes such as goggles and face shields should still be employed at this time. Until more conclusive results are available, preventative measures should reflect the most up to date evidence. We believe that future studies are needed to determine:

1. The potential for viral shedding in tears or secretions of asymptomatic carriers since they play an important role in the pandemic. It has already been shown that COVID-19 patients without any ocular manifestations shed detectable levels of virus but the study of asymptomatic carriers is not yet available.
2. A standardized method for collecting ocular samples for SARS-CoV-2 testing. Heterogeneity in testing techniques are an unnecessary impact on clinical and research outcomes. A standardized approach for sample collection as well as a wider range of sampling time points would provide insightful information.
3. Whether ocular surface tissues can be directly infected by SARS-CoV-2 using in vivo models,

ideally primate models. Animal models would provide pertinent information, such as minimum viral titer and the duration from infection to the onset of ocular symptoms/signs.

4. The risk of SARS-CoV-2 exposure during ocular surgeries. Napoli et al summarized potential risks and potential solutions to minimize viral exposure for eye surgeons.⁵² The authors emphasized the possibility of generating bioaerosols during lacrimal procedures. More research is needed to determine these risk factors and find out effective strategies to protect practitioners. In addition, there have been no studies to determine if the aqueous humor could contain SARS-CoV-2. Different from tears, aqueous humor is not secreted in normal individuals. However, for glaucoma patients who have received trabeculectomy, drainage valves, and similar procedures, their aqueous humor may be a potential source of viral transmission.
5. The association between uveitis and SARS-CoV-2. A recent study showed that IFN induces ACE2 in human airway epithelium.⁵³ Since IFN is used to treat certain uveitis, it may also increase the chance of viral contraction and/or spreading among these patients.

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