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Evolving Consensus Experience of the IUSG-IOIS-FOIS with Uveitis in the Time of COVID-19 Infection

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ABSTRACT

This document summarizes the experience of the International Uveitis Study Group (IUSG), the Intraocular Inflammation Society (IOIS), and the Foster Ocular Inflammation Society (FOIS) and can aid as a guide for the treatment of uveitis patients in the era of COVID-19 pandemic.

This document summarizes the experience of the International Uveitis Study Group (IUSG), the Intraocular Inflammation Society (IOIS), and the Foster Ocular Inflammation Society (FOIS) and can aid as a guide for the treatment of uveitis patients in the era of COVID-19 pandemic. This consensus is published on the website of the IUSG (https://www.iusg.net/uploads/images/IUSG%20Library/001-Consensus-Experience-Document.pdf), the IOIS, and the FOIS. It is therefore accessible to every doctor who seeks advice for her/his uveitis patients.

RISK FACTORS

These are the currently known **risk factors** for severe COVID-19 infection:

1. Age above 60 (in some countries, the limit is placed at 65) years, with a significant risk 70 years and above
2. Co-morbidity: cardiovascular disease > respiratory system disease > systemic hypertension (HTN), diabetes mellitus (DM), obesity (BMI>40)[1]
3. Contact with infected persons (especially within the family) or a recent travel history to severely affected countries or regions (countries with documented community transmission)
4. Health-care workers (increased viral load/exposure due to lack of appropriate personal protective equipment [PPE])
5. Use of moderate to high dose corticosteroids where dose reduction may be required, particularly if COVID develops (see below)[2,3]

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FACTORS LEADING TO AN INDIVIDUAL TREATMENT PLAN

In general, there are three potential uveitis scenarios:

In stable uveitis patient on systemic immunomodulatory therapy (IMT)

A. without clinical signs of COVID-19 infection (presymptomatic or asymptomatic)

B. with either confirmed COVID-19 or showing clinical signs of COVID-19 infection

C. new uveitis patients requiring immunosuppression, or a uveitis patient with an exacerbation requiring an increased dose of IMT.

Uveitis Patients without Confirmation of Clinical Signs of COVID-19 Infection

These patients would have previously been taught how to avoid infection when they were started on IMT. They are expected to already be practicing avoidance of infection through hand washing, personal hygiene, and avoiding crowds.

The ophthalmologist should reinforce the need to use their personal protection protocols, and encourage them to follow all preventative measures proposed at a local or national level. Most effective among these are appropriate social distancing, wearing of masks (guidelines differ depending on the country), and frequent hand washing when in contact with surfaces.

In certain European countries following the start of the pandemic, patients in high risk groups were contacted either personally or by mail/e-mail to re-inforce the recommendations below. Contact by physicians or office personnel, helped ensure that appropriate measures were taken, and that patients were made aware of the steps to be taken in order to avoid becoming COVID positive. These measures include:

- staying at home as much as possible
- practicing social distancing (keeping at 1.5 to 2 m, approximately 6 feet, from other individuals), whether on the street, in stores or waiting rooms
- wearing a mask whenever in the proximity of non-household members or in crowded locations
- washing hands frequently with soap for at least 20 seconds, particularly after touching surfaces such as vending or cash machines, doorknobs, elevator buttons, and light switches. Direct contact from contaminated surfaces is one of the major modes of transmission[4]
- avoidance of face touching if one has not been able to wash the hands
- wearing gloves (even leather or winter gloves can be an option if no latex/vinyl gloves are available in a pharmacy).

If the patient feels unwell, they should contact their doctor's office, who would then be able to advise on the urgency of an appointment. This may or may not be possible depending on the country. In some countries, private offices are allowed to see suspected COVID patients only if they are equipped with isolation rooms, and if appropriate barrier PPE are available (gloves, aprons, N95 or equivalent masks, and face shields or glasses). Alternatively, they may be referred to an appropriate diagnostic center. It is important to keep in mind, particularly in spring and fall, that other viruses may be prevalent in the community, including the common cold and influenza. An appropriate differential diagnosis is therefore mandatory should COVID-19 typical symptoms be present. Depending on local arrangements, patients on immunosuppression may be considered an "at-risk group" and benefit from earlier COVID-19 testing.

In the clinical setting, at-risk patients should preferably be seen earlier in the day and at a separate time from non-risk patients. The number of patients in the waiting room should be kept to a minimum, allowing for appropriate social distancing, and alcohol disinfectant should be provided. Accompanying people should wait outside if possible. Everyone should be wearing a mask. The waiting room examination exam rooms should be frequently ventilated; one may even consider leaving all doors open, including the entry to the office to increase air circulation. Slit lamps should be equipped with shields, and the ophthalmologist should keep a safe distance from the patients when discussing their case. Consultations should be kept brief. The results of laboratory and imaging-based studies should be reviewed prior to seeing the patient. Screening patients a day or two prior to their scheduled visit for risk factors may be beneficial to further minimize risk (see addendum 2). Consider virtual consultations for patients who are low risk for uveitis and are stable.

The first line of defense to any infection is innate immunity. Thus, if the patient's total white blood cell count (WBC) is kept above the lower limit of normal (4,000 per microliter), the risk of infection is reduced (https://www.ncbi.nlm.nih.gov/books/NBK261/).
IMT agents targeting T cells such as CSA are generally safe in moderate doses and do not seem to increase the risk to viral infections, with the possible exception of Varicella-zoster virus (VZV) infections. (https://www.ncbi.nlm.nih.gov/books/NBK47401/) Blood monitoring should be maintained, and preferably done close to home to minimize travel and exposure.

The SARS-CoV-2 virus binds to its target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed on the cell membranes of the lung, intestine, kidney, blood vessels, and even the conjunctiva.[4] The expression of ACE2 is significantly increased in patients with type-1 and type-2 diabetes mellitus (DM), or when patients are being treated with ACE inhibitors or ACE2 receptor blockers (ARBs). ACE2 inhibitors reduce inflammation and have been suggested as treatments for

inflammatory lung diseases, cancer, DM, and HTN. ACE inhibitors cause an up-regulation of ACE-2 and might predispose to infection with SARS-CoV-2 virus. There seems to be a genetic predisposition for an increased risk to SARS-CoV-2 infection due to ACE2 polymorphisms linked to DM, HTN, and stroke, especially in Asian populations. However, the role of ACE inhibitors in relation to the virulence of the infection is not established. Cardiologists do not recommend taking patients off their ACE inhibitors at this time as it may cause more harm than good.[5,6] However, one should recognize that uveitis patients with co-morbidities such as DM, HTN, and cardiovascular disease are at higher risk if they develop COVID-19.[7]

Even if your patients are well informed on how to protect themselves from infections, we recommend that you or your staff contact your patients receiving IMTs by phone to provide them with some guidelines as to what to do in the event they become infected by the SARS-COV-2 virus. The Swiss experience so far has shown that many patients needed to be reassured and reminded of the importance of distancing measures and reassured about the use of IMTs. Some, it was noted, stopped their medications without seeking medical guidance. Such communication is also of importance in a pediatric patients on IMT and gives ophthalmologists the opportunity to discuss the need for treatments and alternative bridging measures. It also allows the ophthalmologist to discuss the need for treatment specific for that individual patient, and possibly to reassess the need for therapy. given uncertainties regarding recurring outbreaks over the coming 18 months.[8]

Therefore, for patients with no evidence of COVID-19, we agree that IMT should be maintained (but reassess the need for continued therapy and minimize the dose of corticosteroids whenever possible).

Patients with either Confirmed COVID-19 Infection or Clinical Signs of COVID-19 Infection

In the event that patients develop clinical signs, whenever possible get confirmation of the diagnosis as there can be other viral causes that may mimic COVID. Please remind the patient to inform their physicians of all the medications they are taking for their uveitis.

If your patient is asymptomatic, continue with IMT along with blood monitoring, and reduce the IMT doses as possible if the white blood cell count falls below 4000/μL.

Symptomatic patients should temporarily stop their conventional IMT and biologic therapies (except for interferon and tocilizumab). Patients taking anti-TNF-drugs should omit their next planned subcutaneous doses until they have recovered.

If needed, consider local treatment options. Systemic corticosteroids may need a slow reduction, but such step should be discussed with the COVID treatment team. Low maintenance doses less than 10 mg/day of prednisolone equivalent may not pose significant risk, and should be maintained. If doses are above 20 mg, these should be tapered if possible, using local therapy to stabilize the uveitis. High dose corticosteroids may predispose the patient to developing high viral loads that could subsequently lead to immune dysregulation.[3]

In most cases, the disease course will be short lived. Symptoms are typically present for 10 to 14 days. If respiratory impairment occurs, it usually becomes evident by day 7 or 8 and is rapidly followed by either recovery or the need for more oxygen support. Once the respiratory impairment has resolved, the initial immunosuppressive regimen may be resumed.

EFFECT OF IMMUNOSUPPRESSIVE DRUGS ON SARS-COV-2

1. Immunosuppression does not appear to increase the risk of contracting an illness. A review of mortality and morbidity reports from prior coronavirus infections failed to reveal any mortalities among transplant unit patients.[10] In Bergamo, Italy, among 522 inflammatory bowel disease patients, none were admitted to the hospital with a SARS-CoV-2 proven infection, when on a statistical basis, 21 such SARS-CoV-2 admissions could have been expected.[9] Bhoori et al. published a series of 111 long-term adult liver transplant patients on minimal immunosuppression, three of whom developed and died from COVID-19. The authors then compared this group to three uneventful SARS-CoV-2 infections occurring in 40 recently transplanted and fully immunosuppressed patients the same center. The three SARS-CoV-2-associated deaths appeared to be related more to known risk factors of severe COVID-19 disease (age and/or the presence of several concomitant comorbidities) rather than the degree of immunosuppression.[11] The authors added that the immunotherapy may, in fact, have been protective.
2. **Interferon-alpha and beta**, and **anti-IL-6** may reduce the possible "Cytokine storm syndrome."[12,13] Cytokine storm syndrome can be one of the factors leading to death during COVID-19 infection; specifically through an excessive release of cytokines (IL-1, IL-6, IL-18, and Interferon Gamma) resulting in multi-organ failure. IL-6 blockade is under investigation as a treatment for COVID-19.

3. New uveitis patients requiring immunosuppression or a patient with an exacerbation requiring an increased dose of immunosuppression. In patients with severe acute uveitis , be it new onset or recurrent, and in whom high doses of corticosteroids such as IV methylprednisolone are traditionally indicated (e.g., Vogt-Koyanagi-Harada disease), periocular or intravitreal corticosteroids should be considered, alone or in

combination with lower doses of systemic corticosteroids. In the case of acute Behcet´s Disease, treatment with interferon-alpha or beta can be considered. To our knowledge, in patients who have contracted SARS-CoV-2 while on anti-TNF, the course has been mild with no severe illnesses or death reported. Several guidelines have been proposed by rheumatologies, links to which are provided in addendum 1.

OCULAR MANIFESTATIONS OF SARS-COV-2

Conjunctivitis, conjunctival injection, and conjunctival chemosis appear to be the common ocular complications of acute SAR-CoV-2 infection.[14, 15, 16, 17] While the vast majority of cases of conjunctivitis have been observed in patients who were known to be SARS-CoV-2 infected, isolated cases of conjunctivitis in SARS-CoV-2 infected yet otherwise asymptomatic patients have been described. Among those with COVID-19, isolation of SARS-CoV-2 ribonucleic acid (RNA) from the conjunctiva appears to be low, at 5-10% of patients or less,[18,19] (and its persistence in tears appears to be short lived at 1 to 2 days.[20] As for tears as a mode of transmission, its role is probably limited[14, 20, 21, 22, 23] – although eye care providers should clearly employ routine standard protective precautions when dealing with patients who might be SARS-CoV-2 infected, including hand hygiene, cleaning and disinfecting of environmental surfaces, and use of PPE.[24] A case of pseudomembranous hemorrhagic conjunctivitis has been described as a late manifestation of COVID-19.[25]

Asymptomatic retinal complications of SARS-CoV-2 infection have also been reported, although their prevalence remains unknown. Marinho et al. [26] used optical coherence tomography (OCT) to examine 12 adults in Sao Paulo, Brazil, 11 to 33 days after the onset of COVID-19, including two who were admitted to the hospital. Of note, 11 of these patients (91.7%) were healthcare providers, including nine physicians. All patients had similar findings, including evidence of microvascular changes in the macula, including isolated cotton wool spots and microhemorrhages. The authors cited studies describing uveitis, retinitis, retinal vasculitis, and optic disc involvement in animals following coronavirus infection. [27, 28] Casagrande et al. [29] reported that SARS-CoV-2 RNA was identified in three of 14 PCR sampled postmortem retina specimens taken from patients who died of COVID-19 in Germany.

LABORATORY MARKERS OF CORONA VIRUS INFECTION[30]

Please be aware that some laboratory parameters (e.g., ESR) are influenced by IMT or are not reliable when using specific IMT drugs (e.g., tocilizumab)

Most frequent:

1. Decrease in lymphocyte count
2. Low albumin
3. Decrease in hemoglobin levels
4. Increase in C-reactive protein (CRP)
5. Increase in Erythrocyte Sedimentation Rate (ESR)
6. Increase in Lactate Dehydrogenase (LDH)
7. Increase in D-dimer

IN SEVERE COVID-19

1. Decrease in lymphocyte count
2. Low albumin
3. Decrease in hemoglobin levels
4. Increase in C-reactive protein (CRP)
5. Increase in Erythrocyte Sedimentation Rate (ESR)
6. Increase in Lactate Dehydrogenase (LDH)
7. Increase in D-dimer
8. Increase in Neutrophil count
9. Increase in Alanine Aminotransferase (ALT)
10. Increase in Aspartate Aminotransferase (AST)
11. Increase in Cardiac biomarkers (e.g., cardiac troponins)
12. Increase in Procalcitonin

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ADDITIONAL RESOURCES AVAILABLE OVER THE INTERNET

1- https://www.iapb.org/news/covid-19-resources-here-is-what-we-know/: international agency for the prevention of blindness has an information page in eight languages with useful links to eye health organizations, editorials, and articles.

2 https://www.aao.org/headline/alert-important-coronavirus-context: American academy of ophthalmology provides a detailed overview of the current American guidelines background information on the virus and environmental cleaning and disinfection recommendations. Also, consider the following site: https://www.aao.org/coronavirus which contains more general information about eyecare.

3- https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen: rolling updates on the WHO site regarding Coronavirus 2019 disease. It also provides information on a WhatsApp campaign in Arabic, French, Spanish, and English where patients can get up to date information on how to protect themselves.

4- https://www.uveitisstudygroup.org/?id=15: UK uveitis national clinical study group has a COVID-19 info hub with information on how to stratify high-risk patients as well as links to other trusted UK sites.

5- https://www.ohsu.edu/sites/default/files/2020-03/CEI%20Clinic%20Protocol%20for%20Suspect%20or%20Confirmed%20COVID-19%20Patients%202020-03-12.pdf best practice for prevention of droplets and contact transmission in ophthalmology clinics

6- https://www.youtube.com/watch?v=Ww0Rf079MZ4 video showing how to put on an remove protective equipment for droplet precautions (donning and doffing)

7- https://msra.org.au/news/ceo-message-covid-19/: information regarding advice for MS patients from the Australian MS Research foundation as well as other related links.