

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

Latest version April 3, 2020 (previous version from March 25, 2020 is outdated)

Problem:

This document summarizes the experience of the IUSG, the IOIS and the FOIS and can help you as a guide in the treatment of your patients through this situation. 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 available to every doctor who seeks advice for her/his uveitis patients. Comments, opinions and suggestions provided by the readers are reviewed by members of the executive boards of all 3 societies before being posted. As additional comments and suggested are sent to us, they will be added every few days. Please use for your comments ONLY Vishali Gupta's mail address vishalisara@gmail.com.

We also provide you with a twitter account to share information on the pandemic and how to handle it. A folder is available on the IUSG website at www.iusg.net/library and very soon on the websites of IOIS and FOIS with additional guidelines and information.

We all are aware of the typical **risk factors** for severe COVID-19 infection:

- a. Age above 50 (in some countries the limit is placed at 60 to 65) years, with a significant risk starting above 70 years-
- b. Co-morbidity: cardiovascular disease > respiratory system disease > arterial hypertension, diabetes, obesity (BMI>40) (1).
- c. Active systemic inflammatory disease. These patients may develop a more vigorous immune response inducing a cytokine storm.
- d. Contact with infected persons (esp. in the family) or even travel to highly infectious countries (in countries with documented community transmission)
- e. Members of medicine related jobs

Factors leading to an individual treatment plan:

In general, we have two different situations:

Patient is on systemic immunosuppression and is

- a. without clinical signs of COVID-19 infection**
- b. with either confirmed COVID-19 or shows clinical signs of COVID-19 infection**

a. Patient without confirmation of clinical signs of COVID-19 infection:

These patients have previously been taught how to avoid infection when they were started on IMT. As these patients should have been practicing avoidance of infection through hand and personal hygiene, avoiding crowds.

They should be encouraged to follow all the preventative measures being proposed (hopefully) at a local or national level. Experience in certain European countries following the start of the pandemic shows that most patients in at risk groups benefit from being contacted, and to be reminded of the measures and their importance. Contact can be by MDs or office personnel. These measures include:

- staying home as much as possible
- practicing social isolation (keeping at 1.5 to 2m, approx.. 6 feet, from other individuals), whether on the street or in store or waiting room.
- wearing a mask when close to people or in risky locations (such as hospitals)
- washing your hands frequently with soap for at least 20 seconds particularly after touching surfaces such as transaction machines, door knobs, light switches. Direct contact from contaminated surfaces is one of the major modes of transmission (2)
- not touching your face if you have not been able to wash your hands
- wearing of gloves, even leather or winter gloves can be an option if no latex/vinyl gloves are available in a pharmacy

If they feel sick, they should contact their doctor's office who should advise them as to the relevance of an urgent appointment. This may or may not be possible depending on the country. In some countries only certain private offices are allowed to see patients if they are equipped with separate room for suspected patients, have appropriate barriers (aprons, N95 masks, and face shields or glasses) or if they need to be referred to an appropriate diagnostic center. At this time of year in Europe and North America, patients may also have the common flu or influenza, an appropriate diagnosis is therefore mandatory should the symptoms worsen. Depending on local arrangements, patients on immunosuppression may be considered an "at risk group" and benefit from earlier COVID-19 testing.

In your offices, if you are still seeing emergency patients within the risk groups defined above should be seen preferably earlier in the day and at a separate time from non-risk group patients. Ideally only 1 or 2 patients should be present at any time in the office or in the waiting area. Safe distances should be maintained between patients, they should all wear masks. Accompanying persons should be asked to wait outside or return when the consultation is finished. Also consider these measures as restrictions are progressively lifted for various segments of the population. In Switzerland, for example, there is talk to first lift restrictions for children and teenagers, but to maintain them for

patients at risk. Anticipating now how to handle a situation where some patients have gained immunity and others not, may become an important consideration.

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 minimized (<https://www.ncbi.nlm.nih.gov/books/NBK261/>). IMT targeting T cells such as CSA are generally safe in moderate doses and do not seem to increase the risk to viral infections (probably with the exception for Varicella-zoster virus (VZV) infections). (<https://www.ncbi.nlm.nih.gov/books/NBK47401/>) Uveitis patients on IMT are already primed to monitor their blood counts regularly; however we may need to reiterate the importance of the same again. Monitoring should be done close to home to minimize travel and exposure.

The virus binds to their target cells through renin angiotensin receptors (ACE2), which is expressed by the epithelial cells of the lung, intestine, kidney, blood vessels and even the conjunctiva. The expression of ACE2 is significantly increased in patients with type-1 and type-2 DM, or who are being treated with ACE inhibitors & ACE2 receptor blockers (ARBs). ACE2 inhibitors reduce inflammation and have been suggested recently for inflammatory lung diseases, cancer, diabetes and hypertension. ACE inhibitors cause an up regulation of ACE2 and this would facilitate infection with COVID-19. There seems to be a genetic predisposition for an increased risk of SARS-CoV-2 infection due to ACE2 polymorphisms that have been linked to DM, HTN, 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. Even when experts first thought that the use of ACE-inhibitors could have a higher risk in COVID-19 infection (4), it now has been published that ACE-inhibitors may be even protective (5)

Consider a higher risk in uveitis patients with co-morbidities such as DM, HTN, and cardiac disease (3).

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. The Swiss experience so far in rheumatology and GP practices is that many patients need to be reminded of the importance of distancing measures and reassured about the use of IMTs, some have stopped them without seeking guidance. This is also of importance in a pediatric population on IMT and gives ophthalmologists the opportunity to discuss the need for treatment and alternative bridging avenues. It will also allow you to discuss their personal need for treatment or potentially reassess the need for therapy. It may be appropriate to accelerate a slow taper, given that the current projections regarding the pandemic call for a series of exacerbations and remissions over an 18-month period (6).

Therefore, for the healthy situation we agree to maintain the IMT (but recheck the type of drug and dosage).

b. Patient with either confirmed COVID-19 infection or clinical signs of COVID-19 infection:

In case of clinical signs, whenever possible get confirmation of the diagnosis as there can be other viral causes.

If your patient is asymptomatic, continue with IMT along with blood monitoring, and reduce the dose if the WBC falls below 4000/ μ L.

In symptomatic patients, they should temporarily stop their conventional IMT and biologic therapy (except for interferon and tocilizumab). Patients taking anti-TNFs should omit their next planned subcutaneous dose until they have recovered.

If needed consider local treatment options. Systemic corticosteroids may need a slow reduction, but this should be discussed with the COVID treatment team. Low maintenance doses <10mg/day of prednisolone equivalent may not pose significant risk, and should be maintained if necessary, for the uveitis (but probably without clear evidence if this is acceptable).

Virus related:

- a. Type and dose of the IMTs. It seems that all IMTs reduce the intensity of the immune response to the virus, which may be in most situations not beneficial.
- b. Exception: **Interferon alpha and beta**, and also **Actemra** (anti-IL-6, Tocilizumab) seem to reduce the possible "Cytokine storm syndrome" (7, 8). Cytokine storm syndrome can be one of the factors leading to death during the COVID-19 infection; through an excessive release of cytokines (IL-1, IL-6, IL-18 and Interferon Gamma) can result in multi-organ failure. IL-6 blockade is under investigation in a protocol in COVID-19 patients in China, results are expected in May.
- c. Additional treatment: A recent article from a health commission in the Guangdong region of China has recommended the use of **chloroquine phosphate** for 10 days in patient without contraindication to the medications in cases of mild, **moderate or severe cases of coronavirus pneumonia** (9). Multiple modes of action have been proposed for Chloroquine/hydroxychlorouine from inhibited binding of viruses to cell surface receptors, alkalinisation of endosomal ph. It inhibits MAPK signaling required for virus replication (10). However, while there is rationale for its use, as well as pre-clinical evidence, there is to date no controlled study that has confirmed its benefit. There are 23 ongoing clinical trials in China. Reference (11) lists in its discussion guidelines China, the Italian Society of Infectious and Tropical Diseases as well as the Dutch Center of Disease control. In addition, other antivirals such as those developed against EBOLA virus and HIV are under study. A first vaccine trial is under way in the US.
- d. In case of fever there is a suggestion (not from the WHO but from the French Health Minister, following a Lancet article) to use **paracetamol** instead of ibuprofen. NSAIDS may interfere with IFN- γ by innate immune cells, an important strategy in antiviral defence (12).

Uveitis related:

In patients with severe acute uveitis (may be as a new uveitis, as recurrence or as a reactivation despite IMT) where high doses of steroids such as IV methylprednisolone are indicated (e.g. intermediate uveitis) local therapy (periocular or intravitreal steroids) might be considered, alone or in combination with lower doses of systemic steroids. This takes into account that patient's response to IMT and their related side-effects during COVID19 pandemic are not clearly predictable. In case of acute Behcet's Disease, treatment with interferon alpha or beta may be even useful against COVID-19 but needs of course the agreement of the COVID-19 treating physician.

Risk analysis based on prior corona virus infections:

A publication in pre-print from Italy indicates that the risk for patients on immunosuppression may be low. Here is an extract from her abstract (13):

“In reviewing the mortality and morbidity reports published on Coronaviruses outbreaks such as Severe Acute Respiratory Syndrome (SARS) that emerged in 2002, Middle East Respiratory Syndrome (MERS, still ongoing) and more recently COVID-19, no fatality was reported in patients undergoing transplantation, chemotherapy or other immunosuppressive treatments, at any age. Risk factors for poor outcome include advanced age, male sex and presence of comorbidities (obesity, diabetes, heart disease, lung disease, kidney disease).“

Indeed, while we should exercise caution in our patient population, there is a need to gather data on the true risk associated with immunosuppression and COVID-19. In the next version of this report, more on the subject.”

Laboratory markers of corona virus infection (14)

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

Most frequent:

- Decrease lymphocyte count
- Decrease albumin
- Decrease haemoglobin levels
- Increase C-reactive protein (CRP)
- Increase Erythrocyte Sedimentation Rate (ESR)
- Increase Lactate Dehydrogenase (LDH)
- Increase D-dimer

In severe COVID-19

- Decrease lymphocyte count

- Decrease albumin
- Decrease haemoglobin levels
- Increase C-reactive protein (CRP)
- Increase Erythrocyte Sedimentation Rate (ESR)
- Increase Lactate Dehydrogenase (LDH)
- Increase D-dimer
- Increase Neutrophil count
- Increase Alanine Aminotransferase (ALT)
- Increase Aspartate Aminotransferase (AST)
- Increase Cardiac biomarkers (e.g. cardiac troponins)
- Increase Procalcitonin

References:

- 1. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020**
- 2. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246-51.**
- 3. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020**
- 4. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450-4**
- 5. https://jamanetwork.com/journals/jama/articlepdf/2763803/jama_patel_2020_vp_200063.pdf**
- 6.). Ferguson NM, Laydon D, Nedjati-Gilani G, Imperial College COVID-19 Response Team. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Imperial College; 2020. DOI:10.25561/77482**
- 7. Zhou Y et al (2020) Pathogenic T cells and inflammatory monocytes incite inflammatory**

storm in severe COVID 19 patients. National Science Review. National Science Review, nwaa041, Available at: <https://doi.org/10.1093/nsr/nwaa041> (accessed 20.3.2020)

8. Mehta P et al (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. Available at: DOI: [https://doi.org/10.1016/S0140-6736\(20\)306280](https://doi.org/10.1016/S0140-6736(20)306280) (accessed 20.3.2020)

9. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Mar 12;43(3):185-188. doi: 10.3760/cma.j.issn.1001-0939.2020.03.009

10. J Crit Care. 2020 Mar 10. pii: S0883-9441(20)30390-7. doi: 10.1016/j.jcrc.2020.03.005

11. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? International Journal of Antimicrobial Agents. 2020

12. Prower E, Hasnain O, Oscier C. H1N1 pneumonitis associated with long-term non-steroidal anti-inflammatory drug abuse. Case Reports. 2015;2015(apr13 1):bcr2014205237-bcr

13. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl. 2020. [Epub ahead of print]

14. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020 Mar 3. pii: /j/cclm.ahead-of-print/cclm-2020-0198/cclm-2020-0198.xml. doi: 10.1515/cclm-2020-0198. [Epub ahead of print] PubMed PMID: 32119647.

15. Seah I, Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in Humans and animals. Ocul. Imm Infl <https://doi.org/10.1080/09273948.2020.1738501>

16. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. 2020 Feb 26. doi: 10.1002/jmv.25725. [Epub ahead of print]

[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(20\)30150-9/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30150-9/fulltext)

<https://blog.cincinnatichildrens.org/safety-and-prevention/covid-19-and-immuno-compromised-patients%3A-guidance-for-parents>

<https://www.unboundmedicine.com/medline/citation/32074550/Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID 19 associated pneumonia in clinical studies>

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30116-8/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30116-8/fulltext)

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 8 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)

5- <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

This is a Consensus Experience information from the International Uveitis Study Group (IUSG), the International Ocular Inflammation Society (IOIS) and the Foster Ocular Inflammation Society (FOIS) (date: April 3, 2020)