# Evolving Consensus Experience of the IUSG with uveitis

# in the time of COVID-19 infection.

Latest version March 23, 2020 (previous version from March 20, 2020 outdated)

## Problem:

This document summarizes the experience of the IUSG 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 (www.iusg.net) and is therefore available for every doctor who seeks advice for her/his uveitis patients. Comments provided by the IUSG members are reviewed by the executive board (Gupta, deSmet, Zierhut) before being posted. We ask for additional comments, and we will add these comments every few days. Please use for your comments (vishalisara@gmail.com)

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

a. Age starting with 50 years: this is because they are more likely to have multiple organ problems due to the higher prevalence of chronic diseases like diabetes mellitus and hypertension, but also possibly because of immune senescence.

b. Co-morbidity: cardiovascular disease > respiratory system disease > arterial hypertension, over weight (1). Patients developing a more vigorous immune response inducing a cytokine storm (hence the possible benefit of tocilizumab) which may aggravate the problem more than brought by the virus itself (see below).

c. Contact with infected persons or even travel to highly infectious countries (in countries with documented community transmission, but the role of travelling is now decreased)

d. Smoking

e. Previous history of infection while on IMT

## 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 they should have learned been practicing avoidance of infection through hand and personal

hygiene, avoiding crowds and the use of masks, they might be actually safer than the general public who are learning these practices during the COVID pandemic. Regarding masks, they should be told to have the mask at hand and if someone coughs or is sick, they should quickly put the mask on and walk away and if they are sick, they should contact a doctor for an urgent appointment. Similarly, they should practice social distancing keeping a 1.5 to 2m distance from surrounding people in areas such as supermarkets or on the streets. They should also sanitize their hands after any manipulation of transaction machines or wear gloves. Direct contact from contaminated surfaces is one of the major modes of transmission (2). If they are sick, they should see a doctor for an urgent appointment. Hence, they may be not more likely to contract COVID infection.

In your offices, if you see mixed populations of patients, patients at risk should be seen preferably early in the day. In the waiting room, distances should be maintained between patients. A minimum number of patients should be allowed to be waiting in office (space appointments), and accompanying persons should be asked to wait outside or return when the consultation is finished.

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 4,000 per microliter, he should not be at increased risk of infection (https://www.ncbi.nlm.nih.gov/books/NBK261/). We should check to ensure the WBC count is not low. 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.

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 by type-1 and type-2 DM, who are 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 upregulation 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. A higher risk is there in uveitis patients with co-morbidities such as DM, HTN, cardiac disease (3). and being treated with ACE2 inhibitors and ARBs (4). They need to be warned and require a consultation with their treating physician for a change of drugs or monitored for the same.

Even if your patients are well informed on how to protect themselves from infections: we recommend that you contact your patients receiving IMTs by phone. The Swiss experience so far from rheumatologists and GPs 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 for importance for 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 (5).

**Therefore, for the healthy situation we have a consensus to maintain the IMT (but recheck the type of drug and dosage) as before.**

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

In this situation we recommend to stop all IMT, as quickly as possible. 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 ok). Exceptions (interferon and anti-interleukin 6 therapy) see next part.

**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 beneficial.

b. Exception: Interferon alpha and beta, and also Actemra (anti-IL-6, Tocilizumab) seem to reduce the "Cytokine storm syndrome". 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: In Singapore, rheumatology patients receiving IMT are given as prophylaxis hydroxychloroquine (2x500 mg/day). 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 (6).
   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-g by innate immune cells, an important strategy in antiviral defense (7).

**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. VKH), 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.

**Laboratory markers of corona virus infection (8)**

**Be aware that some laboratory parameters are influenced by IMT or are not reliable when using specific IMT drugs (eg 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

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