Problem:

We 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.


c. Active systemic inflammatory disease. These patients may develop a more vigorous immune response inducing a cytokine storm.

d. Contact with infected persons or even travel to highly infectious countries (in countries with documented community transmission)
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 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 CORVD-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 WCC falls below 4000/µL.

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/hydroxychloroquine from inhibited binding of viruses to cell surface receptors, alkalinisation of endosomal ph. It inhibits MAPK signaling required for virus replication (9). 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 (10) 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 defense (11).
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.
Laboratory markers of corona virus infection (12)

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:


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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: March 26, 2020)