

# COVID-19 Pandemia - Uveitis Specialist Perspective

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## ABSTRACT

Since several cases of pneumonia of unknown microbial origin that were detected at Wuhan City, China in late December 2019, entire countries are under lockdown to limit the spread of the virus. During this emergency state, accessibility to healthcare services is an increasing challenge. Uveitis population is one of the vulnerable groups which need constant follow-up and guidance because the nature course of their disease. It has been particularly concerning for the patients taking immunomodulatory treatment. Herein, we summarize strategies and preventive measure in the management of uveitis patients during COVID-19.

**Keywords:** Uveitis, Immunomodulatory treatment, Pandemia, COVID-19, SARS-CoV-2.

## INTRODUCTION

On 7 January 2020, a causative pathogen of outbreak was isolated as a novel type of coronavirus (SARS-CoV-2) by Chinese Center for Disease Control.<sup>1</sup> Since then, Coronavirus disease (COVID-19), has escalated and rapidly spread around the world, with World Health Organization (WHO) first declaring a public health emergency of international concern on 30 January 2020, and then a pandemic disease since March 11, 2020.<sup>2</sup>

Since several cases of pneumonia of unknown microbial origin that were detected at Wuhan City, China in late December 2019<sup>3</sup>, entire countries are under lockdown to limit the spread of the virus. Certain measures taken by governments and public will probably be needed for several months, and possibly up to couple years. During this emergency state that we are living in, accessibility to healthcare services and medical equipment is an increasing challenge. The situation is no different for ophthalmic diagnosis and follow up which becomes even worse when it comes to ophthalmic emergencies and chronic ocular diseases which need timely management such as uveitis, glaucoma, diabetes, and such. Patients who have chronic eye diseases are unable to, or afraid to reach hospitals in order to avoid face to face contact and in person encounters.

## Uveitis Patient Management during COVID-19

Uveitis population is one of those vulnerable groups which need constant follow-up and guidance because the nature course of their disease. It has been particularly concerning for the patients taking immunomodulatory treatment (IMT) who are unsure of their risk for severe COVID-19 disease because some or all of those drugs may increase the risk of acquisition or the severity of COVID-19. On the flipside, discussions are ongoing about immunosuppressive drugs, including biologics, potentially being beneficial for late complications by preventing the cytokine storm responsible for development of complications such as ARDS, the most feared complication of this virus.<sup>4</sup> On the hand, there may be an increased risk of COVID-19 for patients with immune-mediated diseases like in BD disease and it is also possible that viral diseases may lead to an exacerbation of these underlying autoimmune conditions.<sup>4</sup> Currently, there is no evidence describing the benefits or risks of cessation of immunomodulators during the COVID-19 pandemic. Expert subspecialty groups are publishing and constantly updating their own recommendations on patient management during this pandemic. Each of those recommendations including WHO<sup>5</sup>, IUSG,<sup>6</sup> ECDC<sup>7</sup>/CDC<sup>8</sup>, EULAR<sup>9</sup>, British Society for Rheumatology<sup>10</sup> regarding COVID-19 put excessive emphasis on preventive measures which are listed as a brief below.

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- a. To adopt social isolation at home, and to practice physical distancing outside at least 2 meters. Besides, gatherings with 5-10 people or more should be avoided.
- b. To wear a mask especially for patients who are on immunosuppressant medication when close to people coughing or in risky locations particularly if in hospital or other clinical setting.
- c. To wash hands frequently with soap for 2 minutes, and to avoid touching own face if not been able to wash hands. Hand cleaning for at least 20 seconds with an alcohol-based hand rub (at least 60% alcohol) is also considered as a proper hand hygiene procedure.
- d. To wear gloves when shopping.
- e. To clean surfaces that are touched on a regular basis, using alcohol-based disinfectants<sup>15</sup>. To the extent possible, touching high-touch surfaces in public places should be avoided, like elevator buttons, door handles, handrails.

Also, there is great emphasize on equipment and/or technology which enables patient care while enabling individual quarantine and social isolation rules, thus preventing spread of coronavirus infection. Because, in this way, the workload of the country and healthcare employees will be reduced in terms of both labors expended and health expenditure indirectly. Being one of those remote healthcare options, telemedicine of all types should be utilized where possible for all uveitic patients, aiming to replace unnecessary office visits. At least, video or telephone consultations can be offered to the patients. By this way, unnecessary travelling, long waiting times with other immunosuppressed patients and possible contact with virus-contaminated surfaces can also be avoided for some of the uveitis population. On the other hand, for the sake of visit stratification, if patients have no treatment side-effects but ongoing remission or low-disease activity, rescheduling the visits may be considered. This may give the uveitis specialist time to inform patients with immunosuppressive drugs over-phone about the virus and to assure that patients adhere to the treatment that the specialist considers to be the best.

### Treatment Considerations in Uveitis Patients

First of all, when treating uveitis patients, one should consider the patient's personal risk factors such as age, comorbidities, health worker status, possible pathogen exposure. Also, degree of community transmission in the area and the individual testing result for COVID-19 should be pursued.

International Uveitis Study Group (IUSG) provided their letter of recommendations regarding patients

who are on immunosuppressive drugs for their uveitic/auto-immune ocular condition.<sup>6</sup> In general, there are three clinical scenarios for patients who are on systemic immunosuppressants.

First scenario is when the patient is healthy and with no exposure to COVID-19. In this scenario IMT can be maintained but should be monitored as usual. These patients should be informed to see a doctor for an urgent appointment if they fell sick, Hence, they may be not more likely to contract COVID infection.

The second scenario is that if the patient has been close to a person who was diagnosed with COVID-19. First of all, this does not mean that the patient contracted the virus. However close monitoring and isolation for 14 days is mandatory. Immunosuppression therapy in these cases should be tuned according to the patient's health status and surfacing symptoms. A much more tailored approach and a case by case decision is needed. Patients should be informed about hospital telephone hotlines and how to get medical attention in case of emergency. They should be warned about clinical signs of the disease especially pulmonary symptoms.

Third scenario is the patient with either confirmed COVID-19 infection or clinical signs of COVID-19. In this situation, immunomodulatory treatment should be stopped. However, systemic steroids may need a slow tapering. <10mg/day of prednisolone equivalent of corticosteroid dose may not pose a definite risk and can be maintained after a discussion with the COVID treatment team. Although scarce, evidence indicates that moderate doses of corticosteroids can be beneficial in early stages of the viral infections with or without pulmonary abnormalities.<sup>11, 12</sup> Local treatments such as steroid drops, subtenon and peribulbar steroid injections, as well as intravitreal steroids can be continued.

If the patient is newly diagnosed with uveitis and treatment is needed, then, if possible, one should prefer local therapy in the form of posterior sub-tenon triamcinolone or intravitreal dexamethasone implant over systemic corticosteroids. High dose oral corticosteroids or immunosuppressants in high risk patients defined as the following: age  $\geq 65$  years, severe chronic lung disease (e.g., asthma, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), etc.), severe heart disease, CD4 count <200, history of diabetes/hypertension/smoking/cardiovascular event should be avoided. Patients need to be explained regarding the additional risk of secondary infections at the time of start of the therapy. A meticulous monitoring is recommended with special precaution to maintain white blood cell count over 4000 per microliter.

### Emphasis on Immunomodulatory treatment (IMT) in a COVID 19 Patient

In general, conventional synthetic IMT drugs (like Azathioprine, Cyclosporin, Methotrexate) are advised to be discontinued in COVID 19 patients especially in case of fever and/ or dyspnea or ARDS. On the other hand, immunomodulatory treatments may act as a double-edged sword and have the potential to reduce the intensity of the late immune response against the virus which may act as a regulatory counteraction.

Among IMT drugs cyclosporin suggested as a first line therapy because it might provide protection against upstream of the cytokine storm in COVID-19 infected patients via its effects against pneumocytes and T lymphocytes' mitochondrial failure besides its antiviral activities in a variety of RNA viruses, including the family of betacoronavirus.<sup>13</sup> This hypothesis is also currently being tested in clinical trials.<sup>13</sup>

The cessation or continuation of biological disease-modifying IMT drug like anti-TNF agents or IL-6 inhibitors depends primarily on whether it is applied for a serious ocular sight threatening inflammation. Some biologics such as interferon alpha and beta, anti-IL6 drugs may reduce the "Cytokine storm syndrome". This is a syndrome where excessive release of certain cytokines such as IL-1, IL-6, IL-18 and Interferon Gamma can result in multi-organ failure.<sup>14</sup> The virus is able to induce a TNF- $\alpha$ -converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, crucial for the penetration of the virus into the cell.<sup>15</sup> This process seems to be strictly coupled to TNF $\alpha$  production, and the use of TNF inhibitors may be effective in reducing both SARS-CoV2 infection and the consequent organ damage.<sup>16</sup> Consequently, a study evaluating adalimumab in COVID-19 infection has recently been registered in the Chinese Clinical Trial Registry (ChiCTR2000030089).

IL-6 and IL-1 also play a pivotal role in this hyperinflammatory condition, suggesting the potential use of their blockers as treatment option for SARS-CoV2 related interstitial pneumonia. Data from a phase 3 RCT of IL-1 blockade (anakinra) in sepsis showed significant survival benefit in patients with hyperinflammation, without increased adverse events. For the treatment of COVID-19 patients, anti-IL-6 drugs are currently under investigation and have mixed results. In CORIMUNO-TOCI trial (NCT04331808) testing Tocilizumab in 129 patients with COVID-19 pneumonia were randomized to receive standard-of-care, either with or without Actemra. Investigators stated that a significantly lower proportion of patients reached the primary outcome in the tocilizumab

arm than in the comparator group. Sanofi and Regeneron Pharmaceuticals said that preliminary results from the phase 2 portion of an ongoing study (NCT04327388) showed that the IL-6 receptor antibody Kevzara (sarilumab) had "no notable benefit" on clinical outcomes versus placebo in hospitalized patients with severe or critical respiratory illness caused by COVID-19. Although these results seem contradictory, the effect of biologic IL-6 inhibitors, if any, seems to be beneficial, rather than being harmful and in uveitis patients which are already on Tocilizumab continuation of the drug may be an option on case by case decision.

Many interferons, particularly interferon beta, have been shown to have modest activity in vitro against SARS-CoV and Middle East respiratory syndrome (MERS)-CoV.<sup>17</sup> In the Lancet, a results of an open-label, randomized, phase 2 trial that examined the effect of a the triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin, compared with single-drug lopinavir-ritonavir in the treatment of patients admitted to hospital with COVID-19 was published recently.<sup>18</sup> Triple therapy was associated with a significant reduction in the duration of viral shedding, symptom alleviation, and duration of hospital stay. With all this evidence interferons seem to be continued to be used or a good option in patients with uncontrolled uveitis. In cases of acute uveitic 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.

Another issue with DMARDs is that they can interfere with blood counts, liver, and bladder functions. Physicians should be aware laboratory markers of COVID-19 and that some laboratory parameters may not reliable when using specific DMARDs. A major study demonstrated that on admission lymphocytopenia in 83.2%, thrombocytopenia in 36.2%, and leukopenia in 33.7% of COVID 19 patients on admission. {Guan, 2020 #14 According to that study, most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and d-dimer. In a uveitic patient on IMT drug, laboratory and hematologic monitoring should be performed in this context.

### CONCLUSION

All patients on disease modifying drugs regardless of their COVID-19 infection state are already considered as they have increased risk for getting an infection. Physicians should warn them about that risk. There is no solid evidence that certain IMT drugs provoke a severe COVID 19, even some of these may be used in later stages of the infection,

however, in the light of current literature they also don't confer a protection against virus transmission. Therefore, all protective measures including social isolation is highly recommended and should be implemented. Ophthalmology practices should be modified and diversified with telemedicine, e-health options, in a way that, it can cope with pandemics like the current one while protecting healthcare providers.

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