



COVID-19 and the Use of Immunomodulatory Agents in Ophthalmology

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Abstract

Immunomodulatory agents are often used in the systemic treatment of non-infectious uveitis. These drugs consist of corticosteroids, conventional immunosuppressives, and biological agents. As it is known that they suppress the immune system, the most important concern associated with immunomodulatory therapy (IMT) is the increased risk of infection. The World Health Organization declared COVID-19 a pandemic on 11 March 2020. Although severe acute respiratory distress syndrome secondary to SARS-CoV-2 infection may develop in all people, patients who receive IMT may be at higher risk in terms of both the transmission of the infection and more severe disease course. Therefore, guidelines on the management of patients receiving IMT due to uveitis during the pandemic are needed. In this review, we examined the immunomodulatory drugs used in the treatment of uveitis in terms of infectious complications and the data of patients who received IMT during the COVID-19 pandemic and discussed recommendations for the use of these drugs. According to the latest information, patients who receive IMT may continue their treatment as long as there are no disruptions in regular complete blood count (especially white blood cell count $>4,000/\mu\text{L}$) and liver and kidney function tests. Patients diagnosed with COVID-19 should be managed with a multidisciplinary approach.

Keywords: COVID-19, immunomodulatory therapy, immunosuppressive, non-infectious uveitis, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in the city of Wuhan (Hubei province, China). After spreading to other cities and countries, the World Health Organization declared it a pandemic on March 11, 2020 (World Health Organization, Situation Report-51). Due to the virus' unclear route of transmission, its rapid spread, and the considerable rate of serious complications it causes, the disease has become a global public health problem of worldwide concern. Although the information we have about COVID-19 is limited, it is steadily increasing. Patients using

immunomodulatory therapy (IMT), both conventional and biological agents, constitute a population that is potentially vulnerable to infectious diseases and require diligent and close follow-up.

The aim of this review was to investigate the safety and use of immunomodulatory drugs for the treatment of ocular diseases during the COVID-19 pandemic.

COVID-19

Genome sequencing revealed that SARS-CoV-2 is very similar to two bat-derived SARS-like coronaviruses and less similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).¹ It has been suggested that SARS-CoV-2 is a novel infectious agent that emerged as a result of

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mutations and recombinations in different genomic regions.

There is still no definite consensus regarding the treatment of patients. Many different drugs have been tried in clinical studies, with hydroxychloroquine and antiviral agents being adopted early in the pandemic.² Corticosteroids were used in an attempt to control the cytokine storm in severe cases, but they were found to delay viral clearance time and had no effect on mortality.³ Tocilizumab, a recombinant human monoclonal antibody developed against interleukin (IL)-6 receptor, was shown to be effective in COVID-19 patients with cytokine storm.⁴ Results are not yet available for clinical studies of sarilumab, another IL-6 receptor antibody. Studies with the Janus kinase inhibitor baricitinib have not yielded favorable results.⁵

Risk Factors for Severe COVID-19

Disease-related mortality rates differ by region (5.6%-15.2%).⁶ The risk of death is higher in older patients and those with comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease.⁷ It was also stated that in previous studies of SARS and MERS infections, which have similar risk factors to COVID-19, immunosuppressed individuals were not found to be at higher risk.⁷ In a retrospective study reporting the clinical course and outcomes of COVID-19 patients, advanced age, need for oxygen support, dementia, and presence of neurological disease at admission were listed as risk factors.⁸ Another study also suggested that the disease is more severe in smokers, but pharmaceutical nicotine may be beneficial in the treatment of COVID-19 due to its immunomodulatory effects.⁹

Immunomodulatory Therapy and COVID-19

It is known that people whose immune systems are suppressed for any reason are at risk of infectious diseases. Ophthalmologists use many different immunomodulatory drugs (conventional immunosuppressants, biological agents, and new small-molecule inhibitory agents) in the treatment of non-infectious uveitis.

The relationship between immunosuppressive drug use and COVID-19 has been a subject of research during the pandemic. Most studies in the literature are case reports and observational studies and involved patients receiving IMT due to organ transplantation and systemic autoimmune diseases. There are few publications on the management of patients with non-infectious uveitis who require IMT.

Systemic Corticosteroids

Systemic corticosteroids are used to control inflammation, especially in cases of vision-threatening acute uveitis. Long-term systemic corticosteroid use causes significant immunosuppression and increases the risk of infection. In three different patients receiving corticosteroid therapy due to organ transplantation, the course of COVID-19 infection was reported to be similar to the normal population.^{10,11,12} A study of 600 patients receiving immunosuppressive therapy for rheumatic diseases showed that patients using corticosteroids (≥ 10 mg/day) had a higher hospitalization rate than patients using other immunosuppressants.¹³

Conventional Immunosuppressive Drugs

Methotrexate: Methotrexate is one of the conventional immunosuppressive drugs and is mostly used in children with chronic anterior and intermediate uveitis.¹⁴ Methotrexate slightly increases the risk of infection but does not pose a risk for the development of serious infection.¹⁵ Although there is no definitive data regarding the effect of methotrexate use on COVID-19 transmission risk and disease course, it is not considered contraindicated.¹⁶

Azathioprine: This drug is most commonly used in ophthalmology practice to treat Behçet uveitis (BU).¹⁷ It can also be used in idiopathic posterior uveitis, Vogt-Koyanagi-Harada disease, and less frequently in cases of uveitis associated with juvenile idiopathic arthritis (JIA).^{18,19} Another study evaluating 230 patients diagnosed with inflammatory bowel disease showed that azathioprine did not increase the risk of upper respiratory tract infection.²⁰ In a retrospective study of 46,030 patients with rheumatoid arthritis (RA), it was reported that although the incidence of influenza was higher than in the healthy population, it was not associated with azathioprine use.²¹ There is no report in the literature regarding the presence of a relationship between azathioprine use and COVID-19 transmission risk and disease course.

Mycophenolate mofetil: Mycophenolate mofetil, another agent previously used in organ transplantation and systemic autoimmune diseases, is used less frequently in the treatment of uveitis than other immunosuppressants. It can be used in patients with panuveitis, posterior uveitis, retinal vasculitis, and scleritis due to various etiologies.^{22,23} Studies in transplant patients have shown that it moderately increases the risk of infection. Ritter and Pirofski²⁴ concluded in their review that the drug especially predisposes to upper respiratory tract infection, urinary tract infection, and herpes virus-related infections. There are no available literature data on the relationship between mycophenolate mofetil use and COVID-19.

Cyclosporine-A: This drug can be used to treat patients with many different panuveitis and posterior uveitis entities, especially BU.²⁵ Studies in dermatology patients have demonstrated a slight increase in the risk of upper respiratory tract infection.²⁶ de Wilde et al.²⁷ showed that cyclosporine-A (Cs-A) suppressed MERS-CoV replication *in vitro*. In a clinic following 2,493 kidney transplant patients, evaluation of the clinical course and outcomes of 19 patients with SARS-CoV-2 revealed that those using Cs-A had a better clinical course than those using other immunosuppressive agents.²⁸ In a multicenter study conducted with kidney transplant patients in our country, examination of patients diagnosed with COVID-19 showed that none of the patients using Cs-A developed severe pneumonia.²⁹ In another study of kidney transplant patients, it was reported that Cs-A could be used as an effective and reliable immunosuppressant when needed in patients diagnosed as having COVID-19.³⁰

Tacrolimus: Tacrolimus is another immunomodulatory agent occasionally used in cases of intermediate uveitis, posterior uveitis, and panuveitis.³¹ It was shown to suppress MERS-CoV replication similar to Cs-A in an *in vitro* study.³² A study

investigating factors associated with mortality in 53 COVID-19 patients with a history of kidney transplantation showed that having dyspnea at admission, being over 60 years old, and tacrolimus use increased the risk of death.³³

Cyclophosphamide: Although not highly preferred in ocular inflammatory diseases today, cyclophosphamide is another immunosuppressant previously used in patients with BU, pars planitis, and sympathetic ophthalmia.³⁴ Durrani et al.³⁵ evaluated the short-term efficacy and safety of intravenous pulse cyclophosphamide in 38 patients with ocular inflammatory disease and reported that 18% of patients in the study developed upper respiratory tract infection. In a study including 7 bone marrow transplant patients with COVID-19, it was noted that 4 of the patients used cyclophosphamide and all of them had mild COVID-19.³⁶

Biologic Agents

Over the last two decades, biologic agents have provided a major advance in the treatment of systemic autoimmune diseases. In later years, they started to be used in the treatment of ocular inflammatory diseases. Etanercept, the first approved anti-tumor necrosis factor alpha (anti-TNF- α) agent, was shown to be ineffective in the treatment of uveitis after some time and to cause uveitis de novo in patients receiving the drug due to systemic autoimmune disease.³⁷

Infliximab: Infliximab, another anti-TNF- α agent, is currently used in patients with uveitis associated with a wide range of etiologies. It is most commonly needed in BU and uveitis in sarcoidosis.³⁸ It was also shown to be effective in the treatment of uveitis associated with JIA, Crohn's disease, and ankylosing spondylitis (AS).^{39,40,41} Infliximab is a low risk agent in terms of infectious complications.⁴² In a study comparing the long-term safety of infliximab and non-biologic agents (systemic corticosteroids, azathioprine, and methotrexate) in the treatment of Crohn's disease, 6273 patients were evaluated and infectious complications were reported to be more common in those using infliximab.⁴³ The incidence of bacterial infection was 2.69% per year and that of viral infection was 0.97% per year. In the study, there is no clear data on the safety of infliximab during the COVID-19 pandemic. A study including 7 patients who used various biologic agents due to psoriasis and were diagnosed as having COVID-19 showed that patients receiving infliximab had a poorer prognosis.⁴⁴ However, there are case reports showing the successful use of infliximab to treat COVID-19 in patients with systemic autoimmune disease.^{45,46} In another study, it was suggested that infliximab could be used in the treatment of patients with ulcerative colitis during the COVID-19 pandemic.⁴⁷

Adalimumab: This drug is another anti-TNF- α agent that has been used to treat uveitis. Successful outcomes have been reported with adalimumab in patients with idiopathic uveitis and uveitis secondary to systemic diseases such as Behçet disease (BD), sarcoidosis, JIA, AS, and Crohn's disease.^{38,48} Adalimumab is the only biologic agent licensed for the treatment of uveitis; others are used off-label. Infections were found to be the

most common drug-related complications in patients using adalimumab for systemic autoimmune disease.⁴⁹ However, it has been shown that advanced age, comorbid diseases, and RA are risk factors, whereas patients with AS, psoriasis, and JIA have a significantly lower risk of serious infection.⁴⁹ In a study of 217 patients with panuveitis, posterior uveitis, and intermediate uveitis of various etiologies, it was reported that non-serious upper respiratory tract and urinary tract infections were more common in patients using adalimumab compared to the placebo group, while the risk of serious infection was similar in the two groups.⁵⁰ There are case reports in the literature regarding the risk of COVID-19 in patients using adalimumab. A 57-year-old psoriasis patient taking adalimumab for approximately 2 years was diagnosed as having COVID-19 manifesting with fever, malaise, and anosmia.⁵¹ According to the report, the patient exhibited no breathing difficulties during follow-up and did not need oxygen support. Adalimumab treatment was continued 3 weeks after discharge and there was no recurrence of symptoms associated with COVID-19 during follow-up. In another 30-year-old patient taking adalimumab for Crohn's disease, COVID-19 infection presented with symptoms of fever and mild dyspnea and resolved rapidly.⁵² The authors attributed this to the patient's young age and the role of TNF- α overproduction in severe respiratory failure. For this reason, they suggested that adalimumab can be used for therapeutic purposes in some COVID-19 patients.

Certolizumab and golimumab: There are no large and long-term studies on the use of certolizumab and golimumab, other anti-TNF- α agents used in systemic autoimmune diseases, in ocular inflammation. In a study examining 30 eyes of 21 patients, it was shown that aqueous flare measurements were significantly reduced and visual acuity was preserved in the long term with both certolizumab and golimumab.⁵³ When the results of three phase 3, randomized, placebo-controlled trials on the long-term safety of certolizumab use in psoriasis patients were analyzed together, the rate of infection was shown to be 1.5% per year, which was reported to be similar to other biologic agents.⁵⁴ There is still no information in the literature regarding the relationship between certolizumab or golimumab use and COVID-19 infection.

In a study evaluating 600 rheumatic patients with COVID-19, it was found that anti-TNF- α use reduced the risk of hospitalization.¹³

Tocilizumab: Tocilizumab, another of the biologic agents more recently used to treat uveitis, is an IL-6 receptor antagonist. In previous years, it was approved for the treatment of RA and JIA. There are reports that it is successful in the treatment of uveitis. In a randomized, controlled, multicenter study, 37 patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis received tocilizumab infusion at one of two different doses.⁵⁵ At both doses, tocilizumab increased visual acuity and decreased vitreous haze and central macular thickness. The efficacy and safety of tocilizumab and methotrexate were evaluated in patients with RA.⁵⁶ During the 24-week follow-up period, serious infectious complications occurred in 1.4%

of patients receiving tocilizumab, similar to methotrexate.⁵⁶ Severe infections requiring hospitalization occurred in 24% of patients using tocilizumab. However, 52% of all patients were also receiving corticosteroid therapy, suggesting that the high incidence of infection was not due to tocilizumab alone. In a study of 141,869 patients comparing tocilizumab with anti-TNF- α agents in terms of risk of serious infection, both groups had similar rates of infectious complications.⁵⁷ It was observed that 4.68% of patients treated with tocilizumab developed serious infections per year. There is currently no known relationship between tocilizumab use and the development of COVID-19 infection. There are publications reporting that for patients who require systemic immunosuppressive therapy and contract COVID-19, tocilizumab may be beneficial for both the comorbid condition and COVID-19.^{58,59} Luo et al.⁴ used tocilizumab to suppress severe systemic immune response in 15 patients with COVID-19. They stated that 11 of the patients responded well to treatment and that tocilizumab may be beneficial for severe patients at risk of cytokine storm.

Secukinumab: Secukinumab, another agent shown to be effective in autoinflammatory diseases, is an IL-17A antagonist. The results of three randomized controlled clinical trials to evaluate the efficacy of subcutaneous secukinumab in the treatment of non-infectious uveitis were analyzed and there was no significant difference in uveitis recurrence between the secukinumab and placebo groups.⁶⁰ In a study of patients with psoriatic arthritis, a dose-dependent increase in the risk of serious infection was observed, with 2.1 of 100 patients in the group receiving the highest dose of secukinumab developing a serious infection within 1 year.⁶¹ Carugno et al.⁶² described a case of COVID-19 in a patient who had been using secukinumab for 2 years due to psoriatic arthritis. They reported that the patient had a mild clinical course and that IL-17 inhibitors may even have a role in the treatment of COVID-19. In another publication, it was reported that IL-17A has a role in lung and heart damage in various diseases and that IL-17A inhibitors may be a potential treatment to prevent damage.⁶³ In contrast, Sharmeen et al.⁶⁴ reported that secukinumab use was associated with severe COVID-19 course. In another study, analysis of clinical course in 41 COVID-19 patients receiving IMT (including secukinumab) due to rheumatologic diseases revealed no difference from the normal population.⁶⁵

Canakinumab: This is another biologic agent that acts as an IL-1 beta inhibitor. It can be used in the treatment of psoriasis, chronic obstructive pulmonary disease, gout, and BD. Anakinra is another biologic agent that exhibits similar activity by binding to the IL-1 beta receptor. In BD patients with ocular involvement, canakinumab and anakinra have been shown to control ocular inflammation.⁶⁶ In a retrospective chart review of 475 patients receiving canakinumab and anakinra for various autoimmune and autoinflammatory diseases, it was reported that 3 patients developed severe bacterial infections, resulting in death for 2 of those patients.⁶⁷ It has been reported that anakinra yields positive results in controlling the cytokine storm in patients with secondary hemophagocytic syndrome and has the

potential to be used in severe COVID-19 cases.⁶⁸ The results of a preliminary study indicated that canakinumab and anakinra are safe during the COVID-19 pandemic and beneficial in COVID-19 patients with cytokine storm.⁶⁹

Interferons: These are a group of cytokines produced by host cells in response to the presence of viruses, bacteria, parasites, and tumor cells. Of the three types, interferon- α and interferon- β reduce autoimmune activity. Systemic recombinant interferon- α -2a therapy has been shown to be effective against the extraocular findings of BD.³¹ It is also effective in the treatment of BU and intermediate uveitis.^{70,71,72} The most common complication associated with interferon therapy is influenza-like symptoms. In fact, the resolution of these symptoms suggests the formation of anti-interferon antibodies.⁷³ No infectious complications related to interferon use have been reported in the treatment of uveitis. Considering its role in the natural immune system, infection related to treatment is not expected. It is thought that interferon could be used in the treatment of COVID-19 because it naturally stimulates an antiviral reaction, and clinical studies on this are ongoing. The use of interferon in combination with other therapies has been reported with no adverse effects in case reports.^{74,75} However, interferon- α preparations are no longer available on the market, only pegylated forms are available. Experience with the use of pegylated interferons in the treatment of uveitis is very limited.

Rituximab: Rituximab, which was first used in the treatment of lymphoma, targets the CD20 antigen on the B cell surface and causes B cell depletion. In subsequent years, it was used in RA and later for the treatment of granulomatous polyangiitis. There are retrospective case series in the literature regarding its role in the treatment of uveitis. It was shown to control inflammation during treatment in 8 patients with uveitis secondary to JIA.⁷⁶ Nine of 11 patients with refractory non-infectious posterior uveitis had improved visual acuity and regression of fluorescein angiography findings.⁷⁷ There are reports that it induced remission in patients with BU.^{78,79} The use of rituximab in multiple sclerosis significantly increases the risk of infection.⁸⁰ However, there are insufficient data demonstrating the side effect profile of rituximab in patients with uveitis.⁷⁷ There are case reports describing a more severe course of COVID-19 in patients using rituximab due to rheumatologic diseases.^{81,82} As rituximab causes B-cell depletion, it was suggested that the risk/benefit ratio should be considered when using the drug during the pandemic, as it may impair the development of immunity in response to SARS-CoV-2 infection or to future vaccines.⁸³ It has been shown that multiple sclerosis patients' rituximab dose interval can be extended during the COVID-19 pandemic with no adverse effect on the course of multiple sclerosis.⁸⁴

Abatacept: This drug inhibits T cell activation by cleaving the bond between cytotoxic T lymphocyte-associated antigen-4 and immunoglobulin G, thereby suppressing T cell-dependent antibody production. It has similar efficacy to anti-TNF- α drugs in the treatment of RA. It can also induce remission in cases of JIA-associated uveitis.⁸⁵ Patients using abatacept generally have an increased risk of infection. A large study evaluating the results

of five different clinical trials showed that the incidence of serious infections was low in RA patients using abatacept.⁸⁶ Literature data regarding the effect of abatacept use on the risk of SARS-CoV-2 transmission or the clinical course of COVID-19 are not yet available.

Alemtuzumab: Alemtuzumab is a monoclonal antibody that reduces T and B lymphocyte counts by binding to CD52 on the cell surface of lymphocytes. The 12-year long-term outcomes of alemtuzumab use in multiple sclerosis patients were recently published.⁸⁷ Its efficacy has been demonstrated both clinically and on magnetic resonance imaging. There are case reports related to its use in the treatment of uveitis. In one report, alemtuzumab induced remission in a case of refractory panuveitis.⁸⁸ It was also shown to induce remission in another patient with refractory intermediate uveitis and macular edema associated with multiple sclerosis. The highest risk of serious infectious complications with alemtuzumab use in patients with multiple sclerosis was reported to be the first year of treatment (3.3%/year).⁸⁷ In the same study, it was observed that the incidence of serious infections decreased in the long term (0.8%/year) in patients with 12-year follow-up. An analysis of 399 patients receiving different treatments for multiple sclerosis (including alemtuzumab) indicated that COVID-19 incidence and disease course were similar to those in the normal population.⁸⁹

SARS-CoV-2 Ocular Involvement

Ocular involvement caused by SARS-CoV-2 was first reported in China.⁹⁰ A patient who tested positive for SARS-CoV-2 after risky contact developed redness of the eyes days before developing pneumonia. After this case, it was thought that the use of protective glasses and/or visors could prevent the spread of the disease. The retina and retinal pigment epithelial cells were shown in previous years to have ACE2 receptors, by which the virus attaches to and infects cells.⁹¹ Recently, ACE2 receptor gene expression has also been demonstrated in conjunctival cells.⁹² This finding supports the hypothesis that SARS-CoV-2 can be transmitted directly through the ocular surface.

Coronaviruses have been shown to cause conjunctivitis, anterior uveitis, retinitis, and optic neuritis in animal models.⁹³ In a study conducted in China, tear and conjunctival secretion samples obtained twice a few days apart from 30 COVID-19 patients were tested for the presence of SARS-CoV-2 and in only one of the patients, both samples tested positive.⁹⁴ Ocular findings have been shown to occur in approximately one-third of COVID-19 patients, with the most frequent being conjunctival hyperemia, chemosis, and epiphora.^{95,96} Clinical risk factors for ocular involvement include advanced age, high fever, increased neutrophil to lymphocyte ratio, and high acute phase reactant levels.⁹⁶ A study evaluating the presence of virus RNA in retinal samples obtained from 14 patients who died from COVID-19 revealed SARS-CoV-2 RNA in 3 of the 14 tested eyes.⁹⁷ In another study evaluating the optical coherence tomography findings of 12 COVID-19 patients aged 25-69 years, hyperreflective lesions in the ganglion cell and inner plexiform layers were observed in

both eyes of all patients and soft exudates and microhemorrhages were observed in the posterior segment examination of 4 patients.⁹⁸ However, in a letter to the editor regarding this article, Vavvas et al.⁹⁹ pointed out that soft exudates can be seen in many diseases and that the exudate in the example image could actually be myelinated nerve fiber and a reevaluation after 6-8 weeks is necessary to differentiate. They also argued that the hyperreflective bands in the images may have been normal vessel shadowing and that these two findings may not be retinal changes associated with COVID-19. Bettach et al.¹⁰⁰ reported a case of bilateral acute anterior uveitis secondary to COVID-19 infection. A 54-year-old woman who was treated for COVID-19 in the intensive care unit presented to the outpatient clinic with blurred vision 2 weeks after discharge. At initial examination, her visual acuity was 0.5 in both eyes and slit-lamp examination revealed bilateral conjunctival hyperemia, central corneal edema, Descemet's membrane folds, keratic precipitates, and +1 cells in the anterior chamber. The patient's findings improved with topical steroid and cycloplegia.

Uveitis Management During the COVID-19 Pandemic

Non-infectious uveitis is a group of sight-threatening inflammatory disorders and may be associated with systemic diseases. Immunomodulatory drugs have long been used in systemic inflammatory diseases and are often used in the treatment of non-infectious uveitis. In addition to corticosteroids (topical, peri-/retrobulbar, intravitreal, systemic), conventional immunosuppressants and biological agents are used to protect against the side effects of corticosteroids, especially in patients who require long-term treatment.¹⁰¹ These drugs are known to suppress the immune system; therefore, the most important problem is the increased risk of infection.

The global SARS-CoV-2 pandemic is a unique phenomenon that has brought many unprecedented challenges. One of these challenges for ophthalmologists is managing non-infectious uveitis patients who need IMT during the pandemic. Opinions and recommendations on this topic are being published from various parts of the world.

In parallel with the recommendations of the International Uveitis Study Group (IUSG), Tugal-Tutkun of our country wrote an article titled "Recommendations for Uveitis Patients Using Immunomodulatory Drugs" and published these recommendations on the website of the Turkish Ophthalmological Association (<https://coronavirus.todnet.org/post/recommendations-for-uveitis-patients-using-immunomodulatory-drugs>). First, the author emphasized that patients using immunomodulatory drugs should adhere strictly to social distancing/isolation and personal protection. It was stated that international uveitis associations do not recommend discontinuing drugs, but depending on the course of ocular inflammation and with physician supervision, the administration interval can be extended, the dose can be reduced, or the drug can be completely discontinued. However, the author also noted that IMT should be discontinued in case of any suspicion of infection or high-risk contact. The vital importance of patients

having regular complete blood count (especially white blood cell count should be $>4,000/\mu\text{L}$) and liver (alanine transaminase, aspartate transaminases, gamma-glutamyl transpeptidase) and kidney function (serum creatinine and urea) tests in terms of the risk of COVID-19 infection was emphasized.

Later, a consensus guide on the management of uveitis during the COVID-19 pandemic prepared by the IUSG, International Ocular Inflammation Society, and Foster Ocular Inflammation Society was published.¹⁰² This guide emphasized that treatment should be adapted based on the patient's COVID-19 status. The recommendations for patients under systemic immunosuppression are divided into two groups. In the first case, the consensus was to continue IMT in patients with no clinical signs of COVID-19. General recommendations for patients were made, such as staying at home as much as possible, complying with social distancing (being at least 1.5-2 m away from others), using masks when in contact with people or in risky areas such as hospitals, washing hands frequently with soap for at least 20 seconds, especially after touching door handles and light switches, and not touching the face without first washing hands. It was stated that a total white blood cell count higher than $4,000/\mu\text{L}$ minimized the risk of infection and that patients should continue to undergo complete blood count tests regularly in the centers closest to their homes. Cs-A was reported to be safe at non-high doses and not predispose to viral infections (except varicella-zoster virus). Finally, it was recommended to contact patients by phone because they could discontinue their medication without being advised by a doctor. In the second case, it was stated that patients with suspected or confirmed COVID-19 can continue immunomodulatory drugs if they are asymptomatic and have a total white blood cell count above $4,000/\mu\text{L}$, while for symptomatic patients, immunomodulatory drugs other than interferon and tocilizumab can be discontinued and local treatment solutions may be considered. It was noted that systemic corticosteroids should not be discontinued abruptly and that dose reduction should be gradual in terms of adrenal suppression. In patients with severe acute uveitis attacks (new-onset uveitis or reactivation) who require high-dose intravenous methylprednisolone therapy, local treatment options (periocular and intravitreal steroids) alone or in combination with low-dose systemic corticosteroids should be considered.

Apart from the consensus guide above, there are publications related to the approach to ophthalmology patients during the COVID-19 pandemic. Gupta et al.¹⁰³ published information and their recommendations on the treatment and follow-up of vitreoretinal and uveal diseases. In addition to the above consensus guideline recommendations for uveitis patients, they reported that the COVID-19 pandemic is not an absolute contraindication to initiating immunosuppressive therapy. Another publication presented recommendations that can be made in the follow-up, diagnosis, and treatment of uveitis patients.¹⁰⁴ Patients with controlled uveitis should be followed remotely (by telephone, etc.) except for emergencies, and routine test results should be evaluated. As few tests as possible should be performed for diagnosis and follow-up. For patients who may

require new treatment or treatment changes, personal protective equipment should be used diligently during examination. Finally, it was stated that IMT should be continued in patients without suspected or confirmed COVID-19, and IMT should be discontinued/reduced and local treatment options considered for infected patients. Similar recommendations were made in a study from Hong Kong.¹⁰⁵ The authors recommended that patients under systemic treatment comply with general prevention measures, be followed up remotely as much as possible, use protective equipment when they need to be examined in person, and postpone elective surgeries. In newly diagnosed cases, they suggested first evaluating local treatment options but stated that biologic agents could be used when necessary in conditions such as BU. They recommended that systemic therapy should be reduced as much as possible or discontinued in patients diagnosed with COVID-19 while receiving IMT.¹⁰⁵ A review investigating the effects of the use of immunosuppressives for ocular inflammatory diseases during the pandemic evaluated the new SARS-CoV-2 virus as well as information obtained during previous SARS and MERS outbreaks.¹⁰⁶ It was stated that immunosuppression does not increase the risk of transmission or clinical severity of COVID-19, and immunosuppressive drugs can even be used to suppress the cytokine storm in severe COVID-19 cases. Similar recommendations were also made in a study reporting the common views of authors from different countries.¹⁰⁷ It was stated that newly diagnosed patients should be followed up regularly until inflammation is controlled and that local treatment options should be preferred whenever possible. However, it was noted that systemic corticosteroids and immunomodulatory drugs can be used in patients with severe sight-threatening uveitis. They reported that treatment should be interrupted in patients who are receiving immunosuppressive treatment and test positive for SARS-CoV-2. In an online survey study, 139 ocular inflammatory disease experts from all over the world were asked questions concerning the use of IMT in non-infectious uveitis cases during the COVID-19 pandemic and a detailed treatment algorithm was created for patients.¹⁰⁸ The experts were presented with patient scenarios divided into different categories and groups and provided yes/no responses in terms of IMT. In the first category, patients were divided into four groups according to COVID-19 signs and symptoms: 1. Healthy, 2. Healthy with a history of contact with a COVID-19 patient, 3. Showing symptoms of COVID-19, and 4. Confirmed COVID-19 diagnosis. In the second category, patients were divided into three groups according to systemic risk factors and immunosuppression level: 1. At-risk patients, 2. High-risk patients, and 3. Very high-risk patients. At-risk patients were defined as those using immunosuppressants other than biologic agents. High-risk patients were defined as patients with one of the following risk factors: biologic agent use, high-dose immunosuppressive use, multiple immunosuppressive use, presence of active systemic inflammatory disease, presence of heart, lung, and/or kidney disease, neutropenia, smoking, pregnancy, being over 60 years of age, or previous history of infection while taking IMT. Very high-risk patients were defined

as those having two or more of the above risk factors. The consensus options for the management of patients classified by risk group are summarized in Table 1, Table 2, and Table 3.¹⁰⁸

Real-life Data During the COVID-19 Pandemic

Information pertaining to patients receiving IMT due to rheumatologic and inflammatory bowel diseases during the COVID-19 pandemic is recorded in international databases.

Experiences with patients using immunosuppressants during the COVID-19 pandemic are also shared in the SECURE-IBD database, which provides current real-life data on inflammatory bowel diseases. Finally, according to data last updated on January 5, 2021, a total of 4,280 cases worldwide were shared (<https://covidibd.org/current-data/>. Updated 01/05/2021). It was observed that 39% of 296 patients who contracted COVID-19 while using oral or parenteral corticosteroids were hospitalized and 14% had a severe course. Thirty-three patients infected with SARS-CoV-2 while using methotrexate were reported. Of those, 10 patients were admitted for inpatient treatment and only 2 patients had a clinically severe disease. Another 362 patients diagnosed with COVID-19 were using azathioprine and 76% of those patients were followed up on an outpatient basis. It was reported that 5% of the patients needed intensive care, 4% received ventilator support, and 8 people died (2%). COVID-19 was diagnosed in 1,418 patients using various anti-TNF- α molecules (monotherapy). Of these, 89% were treated as outpatients and only 2% had severe infection. Of 394 COVID-19 patients using azathioprine or methotrexate in combination with anti-TNF- α , 81% were treated as outpatients, 3% needed intensive care, and 2% required ventilator support. Fifteen patients (4%) died during treatment.

EULAR (European League Against Rheumatism), which conducts studies on rheumatic diseases, collects data pertaining to patients with rheumatic diseases who are diagnosed as having COVID-19. Their latest report (dated: 01/12/2021) presents data from a total of 3,590 patients (https://www.eular.org/myUploadData/files/eular_covid_19_registry_report_1_dec.

pdf). When all patients were considered, it was reported that 46% needed inpatient treatment. Seventy-nine percent of the patients were infected with SARS-CoV-2 while using any immunosuppressant, and of those patients, 56% were using conventional immunosuppressants and 38% used biologics. The proportion of Behçet patients enrolled in this database is 1%, and the report included no separate analysis of Behçet patients. In June of last year, EULAR also published recommendations on the management of rheumatologic and musculoskeletal diseases.¹⁰⁹ It was recommended that patients without suspected or confirmed COVID-19 should continue their treatment unchanged. Patients who have contact with anyone diagnosed as having COVID-19 should have a SARS-CoV-2 test even if they have no symptoms, and a multidisciplinary approach to treatment was recommended for patients with a confirmed COVID-19 diagnosis.

Very recently, two case series of BD patients diagnosed with COVID-19 were published.^{110,111} In a series presenting 4 BD patients with COVID-19 (upper respiratory tract infection in 3 and viral pneumonia in 1 patient), 3 of the patients were hospitalized for treatment and all patients had mild COVID-19 and recovered without any complications. Activation of cutaneous and mucosal findings of BD was observed during COVID-19 infection in one patient and 15 days after recovering from COVID-19 in another patient. Two of the patients in this series were using conventional immunosuppressants (one methotrexate, the other azathioprine) combined with oral corticosteroids at the time of COVID-19 diagnosis, and it was reported that methotrexate therapy was discontinued in the former patient after being diagnosed with COVID-19.¹¹⁰ The other series presented 10 BD patients with COVID-19, of whom 6 developed viral pneumonia, 8 were hospitalized, and 2 were admitted to the intensive care unit. One of the patients died of severe respiratory failure, one developed deep vein thrombosis, and 3 patients had recurrence of oral aphthae and arthralgia associated with BD. All patients except the deceased patient were using colchicine and/or an immunomodulatory drug at

Table 1. Consensus treatment recommendations for at-risk patients* (follow from left to right)¹⁰⁶

| | | | |
|---|-------------------------------|---|--|
| Not using CS | | Healthy patient | Initiate |
| | | COVID-19 patient (suspected or confirmed) | Do not initiate |
| Using oral CS | Using low-dose CS | Healthy patient (with or without contact) | Continue |
| | Using high-dose CS | Healthy patient | Continue |
| | | COVID-19 patient (suspected or confirmed) | Dose can be reduced, drug can be discontinued if confirmed |
| | If considering intravenous CS | COVID-19 patient (suspected or confirmed) | Do not initiate |
| | If considering local CS | Healthy patient with contact or COVID-19 patient (suspected or confirmed) not receiving oral CS | It is preferred over systemic therapy |
| All patients receiving low-dose oral CS | | It is preferred instead of increasing the systemic therapy dose | |
| Using conventional immunosuppressants | | Healthy patient | Continue |
| | | Healthy patient with contact | Continue |
| | | COVID-19 patient (suspected or confirmed) | Dose can be reduced or treatment discontinued |

CS: Corticosteroid, *See text, COVID-19: Coronavirus disease-19

Table 2. Consensus treatment recommendations for high-risk patients (follow from left to right)¹⁰⁶**

| | | | |
|--|-------------------------------|---|---|
| Not using CS | | COVID-19 patient (suspected or confirmed) | Do not initiate treatment |
| Using oral CS | Using low-dose CS | Healthy patient | Continue treatment |
| | | Positive COVID-19 test | Dose can be reduced or treatment discontinued |
| | Using high-dose CS | Healthy patient | Consider continuing treatment |
| | | COVID-19 patient (suspected or confirmed) | Dose can be reduced or treatment discontinued |
| | If considering intravenous CS | Healthy patient with contact or COVID-19 patient (suspected or confirmed) | Do not initiate |
| | If considering local CS | Healthy patient with contact or COVID-19 patient (suspected or confirmed) not receiving oral CS | It is preferred over systemic therapy |
| All patients receiving low-dose oral CS | | It is preferred instead of increasing the systemic therapy dose | |
| Using conventional immunosuppressants | | Healthy patient | Continue |
| | | COVID-19 patient (suspected or confirmed) | Dose can be reduced or treatment discontinued |
| Using or considering treatment with a biologic agent | | Healthy patient (including those using tocilizumab) | Continue |
| | | Healthy patient with contact | Do not initiate |
| | | | Do not change treatment to tocilizumab |
| | | COVID-19 patient (suspected or confirmed) | Discontinue |

CS: Corticosteroid, **See text, COVID-19: Coronavirus disease-19

Table 3. Consensus treatment recommendations for very high-risk patients* (follow from left to right)¹⁰⁶**

| | | | |
|--|-------------------------------|---|---|
| Not using CS | | COVID-19 patient (suspected or confirmed) | Do not initiate |
| Using oral CS | Using low-dose CS | Healthy patient | Continue |
| | | COVID-19 patient (suspected or confirmed) | Dose can be reduced or treatment discontinued |
| | Using high-dose CS | COVID-19 patient (suspected or confirmed) | Dose can be reduced or treatment discontinued |
| | If considering intravenous CS | Healthy patient with contact or COVID-19 patient (suspected or confirmed) | Do not initiate |
| | If considering local CS | All patients not receiving oral CS or receiving low-dose oral CS | It is preferred instead of increasing the systemic therapy dose |
| immunosuppressive drug | | Healthy patient | Continue |
| | | Healthy patient with contact | Do not initiate |
| | | COVID-19 patient (suspected or confirmed) | Dose can be reduced or treatment discontinued |
| Using or considering treatment with a biologic agent | | Healthy patient (including those using tocilizumab) | Continue |
| | | Healthy patient with contact | Do not initiate |
| | | COVID-19 patient (suspected or confirmed) | Discontinue |

CS: Corticosteroid, ***See text, COVID-19: Coronavirus disease-19

the time of COVID-19 diagnosis (colchicine in 5, azathioprine in 3, anti-TNF- α agents in 3, and oral corticosteroids in 2 patients).¹¹¹

Conclusions

In the light of previous clinical experience and the information obtained during the COVID-19 pandemic, albeit short term data, IMT does not appear to increase the risk of SARS-CoV-2 infection or the severity of the disease. Except for patients receiving high-dose systemic corticosteroid therapy and those at risk for severe COVID-19 infection, guidelines

generally recommend continuing IMT for patients who need it. Each patient’s condition should be evaluated individually when making treatment decisions. Patients should be treated using a multidisciplinary approach, taking into account systemic risk factors, the patient’s potential COVID-19 infection status, and the type and severity of uveitis.

Ethics

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Concept: M.F.K.D., F.N.Y., İ.T.T., Design: M.F.K.D., F.N.Y., İ.T.T., Analysis or Interpretation: M.F.K.D., F.N.Y., İ.T.T.,

Literature Search: M.F.K.D., F.N.Y., İ.T.T., Writing: M.F.K.D., F.N.Y., İ.T.T.

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