Implications of COVID-19 infection on patients with uveitis under biologic treatment

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ABSTRACT

Background/aims To investigate the incidence, severity of COVID-19 infection and the outcomes in patients with uveitis treated with biologic agents during COVID-19 pandemic.

Methods In this prospective study, we included all patients with uveitis treated with biologic agents and tested for COVID-19 infection between May 2020 and October 2020.

Results A total of 59 patients were identified. Behçet's disease was the most common diagnosis (64.4%). Infliximab was the most frequent biologic agent used (61%). Nine (15.3%) patients were tested positive for COVID-19. None of the patients with positive COVID-19 test developed any COVID-19-related symptoms during follow-up. Of the nine patients with positive COVID-19 test, only two patients had uveitis flare-up after the biologic suspension.

Conclusion Uveitis patients under biologic therapy can be silent carriers for COVID-19.

INTRODUCTION

A novel SARS-CoV-2, which is responsible for COVID-19, was accepted on 11 March 2020 by the WHO to be a worldwide pandemic.[1 2] Current evidence indicates a greater risk of death in older age patients with concomitant other health-related conditions, including diabetes mellitus, chronic lung disease, hypertension and cardiovascular diseases.[3] Several retinal findings have been reported in patients with COVID-19 including cotton wool spots, intraretinal haemorrhages, dilated veins, tortuous vessels and paracentral acute middle maculopathy.[4–7]

In patients with uveitis, particularly with ongoing biologic therapy, there was a suspicion among uveitis specialists whether those patients have heightened susceptibility to COVID-19 infection.[8] Furthermore, it is also uncertain whether these agents may exacerbate COVID-19 symptoms and convert the infection into a more lethal form.[9 10] This was speculated regarding the relative risk of immunosuppression caused by biologic therapy that can prevent prompt immune response to clear up the virus in the earliest stage of the disease. On the other hand, immunosuppression has been postulated to play a protective role by lessening any exaggerated immune response that might be observed in the later stage of the disease, especially during the cytokine storm.[11–14] The International Uveitis Study Group (IUSG) jointly with the International Ocular Inflammation Society (IOIS) and the Foster Ocular Inflammation Society (FOIS) has similarly indicated the need to continue immunomodulatory therapy (IMT) and biologics in patients without clinical signs of COVID-19 or confirmation of disease.[15 16]

Recently, there have been accumulating data that concomitant therapy with antitumour necrosis factor-alpha (TNF-α) agents is not associated with a worse COVID-19 prognosis.[13 17–21] Moreover, other studies suggest a protective effect of anti-TNF-α agents on the evolution of the disease into severe forms, thereby preventing the damaging effects of the high levels of cytokines.[11 20 22]

In the current study, we aim to report incidence, course of COVID-19 infection and the outcomes of uveitis in patients under biologic therapy.

PATIENTS AND METHODS

This was a prospective study that included all non-infectious uveitis patients treated with biologic agents who were followed up at the uveitis clinic of King Abdulaziz University Hospital, Riyadh, Saudi Arabia, between May 2020 and October 2020. All patients were managed and followed up by one of the authors (AMA). During the period of the pandemic and lockdown, our uveitis service was continued for all patients. Nursing staff and doctors were fully protected using suitable personal protective equipment included N95/surgical mask, eye goggles/face shields, disposable gowns and disposable gloves. Patients were also instructed to wear masks when they come to the clinic. A breathguard was attached to all slit-lamp devices to minimise the transmission of the virus.

Data were collected including demographic data (age, gender) and clinical data, including visual acuity, intraocular pressure and the severity of the anterior chamber inflammation based on the Standardization of Uveitis Nomenclature Working Group.[23] Results of dilated fundus examination, treatment modalities, associated ocular complications and associated systemic diseases were all documented.

At King Abdulaziz University Hospital, a standardised protocol has been adopted for uveitis patients on biologics during COVID-19 pandemic. This included performing a nasopharyngeal swab for the COVID-19 using PCR 2 days before receiving the biologic agent. For those tested positive, the biologics were suspended until the patients were cleared. All patients were seen and evaluated by our medical team after diagnosis of COVID-19. During the clearance time, patients were instructed to continue with other treatments if any.

Table 1 Patients demographics for the whole study group

Variable	n (%) (n=59 patients)
Age	
≤16 years	12 (20.3)
>16 years	47 (79.7)
Gender	
Male	44 (74.6)
Female	15 (25.4)
Body mass index	Mean 25.4±5.9 (range: 16.33–45.2)
Diagnoses	
Behçet's disease	38 (64.4)
Idiopathic panuveitis	9 (15.3)
Chronic recurrent VKH	4 (6.8)
Idiopathic intermediate uveitis	3 (5.1)
Idiopathic anterior uveitis	3 (5.1)
Sarcoidosis	1 (1.7)
Diffuse subretinal fibrosis syndrome	1 (1.7)
Type of biologic therapy	
Infliximab	36 (61)
Adalimumab	14 (23.7)
Rituximab	9 (15.3)
COVID-19 test	
Positive	9 (15.3)
Negative	50 (84.7)

VKH, Vogt-Koyanagi-Harada disease.

RESULTS

A total of 59 patients with uveitis were admitted to receive biologic therapy between May 2020 and October 2020. There were 44 (74.6%) males and 15 (25.4%) females. The age of the patients ranged from 8 to 51 years (mean 26.4±10.9 years). There were 12 (20.3%) patients who were ≤16 years of age. The body mass index of the patients ranged from 16.33 to 45.2 (mean 25.4±5.9). Of the 59 patients included, Behçet's disease was the most common diagnosis in 38 (64.4%) patients. This was followed by idiopathic panuveitis in seven (15.3%) patients, chronic recurrent Vogt-Koyanagi-Harada (VKH) disease in four (6.8%) patients, idiopathic intermediate uveitis in three (5.1%) patients, chronic idiopathic anterior uveitis in three (5.1%) patients, sarcoidosis in one (1.7%) patient and diffuse subretinal fibrosis syndrome in one (1.7%) patient. Infliximab was the most common biologic agent that was used in 36 (61%) patients including 28 (77.7%) patients with Behçet's disease, 4 (11.1%) patients with idiopathic panuveitis, 2 (5.6%) patients with intermediate uveitis, 1 (2.8%) patient with idiopathic anterior uveitis and 1 (2.8%) patient with sarcoidosis. This was followed by adalimumab that was used in 14 (23.7%) patients including 10 (71.4%) patients with Behçet's disease, 3 (21.4) patients with idiopathic panuveitis and 1 (7.1%) patient with intermediate uveitis. Rituximab was used in nine (15.3%) patients including four (44.4%) patients with chronic recurrent uveitis associated with VKH disease, four (44.4%) patients with idiopathic granulomatous panuveitis and 1 (11.1%) patient with diffuse subretinal fibrosis syndrome (table 1).

Clinical management and outcome of uveitis before and after testing positive for COVID-19

Of the 59 patients tested for COVID-19, the test was positive in nine (15.3%) patients. Of those nine patients, one (11.1%) patient was under 16 years of age. The biologic agents were postponed in all patients who were tested positive for COVID-19. However, the patients were instructed to continue with the other medications (table 2). The interval between testing positive

Table 2 Clinical findings before after testing positive for COVID-19

Patient	Diagnosis	Age	Gender	Biologic treatment	BMI	Interval between doses (weeks)	Other treatments	Uveitis status		Was the biologic therapy resumed after clearance from COVID-19	Interval between positive and negative COVID-19 tests	COVID-19 symptoms
								Status of uveitis before testing positive for COVID-19	Was biologic treatment postponed?			
1	Behçet	29	Male	Adalimumab	28.2	2	MMF	Quiet	Yes	Active	Yes	4	Asymptomatic
2	Behçet	38	Male	Infliximab	26.5	8	MMF	Quiet	Yes	Active	Yes	5	Asymptomatic
3	Behçet	48	Female	Infliximab	32.7	10	MMF	Quiet	Yes	Quiet	Yes	3	Asymptomatic
4	Behçet	25	Male	Infliximab	22.3	8	MMF	Quiet	Yes	Quiet	Yes	4	Asymptomatic
5	Behçet	35	Male	Infliximab	25.1	6	Oral steroids	Quiet	Yes	Quiet	Yes	6	Asymptomatic
6	Behçet	38	Male	Infliximab	20.7	8	None	Quiet	Yes	Quiet	Yes	3	Asymptomatic
7	Idiopathic intermediate uveitis	28	Female	Infliximab	25.5	6	Cyclosporine	Quiet	Yes	Quiet	Yes	2	Asymptomatic
8	Idiopathic panuveitis	9	Male	Adalimumab	27.6	2	Topical steroids	Quiet	Yes	Quiet	Yes	2	Asymptomatic
9	Diffuse subretinal fibrosis syndrome	25	Male	Rituximab	23	2*	MMF	Quiet	Yes	Quiet	Yes	2	Asymptomatic

*Patient started on rituximab one dose and found to be COVID-19 positive when presented for the second dose.
BMI, body mass index; MMF, mycophenolate mofetil.

and negative for COVID-19 (clearance time) ranged from 2 to 6 weeks with a mean of 3.4±1.3 weeks. After clearance, clinical evaluation revealed flare-up in two (22.2%) patients with uveitis associated with Behçet's disease and the biologic treatments were resumed in all patients. Patients' characteristics, demographics, treatment modalities and systemic findings of the nine patients with positive COVID-19 test are summarised in table 2.

Clinical details and management of uveitis flares

Of the two patients with flare-ups, the first patient was a 38-year-old male patient with Behçet's disease on infliximab infusions every 8 weeks in addition to mycophenolate mofetil. Because of positive COVID-19 test, infliximab was postponed for another 5 weeks until he was cleared. After clearance, his Snellen visual acuity was hand motions vision in the right eye and 20/40 in the left eye. Intraocular pressure was 51 mm Hg in the right eye and 17 mm Hg in the left eye. Right eye examination revealed anterior chamber inflammation (3+ cells), rubeosis iridis and 360° posterior synechiae causing pupillary block glaucoma. Left eye examination showed quiet eye. The patient underwent right eye peripheral yttrium aluminium garnet iridotomy and the inflammation was treated successfully with resuming the infliximab infusion. The second patient was a 29-year-old male patient with Behçet's disease on adalimumab treatment every 2 weeks in addition to mycophenolate mofetil. Because of positive COVID-19 test, adalimumab was postponed for another 4 weeks until he was cleared. After clearance, his Snellen visual acuity was 20/20 vision in the right eye and 20/200 in the left eye. Intraocular pressure was 14 mm Hg in the right eye and 15 mm Hg in the left eye. Anterior segment examination showed quiet eyes. Dilated fundus examination showed multiple patches of retinitis in both eyes. Optical coherence tomography showed dry macula in the right eye and cystoid macular oedema in the left eye. Fundus fluorescein angiography demonstrated inflamed optic discs in addition to the diffuse vascular leakage in both eyes. The flare-up was treated successfully with resuming adalimumab treatment.

Manifestations of COVID-19 infection

None of the nine patients who were tested positive had symptoms related to COVID-19 infection. Vital signs included temperature and oxygen saturation, were normal in all patients before taking the swabs.

DISCUSSION

The current study was conducted to investigate the incidence, severity of COVID-19 infection and uveitis outcomes in patients receiving biologic treatment. Importantly, due to the sudden, widespread and dynamic nature of the COVID-19 pandemic, our understanding of the SARS-CoV-2 virus is rapidly evolving.[24] Therefore, the administration of biologics in patients with uveitis during the COVID-19 pandemic remains understudied; thus, we conducted our study. During the early stages of this pandemic, a consensus was designed by IUSG, IOIS and FOIS and proposed to continue the use of IMT and biologics in patients without clinical signs or confirmation of COVID-19. Additional recommendations included hand personal hygiene, social distancing and using masks.[15 16]

Interestingly, none of our patients on biologic agents and tested positive for COVID-19 developed any COVID-19-related symptoms. This indicates that the use of biologic agents, particularly anti-TNF-α, might have a protective effect against severe COVID-19 infection symptoms. Therefore, these patients might be silent carriers for the virus. This was in agreement with a previous study.[13]

There is a growing evidence to suggest that the life-threatening cases related to COVID-19 are attributed to a strong upregulation of proinflammatory cytokine production, known as 'cytokine storm syndrome'.[10 17 22 25 26] Therefore, treatment strategies targeting these proinflammatory cytokines, such as inhibition of interleukin-6 and TNF-α with tocilizumab and infliximab, respectively, are currently being investigated by many studies and have shown evidence of clinical benefit in subsets of patients with severe COVID-19.[1 27–36] On the other hand, another study has demonstrated severe bilateral pneumonia in a patient on infliximab treatment, and the symptoms were severe enough to admit the patient to intensive care unit.[10] Therefore, the role of anti-TNF-α agents related to COVID-19 might require further investigation.

In the current study, one patient on rituximab treatment was tested positive for COVID-19. However, this patient did not develop any COVID-19-related symptoms. However, previous studies demonstrated that patients on rituximab treatment for rheumatic diseases had unfavourable prognosis on hospitalisation with COVID-19.[37–39] It has been suggested that high-risk patients on rituximab should have serum immunoglobulin level monitored and the rituximab should be discontinued in those who develop hypogammaglobulinemia.[38]

In the current study, out of nine patients being tested positive for COVID-19, only two patients had uveitis flare-up that was managed by resuming the biologics after medical clearance. Our study indicates that patients on biologic treatment can tolerate delaying the biologic dose few weeks until being cleared from COVID-19 infection. It is essential to know that the consensus strategies in using the biologics during this pandemic may change over time as we learn more about this virus, and the effects of delaying biologics on uveitis outcomes should be revisited regularly.

There are several limitations related to this study including the small number of patients analysed. Even though the sample size in our study is low to draw strong conclusions, this study adds additional data about the safety profile of biologic therapy in patients with uveitis during this pandemic. Moreover, it is crucial to highlight that our data should be interpreted with caution, as all of our patients are from the younger age group with no other concomitant risk factors and therefore might not represent the actual high-risk group.

In conclusion, patients receiving biologic therapy, particularly anti-TNF-α agents, can be silent carriers for COVID-19. In otherwise healthy individuals, biologic treatment can safely treat patients with uveitis during COVID-19 pandemic and can be suspended temporarily for those tested positives. Future research activities might focus on a larger prospective series to determine the safety of biologics in addition to their applicability to reduce the incidence of severe forms of COVID-19.

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