Considerations for the Treatment of Inflammatory Neuro-Ophthalmologic Disorders During the COVID-19 Pandemic

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Abstract: The initiation and continuation of immune-based therapies to treat and prevent complications of inflammatory neuro-ophthalmologic disorders during the 2019 novel coronavirus (COVID-19) pandemic is the subject of considerable debate. In each case, a treatment decision must be reached based on best clinical practices for the disorder, patient comorbidities, the current state of knowledge about the pathogenesis and infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the utilization of hospital and community resources. Unfortunately, the evidence needed to standardize the decision-making process for each neuro-ophthalmologic disorder is currently absent and is likely to require months or years to develop based on the accrual of robust international data sets. In this article, we review the current understanding of SARS-CoV-2 and COVID-19 complications to provide a framework for approaching the treatment of inflammatory neuro-ophthalmic disorders during the COVID-19 viral pandemic.

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BACKGROUND

Coronaviruses (CoVs), first identified in the 1950s, are the largest group of RNA viruses with an extensive range of natural hosts (1). The causative agent of the coronavirus disease 2019 (COVID-19) pandemic is a novel human coronavirus of the beta genus called SARS-CoV-2 or severe acute respiratory syndrome coronavirus 2 (2). Most patients with COVID-19 will have a mild to moderate flu-like illness; a fraction of infected individuals will develop SARS-CoV-2–associated acute respiratory distress syndrome (ARDS) and multiorgan failure. Major risk factors for severe illness include age ≥65 years, residence in a nursing home or long-term care facility, chronic lung disease, moderate to severe asthma, serious heart conditions, Class III obesity (body mass index >40), poorly controlled diabetes, chronic renal disease, renal failure, liver disease, and hypertension (3). The Centers for Disease Control and Prevention (CDC) also notes that for people with "immunocompromised states," such as individuals receiving cancer treatment, smokers, bone marrow or organ transplantation recipients, patients with immune deficiencies, those with poorly controlled HIV or AIDS, and individuals treated with chronic corticosteroids and other "immune-weakening medications," the risk of severe disease may be altered by the degree of immunosuppression (4). However, data from Italy and China have not indicated that immunosuppressed patients are uniformly at higher risk for severe COVID-19 complications (5,6). This finding, seemingly at odds with CDC guidance, raises a number of questions regarding treatment decisions for patients needing acute or chronic treatment for inflammatory neuro-ophthalmic disorders.

Because of the highly infectious and novel nature of SARS-CoV-2, all people are believed to be *at risk* for infection with SARS-CoV-2. The use of immunomodulatory and immunosuppressant therapies for the acute and chronic treatment of inflammatory neuro-ophthalmologic conditions, such as optic neuritis, neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein (MOG)-associated disease, multiple sclerosis (MS), myasthenia gravis, giant cell arteritis (GCA), thyroid eye disease,

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and others can increase both the risk of infection and infectious complications. Guidelines for adjusting treatments, or continuing therapies without changes, are being made by consensus for some disorders such as myasthenia gravis (7), but the evidence guiding these recommendations is limited or nonexistent. To initiate informed conversations with patients regarding acute or ongoing immune-based therapies, neuro-ophthalmologists, neurologists, and ophthalmologists need to have a broad understanding of COVID-19 and the data underlying the infectious risk associated with certain therapies.

SARS-CoV-2, THE NERVOUS SYSTEM, AND PRE-EXISTING NEUROLOGIC DISEASES

Nervous System Invasion

Peer-reviewed data regarding the possible neurotropism of SARS-CoV-2 are not yet available, but previous research on other human coronavirus, including SARS-CoV-1, indicates that central nervous system (CNS) infection is possible, particularly in the brainstem (8). Two potential portals of entry into the CNS by human coronaviruses include 1) hematogenous spread or 2) trans-synaptic spread through neuronal afferents from infected tissue (lung, heart, and nasal epithelium) or sensory neurons of the oronasopharynx. Previous reports, including postmortem human studies, have shown that SARS-CoV-1 can enter the CNS and likely does so by trans-synaptic neuronal spread from the respiratory epithelium or the olfactory bulb (8), although infected circulating immune cells in SARS-CoV-1 make it plausible that hematogenous spread can contribute to neuronal infection as well (8). Studies in primates infected with coronaviruses have demonstrated direct hematogenous spread into the primate CNS with perivascular tissues showing the greatest concentration of the viral material. Indeed, autopsy tissue from patients with SARS-CoV-1 have demonstrated systemic vasculitis (9,10).

Early data from China are shaping our understanding of central and peripheral nervous system signs and symptoms in patients with COVID-19. Mao et al (11) conducted a retrospective chart review of 214 hospitalized patients with COVID-19 in Wuhan, China, and reported neurologic issues in roughly 36% of patients. Signs and symptoms included headache, dizziness, anomia, dysgeusia, ataxia, vision impairment, and altered consciousness associated with disorders such as stroke, seizure, and myopathy (11). The authors did not localize the vision impairment or provide additional clinical details about the patients, as the data were collected by chart review, and clinical documentation was limited by the logistical constraints of the pandemic (personal communication). Many neurologic signs and symptoms, such as altered consciousness, stroke, and seizure, could have been the result of critical illness and/or systemic inflammatory changes; however, others findings, such as abnormal taste and smell, which are now commonly reported, could be the result of direct nervous system involvement, particularly abnormal taste since anosmia is potentially related to infection of the nasal epithelium. A recent report of acute necrotizing encephalitis (12) in a patient with polymerase chain reaction-documented COVID-19 raises the question of direct CNS infection vs hyperinflammatory, immune-based injury; unfortunately, the analysis of the cerebrospinal fluid (CSF) was limited because of a traumatic lumbar puncture (11,12). A patient from Japan was recently reported with altered mental status and meningoencephalitis in association with COVID-19 pneumonia (13), and viral RNA from SARS-CoV-2 was isolated from the CSF, demonstrating the potential neuroinvasive nature of the virus. In fact, it has been proposed that direct infection of the brainstem could contribute to respiratory failure in COVID-19 resulting in prolonged time to extubation in some patients recovering from viral-induced pneumonia, although the contribution of central hypoventilation from SARS-CoV-2 infection remains to be proven (14). Finally, there is evidence that the hyperinflammatory innate immune response contributes to ARDS in SARS-CoV-2, and SARS-CoV-1 could potentiate CNS invasion (10,15). Nearly weekly, new cases of CNS involvement in association with COVID-19 are being reported, including encephalopathy, confusion, agitation, corticospinal tract sign (16), demyelinating peripheral neuropathy, flaccid paresis of extremities and the face (17), cerebrovascular disease (18), and seizures (19). Additional clinical data collection is required to determine the true rate of direct nervous system invasion by SARS-CoV-2 in patients with severe COVID-19.

Pre-Existing Neurologic Diseases

For those with pre-existing neurologic disease, there are no data at this time that indicate whether isolated and pre-existing nervous system disorders, without other known risk factors, increase the risk for SARS-CoV-2 infection or infectious complications, neurologic or otherwise. As noted, systematic tracking of large number of patients will be critical to address such issues. The COVID-19 Global Rheumatology Alliance is currently collecting data to understand how those with pre-existing rheumatic disease on immunomodulatory and immunosuppressive therapies fare with SARS-CoV-2 infection (20). These data have potential to inform our decision about risks associated with immunomodulatory and immunosuppressive agents in nonrheumatologic conditions, although given the complexity of the immune response to SARS-CoV-2, the results might not be generalizable to people with pre-existing nervous system disorders on the same therapies. More recently, the National MS Society and the Consortium of MS Centers developed a reporting and tracking system for COVID-19 in MS and Related Diseases (COViMS); case reporting forms and additional information are available online at https://www.covims.org/. Other registries are taking shape as well (see https://clinicaltrials.gov/ for an updated list).

Another challenge is whether COVID-19 increases the risk for exacerbation of pre-existing inflammatory neuro-ophthalmic conditions. COVID-19 is a novel illness for humans, and careful patient observations will be necessary to understand the role it might have in altering the course of inflammatory nervous system disease. Past observations and reports indicate that some conditions, such as MS, are likely to have an increased risk of disease activity during times of infection (21–24). For COVID-19, the dramatic elevation in acute phase reactants and cytokines may impact disorders such as NMOSD in which IL-6 signaling and complement play a prominent role in relapse activity (25–27). If the seroprevalence remains relatively low for SARS-CoV-2 infection in the general population, then hundreds of patients will need to be evaluated to systematically address questions regarding infectious complications. Therefore, tracking outcomes for patients with pre-existing neurologic disease through collaborative efforts such as COViMS is preferred over single-institution data to inform clinical decision making.

It is clear from epidemiologic data regarding COVID-19 that age is one of the most significant risk factors for severe complications and mortality. The adjusted fatality rate for those younger than 50 years is $<0.5\%$, and it is even lower for those younger than 19 years. Adjusted fatality rates for age above 50 years are: 50–59 years, 1.25%; 60–69 years, 3.99%; 70–79 years, 8.61%; and >80 years, 13.4% (28). Therefore, during the care of patients with neuroinflammatory disorders during the SARS-CoV-2 pandemic, age is an important factor when making treatment decisions during the pandemic.

THE IMMUNOLOGY OF SARS-CoV-2 AND COVID-19: OUR CURRENT UNDERSTANDING

The investigation of SARS-CoV-2 has taken place at a rapid pace, and our understanding will continue to grow beyond our current summary. In vitro research demonstrates that the surface spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) in pigs, ferrets, cats, nonhuman primates, and human cells (29). The SARS-CoV-2 virus shares approximately 80% of its sequence with SARS-CoV-1 and 97% of its sequence with a bat coronavirus (29), lending evidence to its species origin. The spike protein engagement with ACE2 reduces ACE2 expression and facilitates viral entry into the cell (30), and novel mutations in the SARS-CoV-2 spike protein appear to facilitate ACE2 binding affinity and infectivity (29,31). For SARS-CoV-2, a driver of ARDS and destruction of lung tissue appears to be the host's innate immune system. An analysis of inflammatory biomarkers and lymphocyte subsets in 452 patients with laboratory-confirmed COVID-19 (26) revealed that specific inflammatory markers, including procalcitonin and C-reactive protein, were significantly elevated. Another study showed that procalcitonin was normal in patients with COVID-19 on admission and then increased with secondary infections (32,33). A cytokine storm appears to take place in patients with severe disease, and studies have shown elevated levels of IL-1B, IL-1RA, IL-6, IL-7, IL-8, IL-9, IL-10, and fibroblast growth factor, granulocyte-colony stimulating factor (GSCF), granulocyte-macrophage colony-stimulating factor, interferon gamma, IP10, MCP-1, MIP1A, MIP1B, platelet-derived growth factor, TNFα, and vascular endothelial growth factor in intensive care unit (ICU) and non-ICU patients compared with healthy adults (32,33). ICU patients had plasma concentrations of IL-2, IL-7, IL-10, GCSF, IP10, MCP-1, MIP1A, and TNFα that were higher than those of non-ICU patients, and hospitalized patients with COVID-19 can have decreased circulating leukocytes, particularly $CD4^+$ T lymphocytes, early in the disease course (32,33). Investigations show particular elevation of IL-6 in hospitalized patients with COVID-19, including ICU and non-ICU patients (33). The number of B cells, polymorphonuclear leukocytes, and immunoglobulins (IgA, IgG, and IgM) does not appeared to be altered (33), although this might vary with the patient and disease course (34). Given these data, there are numerous trials underway investigating methods to diminish the innate immune response to COVID-19, such as anti–IL-6 receptor therapies. Destruction of lower respiratory tract tissue may be at least partially due to the hyperinflammatory response in COVID-19. One report indicated that COVID-19 ARDS patients treated with an IL-6 receptor inhibitor had better outcomes, improved fever, and lower oxygen requirement (35); randomized controlled trials (RCTs) using the IL-6 receptor blockade with tocilizumab (Actemra, Roche-Genentech) or sarilumab (Kevzara, Regeneron) are now underway in the United States, and a multicenter RCT with tocilizumab was also approved in China for patients with COVID-19 pneumonia and elevated IL-6 (32). Similar approaches aimed at dampening the innate immune response have been proposed (36,37). Early reports have indicated that some people with COVID-19 who were on immunosuppressive agents for immune-related disorders or prevention of transplant rejection seem to have performed well despite their immunocompromised status (5,6). Data suggest that B-cell–depleting or nonlymphopenic therapies could decrease or even ameliorate detrimental consequences of an overreactive innate immune response (26). Although far from definitive, anecdotal data from a hospital in Lombardy, Italy, that is located in the "red zone" of the Italian COVID-19 outbreak reveal that immunosuppressed patients are not at an increased risk of severe pulmonary disease compared with the general population (5). Another example is a case report of a 52-year-old male patient with a history of kidney transplant on a broad immunosuppressant regimen (mycophenolate, tacrolimus, and prednisone) with laboratory-confirmed COVID-19 pneumonia, who was treated with 40 mg of intravenous methylprednisolone in combination with supportive management without significant side effects (6). As the pandemic continues, a review of the clinical course of the immunocompromised will be important to help guide therapy.

IMMUNOMODULATORY AND IMMUNOSUPPRESSIVE AGENTS USED IN NEURO-OPHTHALMIC DISORDERS

Table 1 lists therapies used for the acute or chronic treatment of common inflammatory disorders encountered by the neuro-ophthalmologist. Owing to their direct and indirect effects on immune cells and their interactions, there are potential concerns regarding the use of these medications and the risk of severe COVID-19 complications. It is critical that treating physicians discuss the benefits and risks of using these medications with their patients during the pandemic to be sure patients are not placing their health at risk by discontinuing their medications out of fear.

Fortunately, to date, the risk of serious acquired viral infections remains relatively low with commonly used medications in inflammatory neuro-ophthalmic conditions, whereas the risk for viral reactivation, such as with herpes zoster, varicella zoster virus, John Cunningham virus, and hepatitis B, may be increased with a number of agents (9). The effects of high-dose corticosteroids on immune function are pleiotropic; however, their effect on macrophage production of IL-1, IL-6, and tumor necrosis factor may be particularly relevant for the management of ARDS in patients with COVID-19 pneumonia (38). Variables such as the duration and dosage of corticosteroids, concomitant medications, and underlying medical comorbidities contribute to the higher incidence of opportunistic infections and reactivation of latent herpes zoster and tuberculosis (39) with the use of corticosteroids. Importantly, after discontinuation of short-term use of corticosteroids, such as used for typical optic neuritis, reconstitution of immune function is believed to occur rapidly. For patients with inflammatory neurologic conditions receiving B-cell–depleting anti-CD20 agents, there has been no safety signal indicating an elevated risk for acquired viral infections. In the randomized Phase III clinical trials of ocrelizumab for the treatment of relapsing and progressive forms of MS, there was no significant increase in serious infections observed in the ocrelizumab arms, although there was an apparent *association* between decreased levels of IgG and serious infections (40) in patients on ocrelizumab. Based on the results from the aforementioned clinical trials, the overall prevalence of serious infections in patients with MS who are treated with ocrelizumab is similar to that of the population with MS in general, and the types of serious infections are also consistent with those observed in MS registries. Among the infections reported in both trials, most viral infections were reactivation of herpes zoster, and the incidence of other respiratory infections, such as flu-like illnesses, was not significantly elevated when compared with placebo or IFN-1a (40,41). Similarly, the addition of rituximab to standard lymphoma chemotherapy regimens did not increase the infection risk in a focused meta-analysis (42).

Special Considerations

An abundance of caution should be given when using agents that can generate profound lymphopenia, including alemtuzumab and cladribine. Alemtuzumab exerts its clinical efficacy by lymphocyte depletion (43,44). Although broader effects on the adaptive and innate immune system remain unknown, absolute lymphocyte counts are profoundly decreased by the first day of infusion and may remain low, or even undetectable, for up to 2 years. Because T-cell depletion has the potential to promote the risk of viral infection, prophylaxis with antivirals during the post-infusion phase is advised for patients on alemtuzumab (43,44). Similar caution should be taken with cladribine, where the reduction of T cells tends to be rapid and dose dependent. T-cell depletion by 20% occurs following the first dose and increases to 45% following the second dose; depletion may be prolonged (43).

TREATMENT CONSIDERATIONS

Before initiating any therapy with immunosuppressive or immunomodulatory effects, patients should be screened for signs and symptoms of COVID-19. It would be prudent to avoid starting new treatments in patients acutely ill with COVID-19 out of obvious safety concerns. Physicians should counsel all patients before initiating new treatments that they must adhere to standard precautions for the prevention of exposure to SARS-CoV-2 (i.e., social distancing and avoiding people who have a higher chance of being an asymptomatic carrier) and minimize risk for infection (i.e., handwashing). Even in the absence of SARS-CoV-2 exposure or COVID-19 symptoms, patients should remain vigilant about their risk of contracting an infection, and neuro-ophthalmologists should be prepared to counsel them regarding these concerns. Integrating the issues discussed previously, we provide the following considerations for acute treatment and chronic therapy for some of the most common inflammatory conditions treated by neuro-ophthalmologists (Table 2).

MANAGEMENT OF ACUTE OPTIC NEURITIS

Acute optic neuritis can be due to a variety of underlying diseases, including MS, NMO, and MOG antibody disease. High doses of corticosteroids or adrenocorticotropic hormone are standard treatments for acute optic neuritis (45,46). Currently, there is no evidence that a short course of steroid treatment increases the risk or severity of SARS-CoV-2 infection.

Optic Neuritis Associated With Multiple Sclerosis or Idiopathic Optic Neuritis

Although corticosteroid therapy does not alter the final visual acuity or reduce retinal nerve fiber layer (RNFL) loss in MS-associated optic neuritis, it hastens the speed of visual

TABLE 1. Frequently used FDA-approved immunosuppressive therapies and their risk of infection

Treatment	Typical Dosage	Mode of Action	Risk of Infection	Comments
Ocrelizumab	Induction followed by 600 mg, every 6 mo	B-cell depletion	Viral infections and reactivation of HSV and VZV	Associated with the low IgG level
Tocilizumab	8 mg/kg every 4 weeks	IL-6 receptor inhibitor	Diverticulitis, bacterial infections, and viral upper respiratory infection	Theoretical benefits during cytokine storm in SARS-CoV-2 with randomized clinical trials ongoing
Teriflunomide	7 mg or 14 mg po daily	Inhibits the proliferation of activated T and B lymphocytes through the inhibition of DHODH	Zoster reactivation and opportunistic infections	Decreases the release of IL-6, IL-8, and MCP-1 from monocytes Inhibits lymphocytes proliferation (dose-dependent)
Eculizumab	900 mg IV weekly for 4 weeks, then 1,200 mg every 2 weeks	Humanized monoclonal antibody targeted against complement C5	Serious meningococcal infections	Modulate the activity of the distal complement by preventing the formation of MAC; hypothetically could be beneficial Does not hinder the viral fighting component of the immune system
Fingolimod	0.5 mg po daily	Binds the S1P receptor, causing lymphoid cell retention in the secondary lymphoid tissue	Viral infections (VZV and HSV) and HPV infections. PML	Risk for viral infections is dose-dependent and increased with the concomitant use of immunosuppressant therapies
Natalizumab	300 mg monthly infusion	Targets integrin $\alpha 4\beta 1$ (VLA-4), restricts T-cell and NK-cell extravasation and migration into the CNS	Small risk of upper respiratory tract infection	Does not suppress the immune system and does not place patients at greater risk for infections
Alemtuzumab	12 mg intravenous infusion once daily for 5 days at Month 0 and then once daily for 3 days at Month 12	Monoclonal antibody that selectively binds to CD52, highly expressed on lymphocytes (T and B cells), depleting these cells from circulation in the periphery	EBV and EBV-associated lymphoproliferative disorder, PML, and reactivation of latent viruses Opportunistic infections	Lymphopenia with unaltered innate response Theoretical increased risk for infection and infectious complications, including COVID-19
Cladribine	3.5 mg/kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg/kg per treatment course)	Purine antimetabolite cytotoxic effects on B and T lymphocytes through the impairment of DNA synthesis	Reactivation of latent viruses; viral infections	Lymphopenia Theoretical increased risk for infection and infectious complications, including COVID-19

CNS, central nervous system; DHODH, dihydroorotate dehydrogenase; EBV, Epstein-Barr virus; FDA, Food and Drug Administration; HPV, human papillomavirus; HSV, herpes simplex virus; MAC, membrane attack complex; MCP-1, monocyte chemoattractant protein 1; NK, natural killer; PML, progressive multifocal leukoencephalopathy; po, by mouth; VLA-4, very late antigen 4; VZV, varicella zoster virus.

TABLE 2. Common off-label immunomodulatory and immunosuppressive therapies and their risk of infection

Treatment	Typical Dosage	Mode of Action	Risk of Infection	Comments
For acute attack and relapses				
Methylprednisolone	1,000 mg daily for 3–5 days	Multiple mechanisms on most immune cells—dependent on the activation state; inhibits lymphocyte activation Suppressed production of IL-1, IL-6, and TNF	No evidence of increased risk of viral infections other than reactivation of VZV	Dependent on the duration of the therapy and dose
Plasma exchange	5 cycles over 5–7 days	Cytokine modulation, autoantibody depletion	No known risk for infections outside of central line placement	
IVIg	400 mg/kg/day for 5 days	Contains antibodies and antagonists to proinflammatory cytokines. IVIg is thought to interfere and prevent the passage of autoimmune T cells into the blood–nerve barrier	No known risk for infections	Probably beneficial as adjunctive therapy
Long-term therapies				
Azathioprine	2.5–3.0 mg/kg daily	Block adenine and guanine synthesis; inhibits T- and B-cell activation and mitosis	Leukopenia; no increase in the risk of viral infection	The risk for infection is higher after organ transplant and in patients with IBD rather than those with neurologic disorders
Methotrexate	7.5–25 mg weekly	Folic acid antagonism; inhibits DNA replication	Potential risk for opportunistic infections	Increased risk for infections if significant myelosuppression occurs
Mycophenolate	750–3,000 mg daily	Inhibit guanosine nucleotide biosynthesis; inhibits T- and B-cell activation and mitosis	Urinary tract infection and rare opportunistic infections	No known risk for viral infections
Rituximab	Induction followed by 1,000 mg every 6 months	B-cell depletion	Reactivation of herpes simplex and VZV	Associated with the low IgG level
Cyclophosphamide	2 g daily for 4 days	Inhibits mitosis	Increases the risk for opportunistic infections and VZV reactivation	Heighten the risk for serious viral infections

IBD, inflammatory bowel disease; IVIg, intravenous immunoglobulin; TNF, tumor necrosis factor; VZV, varicella zoster virus.

recovery and improves short-term relapse risk. Thus, treatment with IV corticosteroids should be considered if therapy can be delivered with low risk of contact with those potentially infected by SARS-CoV-2. To avoid unnecessary hospital or infusion center stays, patients can receive steroid infusions through a home-health agency or receive a high-dose oral prednisone (21,45). Alternatively, an intramuscular repository corticotropin injection can be self-administered in the home setting.

Optic Neuritis Associated With Anti–Myelin Oligodendrocyte Glycoprotein IgG

Vision loss can be exquisitely steroid-responsive in MOG antibody disease and patients can require prolonged, low-dose corticosteroids to prevent relapse and further loss of the RNFL (47). We recommend initial treatment with IV corticosteroids. If prolonged treatment is necessary, testing for active SARS-CoV-2 infection or an immune response to SARS-CoV-2, such as positive anti–SARS-CoV-2 antibodies, might be helpful in guiding therapy.

Optic Neuritis Associated With Aquaporin-4 IgG Antibodies

We recommend initial treatment with IV corticosteroids with a low threshold for advancement to plasma exchange (PLEX), which has been shown to improve visual outcomes in cases of severe corticosteroid-refractory NMOSD (27,48,49). The early use of PLEX is critical for an optimal response (27,49), but its use should be considered very carefully during the COVID-19 pandemic given the need to minimize the use of potentially scarce hospital resources for non–life-threatening conditions and to prevent increased exposure to SARS-CoV-2. Thus, if PLEX can be arranged through an infusion center, without hospitalization and with minimal risk of SARS-CoV-2 exposure, it should be considered on a case-by-case basis. An alternative treatment to PLEX is intravenous immunoglobulin (IVIg), although its use for recalcitrant cases of optic neuritis is not supported in large studies (50). As with other infusions, the decision to use IVIg must be weighed carefully to avoid exposure and the utilization of hospital resources.

Acute Optic Neuritis in Symptomatic COVID-19

In the setting of symptomatic COVID-19 infection associated with any type of acute optic neuritis, it is currently unclear whether it is safe to treat with corticosteroids. Despite the lack of data on the risks of steroid use in patients with symptomatic COVID-19, the CDC and World Health Organization have cautioned against the use of corticosteroids in the management of patients with COVID-19 based on experience from patients with SARS-CoV-1 and patients with Middle East Respiratory Syndrome (51,52). Nevertheless, SARS-CoV-2 is a novel virus, and many patients are anecdotally receiving corticosteroids in the acute setting in an attempt to treat COVID-19–associated ARDS. In a study conducted in China on 72 patients with probable SARS-CoV-1 illness, 17 patients received methylprednisolone 500 mg intravenously and showed diminished oxygen requirements and improved radiographic outcomes (53).

MANAGEMENT OF OTHER ACUTE INFLAMMATORY DISORDERS WITH NEURO-OPHTHALMIC CONSEQUENCES

It is not possible to provide exhaustive and specific advice for the management of every immune-mediated or inflammatory neuro-ophthalmic disorder. However, the approach to the treatment of temporal arteritis and myasthenia gravis can serve as a model, and the principles that guide the approach to treatment can be applied to other disorders. In a manner not dissimilar to considerations for the treatment of optic neuritis, the patient and the physician must balance the potential response to therapy of acute neuro-ophthalmic symptoms with apparent infectious risk and complications. Avoidance of immunosuppressive therapies for these disabling neurologic disorders during the pandemic might carry devastating consequences, including additional risk of hospitalization for patients, and for these reasons, fear of COVID-19 should not inform the approach to treatment for conditions with severe consequences that can occur due to inadequate or delayed treatment.

Acute Vision Loss Associated With Giant Cell Arteritis

Patients with acute monocular vision loss from GCA may rapidly lose vision in the fellow eye and/or suffer systemic ischemic consequences if prompt treatment does not occur (54). Thus, all patients, regardless of risk factors for COVID-19, should be counseled about the risks associated with untreated GCA in the setting of acute vision loss and should be offered standard-of-care treatment. Given that immunosuppression for GCA will be acute as well as chronic, and that GCA occurs commonly in elderly patients with other comorbidities, working closely with the patient's primary care provider or rheumatologist during the COVID-19 pandemic is advised. Recent reports indicate that the severity of COVID-19 infection is related to the degree of glycosylated SARS-CoV-2 viral particles, and several reports have suggested that hyperglycemia, and not simply a history of diabetes, has the potential to worsen outcomes by altering viral pathogenesis and facilitating immune evasion (55). In fact, there is evidence that infection with SARS-CoV-1 results in pancreatic islet cell dysfunction and infection with SARS-CoV-2 could be displaying the same phenomenon given the high incidence of hyperglycemia in patients hospitalized with COVID-19 (55). During steroid treatment for GCA, the goal should be to suppress vasculitis while minimizing steroid-induced side

effects. In GCA, short-term treatment with high-dose corticosteroids is typically transitioned to long-term steroid therapy, and in the face of steroid-induced diabetes, a steroid-sparing agent, such as methotrexate and tocilizumab, should be strongly recommended for long-term treatment. There are additional considerations for the use of tocilizumab during the COVID-19 pandemic. As previously discussed, IL-6 receptor inhibition might be useful in diminishing the cytokine storm effects involved in the hyperinflammatory response associated with ARDS in COVID-19, but the timing of the treatment could be critical and results from randomized clinical trials are not yet available. The rapidly evolving data regarding COVID-19 complications and pathogenesis argue for collaboration with internists and rheumatologists when determining long-term treatment strategies for patients with GCA during the pandemic.

Acute Presentation of Ocular Myasthenia Gravis

The treatment of the patient with ocular myasthenia gravis (OMG) should be given careful consideration during the COVID-19 pandemic. Again, counseling the patient on COVID-19 mitigation and the risks and benefits of immunosuppressive treatment for acute OMG symptoms will be important because symptomatic treatment (i.e., with acetylcholinesterase inhibitors, patching, and prisms) may provide some benefit and allow for the delay or temporary avoidance of immunosuppression. All patients, and particularly patients at risk for severe COVID-19 complications (i.e., older age, diabetes, and heart disease), should be counseled about the lack of definitive evidence that early immunosuppressive treatment of OMG prevents generalized myasthenia gravis, although it might prevent inflammatory changes at the neuromuscular junction that can lead to persistent symptoms. If immunosuppressive treatment is delayed, patients with newly diagnosed OMG should be monitored closely and educated about other bulbar symptoms and extremity weakness that could indicate generalized MG and the need to initiate immunosuppressive treatment.

CONTINUATION OR INITIATION OF LONG-TERM IMMUNE-BASED TREATMENTS

There are many disorders that require chronic immunotherapy, and several specific pharmaceutical treatment options are reviewed in Table 1. Data regarding the potential consequences of long-term immune therapy and COVID-19 are lacking, and the physician must weigh the risk of inflammatory injury from the underlying disease activity with the unknown risks of COVID-19 complications associated with treatment during the pandemic. For patients who develop signs and symptoms of COVID-19 or are confirmed to have SARS-CoV-2 infection while on therapy, it is prudent to consider discontinuing immunosuppression, but data to support this action are not available. In a case series of 86 patients in New York City with identified immune-mediated inflammatory disease who had confirmed or highly suspected COVID-19 on biological or JAK inhibitors were followed over time either in the outpatient or in the inpatient setting, revealing that the incidence of having serious disease and complications among those patients was consistent with the general population (56). Data collected from multiple MS centers across Italy suggested that the use of disease-modifying therapies is not associated with worse COVID-19 outcomes (57). Indeed, sudden cessation of chronic therapy may expose the patient to the risk of disease relapse and long-term morbidity; thus, continued therapy at the lowest effective dose may be advisable. Decisions must be made on a case-by-case basis in conjunction with the physician managing the COVID-19 infection.

At this time, there is no evidence that initiation of long-term immunomodulating therapies should be postponed or stopped in disorders that have the potential for significant future disability. As noted, there is a possibility that some therapies may decrease the overactivation of the innate immune system to the benefit of the infected patient (5,6). The major caveat is that data have not been collected systematically. Nonetheless, the US Centers for Disease Control and Prevention and the American College of Rheumatology suggest that patients should continue with their normal treatment regimens (20), particularly if it is clear that stopping therapy would increase disease activity in an individual patient. Furthermore, cessation of therapy may take months to reverse any immunomodulatory or immunosuppressive effects. As noted, only the initiation of agents associated with profound immunodepletion (such as alemtuzumab and cladribine) should be avoided during the COVID-19 pandemic until additional data become available to the contrary. Meanwhile, all patients found to have COVID-19 while on chronic treatment should be enrolled in a previously mentioned appropriate disease registry, so that outcomes can be tracked and more definitive recommendations about treatments formulated.

CONTINUATION OF TREATMENTS IN HOSPITALIZED PATIENTS WITH COVID-19

This is one of the most vexing problems to consider. We believe there is no simple answer that can apply equally to every drug, disorder, or patient condition. Multiple factors must be taken into consideration at the time of the presentation of the patient, including age, comorbid lung and cardiac disease, neurologic disorders that might affect respiration (i.e., myasthenia), and factors that may impact COVID-19 treatment outcomes. For intubated and critically ill patients, the most important treatment is what is deemed necessary to save the life of the patient.

CONCLUSIONS

Medical decision making regarding the treatment of patients with inflammatory neuro-ophthalmic conditions during the COVID-19 pandemic must be carefully weighed and individualized for each patient. In all cases, the benefits of standard-of-care treatment must be balanced against the potential impact on the adaptive and innate immune systems needed to defend against SARS-CoV-2 infection and coinfections. In addition, hospital and community resources should be considered. Fear of COVID-19 should not be the leading factor in therapeutic decision making. The long-term sequelae of delaying or stopping immune-based therapies in disorders of the nervous system must always be considered in light of the unknown consequences of infection. At this time, profound immunodepletion with medications such as alemtuzumab and cladribine should be avoided during the COVID-19 pandemic. It is also important to avoid hyperglycemia during treatment with steroids because of the potential role of hyperglycemia in the pathogenesis and severity of COVID-19. All patients on immunosuppressive agents should be appropriately counseled regarding CDC and state guidelines for social distancing and the prevention of infection with SARS-CoV-2. Finally, patients should be encouraged to seek immediate medical attention if they experience neurological symptoms despite any fear they may have of contracting COVID-19.

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