COVID-19 and immunosuppression: a review of current clinical experiences and implications for ophthalmology patients taking immunosuppressive drugs

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan city, Hubei province, China. This is the third and largest coronavirus outbreak since the new millennium after SARS in 2002 and Middle East respiratory syndrome (MERS) in 2012. Over 3 million people have been infected and the COVID-19 has caused more than 217 000 deaths. A concern exists regarding the vulnerability of patients who have been treated with immunosuppressive drugs prior or during this pandemic. Would they be more susceptible to infection by the SARS-CoV-2 and how would their clinical course be altered by their immunosuppressed state? This is a question the wider medical fraternity—including ophthalmologists, rheumatologists, gastroenterologist and transplant physicians among others—must answer. The evidence from the SARS and MERS outbreak offer some degree of confidence that immunosuppression is largely safe in the current COVID-19 pandemic. Preliminary clinical experiences based on case reports, small series and observational studies show the morbidity and mortality rates in immunosuppressed patients may not differ largely from the general population. Overwhelmingly, current best practice guidelines worldwide recommended the continuation of immunosuppression treatment in patients who require them except for perhaps high-dose corticosteroid therapy and in patients with associated risk factors for severe COVID-19 disease.

BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan, the largest city in Hubei province, China. This is the third and largest coronavirus outbreak since the millennium, after SARS in 2002 and Middle East respiratory syndrome (MERS) in 2012.The COVID-19 arising with SARS-CoV-2 has infected over 3 million patients and caused more than 217 000 deaths as of 10 April 2020.[1]

Most patients with COVID-19 do well but 19% of them develop severe or critical disease with significantly higher mortality rates. The largest case series published by the Chinese Centre for Disease Control and Prevention reported a 49% mortality rate in critically ill patients with COVID-19.[2] The risk factors include older age (highest risk group is above 80 years with mortality rate between 10% and 15%), cardiovascular disease, diabetes, chronic respiratory disease, hypertension, obesity and cancer.[3]

A particular concern exists regarding the vulnerability of patients who have been pharmacologically immunosuppressed prior or during this pandemic. For ophthalmologists, they include patients with ocular surface disease, scleritis and uveitis. Our colleagues in the fields of rheumatology, oncology, gastroenterology and organ transplantation share the same concern. This review attempts to answer, at least in part, the question which arises in many a physician's mind—'Am I putting my patients at increased risk of COVID-19 if they are on immunosuppression?'

Virology of SARS-CoV-2 and its implications

The SARS-CoV-2 is an enveloped RNA β-coronavirus likely originating from bats and have transmitted to humans via unknown intermediate hosts.[4] The structure of its receptor-binding gene that codes for its spike proteins is similar to that of SARS coronavirus and it has been shown to use the same receptor, the ACE2 for host cell entry via endocytosis.[5] Primary targets of SARS-CoV-2 include airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, type II pneumocytes and macrophages.[5] Viral replication likely causes high levels of host cell pyroptosis with localised inflammation which enables the eradication of the pathogen. The immune response then recedes and the patient recovers. In others, a dysfunctional immune response triggers the massive proliferation of immune cells and the overproduction of cytokines interleukin-6 (IL-6), IL-1β, IFN-γ, MCP-1, IP-10, IL-4 and IL-10 leading to a downward spiral of immune-mediated end-organ damage.[6] Thus, interesting propositions have been made to use immunosuppressive agents to limit this aberrant immune-mediated damage and to target viral receptor binding and endocytosis mechanisms and these will be discussed in later.

Experiences from SARS and MERS

The similarities are striking between all three coronavirus outbreaks. Like the SARS and MERS

outbreak, the current COVID-19 pandemic was initiated by zoonotic transmission of a novel coronavirus.[4] Clinically, infected patients commonly present with upper respiratory tract symptoms which may then progress to pneumonia. In COVID-19, a three-stage classification model has been proposed consisting of an early infection phase with mild constitutional symptoms and evidence of moderate lymphopenia; a pulmonary stage characterised by dyspnoea, hypoxia, abnormal chest X-ray and transaminitis and a hyperinflammation phase with acute respiratory distress syndrome (ARDS), shock, cardiac failure and extremely high inflammatory parameters including proinflammatory cytokines also referred to as a cytokine storm.[7] Similarly, in SARS, the acute lung injury resulted from an aggressive immune response initiated by viral replication.[8] Pathologically, those that succumb show microscopic and gross features of ARDS, hypercoagulability, multiple organ damage and atrophy of the spleen and lymph nodes.[9 10]

WHO consensus on SARS reported risk factors for infection that include male gender, older age and concomitant disease.[11] Similarly, a systematic review on the epidemiology of MERS reported older age and concomitant disease as risk factors for infection and mortality.[12] Concomitant disease included diabetes, chronic cardiac, respiratory and renal diseases. Encouragingly, immunosuppression, drug induced or otherwise, did not appear to be a risk factor for morbidity or mortality in the previous two coronavirus outbreaks. The few studies available serve to illustrate this well. In a study by Chiu, only one immunosuppressed renal transplant patient was reported to have been afflicted with SARS.[13] The author concluded that it is unlikely immunosuppressant regimens require tailoring in the face of the SARS threat. AlGhamdi *et al* reported two cases of immunosuppressed renal transplant patients infected with MERS and did not find any significant difference in terms of clinical presentation and disease progression as compared with the general population.[14] Patients with autoimmune diseases, retroviral infections, organ transplants, cancer treatment or any form of immunosuppression have not been reported to be at higher risk in over 10 000 cases of SARS and MERS infections combined to date.

Contradicting evidence arise when the research into treatments for SARS and MERS are considered. Immunosuppression in the form of corticosteroids given to patients with SARS and MERS relieved symptoms from ARDS but delayed viral clearance and did not improve mortality rates.[15 16] However, one needs to exercise caution in the interpretation as these studies were based on significantly high doses of corticosteroids in patients with severe disease and the results have limited value in extrapolation to milder disease in patients on maintenance immunosuppression for immune-based diseases.

The lessons from SARS and MERS thus offer some degree of confidence that immunosuppressive drugs are largely safe in the current COVID-19 pandemic. Physicians must be mindful of the potential effects of such therapy especially in those at risk of severe disease.

What do we know about COVID-19 and the immunosuppressed?

The current literature regarding COVID-19 and immunosuppression therapy stems from the increasing number of case reports and observational studies emerging from China and Europe and concerns largely transplant patients and those with systemic autoimmune diseases.

Li *et al* reported two cases of COVID-19 among 200 heart transplant patients in Hubei, China. Both patients were significantly immunosuppressed with tacrolimus and mycophenolate mofetil yet their clinical presentation, disease course, laboratory findings and CT imaging mirrored that of non-immunosuppressed patients. Both survived the event.[17]

Single case reports by Zhu *et al*, Guillen *et al* and Liu *et al* separately describe renal and liver transplant patients immunosuppressed with varying combinations of tacrolimus, mycophenolate mofetil and prednisone.[18–20] All three groups separately concluded their patients did not deviate from the normal clinical course seen in non-transplanted adult patients with COVID-19.

Favourable outcomes have also been observed in larger cohorts of immunosuppressed patients in the hotspots of Lombardy, Italy and Wuhan, China. D' Antiga reported three cases of SARS-CoV-2 infection with none progressing to pneumonia among over 300 paediatric patients with liver transplants or autoimmune liver disease.[21] No change in immunosuppression regimen was mandated in his centre. In keeping with this data, Bhoori published a series of 111 long-term adult liver transplant patients on minimal immunosuppression with three COVID-19 fatalities and compared them to three uneventful SARS-CoV-2 infections in 40 recently transplanted and fully immunosuppressed patients at his centre.[22] The deaths recorded appeared to be related more to the known risk factors of severe COVID-19 disease (age, presence of several concomitant comorbidities) rather than the degree of immunosuppression and that immunotherapy might have been protective against severe disease.

Norsa *et al* followed up 522 patients with inflammatory bowel disease (IBD) with 22% on oral immunosuppression such as corticosteroids and antimetabolites and 16% on biologics.[23] During the study duration, a separate 479 non-IBD patients were admitted to his hospital for severe COVID-19 pneumonia yet there were no reports of SARS-CoV-2 infection in the patients with IBD despite mathematical modelling predicting at least 21 cases. Lending further weight, Mao *et al* also reported no cases of SARS-CoV-2 infection in over 20 000 patients with IBD from the seven largest IBD centres in China.[24] Importantly, no cases were also reported from the three largest IBD centres in Wuhan, the original hotspot of this pandemic.

Looking at this issue from a slightly different perspective, various retrospective studies on patients with COVID-19 suggest little evidence that immunosuppression is a significant risk factor for infection and severe disease. Chen *et al* reported on the first 799 people with severe or critical COVID-19 disease in Wuhan and analysed the difference between the 113 morbidities and 161 patients who recovered as of 28 February 2020.[25] The major risk factors were older age, male gender and comorbidities of hypertension, diabetes, cardiovascular disease or chronic lung disease. Immunosuppression was not one of them. A subsequent meta-analysis of eight studies including 46 248 patients indicated that those with the most severe disease were more likely to have hypertension, respiratory disease and cardiovascular disease.[26] The authors noted the similarities between the risk factors of the current pandemic with that of SARS and MERS and importantly, there was no report of higher incidence in immunosuppressed patients.

To determine the exact risk of infection and severe COVID-19 disease in immunosuppressed patients will require specific large-scale prospective epidemiological investigations. But these preliminary findings suggest like in SARS and MERS, the incidence, morbidity and mortality rates in immunosuppressed patients may not differ largely from the general population.

Can immunosuppression be paradoxically considered protective or as treatment?

A provocative area of research is the usage of immunosuppression in treating COVID-19 pneumonia. This is currently focused on biological agents and small molecule inhibitors. In the age of precision medicine, our armamentarium now consists of such drugs that can target specific steps in the pathophysiology of SARS-CoV-2 infection without the widespread blunting of the protective host immune response.

IL-6 inhibitors specifically tocilizumab, a humanised monoclonal antibody, has been one of the leading agents studied due to the key role IL-6 plays in the late hyperinflammatory phase of the disease and experience with this drug in the treatment of cytokine release syndrome caused by chimeric antigen receptors redirect T cells.[27] An initial retrospective study by Xu *et al* in Anhui, China of 21 patients with severe or critical COVID-19 disease showed 52.6% had resolution of lymphopenia and normalisation of C reactive protein levels and 90.5% had resolution of lung opacification on imaging after 5 days of treatment without significant side effects.[28] The authors are currently conducting a clinical trial with over 500 patients and initial results are promising, showing rapid resolution of fever and improving respiratory function after tocilizumab infusion.[29] While acknowledging the paucity of high-quality randomised control clinical trials, Chinese and Italian COVID-19 guidelines have included tocilizumab as a treatment option for selected patients with severe COVID-19 pneumonia.[30 31]

At the other spectrum, Janus-associated kinase inhibitors like baricitinib have also been touted as potential early treatment options to reduce viral infective load.[32] Baricitinib has a high affinity to and can inhibit adaptor-associated protein kinase 1 which is involved in receptor-mediated endocytosis thereby possibly interrupting the passage of SARS-CoV-2 into lung alveolar epithelial cells. To date, two trials of baricitinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature soon.[33 34]

A discussion of immunosuppression cannot be complete without understanding the role of corticosteroids in COVID-19 disease. In a series of 99 COVID-19 patients in Wuhan, China by Chen *et al* where 19% of patients were treated with intravenous corticosteroids, they concluded methylprednisolone (1–2 mg/kg/day) is recommended for patients with ARDS from COVID-19 pneumonia.[35] Similarly, Wu *et al* studied 201 patients and among those with ARDS, patients who received corticosteroids were associated with a lower risk of mortality (46% mortality rate with corticosteroids vs 62% without).[36] A larger series of 244 patients by Lu *et al* reported the corticosteroid therapy in severe or critically ill patients with COVID-19 did not affect 28 day mortality rates after multivariate analysis adjusted for all major mortality risk factors. However, they cautioned there was increased mortality risk with increasing corticosteroid dosage. Every 10 mg increase in hydrocortisone-equivalent dosage was associated with additional 4% mortality risk and proposed keeping dosages to a minimal and only when absolutely required.[37] This conservative stance is also highlighted in WHO guidance which clearly states that corticosteroids are not to be given unless there is a clear and separate indication from COVID-19 disease such as asthma.[38]

As it stands, there is encouraging early data that suggest immunosuppressants with the exception of high-dose corticosteroids have a role in treatment of COVID-19 disease and by extension, the immunosuppressed patient may paradoxically be conferred a protective effect or at the least, not be predisposed to a poorer clinical outcome as conventional wisdom may suggest. Until such time good quality evidence from clinical trials emerge, this will continue to be an area where the most difficult decisions will have to be made regarding the usage, timing, dosing and duration of immunosuppressants in a patient with COVID-19.

Current best practice guidelines regarding immunosuppression in the COVID-19 pandemic

While the pathogenesis of SARS-CoV-2 infection and its interaction with the host immune system remains to be fully elucidated, each passing day yields an abundance of clinical and laboratory evidence which physicians should critically review to shape their response in this COVID-19 pandemic.

As alluded to earlier, immunosuppression may have a role in modulating the host inflammatory response seen in severe COVID-19 infections. Moreover, ceasing immunosuppression risks causing the underlying condition to flare and to that end many medical societies in Europe and more recently the USA across various disciplines and specialties have opted to continue patients on their existing immunosuppression regimens.[39]

The British Society of Rheumatology (BSR) has developed a risk stratification guide and scoring grid to address the management of immunosuppression during this pandemic.[40] The recommendation is for all patients who are well and on immunosuppression therapy to continue with their medications with appropriate social distancing and infection prevent strategies pegged to differing levels of risks. Those who are on ≥20 mg/day of oral prednisone or its equivalent, alkylating agents or two or more drugs (one of which is a corticosteroid) fall into the highest risk category and are recommended to be shielded.[38 41] Patients on ≥5 mg/day but <20 mg/day of oral prednisone or its equivalent, two or more non-corticosteroid drugs fall into the moderate risk category and recommended to at least practice social distancing. Lastly, patients on single non-corticosteroid drugs are of the lowest risk similar to patients with comorbidities like diabetes. Special emphasis has been placed on corticosteroids by the National Health System of England (NHS) as well because of the disappointing experience with corticosteroids in the treatment of SARS and MERS.[42] The NHS guidelines recommend physicians to exercise caution in starting patients during the pandemic, use the lowest possible dose and taper corticosteroid therapy as fast as possible in the clinical context.

The British Society of Gastroenterology (BSG) in their guidelines regarding immunosuppression in patients with IBD has largely concurred with the BSR and NHS.[43] Apart from minor differences, the BSG also recommends the continuation of IBD patients on all immunomodulators (ie, antimetabolites) and biologics as there is no current evidence these groups of drugs increase COVID-19 infection risk. Corticosteroids are best to be avoided but in those who require, NHS guidelines of shielding and social distancing should be adhered to at the same dosages.

Likewise, based on expert opinion and emerging research, the American Gastroenterological Association clinical practice update reports no evidence of increased risk of infection and severity of COVID-19 disease in patients with IBD.[44] Their recommendation is for well patients to stay on IBD therapies with a goal of sustaining remission, avoiding the necessity of high dose corticosteroid therapy or hospitalisation that are all much worse than known risks of existing IBD therapies. For the asymptomatically infected patient with IBD, corticosteroids should be reduced to <20 mg/day of oral prednisone, immunomodulators (ie, antimetabolites) temporarily withheld and biologic therapies delay for 2 weeks while monitoring for COVID-19 disease

and resumed if the patient remains asymptomatic. For patients with IBD with COVID-19, no easier answer exists but a general approach will be to adjust IBD therapies to focus on reducing immune suppression during active viral replication in an attempt to reduce the likelihood of complications.

The American Academy of Dermatology elegantly argued for the continued use of biological agents during this period in their interim guidelines.[45] With no data on the specific risk of COVID-19 infection with biological therapy, their priority is to keep patients out of emergency units so as not to tax the healthcare system unnecessarily. Balancing the risk of immunosuppression with the risk of disease flare requiring urgent intervention, they propose all well patients to continue biologics, consider deferring initiation of biological therapy in those with known COVID-19 risk factors and discontinue biologic therapy in patients who are infected.

The International Uveitis Study Group jointly with the International Ocular Inflammation Society and the Foster Ocular Inflammation Society has similarly indicated the need to continue immunosuppression in patients without clinical signs of COVID-19 or confirmation of disease.[46] Social isolation should be practiced as much as possible, and while follow-up for stable patients can be achieved through telemedicine, patients with active uveitis should be seen with appropriate adjustment in therapy. Tapering corticosteroids as quickly as possible should be attempted in all cases. In symptomatic patients, a confirmation of the diagnosis should be requested as the patient is considered in an 'at risk' group. Corticosteroids dose should be reduced as much as possible to under 20 mg/day of oral prednisone or equivalent. If corticosteroids are required to treat a de novo uveitis or a flare-up, local intraocular therapy (if required, bilateral) should be considered as it should provide adequate treatment for the duration of the COVID-19 infection and beyond. For patients on biologic agents other than interferon or IL-6 blocking agents, the medication should be interrupted until there are clear signs of recovery, at which point the medication can be reinstated. For other systemic immunosuppression, the dosage should remain intact, but monitored in case of progression to a higher level of COVID-19 severity. Recommendations are likely to evolve as more information becomes available the relationship between induced immunosuppression and COVID-19 disease.

CONCLUSION

Immunosuppression is a double-edged sword. While it has been a tool much used by many physicians in combating chronic inflammatory diseases, it does come with significant trade-offs with increased risk of infections being one of them. In this current climate of the COVID-19 pandemic, it is imperative that prescribers of such medications take the time and effort to consider their usage and educate their patients on the actions to take if they unfortunately fall ill.

The initial clinical experiences to date seem to allay worries that immunosuppression might increase the risk of patient getting infected with SARS-CoV-2 and developing severe complications. Overwhelmingly, the best practice guidelines worldwide currently recommended the continuation of immunosuppression treatment in patients who require them except for perhaps high-dose corticosteroid therapy, and in patients with associated risk factors for severe COVID-19 disease.

There is a pressing need for more research to be done to confirm these preliminary findings and allow refinement of guidelines on the management of immunosuppressed patients during this COVID-19 pandemic.

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