Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Multiple sclerosis and COVID-19: A great opportunity for databases promoting research and collaboration

Coronavirus disease 2019 (COVID-19) is a disease caused by the novel SARS-CoV-2 virus that has resulted in a worldwide pandemic. While the resultant respiratory disease is mild in the majority of patients, a subset of patients can develop severe disease with significant respiratory compromise that may require ventilation and intensive care. Elderly patients and patients with co-morbidities such as diabetes and obesity appear to be more severely affected and are at high risk for a fatal outcome. Patients with multiple sclerosis (MS), who are often treated with immunosuppressive agents, might be more susceptible to complications of COVID-19 because of their inability to make a robust immune response against the virus. Alternatively, it is also possible that immunosuppression might be beneficial in limiting the cytokine storm complications caused by the virus, thereby having some protective effect against the virus.

It has been established that MS patients have an increased risk of infections compared to the general population. These infections can lead to increased morbidity and may also contribute to provoking relapses as well as transiently worsening patients' baseline neurologic symptoms (pseudorelapse). First line treatments such as interferon-beta and glatiramer acetate are not thought to result in an increased risk of infection. However, the higher efficacy disease modifying therapies (DMTs) have effects on the immune response that result in an increased risk of infection, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML). In the context of the current COVID-19 pandemic, it has become of utmost importance to understand how this infection affects patients with MS and how DMTs might affect a patient's immune response against the novel coronavirus. Moreover, it is of great interest to clinicians caring for MS patients, how specific DMTs may differentially effect not only the risk of developing COVID-19, but also whether there is a difference in morbidity and severity of the infection based on DMT or treatment strategy (high-efficacy versus others).

Because there is limited published information on the effects of COVID-19 on MS, little is known about the effects of the infection on the clinical course of MS and how a DMT might affect the clinical course of COVID-19. In this issue of the *Journal of Neuroimmunology (JNI),* a case of COVID-19 in a patient with MS treated with fingolimod is presented (Chiarini et al., 2020). While there have been two case reports published to date of MS patients developing COVID-19 while on fingolimod which also showed that a patient can survive in the context of recent treatment with fingolimod and experience a milder disease course (Barzegar et al., 2020), this case was also instructive because the authors attempted to determine some of the effects of fingolimod and the SARS-CoV-2 virus on the immune response. Despite being lymphopenic on admission as a result of the fingolimod treatment and potentially also the SARS-CoV-2 virus, the patient was still able to mount an antibody response, presumably directed against the virus, resulting in a favorable outcome for this patient. Of note, the patient's fingolimod treatment was discontinued when hospitalized which could have played a role in impacting the immune response observed. The immune reconstitution appears faster in the context of stopping fingolimod compared to other oral and infusible therapies. Although, it is not clear whether other potent immune therapies result in a less robust immune response in the setting of COVID-19. This is an area of needed research since this could help further our understanding of the differential impact of specific DMTs on COVID-19 infected patients. Also, it is unclear if there may be an independent protective or deleterious effect with sphingosine-1-phosphate (S1P) receptors modulators in MS patients with COVID-19 since there are S1P receptors within the lungs (Ebenezer et al., 2016). If there is truly a protective effect, then it could be secondary to a reduction in pro-inflammatory cytokines in the setting of DMT use that results in a less robust cytokine storm. It is speculated that the host immune response towards COVID-19 may be worse than the infection itself which has been observed with other infections (e.g., PML immune reconstitution inflammatory syndrome).

Other case reports on the coexistence of COVID-19 and MS have been reported with patients receiving other immunosuppressive drugs (Suwanwongse and Shabarek, 2020; Borriello and Ianniello, 2020). In a patient receiving ocrelizumab, despite being impaired in the ability to mount a normal antibody response based on this medication's main mechanism of action, the patient had a mild disease course and recovered uneventfully from COVID-19 (Suwanwongse and Shabarek, 2020). One has to speculate that maybe this patient did better than expected because B-cells are a major source of Interleukin 6 (IL-6) production and depleting B-cells may help dampen the typical cytokine storm effects with lower IL-6 levels. Another patient with MS being treated with natalizumab also had an uneventful disease course, although this patient did receive an extended interval dosing of natalizumab (Borriello and Ianniello, 2020). A recent case series of patients treated with rituximab or ocrelizumab from Madrid also suggested that patients with MS and COVID-19 on these medications may have an uneventful disease course (Montero-Escribano et al., 2020)). In none of these instances were there any immunologic studies performed to evaluate the effects of the SARS-CoV-2 infection on the immune response and how the DMT may have affected the immune response against the virus.

While such case reports are able to illustrate a particular point, more information is needed to understand the full effects of COVID-19 on the disease course in MS and whether there are particular instances where a specific treatment might affect the clinical course/outcome either in a

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positive or negative direction. For example, there is a program in Italy that is obtaining important data from neurologists about their patients with MS and COVID-19 (Sormani et al., 2020). As of April 7, 2020, there were 232 patients entered in this registry, including 31 patients that had been treated with fingolimod. Of these 31 patients, 8 had been confirmed by PCR testing to have COVID-19, while 23 patients were suspected of having the disease based on clinical characteristics.

In North America, a registry of MS patients and patients with other central nervous system inflammatory diseases (neuromyelitis spectrum disorders and myelin oligodendrocyte glycoprotein associated disorders) has been established through a collaboration of the National Multiple Sclerosis Society and the Consortium of Multiple Sclerosis Centers. As of May 7, 2020, 156 patients with MS had been enrolled and 6 deaths had been recorded. The majority of deaths thus far have occurred in older patients (> 50) who had higher levels of disability (e.g., non-ambulatory), longer disease duration, and co-existing medical comorbidities that were previously noted to have increased mortality for patients with COVID-19 in the general population. These demographics are in contrast to some of the patient's characteristics in this report (younger age and less overall disability). In this registry, known as COViMS, no deaths had been recorded in the 11 patients being treated with fingolimod, 1 death recorded in the 48 patients treated with ocrelizumab, and no deaths in 18 patients treated with natalizumab.

While both these registries are in their early stages of data collection, it seems that the earlier concerns regarding high efficacy DMTs making MS patients more susceptible to developing a severe COVID-19 disease course, including death, does not appear to be the case based on what we know at this point. However, more work will need to be done with regard to studies like that published in this issue of JNI to further examine how the immune response to SARS-CoV-2 is affected by specific MS DMTs and treatment strategies (e.g., high efficacy vs. others). In addition, there is an urgent need for clinicians to help the MS community in collecting this important clinical data. If you are a neurologist/clinician taking care of a patient with MS who has developed suspected or definite COVID-19, you can enter their clinical data into the COViMS registry at COViMS.org.

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