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Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic

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The emergence of novel Coronavirus 2019 (COVID-19)[1] and the subsequent pandemic present a unique challenge to Neurologists managing patients with multiple sclerosis (MS) and related neuroinflammatory disorders, such as neuromyelitis spectrum disorder (NMOSD).

National professional bodies (e.g., Italian Society of Neurology, Association of British Neurologists) and patient organisations (e.g., National MS Society, MS International Federation, UK MS Society, MS Australia) have responded rapidly by issuing guidelines for the COVID-19 pandemic, primarily focussed on MS disease-modifying therapies (DMTs). In this commentary we highlight the implications of COVID-19 for people with MS and related disorders, including the risk of respiratory infections, general health advice, and recommendations (from consensus-based guidelines) for immunotherapies, relapse management and service delivery during the COVID-19 pandemic.

Risk of respiratory infections

Whether people with MS and NMOSD are at increased risk of COVID-19 infection, or at higher risk of more severe infection, is unknown. There is no data available on whether the rate of mild, self-limiting respiratory infections that do not require a medical encounter is increased in people with MS. However, there is increased infection-related health care utilization across all age groups in people with MS compared with the general population.[2] These infections include pneumonia[2,3] (particularly in people with bulbar weakness resulting in aspiration and impaired pulmonary function due to severe quadriparesis) and influenza[3], but not upper respiratory tract infections.[2] Older age, male sex, worse physical disability, and

lower socioeconomic status are associated with increased hospitalization rates in MS.[3] People with MS have a higher risk of intensive care unit admission with infections, and higher 1-year mortality after admission than the general population.[4] In addition to the higher background risk of infection-related health care utilization, people with MS treated with the second generation DMTs are exposed to a further increased risk of infections.[5] These factors should be considered when counselling individuals about the risks of COVID-19 infection.

General health advice

People with MS and related disorders should follow World Health Organization (WHO) and national or local health authority guidance on preventative measures to reduce transmission of COVID-19 in the general population. These include social-distancing, frequent hand-washing with soap and water or an alcohol-based hand rub and respiratory hygiene. Face masks are only recommended for people who are coughing or sneezing, or for those caring for a patient with suspected COVID-19 infection. Advice from WHO is updated regularly (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Patients should be educated about the symptoms of COVID-19 infection, including fever, cough, and shortness of breath. People with MS and related disorders should be advised not to make changes to their MS treatment without discussion with their neurologist.

Managing patients with COVID-19 infection

In people with MS and related disorders taking immunotherapy, treatment is generally continued during mild, viral infections. In those with documented mild COVID-19 infection it may be reasonable to continue treatment. Neurologists should have a lower threshold for stopping treatment in people taking therapies with greater immunosuppressive effects and

those with risk factors for a more severe disease (older age, comorbidities[6]), or if COVID-19 symptoms are deteriorating.

Consideration should be given to stopping treatment in those who are hospitalised with severe or complicated COVID-19 infection. Treatment can be restarted after 4 weeks, or when symptoms have fully resolved, keeping in mind the risk of rebound MS activity with S1P modulators and natalizumab. Neurologists should alert intensive care physicians to the importance of fever management in people with MS.

Managing patients with multiple sclerosis without COVID-19 infection

Acute relapses

MS relapses are frequently treated with a short-course of high-dose intravenous methylprednisolone. Chronic use of corticosteroids is associated with an increased risk of infections, and short-term use of high-dose corticosteroids may increase the risk of herpes virus reactivation.[7] High-dose steroids hasten the recovery from MS relapses, but do not influence the final degree of recovery.[8] Neurologists should consider having a higher threshold for offering steroid treatment during the COVID-19 pandemic.

An acute infection will sometimes lead to a transient worsening of symptoms in MS and other disorders (pseudo-relapse).[9] Patients should be carefully screened for symptoms of active COVID-19 infection before receiving corticosteroid treatment.

Disease-modifying therapies

A few MS therapies (interferon-β, glatiramer acetate) exert immunomodulatory effects with no increase in the risk of systemic infections. Other treatments used in contemporary MS practice do have immunosuppressive effects with alterations in lymphocyte number, trafficking, proliferation and function[9], with an increased risk of infections, including viral infections and respiratory infections.[7, 9] It is reasonable to hypothesise that these therapies may predispose to a greater risk of COVID-19 infection, and potentially more severe infection. However, at the present time there is no evidence to support this. People with MS who are profoundly lymphopenic, for example, after treatment with alemtuzumab or less commonly during treatment with cladribine, fingolimod or dimethyl fumarate, may be at higher risk

In most people with MS the benefits of continuing treatment will outweigh the risks of stopping an MS therapy because of concerns over COVID-19 (Table 1). Alemtuzumab and, to a lesser extent, cladribine lead to a transient and variable period of lymphopenia after each course of treatment. We recommend delaying treatment with these therapies in patients due to receive a second or subsequent course (Table 1). Anti-CD20 therapies, including ocrelizumab and rituximab, are typically dosed regularly every 6 months. B-cell depletion frequently lasts much longer than the scheduled dosing interval and extended interval dosing should be considered, especially in patients who are B-cell depleted (as measured by CD19/CD20 lymphocyte counts) at the time of the next scheduled dose, or those with low levels of immunoglobulin-G (IgG). Extended interval dosing is already widely used in patients treated with natalizumab because of observational data showing a reduced risk of progressive multifocal leukoencephalopathy.[10] Whether this approach reduces the risk of other infections is unknown, but should be considered during the COVID-19 pandemic to reduce hospital visits.

The counselling of patients with MS who want to discuss delaying or even stopping an MS therapy will be influenced by: (1) patient factors, such as age and comorbidities that increase the risk of severe COIVD-19 infection[6]; (2) disease factors, including disease activity prior to starting treatment and in the previous 12 months, disease course and disability; (3) drug factors, including the potential for rebound disease activity if treatment is stopped (e.g. S1P modulators, natalizumab).

Decisions over initiation or switching DMTs during the COVID-19 pandemic should take into account the same patient, disease and drug factors noted above. It is safe to initiate treatment with interferon-β, and glatiramer acetate, and perhaps safe to start teriflunomide and dimethyl fumarate in children and young adults who are otherwise healthy (Table 1). The burden of treatment monitoring should be taken into account when initiating a new MS therapy, for example, monthly (or 2-weekly in Europe) liver function tests in patients starting teriflunomide may be impractical during the COVID-19 pandemic. If a high-efficacy treatment is required for patients with severe, or breakthrough disease then starting or switching to natalizumab is preferable to alemtuzumab, cladribine or ocrelizumab, because the risk of systemic immunosuppression is lower and prolonged lymphocyte depletion does not occur. Treatment with natalizumab for 12-18 months is associated with a low-risk of progressive multifocal leukoencephalopathy (including in patients who are JC virus antibody positive), and can be considered as a bridging therapy. There is a general consensus against autologous haematopoietic stem cell transplantation, as it represents the highest risk of infections to patients.

Managing patients with neuromyelitis optica spectrum disorder without COVID-19 infection

Relapses in patients with NMOSD may be devastating and patients should be encouraged to continue therapies for attack-prevention including corticosteroids, azathioprine, mycophenolate mofetil, rituximab, tocilizumab and eculizumab. If there is a clinical need to stop or delay treatment in patients with NMOSD then moderate dose corticosteroids (e.g. prednisolone 20mg) can be used to prevent relapses in the short to medium term.

Managing special patient groups

The risk of COVID-19 infection appears lower in children and infections appear milder. There are no special considerations in children with MS and related disorders.[11] Severe COVID-19 infections are more common in older adults (>60 years) with a higher case-fatality rate.[6] Treatment decisions in this age group should be individualized, taking into account other comorbidities that increase the risk of death (cardiorespiratory disease, diabetes)[6], and the more modest benefits of disease-modifying treatment in older patients[12] and/or those with progressive forms of MS. Pregnant women should follow general health advice during the COVID-19 pandemic, with no special considerations.

Implications for service delivery

Many MS centres are utilising telemedicine to avoid non-essential hospital visits during the COVID-19 pandemic. Telemedicine has previously been validated as a tool for assessing disability in MS with high patient acceptability.[13] Other steps to reduce hospital visits like home delivery of medications, delaying follow-up MRI scans in stable patients and reducing the frequency of routine laboratory monitoring should also be considered. Oral corticosteroids may be preferable to treat acute relapses, given the equivalent efficacy to intravenous corticosteroids, at least in patients with MS.[14] Less frequent dosing of infusion therapies (e.g. natalizumab, ocrelizumab) may also relieve pressure on infusion centres that may be understaffed due to redeployment or illness. MRI and infusion centres have

implemented additional measures to reduce the risk of COVID-19 transmission in these settings.

Conclusions

As for the general population, most patients with MS are expected to experience only mild symptoms with COVID-19 infection. Some immunotherapies may increase the risk of more severe infection and individualised risk assessment is required, taking into account the immunosuppressive effects of the treatment, as well as other patient factors (e.g. age, physical disability, comorbidities) and the healthcare setting. Collecting data on the impact of COVID-19 on people with MS and related disorders, and particularly the risks of a novel pathogen in patients on immunosuppressive treatments is a priority for national and international registries. We would recommend all neurologists who become aware of a person with MS being confirmed as COVID-19 positive notify their local registry.

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Table 1. Recommendations for use of multiple sclerosis disease-modifying therapies during the COVID-19 pandemic

	Patients initiating treatment	***Patients already on treatment***
No risk of systemic immunosuppression		
Interferon-β preparations	Initiate treatment as usual	Continue treatment
Glatiramer acetate	Initiate treatment as usual	Continue treatment
Low-risk of systemic immunosuppression		
Teriflunomide	Initiate treatment as usual	Continue treatment; ensure neutrophil count >1000/mm^3
Dimethyl fumarate	Initiate treatment as usual	Continue treatment; ensure lymphocyte count >500-800/mm^{3*}
Natalizumab	Initiate treatment as usual	Continue treatment; consider extended interval dosing
Moderate-risk of systemic immunosuppression		
S1P modulators e.g. fingolimod, siponimod, ozanimod	Consider delaying initiation of treatment or an alternative DMT, taking into account the risks and benefits	Continue treatment; ensure lymphocyte count >200-300/mm^{3*}
Anti-CD20 agents e.g. ocrelizumab, rituximab	Consider delaying initiation of treatment or an alternative DMT, taking into account the risks and benefits	Consider extended interval dosing guided by CD19 lymphocyte counts, taking into account the risks and benefits, and reassess periodically
High-risk of systemic immunosuppression		
Cladribine	Do not initiate treatment, consider an alternative DMT	Delay further courses of treatment, taking into account the risks and benefits, and reassess periodically
Alemtuzumab	Do not initiate treatment, consider an alternative DMT	Delay further courses of treatment, taking into account the risks and benefits, and reassess periodically
Autologous haematopoietic stem cell transplantation	Do not initiate treatment, consider an alternative DMT	Not applicable

*Some neurologists advise dose reduction if lymphocyte counts are approaching cut-off values for discontinuing treatment, although no evidence is available to guide these decisions.