

# Consensus Statement On Immune Modulation in Multiple Sclerosis and Related Disorders During the COVID-19 Pandemic: Expert Group on Behalf of the Indian Academy of Neurology

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## Abstract

Knowledge related to SARS-CoV-2 or 2019 novel coronavirus (2019-nCoV) is still emerging and rapidly evolving. We know little about the effects of this novel coronavirus on various body systems and its behaviour among patients with underlying neurological conditions, especially those on immunomodulatory medications. The aim of the present consensus expert opinion document is to appraise the potential concerns when managing our patients with underlying CNS autoimmune demyelinating disorders during the current COVID-19 pandemic.

**Keywords:** COVID 19, disease modifying therapy, immunotherapy, MOG, MS, NMOSD

## INTRODUCTION

In December 2019, health authorities recognized an outbreak of pneumonia occurring in Wuhan in the Hubei Province, China,<sup>[1]</sup> which soon transformed itself into a global pandemic and a massive public health threat.<sup>[2,3]</sup> Scientists found it to be related to a novel beta coronavirus, named severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2) or 2019 novel coronavirus (2019-nCoV), which shares a significant similarity to the SARS-CoV, responsible for the severe acute respiratory syndrome (SARS) epidemic in 2003.<sup>[2]</sup> The virus attaches itself through the angiotensin converting enzyme 2 (ACE2) receptor to enter the cells expressed in airway epithelial, vascular, kidney and small intestinal cells.<sup>[4]</sup> As on the day of submission of this paper, the estimated numbers of globally confirmed cases of COVID-19 are 1,136,862 including 63,025 deaths (WHO, Last updated: 2020/4/6, <https://experience.arcgis.com/experience/685d0ace521648f8a5beeee1b9125cd>, accessed 6.4.2020). Within this relatively short period of the ongoing pandemic, there has been a surge of publications (more than 2000 on the day of submission of this paper) on the clinical patterns, imaging findings, virus biology and therapeutic strategies, for COVID-19. In an initial description of 41 hospitalised people in Wuhan, China,<sup>[1]</sup> 73% were men with a median age of 49 years. Diabetes, hypertension and cardiovascular disease were common underlying conditions observed. The most common clinical features were fever,

cough, myalgia and headache with acute respiratory distress syndrome (ARDS) being the most frequent complication, inducing mortality in six (15%) patients. Leucopenia ( $<4 \times 10^9/L$ ) was observed in about 25% patients and lymphopenia ( $<1.0 \times 10^9/L$ ) in 63% patients.<sup>[1]</sup> In a recent systematic review of 19 studies, the authors found lymphopenia in 43.1% patients (95%CI 18.9-67.3).<sup>[5]</sup>

Neurological complications have been sparsely described across the published reports including cerebrovascular disease, impaired consciousness, anosmia, headache and skeletal muscle injury.<sup>[1,6]</sup> A recent report has described a patient with acute necrotising encephalopathy.<sup>[7]</sup> Interestingly, authors have suggested a putative role of neuroinvasion in the occurrence of respiratory failure.<sup>[4]</sup>

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## Concerns related to MS and related disorders during the current COVID 19 pandemic

MS, NMOSD, MOG antibody disease and related disorders are a group of autoimmune inflammatory disorders of the central nervous system (CNS). Most patients with these illnesses are treated with long-term immunomodulatory therapy to prevent acute relapses and disability. Our review is driven on the premise that most people with autoimmune neurological disorders are on immunomodulatory treatments, some of which may predispose to infections. We currently do not know whether people with autoimmune demyelinating neurological disorders are at an increased risk of acquiring COVID-19 infection; whether the disease has different severity and whether COVID-19 modifies the clinical behaviour of these disorders. We also lack any current understanding on how the use of ongoing treatments for autoimmune demyelinating neurological disorders modifies the risk and manifestations of COVID-19 infection episodes. We therefore intend to address the following concerns: (1) Is it safe to continue ongoing treatments/start treatment for the underlying neurological disorders during and after COVID-19 infection episodes? (2) Do people with CNS autoimmune demyelinating disorders need to follow usual or special precautions during the COVID epidemic? and (3) What is the influence of the coexisting conditions in the decision-making? Answers to these are not known succinctly, but an indirect application and corroboration of current understanding may provide us with steps to optimise patient care during the current global crisis.

Lymphopenia and potential reduced T cell activity has been observed in the clinical reports of patients with COVID-19, mechanism of which is unclear.<sup>[1,5]</sup> This is especially important in the context of patients with autoimmune diseases where lymphopenia could potentially be made worse with therapy. Medications influence lymphocyte levels variably and by different mechanisms.<sup>[8]</sup> Although data from previous studies have suggested that lymphopenia may not necessarily correlate with increased risk of infection,<sup>[9]</sup> it becomes imperative to monitor patients during this time and choose medications with lowest cytopenic potential for newly diagnosed cases. Cytokine overactivity also occurs in patients with COVID-19 infection,<sup>[10]</sup> leading to a potential discussion on experimental therapies with immunomodulatory agents.<sup>[11]</sup> How this would potentially affect a patient with a known CNS demyelinating disorder is currently not understood.

International advisories from the Multiple Sclerosis International Federation (MSIF),<sup>[12]</sup> Association of British Neurologists (ABN)<sup>[13]</sup> and Italian Neurological Association<sup>[14]</sup> have also been recently released, and suggested safe and avoidable therapies during the ongoing pandemic.

## Review of medications used: Potential mechanisms of action and putative implications [Table 1]

### Beta interferons

Interferons have been one of the earliest and most common medications used in patients with MS. Exact mechanism

of action is not well known, although they are believed to reduce inflammation by inhibiting T-cell activation and proliferation, reducing cytokine production and regulating endothelial adhesion molecules involved in blood–brain barrier permeability. Common side effects include fever, headache and flu like symptoms. Less common side effects include raised liver enzymes and lymphopenia. Long-term use of these agents have been shown to be safe with no defined increase in the risk of serious infections.

### Recommendation:

- The drug seems to pose minimal risk of immunosuppression or infections and should be continued as a therapy, and can be started in patients with a newly diagnosed MS during the COVID-19 pandemic.

### Glatiramer acetate (GA)

Glatiramer acetate is an amino acid copolymer used in the management of MS. GA treatment is believed to promote development of Th2-polarized GA-reactive CD4(+) T-cells. It is considered to be a potentially safe agent and with no long-term increase in the risk of infections.

### Recommendation:

- The drug seems to pose a minimal risk of immunosuppression or infections and should be continued as a therapy, and can be started in patients with a newly diagnosed MS during the COVID-19 pandemic.

### Dimethyl fumarate (DMF)

DMF is an oral Nrf2 pathway activator indicated for relapsing forms of MS.<sup>[15]</sup> It reduces expression of NF-κB-dependent genes, leading to modulation of inflammatory cytokines, chemokines and cell adhesion molecule expression. Most commonly encountered side effects include gastric discomfort and flushing. It does not significantly increase the risk of systemic viral infections. Lymphopenia is a dose limiting side effect and is a potential concern that needs monitoring, especially in the current situation. A previous study with BG-12 did not confirm the risk of greater chance of infections with lymphopenia related to DMF. Risk of progressive multifocal leukoencephalopathy (PML) is increased in patients with persistent lymphopenia.

### Recommendations:

- The drug seems to pose low risk of infections or immunosuppression. However, monitoring for lymphopenia is necessary.
- Patients taking this drug should continue to take this medication.
- Among newly diagnosed MS patients, the drug could potentially be started as the first line therapy during the COVID-19 pandemic, with close monitoring of the lymphocyte counts.

### Teriflunomide

It is an immunomodulatory drug used as first line therapy in MS. Teriflunomide blocks the enzyme dihydroorotate dehydrogenase,<sup>[15]</sup> a key mitochondrial enzyme essential

**Table 1: Classification of immunomodulatory drugs based on mechanism of action<sup>[25,35-38]</sup>**

Class and drug	Immuno-suppressant*	Effect on peripheral immune cells
Agents with pleiotropic effects		
Glucocorticoids	Yes	Increased neutrophils, reduced lymphocytes
Interferon beta 1a and 1b, pegylated interferon beta 1a	No	Mild leukopenia, specifically lymphopenia
Glatiramer acetate	No	Mild or no reduction in leukocyte count
Dimethyl fumarate	Possible	~30% reduction in lymphocyte count
Antimigratory agents		
Natalizumab	No#	Increase in circulating lymphocytes, monocytes, basophils, and eosinophils
Fingolimod	Yes	20-30% reduction in lymphocyte count
Siponimod	Yes	20-30% reduction in lymphocyte count
Antiproliferative agents		
Teriflunomide	Possible	15% reduction in lymphocyte and neutrophil counts
Azathioprine	Yes	Moderate to marked reduction in lymphocyte and leukocyte counts
Mycophenolate mofetil	Yes	Mild to moderate reduction in lymphocyte count
Mitoxantrone	Yes	Reduction in lymphocyte and leukocyte counts
Immunodepletors		
Alemtuzumab (antiCD52 MAb)	Yes	98 - 99.8% depletion of circulating T and B lymphocytes in 7 days, repopulation in 3 - 6 months
Rituximab (antiCD20 MAb)	Yes	Marked reduction of CD20+B lymphocytes, neutropenia
Ocrelizumab (antiCD20 MAb)	Yes	Rapid depletion of CD20+B lymphocytes in 2 weeks, mild to moderate lymphopenia
Cladribine	Yes	Moderate to severe lymphopenia

\*Classification as immunosuppressant indicates tendency to cause significant lymphopenia, association with opportunistic infections, reduction in the antibody response to vaccines and/or increase in the risk of secondary malignancies. (Giovannoni, 2018<sup>[35]</sup>). # No increased risk of systemic infections. MAb: Monoclonal antibody

for de novo pyrimidine synthesis resulting in reduction of activated T cells. Nearly 10% of patients on Teriflunomide have had upper respiratory tract infections and influenza-like illness, which were self-limiting. The other side effect that is relevant to this discussion includes haematological abnormalities such as neutropenia. Monitoring patients on Teriflunomide needs to be more rigorous compared to other first line DMTs.

#### Recommendations:

- Patients taking this drug should continue to take this medication with adequate monitoring.
- In newly diagnosed MS patients, it is advisable to start Teriflunomide with caution and monitoring as the first line DMT during the ongoing COVID-19 pandemic. International advisories have also suggested its use.<sup>[13,14,20]</sup>

#### Fingolimod

This is a sphingosine 1-phosphate (S1P) receptor antagonist and blocks the egress of lymphocytes (mainly, CCR7+ CD4+ naive and central memory T cells) from the lymph nodes. The lymphocytes are redistributed and retained in the secondary lymphoid tissue and entry into CNS is prevented. The drug can produce lymphopenia and leukopenia and this needs monitoring. An increased risk of infections have been reported with Fingolimod use including reactivation of herpes simplex 1 and varicella zoster, human papilloma virus infection and opportunistic infection by JC virus (progressive multifocal leukoencephalopathy).

#### Recommendation:

- Patients taking Fingolimod should continue to take this medication with adequate monitoring. Fingolimod poses a risk of rebound disease if stopped and this should be given due consideration in the decision-making.
- In newly diagnosed MS patients, it is advisable not to choose Fingolimod during the current COVID-19 pandemic.

#### Siponimod

This new drug, which is presently not available in India, is a congener of Fingolimod and selectively binds to subtypes of S1P receptor (S1P1 and S1P5). The mechanism of action is similar to Fingolimod and the receptor-binding inhibits the migration of the lymphocytes to the location of the inflammation within CNS. Siponimod can produce lymphopenia and leukopenia.

#### Recommendations:

- Patients taking Siponimod should continue to take this medication with adequate monitoring. The risk of rebound disease on drug cessation probably outweighs the risk of infection.
- In newly diagnosed MS patients, it is advisable not to choose Siponimod during the current COVID-19 pandemic.

#### Azathioprine (AZA)

It is a purine analogue that impairs DNA synthesis in rapidly multiplying cells, particularly T and B lymphocytes.

**Table 2: Summary table of expert consensus of IAN for use of Immunomodulators during the COVID 19 Pandemic in patients with MS, NMO and MOG-related Disorders in Non-COVID positive patients**

Medications	Therapy in newly diagnosed patients	Maintenance Therapy in already diagnosed patients
<b>Multiple Sclerosis</b>		
Pulse steroids ( for relapse)	Yes	No
Plasmapheresis (for severe relapse in select cases)	Yes. Limited evidence. <sup>[39-41]</sup>	No.
IVIG ( for severe relapse in select cases)	Uncertain. Limited evidence. <sup>[39,40,42,43]</sup>	Limited evidence. Uncertain benefit. <sup>[42,43]</sup>
Interferons	Yes	Yes
Glatiramer	Yes	Yes
Dimethyl fumarate	Yes	Yes
Teriflunomide**	Yes (With caution)	Yes
Fingolimod	No	Yes
Natalizumab	Yes	Yes
Alemtuzumab	No	Withhold/delay
Ocrelizumab	No	Withhold/delay
Rituximab	No	Withhold/delay
Azathioprine	No	Yes
Mycophenolate Mofetil	No	Yes
<b>NMOSD, MOG and related disorders</b>		
Steroids	Relapse: Yes	##,^^ Possibly (With Close Monitoring. Consider alternate if possible)
Plasmapheresis	Relapse: Yes. <sup>[41,44-48]</sup>	Yes (Could Be Considered As An Option During The Current Pandemic, Weighing The Feasibility And Potential Risk Of Infection, frequent visits and Hospitalisation )
IVIG	Relapse: Yes. <sup>[43,45,47-50]</sup>	Yes (Could Be Considered as a Safe Option During The Current Pandemic. Consider cost and feasibility) <sup>[43,45,47-50]</sup>
Rituximab	Uncertainty exists. Could be potentially considered in individual circumstances, in view of risk of preventing breakthrough disease versus risk of COVID 19 infection if no other option seems feasible. Discussion with infectious disease expert is important.	Prudent to delay if patient is stable. Could monitor CD19/20/ and CD 27 (if available) blood cell counts. <sup>[51,52]</sup>
Azathioprine	No	Yes
Mycophenolate Mofetil	No	Yes

\*\*This has been considered to be a potential therapy that can be offered to a newly detected patient by other advisory summaries listed above.<sup>[13,14,20]</sup> ## For patients who have been on low dose maintenance, it must be taken into consideration if any other long-term immunosuppression is being given and risk of relapse. Accordingly depending upon the dose, modification or withdrawal of the therapy could be decided. ^^ Low dose maintenance has also been suggested as a continuation treatment during this pandemic in absence of alternate treatment for patients where immunosuppressive therapy has to be stopped or delayed.<sup>[20]</sup>

Therapy with AZA is expected to produce lymphopenia and the recommendation is to keep absolute lymphocyte count around 600- 1000 cells/ul for therapeutic efficacy.<sup>[16]</sup> Therapy with AZA is known to cause gastrointestinal and haematological side effects. Opportunistic infections are uncommon in patients on long term treatment with AZA and is not associated with severity of lymphopenia.<sup>[17]</sup>

#### Recommendation:

- The patients on chronic therapy may continue the treatment with close monitoring.
- It advisable not to choose Azathioprine in newly diagnosed patients during the current COVID-19 pandemic.

#### *Mycophenolate mofetil (MMF)*

It has a similar mechanism of action as AZA, a purine analogue that interferes with cellular proliferation, but unlike the latter, it targets guanosine rather than adenosine which limits side effects including treatment related lymphomas. An optimized dose of MMF causes absolute lymphocyte count to reduce to 1000- 1500 cells/ul. Mycophenolate therapy has been shown to be associated with opportunistic infections particularly cytomegalovirus and BK virus in transplant recipients. Paradoxically it also exhibits antimicrobial activity against hepatitis C and human immunodeficiency virus (HIV).<sup>[18]</sup>

*Recommendation:*

- The patients on chronic therapy may continue the treatment with close monitoring.
- It is advisable not to choose MMF in newly diagnosed patients during the current COVID-19 pandemic.

**Cladribine**

It is considered amongst the ‘pulsed immune reconstituting therapy’ (PIRT) agents. It is administered orally in annual cycles of 8–19 days and exerts a prolonged lymphopenia, occurring soon after the first cycle. Both CD4 + and CD8 + T cell concentrations get markedly low for prolonged periods, although the reduction is gradual in contrast to the monoclonal antibodies.<sup>[19]</sup>

*Recommendation:*

- Based in its high lymphopenic properties, it is advised not to start this agent for treatment in MS during the COVID-19 pandemic.
- In case patient has been previously given a dose, it is prudent to delay the next dose.<sup>[20]</sup>

**Mitoxantrone**

Mitoxantrone, originally an antineoplastic agent, acts as a type II topoisomerase Inhibitor and also inhibits DNA synthesis and repair in rapidly proliferating T and B cells. Mitoxantrone is approved for the treatment of secondary progressive MS and ‘progressive-relapsing’ MS.<sup>[21]</sup> It has significant cardiotoxicity and myelotoxicity which mandates close monitoring and associated teratogenicity mandates contraceptive measures during therapy and thereafter for 6 months.

*Recommendation:*

- Due to its significant toxicity and being a strong lymphopenic agent, its use during the COVID-19 pandemic is not recommended or if already being prescribed, further doses should be withheld till the pandemic subsides.

**Natalizumab**

Natalizumab is an injectable humanized IgG4 monoclonal antibody targeting the alpha-4 integrins expressed on the surface of all leukocytes except neutrophils. It prevents entry of both T and B lymphocytes into the brain parenchyma. Peripheral leukocyte subsets are increased and normal immune response to influenza vaccine has been demonstrated.<sup>[22]</sup> As the mechanism is antimigratory, Natalizumab predisposes to CNS viral infections, especially, progressive multifocal leukoencephalopathy (PML).<sup>[23]</sup> A few cases of herpes simplex and varicella encephalitis and meningitis have also been reported with Natalizumab.<sup>[22]</sup> There was no significant difference in the frequency of systemic infections compared to placebo in the AFFIRM and SENTINEL trials of Natalizumab.<sup>[23,24]</sup> No increased risk of infections was noted compared to interferons or Glatiramer acetate in a recent study.<sup>[25]</sup>

*Recommendation:*

- Natalizumab infusions can be continued. There is no current significant evidence of neurotropism of

SARS-CoV-2 and therefore theoretically Natalizumab does not pose any risk.

- Although there is a potential concern of rebound disease activity,<sup>[26]</sup> it is reasonable to consider extended interval dosing (from 4 weeks to 6-8 weeks) in patients with well controlled disease during this COVID-19 pandemic to mitigate even the very low risk of systemic infections with Natalizumab. This would also reduce hospital visits.
- Among newly diagnosed patients, Natalizumab could be considered as a potential therapy for aggressive or highly active MS only.

**Rituximab**

This is a selective immune depletor of Anti-CD 20 B cells. Effect of Rituximab starts as early as 1-3 days and the effect lasts up to 6 to 12 months. Rituximab is used in the treatment of autoimmune demyelinating neurological diseases like MS, NMOSD and MOG spectrum disorders.<sup>[36,51,52]</sup> Patients on Rituximab treatment probably have a slightly increased risk of acquiring infections especially viral infections like herpes.

*Recommendation:*

- MS and NMOSD patients who are on Rituximab may delay their maintenance dose of Rituximab by a few weeks based on the severity of their disease, previous relapse rate and disability status. All decisions should be made in consultation with the treating doctor, who will weigh the risks and benefits of delaying the treatment. Monitoring of CD 19+/20+ and where available CD27+ cell counts can be performed in these patients to help guide treatment in practice.<sup>[51,52]</sup>
- If CD 19+/20+ cell counts are less than 1%, the maintenance dose of rituximab may be delayed. For patients with higher levels of CD 19+/20+ cell counts, the decision should be individualised based on risk benefit assessment during the current pandemic.
- It may be prudent to delay the initiation of Rituximab in patients with MS and related disorders during the ongoing COVID-19 pandemic.
- In patients with NMOSD, a decision to initiate rituximab should be strictly individualized based on the severity of attacks, number of relapses and disability and absence of alternative choice of medication.
- Patients on Rituximab and their care givers should take all the necessary precautions as recommended during this pandemic.

**Ocrelizumab**

Ocrelizumab is also an anti-CD 20 B cell depleting agent approved by FDA for the treatment of RRMS and PPMS. Currently Ocrelizumab is not available in India. The risk of acquiring a viral infection is probably moderately increased in patients on Ocrelizumab. As duration of action is long, the patients may remain susceptible to COVID-19 virus for prolonged periods.

*Recommendation:*

- Patients already on Ocrelizumab may delay the maintenance dose of Ocrelizumab for some time till the

pandemic subsides or more information gets available on the real risk of COVID -19 infection in patients on anti-CD 20 drugs.

- It is advisable not to initiate Ocrelizumab during the ongoing COVID-19 pandemic.

### *Alemtuzumab*

Alemtuzumab is a humanized monoclonal antibody targeting the CD52 antigen expressed on effectors of adaptive and innate immunity, principally, lymphocytes, monocytes and dendritic cells. Alemtuzumab rapidly depletes circulating T and B lymphocytes by antibody and complement-dependent cytotoxicity followed by repopulation and remodeling of adaptive immunity over weeks to months.<sup>[27]</sup> Recovery starts within one month with CD8+ T cells and B cells improving to near normal in 3 to 6 months, CD4+ T cell recovery is delayed by 2 years.<sup>[28]</sup>

Alemtuzumab is associated with an increased risk of systemic and CNS viral infections.<sup>[27]</sup> The risk of viral infections is significantly increased for 3 to 6 months after Alemtuzumab therapy. Respiratory infections and urinary tract infections were the most common, usually mild to moderate in severity. There was higher incidence of herpes infections. An increased risk of reactivation of latent pulmonary tuberculosis contributes to the pulmonary morbidity.<sup>[27-29]</sup> The risk of infectious complications are maximum in the first two years, but declines thereafter.<sup>[30]</sup>

#### *Recommendation:*

- For patients already on treatment with Alemtuzumab, it is advised to delay the second course until the risk of COVID-19 infection has subsided. A delay in reinfusion till 18 months may be considered as this confers a low risk of re-emergent MS activity.
- Alemtuzumab infusion should not be initiated in patients during the ongoing COVID 19 pandemic.

### *Autologous hematopoietic stem cell transplantation (AHSCT)*

AHSCT would be associated with the highest risk of infections to patients and therefore there is a general consensus against it during the ongoing COVID 19 pandemic.<sup>[20]</sup>

### *Corticosteroids*

Glucocorticoids exert anti-inflammatory activity through multiple mechanisms, predominantly at the level of inflammation controlling genes by interaction with glucocorticoid receptors. They induce apoptosis of T and B cells and inhibit T cell signalling and inflammatory cytokine release. Maintenance corticosteroids are likely associated with a higher risk of infections and specifically lower respiratory tract infections,<sup>[31]</sup> but could vary with the primary underlying disease and concomitant immunosuppression. The increased risk is demonstrated even for low doses (equivalent to 5 mg prednisolone) and increases with increasing dose.<sup>[32]</sup> No specific data from COVID 19 cohorts is available, although data on low dose early use of methylprednisolone from a recent

published Chinese study (not peer reviewed, pre- print) among patients with COVID 19 pneumonia, was associated with a faster clinical improvement and lung features.<sup>[33]</sup>

#### *Recommendation:*

- Use of pulse methylprednisolone for an acute demyelinating event should be considered but individualised as per need (see summary of recommendations below)
- Patients on maintenance corticosteroid could be at an increased risk of infections and warrants general care to minimize the risk of infection.
- A higher dose of steroid may confer a higher risk of infection.
- The continuation or withdrawal of the drug should be individualized based on the risk of relapse of the primary disease.

### **Summary and overview of recommendations of the expert group [Table 2]**

#### *Specific Recommendations*

- *Practice of optimal health safety norms is mandatory.*
- *It may be prudent to involve the local infectious disease expert for shared decision making*
- *It is important to screen a patient for symptoms of active COVID-19 infection before starting any immunomodulatory therapy.*

#### *Starting medications:*

- Shared decision making is critical during this period, and the treating expert may discuss with the patient about the options of starting treatment versus delaying the treatment. Factors like disease type, severity of disease, relapse rate and disability status may help to make appropriate decisions.
- The patient must be explained on the risks with each medication and need of monitoring. The standard precautions during the current pandemic must well be explained.
- Among patients with MS and in situations where starting a DMT is imperative, medications with lowest immunosuppressive properties and risk of infection should be preferred. These include IFN, GA, and probably DMF (opinion differs in international advisories). For aggressive cases demanding institution or switch of treatment, Natalizumab may be reasonable in a patient with negative JC virus serostatus. Close monitoring of biochemical and haematological adverse events is recommended.
- For patients with NMOSD, MOG antibody associated disease and other related disorders, who require immunosuppressive medications, it may be prudent to consider use of intravenous immunoglobulin (IVIG) (as it seems safest), maintenance steroids alone, rituximab, or plasmapheresis maintenance, based on the individual circumstances.<sup>[20,43,47,48,50]</sup>
- However, patients with an aggressive disease would require standard treatment protocols with adequate practice of COVID 19 preventive norms.

*Continuing medications:*

- Patients on DMTs may continue with the medications.
- Patients whose disease is stable on immunosuppressant therapy with azathioprine or mycophenolate mofetil should continue the treatment and follow all general precautions against exposure to COVID-19.
- Medications with potential risk of lymphopenia need close monitoring and a strict advice to practice health safety norms in this period.
- For medications like rituximab or similar medications requiring continuation dose, it may be prudent to consider delaying the maintenance dose. Monitoring of CD19+ and CD27+ cell count levels and CD27+ cell counts where available, may help in assessing the need for maintenance dose.<sup>[51,52]</sup>

*During a potential COVID 19 infection in a patient:*

- The risk of stopping versus continuing should be individualised based on discussion with the treating neurologist and infectious disease expert.
- Drugs with high risk of lymphopenia and immunosuppression [Table 1] should be preferably withheld and all infusions postponed. Some International advisories have suggested stopping all medications.<sup>[13,14]</sup> Concern for drugs with rebound effect needs close monitoring. For patients on drugs like interferons, there may be a consideration to continue treatment after discussion with the infectious disease team.

*Management of a relapse:*

- There is a potential concern regarding the use of steroids during a relapse or disease exacerbation due to concerns of immunosuppression. Disease exacerbation will require optimum adjudication, severity judgement, risk related to the underlying disease and appropriate discussion with the patient regarding various treatment options.
- It is important to differentiate a relapse from any fluctuation and pseudorelapse.
- It is advised to screen a patient for symptoms of active COVID-19 infection before starting steroids.<sup>[20]</sup>
- For patients with MS, based on severity of the relapse, the neurologist may take a decision on observation or treatment with steroids during this pandemic. For symptoms that are very mild, more subjective, with negligible objective findings and disability, observation over the next 48-72 hours may be considered. For worsening symptoms, or a moderate to severe relapse, it may be prudent to start immediate acute immunomodulation. The drug of choice for relapse treatment is pulse intravenous methylprednisolone in usual doses,<sup>[39,40]</sup> although other potential choices in the current situation could include intravenous immunoglobulin therapy or plasmapheresis, albeit with issues of cost, feasibility, low evidence and probably uncertain efficacy.<sup>[39-42]</sup>
- For patients of NMOSD, MOG disease and related disorders, a relapse may suggest more severe disease behaviour and risk of disability. Therefore, it is prudent to

start acute treatment. As mentioned above, steroids remain the mainstay of treatment but since plasmapheresis has a significant role in NMOSD relapses and probably in MOG related disease too and is generally considered in patients with severe relapses as an early add on or sometimes a primary therapy to reduce disability, it remains a potentially effective alternative in this situation.<sup>[41,44-47]</sup> However, invasive nature of this treatment and its potential risks, availability and feasibility in the current situation should be borne in mind. IVIG remains an alternative option in this scenario.<sup>[45,47-50]</sup>

*Switching therapy*

Principles of switching therapy involve relapse rate, disability progression and imaging evaluation. For relatively stable patients, it is prudent to delay the switching as the new agent may require biochemical/haematological and adverse effect monitoring, which may become difficult during the current period. In case it is imperative, then a suitable drug as discussed above with least immunosuppressive/lymphopenic potential. For highly aggressive patients and for those with high disease activity, Natalizumab could be used in JCV negative patient.

*Utilization of telemedicine*

This would be prudent during the COVID-19 pandemic to avoid non-essential hospital visits and also during the periods of lock down. Telemedicine has also been validated as a tool for assessing disability in MS with high patient acceptability.<sup>[34]</sup> Hospital visits may be also be reduced by facilities like home delivery of medications, delaying follow-up MRI scans in stable patients and reducing frequency of routine laboratory monitoring.<sup>[20]</sup>

*Recommendations – for patients*

- Strictly follow guidelines of health authorities.
- Wash your hands frequently with soap and water or an alcohol-based hand rub. Each hand-wash should last for a minimum period of 30 seconds before rinsing with water.
- Avoid touching your eyes, nose and mouth unless your hands are clean
- Try to keep at least 1-meter distance between yourself and others, particularly those who are having fever, cough, sneezing or any other medical illnesses with fever.
- Use Masks when going outside: Advice from local health authorities and Ministry of Health and Family welfare, Govt of India (<https://www.mohfw.gov.in/>) as well as WHO is updated regularly, so kindly keep a check. (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>, accessed on 05.04.2020). Since you are on medications and probably at a higher risk than normal population, it may be prudent to use mask. A manual for making homemade masks is also available from the office of Principal Scientific Advisor, Government of India for routine use and prevention, although guidelines are being updated regularly. (<http://164.100.117.97/WriteReadData/userfiles/FINAL%20MASK%20MANUAL.pdf>, accessed on

05.05.2020). Teaching video to use and maintain reusable face covers is also available at <https://www.mohfw.gov.in/>.

- Avoid meeting relatives/friends/public gatherings/crowds.
- Avoid using public transport
- Do not go out for shopping, leisure or travel and, when arranging food or medication deliveries, these should be left at the door to minimize contact
- Good Food Hygiene Practice:
  - Avoid outside foods
  - Use home-made fresh foods
  - Avoid tinned foods
- Do's at Home:
  - Clean any shared spaces in between use.
  - Use separate towels from the other people in your house.
  - Kindly keep your toilet and bathrooms clean and ventilated.
- *Caregivers and family members who live with a person with autoimmune neurological disorders should also follow standard practices as recommended during the ongoing pandemic.*

### Medication Guidelines

- People currently taking the medications should continue their treatment and discuss with their neurologist regarding the same.
- Patients with other co-morbidities like hypertension, diabetes, hypothyroidism should continue taking their medications. Before changing/stopping any medication, the primary physician should be consulted. Adherence to medications is emphasized since poor management of these co-morbidities has been linked to worse prognosis with COVID-19.
- There is a potential concern you may be at an increased risk of an infection in view of the immunomodulatory medications being used. General precautions should be strictly followed.
- Don't stop medications without consultation, as there may be a risk of flare/attack/relapse and the disease may worsen/progress.
- If you develop any symptoms that may suggest a new infection, contact your health care provider immediately.

### Disclaimer:

1. Knowledge related to SARS-CoV-2 or 2019 novel coronavirus (2019-nCoV) is still emerging and rapidly evolving. We know little about the effects of this novel CoV on various body systems and its behaviour among patients with a variety of underlying medical and neurological conditions, especially those on immunomodulatory medications.
2. The aim of the present document is to appraise the potential concerns when managing our patients with underlying CNS autoimmune demyelinating disorders during the current COVID-19 pandemic.
3. The statement shall cover Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum disorders

(NMOSD), Myelin Oligodendrocyte Glycoprotein (MOG) antibody associated disease and other related disorders.

4. The advisory is based on our current knowledge of the medications and known risks of immunosuppression. It is unclear at this juncture whether disease modifying therapies (DMT) for MS and immunosuppressants (IS) prescribed for MS and related disorders including NMOSD and MOG antibody associated disease have a potential risk of increasing the likelihood of COVID-19 infection and its related complications. This consensus statement can be used to guide decisions on balancing the risk of infection with the risks of both starting and stopping immunomodulatory therapy. In the absence of evidence-based data specifically for COVID 19 and these disorders, this review comprises the consensus opinion of experts rather than a systematic elaboration of evidence-based guidelines.
5. The statement is written specifically from the perspective of ongoing COVID 19 pandemic and is not intended to be a generic guideline to manage patients with these disorders.
6. The treating neurologist should individualize the decision-making in consultation with an infectious disease specialist and after discussion with the patient and his family members.
7. It is prudent to screen a patient for symptoms of active COVID-19 infection before starting any immunomodulatory therapy.
8. The opinion and advisory may vary across different countries.

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### Conflicts of interest

There are no conflicts of interest.

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