










Managing Disease-Modifying Therapies and Breakthrough Activity in Multiple Sclerosis Patients During the COVID-19 Pandemic: Toward an Optimized Approach

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Abstract: The emergence of the novel coronavirus disease 2019 (COVID-19) pandemic has become a major public health challenge of global concern since December 2019, when the virus was recognized in Wuhan, the capital city of Hubei province in China and epicenter of the COVID-19 epidemic. Given the novelty of COVID-19 and the lack of specific anti-virus therapies, the current management is essentially supportive. There is an absence of consensus on guidelines or treatment strategies for complex disorders such as multiple sclerosis (MS), in which the risk of infections is higher than in the general population. This is due to the overall impairment of the immune system typical of autoimmune diseases, in addition to accumulation of disabilities, and the iatrogenic effect generated by corticosteroids and the recommended disease-modifying therapies (DMTs). DMTs have different modes of action, but all modulate and interfere with the patient's immune response, thereby raising concerns about adverse effects, such as an increased susceptibility to infections. In this review, we analyze the evidence for use of DMTs during the current critical period and ratify an algorithmic approach for management to optimize care between keeping DMTs, with their infection hazards, or coming off them, with the risk of disease activation. We also provide an algorithmic approach to the management of breakthrough activity during the COVID-19 pandemic.

Keywords: COVID-19, multiple sclerosis, disease-modifying therapies

Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic is a world-shattering infection that affects all geographical areas. The current situation is changing rapidly, with increasing numbers of cases arising across more than 200 countries and territories around the world.¹ The number of confirmed coronavirus patients has grown substantially, with higher day-to-day increases and evidence of sustained transmission in six continents.²

The novel coronavirus is a member of the beta group of coronaviruses, which was named by the International Committee on Taxonomy of Viruses (ICTV) as severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) and the disease as COVID-19.³ Accumulating evidence suggests that a subgroup of patients with severe COVID-19 may have alveolitis cytokine storm syndrome.⁴ Secondary hemophagocytic lymphohistiocytosis (sHLH) is an underrecognized, hyperinflammatory syndrome

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characterized by a fulminant and fatal hypercytokinemia with multiorgan failure, which is most commonly triggered by viral infections⁵ and characterized by an increase in pro-inflammatory mediators.⁶

There is a great complexity of host immune defenses against viral infections. Activation of cytotoxic and other T lymphocytes (cell-mediated immunity) occurs as early as 3–4 days,⁷ then decreases rapidly within 5–10 days of elimination of the virus. In contrast, humoral immunity appears later (after 7 days) and persists for much longer (often for years).⁸

The knowledge that COVID-19 can cause critical illness and death is a particular concern among patients with chronic illnesses, including multiple sclerosis (MS).⁹

COVID-19 Infection Risk Stratification in Patients with Multiple Sclerosis

Patients with multiple sclerosis (pwMS) seem to be at higher risk of infection compared with the general population,¹⁰ and constitute a susceptible population for contracting COVID-19 and frequently developing respiratory insufficiency as a result of their reduced muscle strength, bulbar dysfunction and ineffective secretion clearance;¹¹ however, not all patients carry the same risk. Nevertheless, COVID-19 risk can be increased by comorbidities, older age and degree of disability. Moreover, many disease-modifying therapies (DMTs) with various modes of action modulate or interfere with the patient's immune response, raising uncertainties about the increased risk of infection.¹² According to their risk category, patients should be advised about the appropriate mitigation measures, by practicing social distancing for patients with low risk, social stringency for patients with intermediate risk or shielding for patients with high risk (Table 1).

During the current COVID-19 pandemic, pwMS as well as MS specialists are faced with many challenges: (1) concerns about the use of DMTs in MS patients; (2) delay or deferral in DMT dispensing due to logistic difficulties; (3) shortage of available hospital beds; (4) patients' worries about using immunosuppressive/immunomodulatory treatments; (5) absence of blanket recommendations or consensus regarding maintenance therapy and relapse management; and (6) the need for coordinated efforts to raise awareness among patients and medical society about general and specific infection control

measures according to World Health Organization (WHO) recommendations.

The present review discusses the general prophylactic measures for pwMS to mitigate the risk of infection, initiation/maintenance of DMTs and acute relapse management, and tries to design strategies for MS management during the current COVID-19 pandemic.

General Infection Risk Mitigation Measures

PwMS should adopt the recommended general and national public health measures, including frequent handwashing/sanitation, social distancing and adequate nutrition.¹³ For patients who have interactive audio/video telecommunications facilities, telehealth services, e-visits and virtual check-ins are implemented. In the absence of such means, especially in rural settings, phone calls/WhatsApp texting with the MS team should be available for regular follow-up and for answering patients' queries. Public awareness should be raised through social media campaigns to provide essential information and knowledge about COVID-19, and to reinforce key messages to shape patients' behavior to prevent/minimize the spread of infection.

Initiation/Maintenance of DMTs

The initiation and maintenance of DMTs in pwMS can be very challenging, especially during this critical period. A few DMTs exert immunomodulatory effects with almost no increase in the risk of systemic infections. Other agents used in MS management have immunosuppressive effects with considerable effects on lymphocyte count, trafficking, proliferation, differentiation and function, leading to an increased risk of infections.¹⁴ Table 2 summarizes the modes of action, doses and routes of administration of currently approved DMTs.

Interferon-Beta (INF-β)

The therapeutic efficacy of INF-β in MS is not only related to its immunoregulatory characteristics, but also to its in vivo anti-viral properties, evident by their significant inhibition on the viral replication of human herpesvirus 6 (HHV-6), which was studied as an example of a latent neurotropic virus.¹⁵

Leukopenia/neutropenia and, to a lesser extent, lymphopenia are among the very rare hematological abnormalities associated with INF-β use; thus, they are usually clinically insignificant.¹⁶ INF-β initiation can be

Table 1 Stratification of COVID-19 Risk in Multiple Sclerosis Patients

Risk Factor	Low Risk (Social Distancing)	Intermediate Risk (Social Stringency)	High Risk (Shielding)
Age ^{93–95}	<40 years	40–49 years	≥50 years
Comorbidities ⁹⁶ (eg, diabetes mellitus, hypertension, cardiovascular disease)	Absent	One	Two or more
Smoking ⁹⁷	Non-smokers	–	Smokers
Type of MS ^{10,98}	RRMS on one of the low-risk medications	RRMS on one of the intermediate-risk medications	SPMS/PPMS (EDSS >4)
Ambulation index score ^{11,98,99}	0–3 (walks independently)	4–5 (unilateral support or bilateral support, walks 25 feet in ≤20 seconds)	6–9 (bilateral support, walks 25 feet in >20 seconds or unable to walk 25 feet, uses wheelchair on occasions/most of the time or restricted to it)
Bulbar or respiratory symptoms related to MS ^{99,100}	No bulbar symptoms	Bulbar symptoms	Bulbar and respiratory symptoms
Pregnancy ¹⁰¹	–	Yes	–
Obesity ¹⁰² (body mass index)	Normal or overweight (18.5–29.9 kg/m ²)	Obese (30–39.9 kg/m ²)	Morbidly obese (≥40 kg/m ²)
Disease-modifying therapies ⁹⁹	Interferons, glatiramer acetate, natalizumab, dimethyl fumarate, teriflunomide	Alemtuzumab or cladribine in the past 6 months, fingolimod, ocrelizumab or rituximab in the past 12 months	Alemtuzumab or cladribine in the past 12 weeks, AHSTCT in the past 12 months, any other immunosuppressant
Lymphopenia ^{2,29,93}	Grade 0–1	Grade 2	Grade 3–4
Visited or living in a high-risk area for COVID-19 ¹⁰³	No	Yes (≥14 days)	Yes (<14 days)
Working in a health-care facility ¹⁰⁴	No	–	Yes

Abbreviations: AHSTCT, autologous hematopoietic stem cell transplantation; COVID-19, coronavirus disease 2019; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

associated with influenza-like symptoms, including fever, bone aches, headaches and dyspnea, which usually fade away by 3 months.¹⁷ However, such symptoms may be confused with COVID-19 symptoms, and thus strict risk mitigation including prolonged dose titration and the use of paracetamol is recommended. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is currently controversial as there have been some reports stating that NSAIDs may exacerbate symptoms in COVID-19 patients.¹⁸

Recommendations

INF-β can be initiated or maintained safely. Dose titration and the use of paracetamol in starters is recommended. Those who

redevelop influenza-like symptoms should be checked for COVID-19 and stop INF-β until a clear diagnosis is established. Those who are still experiencing injection-related symptoms should report if the symptoms are exaggerated or different from usual.

Glatiramer Acetate

Glatiramer acetate (GA) is an MS immunomodulating drug which is not associated with an increased systemic risk of infection.^{19,20} Furthermore, GA tends to be beneficial in the Theiler's murine encephalomyelitis virus model by inducing anti-inflammatory immune responses. It neither increases viral loads nor decreases anti-viral immunity.

Table 2 Summary of Disease-Modifying Therapies Approved for Use in Multiple Sclerosis^{16,51,105}

	Route of Administration	Dose	Principal Proposed Mechanism of Action
Interferon β -1a	IM	30 μ g once per week	Down-regulation of MHC expression on APCs, decrease pro-inflammatory cytokines, inhibit T-cell proliferation, inhibition of leukocyte migration across the BBB
Interferon β -1b	SC	22–44 μ g 3 times per week	
	SC	0.25 mg every other day	
Glatiramer acetate	SC	20 mg once daily or 40 mg 3 times per week	Shifts pro-inflammatory T-helper-1 lymphocyte to regulatory T-helper2 lymphocyte
Teriflunomide	PO	7–14 mg once daily	Selective reversible inhibition of dihydroorotate dehydrogenase, T-cell activation and cytokine production inhibitor
Dimethyl fumarate	PO	120 mg bid for 1 week then 240 mg bid daily	Decreases pro-inflammatory cytokines and decreases entry of lymphocytes into the CNS (inhibits expression of adhesion molecules)
Fingolimod	PO	0.5 mg once daily	Lymphocyte sequestration in secondary lymphoid tissues
Natalizumab	IV	300 mg every 4 weeks	Interaction with α -integrins preventing lymphocytes from crossing BBB
Cladribine	PO	3.5 mg/kg body weight divided into 2 yearly treatment courses (1–2 tablets/day over 4–5 consecutive days)	Cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in long-lasting depletion of lymphocytes
Ocrelizumab (anti-CD20)	IV	Initially 300 mg once repeated after 2 weeks, then 600 mg every 6 months	Anti-CD20 and depletion of B lymphocytes
Mitoxantrone	IV	12 mg/m ² q3m (maximum cumulative dose 140 mg/m ²)	Inhibits B cells and T cell and macrophage proliferation
Alemtuzumab	IV	12 mg daily for 5 days, then 1 year later 12 mg daily for 3 days	Anti-CD25 and depletion of lymphocytes

Abbreviations: APC, antigen-presenting cell; BBB, blood–brain barrier; bid, twice a day; CNS, central nervous system; DNA, deoxyribonucleic acid; IM, intramuscular; IV, intravenous; μ g, microgram; mg, milligram; MHC, major histocompatibility complex; PO, per oral; SC, subcutaneous.

Recommendations

GA can be initiated or maintained safely during the COVID-19 pandemic.

Teriflunomide

Teriflunomide selectively and reversibly targets activated T and B lymphocytes inducing a cytostatic effect, thus limiting their contribution to the inflammatory processes of MS pathogenesis without either compromising the adaptive immunity or increasing the incidence of serious infections in long-term follow-up.^{21–23} Accordingly, teriflunomide is not considered an immunosuppressant; however, it may lead to a mild lymphopenia²³ (grade 1 and 2), which usually occurs early in the treatment course and persists for an extended period. Therefore, suspension of teriflunomide treatment with an accelerated elimination procedure should be considered if a patient develops a serious infection.²⁴ Mild leukopenia/neutropenia has also been reported.²⁵

It is worth mentioning that teriflunomide and its parent compound, leflunomide, have demonstrated both in vitro and in vivo activity against several viruses, including the BK virus, cytomegalovirus, Epstein–Barr virus, herpes simplex virus, Theiler's virus and John Cunningham virus (JCV).^{26,27} Teriflunomide is slowly eliminated from plasma; it takes 8 months to 2 years to reach a plasma concentration less than 0.02 mg/L. Accelerated elimination of teriflunomide should be considered after discontinuation in cases where a serious infection develops. For accelerated elimination, the use of cholestyramine 8 g administered three times daily or 50 g of activated powdered charcoal every 12 hours for 11 days is recommended.²⁴

Recommendations

Teriflunomide can be started and maintained during the COVID-19 pandemic in the absence of concurrent infection. Routine laboratory tests should be performed according to the product information. Accelerated elimination

should be considered if the patient has COVID-19 and teriflunomide is to be discontinued.

Dimethyl Fumarate (DMF)

The mechanisms of action of DMF include induction of apoptosis of activated T cells, shift of CD4⁺ T cells toward a Th2 profile, and reduction of dendritic cell (DC) maturation. DMF has been shown to selectively reduce memory T cells in MS and decrease the overall B-cell population, in particular mature B cells.²⁸ Accordingly, it can potentially induce lymphopenia, which is reported as a worrisome sign in the COVID-19 pandemic.²⁹ The frequency of grade 1 lymphopenia was reported to occur in approximately 16.5% of DMF-treated patients and grade 3 (200 to <500 cells/ μ L) in 2.4–7%.^{30–32} Lymphopenia is mainly encountered during the early treatment course, yet it can be severe and may persist even after DMF withdrawal.³² PwMS with a lymphocyte count above 800 cells/mm³ can deal with viral infections reasonably well, provided they are relatively young and have no other comorbidities. Notwithstanding, there is no current evidence of an increased risk of COVID-19 infection with DMF.³³

Recommendations

DMF can be initiated and maintained during the COVID-19 pandemic provided there is no significant lymphopenia (grade ≥ 3). The usual monitoring guidelines for DMF include complete blood count (CBC) with differential leukocytic and lymphocytic counts before treatment initiation and every 3 months during the first year of treatment, followed by every 6 months thereafter, or as clinically indicated, and it should be discontinued in cases of persistent grade 3 lymphopenia for 6 or more months.³⁴ In MS patients with confirmed active COVID-19, interruption of DMF should be considered.^{33,35}

Fingolimod

Fingolimod has been associated with increased risk of infections compared with placebo or IFN- β and GA in randomized clinical trials and post-marketing surveillance.^{36–40}

Given its effects on lymphocyte trafficking, fingolimod could theoretically increase the risk of infections; yet, definite correlation between reduction of circulating lymphocyte count and the frequency of serious or opportunistic infections was critiqued by some reports, which emphasized that infection was not significantly increased even in patients whose lymphocyte counts had decreased to <200 cells/mm³.⁴¹ If the total leukocyte count is <4000 and >2500

cells/mm³ and/or the lymphocyte count is <600 and >200 cells/mm³, the dose can be reduced to every other day.⁴²

According to some pathological findings of pulmonary edema and hyaline membrane formation in COVID-19, the use of immune modulators, together with ventilator support, should be considered for patients with severe symptoms to prevent the development of acute respiratory distress syndrome (ARDS). Currently, there is an ongoing trial that aims to determine the efficacy of fingolimod in the management of COVID-19.⁴³

Recommendations

Delaying initiation of fingolimod may be considered during the coronavirus pandemic.³² For those who are on stable treatment with regular follow-ups, it is recommended to advise patients to closely monitor themselves for any symptoms or signs of infection. In case of any infection, CBC should be performed to exclude significant leukopenia or lymphopenia. If grade 3–4 lymphopenia occurs at any time during the current specific circumstances, other treatment options should be considered. Sudden fingolimod cessation is not recommended owing to the rebound effect that occurs approximately 2–4 months after treatment discontinuation, unless the patient is confirmed to have COVID-19.^{44,45} In MS patients with confirmed active COVID-19, interruption of fingolimod may be considered.

Natalizumab (NTZ)

NTZ selectively compromises immune surveillance only in the central nervous system by playing a major role in active lymphocyte trafficking across the blood–brain barrier, through binding to the α_4 -subunit of $\alpha_4\beta_1$ - and $\alpha_4\beta_7$ -integrins expressed on the surface of human leukocytes and vascular cell adhesion molecule-1.⁴⁶ It is one of the treatment options for patients with aggressive MS or sub-optimal response to first line therapies.⁴⁷

Despite the increased risk for progressive multifocal leukoencephalopathy, an opportunistic life-threatening brain infection caused by JCV, the risk of acquiring systemic infections with NTZ is considered relatively low compared to other high-efficacy medications.⁴⁸

NTZ discontinuation may trigger a rebound effect, frequently occurring within 3–6 months of discontinuation; therefore, careful evaluation of risk–benefit should be considered prior to NTZ cessation.⁴⁹

Recommendations

NTZ is currently viewed among the safest high-efficacy therapies to use during the COVID-19 pandemic and could be started and maintained in patients with no current or potential infection, especially in those with aggressive MS.³³ For patients with active COVID-19 infection, delaying the next infusion should be considered.

Cladribine

Cladribine causes selective and transient reductions of CD19⁺ B cells and T cells, followed by reconstitution of adaptive immune function. The hazard of viral infections is significantly higher in the 3–6 months after cladribine intake as the lymphopenia nadir is 9 weeks with up to 12 weeks to recover.⁵⁰

In the integrated analysis of cladribine safety, median absolute lymphocytic count (ALC) reached a nadir of 1.00×10^9 cells/L at 2 months after the start of treatment during year 1. At the end of year 1 (48 weeks), median ALC had increased to 1.21×10^9 cells/L. During year 2, median ALC reached a nadir of 0.81×10^9 cells/L at 55 weeks (week 7 in year 2). Median ALC returned to the normal range by 84 weeks (week 36 in year 2). Median ALC returned to the normal range in 75% of patients by 144 weeks. Grade 3 lymphopenia was experienced by 25% of patients and grade 4 lymphopenia by <1% of patients treated with cladribine tablets.⁵¹

Recommendations

Delaying initiation of cladribine should be considered during the coronavirus pandemic. For those who have already started treatment, delaying the second cycle⁵² for 3–6 months or until the risk of coronavirus infection has passed may be considered. For patients with active COVID-19 infection, delaying the second cycle of cladribine should be considered.³³

Anti-CD20 Therapies

The first therapeutic anti-CD20 monoclonal antibody (mAb), rituximab (used off-label in MS), is a murine–human chimera to which many patients develop antibodies and/or experience infusion-related reactions. Ocrelizumab is a second generation recombinant humanized mAb, which selectively binds to CD20-expressing B cells and triggers antibody-dependent cellular cytotoxicity and complement-mediated lysis. Lymphoid stem cells and plasma cells do not express CD20 and therefore are not directly targeted.⁵³

B-cell counts are reduced within 2 weeks and remain depleted throughout ongoing treatment. The duration of B-cell depletion was initially estimated to be 6–9 months with rituximab treatment alone^{53,54} and it is now obvious from Swedish experience that rituximab remains effective at controlling disease activity beyond 6 months.⁵⁴ Anti-CD20 therapies leave the T-cell compartment of the immune system relatively intact and there have been no severe viral infections in the clinical trial programs. The main viral infection noted with anti-CD20 therapies is herpes zoster or shingles, and even then, these cases tend to be mild or moderate.⁵⁵

Recommendations

Delaying initiation of ocrelizumab and rituximab may be considered during the COVID-19 pandemic. In patients who are stable on treatment, one should consider delaying the next infusion.

Other Immunosuppressant Drugs

Some other immunosuppressant drugs are used off-label for managing pwMS, especially in low-income countries. A large MS Egyptian cohort, in 2017,⁵⁶ showed that about 23.6% of pwMS were receiving those drugs, including cyclophosphamide (CPM), methotrexate (MTX), azathioprine (AZA) and mitoxantrone, as induction/maintenance therapies.^{56–59}

Both CPM and MTX are cytotoxic drugs causing damage to immune cell DNA, thus possessing a potent immunosuppressant effect. AZA acts through inhibition of DNA, RNA and protein synthesis.^{60–62} The main safety concerns of those drugs are lymphopenia, potential risk of infections and hepatotoxicity.^{63,64}

Mitoxantrone interacts with the enzyme topoisomerase-2 and causes single- and double-strand breaks by intercalating the DNA through hydrogen bonding.^{64,65} As has been well established for decades, mitoxantrone is a potent immunosuppressive agent targeting proliferating immune cells. It inhibits proliferation of macrophages, B lymphocytes and T lymphocytes.⁶⁶

AZA has a delayed onset of action, with the nadir lymphocyte count being reached at 135 days. Overall, lymphopenia tends to spontaneously resolve with no change in AZA dosing. Lymphopenia is a direct effect of AZA treatment, but lymphopenia-related complications have not been commonly reported. The usual monitoring strategies include weekly monitoring of CBC and liver enzymes for the first 4 weeks of therapy, or until the maintenance dose is achieved, and then every 3 months.⁶⁷

Recommendations

Clinicians should consider delaying initiation of CPM, MTX and mitoxantrone during the COVID-19 pandemic. Interruption of CPM, MTX and mitoxantrone may be considered. AZA can be started with weekly monitoring of CBC and transaminases for the first 4 weeks of therapy.

Alemtuzumab (AMZ)

AMZ is a humanized anti-CD52 mAb.^{68,69} It induces lysis and apoptosis of cells highly expressing CD52, namely T and B lymphocytes,⁷⁰ via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity, leading to a marked global lymphocyte depletion.^{71,72} AMZ-treated patients exhibit a nearly complete depletion of circulating CD4⁺ lymphocytes within a few hours of administration, with a nadir between days 3 and 7.^{73,74} The repopulation of T lymphocytes starts by month 3 and the return to the lower limit of the normal values occurs by month 6–12; however, this could be delayed for up to 24 months. B cells start to repopulate from 6 weeks onward, return to baseline by 3 months and exceed baseline levels from 6 months.^{75–78}

Overall, in key clinical trials, infections were more common in AMZ-treated patients compared to those treated with INF β -1a.^{73,74,79,80} The accumulations of herpes infections during the CARE-MS studies led to the implementation of prophylactic acyclovir treatment (0–4 weeks after AMZ infusion).⁸¹ The treating physician should be vigilant to possible opportunistic infections, particularly in the first few months after AMZ infusion.⁸²

AMZ administration is associated with acute induction of some pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and interferon-gamma (INF- γ), which peaks 2–6 hours after infusions and causes the “cytokine-release syndrome”.⁸³

Thus, in the COVID-19 pandemic AMZ carries a significant risk of catching the infection, besides the theoretical potential of aggravating the inflammatory phase of the disease caused by the cytokine storm.

Recommendations

Clinicians should consider delaying initiation of AMZ during the COVID-19 pandemic. In patients with highly active relapsing–remitting multiple sclerosis (RRMS), the use of an alternative treatment is to be considered, eg, NTZ (or DMF if serum anti-JCV antibodies are positive). If the first or second cycle has already been administered, the patient

should adhere to strict social stringency or shielding, or even self-isolation for 3 months or until a CBC demonstrates lymphocytic recovery. If another treatment cycle is due, it could be postponed.

Recommendations for the initiation and maintenance of DMTs in MS patients are summarized in [Figure 1](#).

Management of Relapse

Patients who present with new or worsening of neurological symptoms and have symptoms suggestive of COVID-19 (fever, dry cough, sore throat, headache or bone pains, loss of smell and/or taste) are to be sent for nasopharyngeal and oropharyngeal swab or wash and PCR testing. If the diagnosis of COVID-19 is confirmed, health authorities should be notified according to national requirements. If tests are repeatedly negative, other causes of fever should be searched for and treated accordingly.

If there are no symptoms or signs of any infection, a diagnosis of a true relapse can be made, and standard treatment should be applied. Caution is warranted that pseudo-relapse might be followed by a bona fide MS relapse.⁸⁴

A telephone questionnaire can be used to assess the Expanded Disability Status Scale (EDSS) score in cases where patients are unable to attend at their health facility owing to quarantine or curfew.⁸⁵

Relapses that do not or only minimally affect activities of daily living and affect only sensory functional domains are considered mild and do not require steroid treatment under the current pandemic circumstances. Any other relapse, considered moderate or severe,⁸⁶ should receive appropriate treatment.

It is advisable to limit the use of steroids during the COVID-19 pandemic. Pulsed high-dose/continuous oral steroids are immunosuppressive and may, at least theoretically, increase the risk of a COVID-19 viral infection or severity of related symptoms. If steroids are to be given anyway, patients are encouraged to receive standard high-dose corticosteroids intravenously at home⁸⁷ with strict self-isolation. Following high-dose corticosteroids, oral tapering is not necessary unless considerable residual symptoms are still encountered. Early clinical trials used steroid tapering after high-dose intravenous corticosteroids to combat potential acute adrenal insufficiency or to maintain the therapeutic effect; however, subsequent studies have shown that this tapering is not necessary after a brief steroid course that does not significantly suppress the hypothalamic–pituitary–adrenal axis,⁸⁸ nor does tapering contribute to recovery.⁸⁹

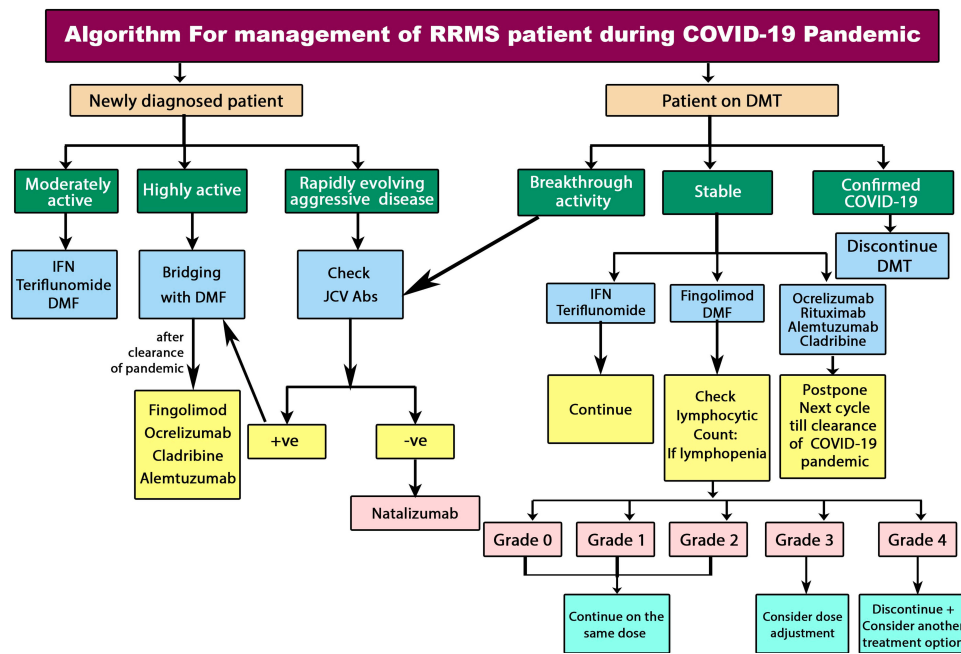


Figure 1 Algorithm of initiation and maintenance of DMTs in RRMS patients during COVID-19 pandemic.¹⁰⁶

Abbreviations: COVID-19, coronavirus disease 2019; DMF, dimethyl fumarate; DMT, disease-modifying therapy; IFN, interferon; JCV, John Cunningham virus; RRMS, relapsing–remitting multiple sclerosis.

Intravenous immunoglobulin (IVIg) exhibits anti-inflammatory effects via inhibition of complement-mediated tissue damage and modulation of the cytokine network. It suppresses the production of pro-inflammatory

cytokines while increasing the production of anti-inflammatory mediators.⁹⁰ Also, it has an immunomodulatory influence on different cells of the innate and adaptive immune compartments.⁹¹

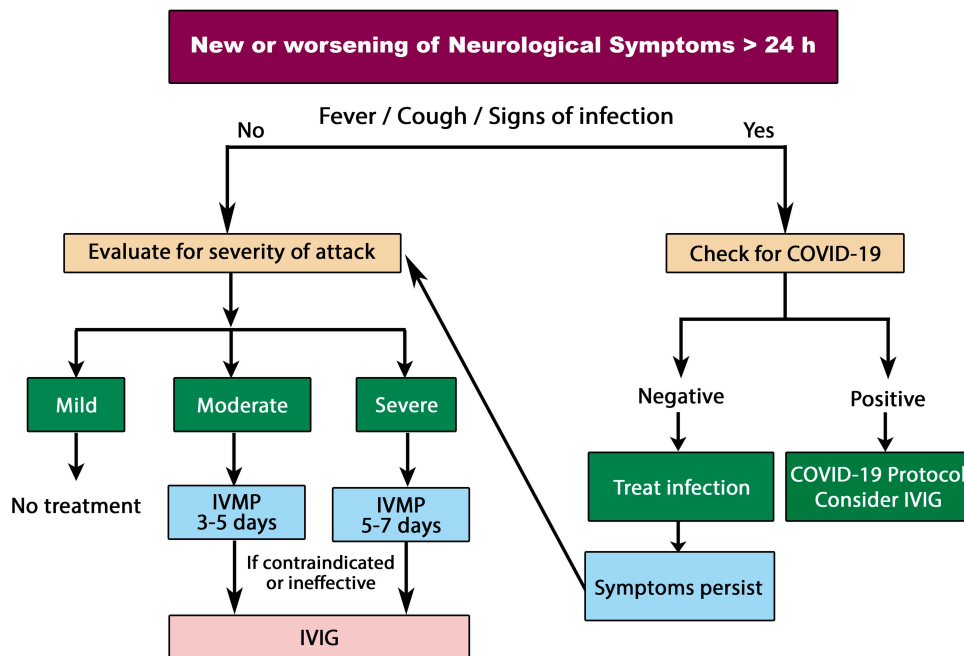


Figure 2 Algorithm of relapse management in RRMS patients during COVID-19 pandemic.

Abbreviations: COVID-19, coronavirus disease 2019; IVIG, intravenous immunoglobulins; IVMP, intravenous methylprednisolone; RRMS, relapsing–remitting multiple sclerosis.

IVIG therapy has a minimal impact on immune function.⁹² Therefore, IVIG can currently be considered as a good alternative if steroids are contraindicated, poorly tolerated or ineffective, or if hospitalization is impossible.

Plasma exchange may not be a suitable option in the treatment algorithm because of its invasive nature and the need for prolonged hospital stay.

Recommendations for the management of relapse during COVID-19 are summarized in Figure 2.

Summary of Recommendations

- Before initiating a DMT that may lower immunity, PwMS should remain in quarantine for at least 14 days to exclude potential COVID-19 infection.
- pwMS would not normally need to stop taking their DMT as a result of the threat of the virus.
- Patients on a “treatment-escalation/modification” pathway are not under immediate pressure to change, unless there are other factors (disease activity, JCV positivity, etc).
- Patients on immune reconstitution DMTs can rely on their long-term effect with delaying re-dosing.
- It seems wiser to select a treatment that does not reduce specific immune cells (lymphocytes) (eg, interferons, glatiramer acetate or natalizumab). Medications that reduce lymphocytes over longer intervals (eg, alemtuzumab, cladribine, ocrelizumab and rituximab) or those which may reduce the ability of the immune system to respond to infection (eg, fingolimod, dimethyl fumarate, teriflunomide and siponimod) should carefully be considered with regard to the risks and benefits during the COVID-19 pandemic.
- pwMS who are currently on alemtuzumab, cladribine, ocrelizumab, rituximab, fingolimod, dimethyl fumarate, teriflunomide or siponimod and are living in a community with a COVID-19 outbreak should isolate as much as possible to reduce their risk of infection.
- For patients with active COVID-19 infection, it is mandatory to stop all DMTs. The timing of resuming treatment is not well defined but may depend on serial COVID-19-negative PCR tests within 3–4 weeks of resolution of symptoms.

Although these recommendations can offer guidance toward optimized practice, management of patients with multiple sclerosis during the COVID-19 pandemic is still very challenging given the uncertainty of the current situation and the lack of evidence.

Disclosure

Thomas Berger has participated in the last 2 years in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Biogen, Bionorica, Celgene, MedDay, Merck, Novartis, Roche, Sanofi Aventis/Genzyme, TG Therapeutics and TEVA. His institution has received financial support in the last 2 years by unrestricted research grants (Biogen, Novartis, Sanofi Aventis/Genzyme, Roche, TEVA) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, Merck, Novartis, Roche, Sanofi Aventis/Genzyme, TEVA. The authors report no other conflicts of interest in this work.

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