Multiple sclerosis treatment during the COVID-19 pandemic

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MULTIPLE SCLEROSIS TREATMENT DURING THE COVID 19 PANDEMIC

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
AHSCT	Autologous hematopoietic stem cell transplantation
ARDS	Acute respiratory distress syndrome
ADWP	Autoimmune Diseases Working Party
CNS	Central nervous system
CIS	Clinically isolated syndrome
CSF	Cerebrospinal fluid
CT	Computed tomographic imaging
COVID-19	Coronavirus disease 2019
DMTs	Disease-modifying treatment
DMF	Dimethyl fumarate
DIS	Dissemination in space
DIT	Dissemination in Time
EID	Extended interval dosing
EDSS	Expanded Disability Status Scale
EBV	Epstein Barr-Virus
ERGIC	Endoplasmic reticulum Golgi intermediate compartment
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
IL-1	Interleukin- 1
IL-2	Interleukin- 2
IL-6	Interleukin- 6
IL-7	Interleukin- 7
IL-8	Interleukin- 8
IL-10	Interleukin- 10
IFNs	Interferons
IRT	Immune reconstitution therapy
MRI	Magnetic resonance tomography
MS	Multiple Sclerosis
MERS	Middle East respiratory syndrome
MuSC-19	Multiple Sclerosis and COVID-19

MSIS-29	Multiple Sclerosis Impact Scale
NK	Natural killers
PPMS	Primary progressive MS
pwMS	Patients with multiple sclerosis
PDDS	Patient Determined Disease Steps
PML	Progressive multifocal leukoencephalopathy
RRMS	Relapsing-remitting MS
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SPMS	Secondary progressive MS
S1PR	Sphingosine 1-phosphate receptor
TNF	Tumor necrosis factor
TGF	Transforming growth factor
URT	Upper respiratory tract
WHO	World Health Organization

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Abstract

Title: Multiple sclerosis treatment during the COVID-19 pandemic.

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), and the current treatment is centered on immunomodulatory and immunosuppressive medications. The ongoing COVID-19 pandemic has raised concerns about the risk of infection in the general population and vulnerable patients such as those with MS. High-dose pulse steroid therapy and disease-modifying treatments (DMTs) modify the immune response, and concerns have been raised about the effects of these treatments may have on COVID-19 outcomes.

MS and COVID-19 share immune system dysfunction, characterized by the inappropriate activity of major immune cells, such as T lymphocytes, and their imbalance in the level of released anti- and pro-inflammatory cytokines. Therefore, it is reasonable to draw some conclusions regarding the influence of MS medications on COVID-19 using data from international registries of COVID-19 among patients with multiple sclerosis (pwMS) and known pharmacology of DMTs.

There is no single therapy that is successful in all cases of COVID-19 disease, and vaccination is the best strategy to combat the pandemic. Some DMTs may reduce the vaccine's effectiveness, although they may still give some protection against COVID-19 infection. A risk/benefit analysis should be performed before a decision is made about when to provide the vaccination and whether to defer the administration of the DMT dosage or not.

Keywords: Disease-modifying therapy, Multiple sclerosis, COVID-19 pandemic, Vaccines.

Sažetak

Naslov rada: Liječenje multiple skleroze tijekom pandemije COVID-19

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Multipla skleroza (MS) je autoimuna bolest središnjeg živčanog sustava (CNS), a trenutno liječenje usmjereno je na imunomodulatorne i imunosupresivne lijekove. Pandemija COVID-19 koja je u tijeku izazvala je zabrinutost zbog rizika od infekcije u općoj populaciji te kod ranjivih bolesnika poput onih s MS-om. Terapija visokim pulsnim dozama kortikosteroida kao i lijekovima koji modificiraju tijek bolesti (DMT) vezana je uz moguće negativne učinke koje navedeno liječenje može imati na ishode COVID-19 infekcije.

MS i COVID-19 dijele disfunkciju imunološkog sustava, koju karakterizira neprikladna aktivnost glavnih imunoloških stanica, kao što su T limfociti, te njihova neravnoteža u razini oslobođenih protuupalnih i proupalnih citokina. Stoga je razumno donijeti neke zaključke o utjecaju lijekova za MS na COVID-19 koristeći podatke međunarodnih registara osoba s MS-om oboljelih od COVID-19 te poznate farmakologije različitih DMT-a.

Ne postoji jedinstvena terapija koja je uspješna u svim slučajevima bolesti COVID-19, a cijepljenje je najbolja strategija za borbu protiv pandemije. Neki DMT-i mogu smanjiti učinkovitost cjepiva, iako i dalje mogu pružiti određenu zaštitu od infekcije COVID-19. Prije donošenja odluke o tome kada provesti cijepljenje i treba li odgoditi primjenu doze DMT-a ili ne, potrebno je provesti analizu rizika/koristi.

Ključne riječi: terapija koja modificira bolest, multipla skleroza, pandemija COVID-19, cjepiva.

Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) originated in late 2019 in Wuhan, China, and has since spread worldwide. The World Health Organization (WHO) confirmed on March 11, 2020, that COVID-19, the disease caused by SARS-CoV-2, has become a global pandemic[1].

The ongoing pandemic has raised numerous concerns about the risk of infection in the general population and vulnerable patients such as those with Multiple Sclerosis (MS), an autoimmune disease of the CNS. Because of the disease's autoimmune-mediated inflammatory nature, treatment is centered on immunomodulatory and immunosuppressive medications[3]. Current MS treatment guidelines recommend long-term DMTs for patients with varying disease phenotypes and additional short-term steroids for flare-ups[4]. Due to the fact that both high-dose pulse steroid therapy and DMTs modify the immune response, specific concerns have been raised about the effects of DMTs or high-dose steroid therapy on COVID-19 outcomes[5].

Moreover, the COVID-19 pandemic has placed a significant burden on healthcare systems, medical resources, and emergency services[95]. The strain on primary care was particularly great, and treating MS required a reframing of the way patients are cared for. In addition, vaccination was also an issue in patients with MS (pwMS) due to its possible effect on the immune system. Furthermore, fears related to COVID-19 had led to concerns that resulted in a shift in the neurologists' mindset regarding the prescription of DMTs[169]. As a result, they had to consider the risk of severe COVID-19, as well as the possibility of impairment from MS under-treatment. An additional challenge was the recommendation of a vaccination strategy based on the patient's treatment plan.

Apart from the issues mentioned above, the current pandemic has highlighted a slew of other issues; (i) Do DMTs affect the clinical course of COVID-19 and/or should they be discontinued; (ii) Do MS treatments affect vaccination efficacy; (iii) Does COVID-19 vaccination worsen MS; (iv) How will pwMS and newly diagnosed individuals be managed throughout the pandemic[2]?

The following graduate thesis aims to evaluate the pertinent issues in the course and management of MS during the COVID-19 pandemic.

Literature review

1 Multiple sclerosis - phenotype and diagnosis

MS is characterized as a chronic inflammatory disease of the CNS that causes sclerotic lesions in the brain, which progressively result in motor and sensory impairments[6]. MS develops in young adults and affects around 2.8 million individuals worldwide[7]. It is the most prevalent demyelinating disease in high-income countries, but it varies globally. MS has the highest prevalence in North America (140 per 100,000 inhabitants) and Europe (108 per 100,000) and the lowest in East Asia (2.2 per 100,000 inhabitants) and sub-Saharan Africa (2.1 per 100,000 inhabitants)[7]. In Croatia, the MS prevalence is 143.8 per 100,000 inhabitants[8].

The etiology of MS is not entirely known; nevertheless, environmental, genetic, and epigenetic variables all contribute to the pathogenesis of MS and may interact with modifiable risk factors[9]. Nowadays, there is a more excellent knowledge of the risk factors that contribute to the disease's development, including genetic (e.g., HLA DRB1), environmental (e.g., vitamin D, Epstein Barr-Virus (EBV) particularly during adolescence), and lifestyle (e.g., smoking, sunshine -UVB) variables[9]. Lastly, the disease is caused by dysregulation of the immune system, namely the microglia, activated macrophages, and B and T lymphocytes[3,10].

EBV has been strongly linked to MS, yet there is a substantial quantity of contradictory data[11]. Higher titers of EBV antibodies have been linked to an increased risk of MS development[12], and pwMS have been shown to have an overall altered immune response to EBV in their peripheral blood and CNS. These are some of the pieces of evidence supporting EBV involvement in MS. Other evidence includes a correlation with infectious mononucleosis (an acute EBV infection) and an almost universal history of EBV infection among MS patients[13]. There have been several suggestions put forth to explain how EBV can be involved in MS, including (i) Molecular mimicry; (ii) Mistaken self; (iii) Bystander damage and (iv) Autoreactive B cells infected with EBV. However, MS development may result from a failure of viral clearance in general if EBV is not the predominant causative agent but is instead one of the numerous viruses or infectious agents capable of evoking a comparable altered immune response[11].

MS is classified clinically as relapsing-remitting, primary progressive, or secondary progressive. In around 80% of MS patients, a clinically isolated syndrome (CIS) is the first presentation (Table 1)[15]. CIS is a clinical term that refers to an acute clinical event that affects one or more CNS regions and can progress to

relapsing-remitting MS (RRMS)[14]. Depending on the area of the eloquent lesion, CIS may be uni- or multi symptomatic. Optic neuritis (vision problems, such as double vision), brainstem (dizziness, difficulty with walking and coordination and spasticity or stiffness of the muscles) and spinal cord syndromes (partial myelitis - numbness or tingling) are the most prevalent presentations; nevertheless, there are various additional less common presentations, including cortical presentations such as dominant parietal lobe syndromes[17]. At 20 years, the conversion rate from CIS to RRMS is 21% in patients with a normal baseline MRI scan versus 82% in those with one or more clinically silent white matter lesions on MRI[16,17]. The majority of MS patients have recurring acute/subacute focal neurological impairments in various parts of the CNS. This most prevalent phenotype of MS is referred to as RRMS. Around 35–50% of patients with RRMS undergo a progressive neurological impairment unrelated to previous inflammatory episodes referred to as the secondary progressive phase (SPMS). Without apparent clinical relapses, around 15% of MS patients have a steady, progressive deterioration from the start, a condition known as primary progressive (PPMS). The classifications are based on the clinical course of the disease and do not include information on the disease's underlying pathophysiology. Although the severity of the disease varies, data from relevant studies evaluating the normal course of MS clearly demonstrate that neurological damage increases within 10–20 years in the majority of untreated patients[18,19].

Table 1. Clinical syndromes typical and atypical for MS–related demyelination. According to: Solomon AJ, et al. Neurology (2019); (23).

Typical for MS	***Atypical for MS***
Unilateral optic neuritis, mild and with partial/full recovery	Bilateral optic neuritis; severe optic neuritis; poor recovery from optic neuritis
Diplopia due to internuclear ophthalmoplegia	Headache, with/without diplopia, or visual obscuration
Facial sensory loss or trigeminal neuralgia in young patient	Acute/subacute cognitive impairment
Cerebellar syndromes that include ataxia and nystagmus	Dizziness/vertigo without brainstem or cerebellar findings
Sensory impairment or motor weakness localizing to the spinal cord, with partial/full recovery	Sensory loss in extremities without a clear CNS pattern
	Complete transverse myelopathy

The simultaneous inflammation in different regions of the CNS is called dissemination in space (DIS). Dissemination in time (DIT) describes the recurrent inflammation of the CNS. Both criteria (Table 2) must be fulfilled to diagnose MS either in terms of clinical disease progression or pathological changes (perivascular infiltrates of mononuclear cells, demyelination, axonal loss, and gliosis with the formation of multiple plaques in the brain and spinal cord) on magnetic resonance imaging (MRI)[20]. MS is diagnosed using a combination of clinical, laboratory, and MRI evidence, in accordance with the McDonald criteria[21]. Diagnostic criteria have evolved in tandem with technological advancements, and definitions have been modified to make them more accessible and applicable to a broader proportion of the population while preserving sensitivity and specificity[21]. In 2017, the McDonald criteria (Table 3) were revised to incorporate evidence-based improvements and to reinstate the significance of cerebrospinal fluid (CSF) oligoclonal bands[22]. As a result, MS may now be diagnosed more frequently during the early clinical presentation as compared to the 2010 McDonald criteria[23]. The differential diagnosis in other cases depends on the clinical presentation and is outlined in Table 4.

Table 2. 2017 McDonald criteria for demonstration of DIS and DIT by MRI in a patient with a CIS. According to: Thompson AJ, et al. Lancet Neurol (2018); (22).

DIS can be demonstrated by one or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in 2 of the 4 areas of the CNS: periventricular, † cortical or juxtacortical, and infratentorial brain regions, and the spinal cord
DIT can be demonstrated by the simultaneous presence of *gadolinium-enhancing* and *non-enhancing lesions** at any time Or By a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. †For some patients: e.g., individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.

Table 3. The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset. According to: Thompson AJ, et al. Lancet Neurol (2018); (22).

Clinical presentation	***Additional criteria to make MS diagnosis***
Patients who have experienced a typical attack/CIS at onset.	
• 2 or more attacks and clinical evidence of 2 or more lesions. OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in a different location	None. DIS and DIT have been met.
• 2 or more attacks and clinical evidence of 1 lesion	***DIS*** *showed by one of these criteria:* • Additional clinical attack implicating different CNS site • 1 or more MS-typical T2 lesions in 2 or more areas of CNS (periventricular, cortical, juxtacortical, infratentorial or spinal cord)
• 1 attack and clinical evidence of 2 or more lesions	***DIT*** *showed by one of these criteria*: • Additional clinical attack • Simultaneous presence of both enhancing and non-enhancing MS typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) • CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	***DIS*** *showed by one of these criteria:* • Additional attack implicating different CNS site • 1 or more MS-typical T2 lesions in 2 or more areas of CNS (periventricular, cortical, juxtacortical, infratentorial or spinal cord) ***AND*** ***DIT*** *showed by one of these criteria:* • Additional clinical attack • Simultaneous presence of both enhancing and non-enhancing MS typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) • CSF oligoclonal bands

Table 3. *Continuation.*

Clinical presentation	***Additional criteria to make MS diagnosis***
Patients who have a steady progression of disease since onset (primary progressive multiple sclerosis)	
• 1 year of disease progression (retrospective or prospective)	***DIS*** *shown by* ***at least 2*** *of these criteria:* • 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) • 2 or more T2 spinal cord lesions • CSF oligoclonal bands

Abbreviation: CNS= central nervous system; CSF= cerebrospinal fluid; DIS= dissemination in space; DIT= dissemination in time; MRI= magnetic resonance imaging; MS= multiple sclerosis; T2 lesion = hyperintense lesion on T2-weighted MRI.

Table 4. Differential diagnosis of multiple sclerosis. According to: Dobson R, et al. Eur J Neurol (2019); (15).

Autoimmune/inflammatory conditions
• Neuromyelitis optica spectrum disorder (NMOSD) • Acute disseminated encephalomyelitis (ADEM) • Sjogren's Syndrome • CNS lupus • Sarcoidosis • Neuro-Behçet's syndrome • CNS vasculitis
CNS infections
• Neuro-syphilis • Lyme disease • Human T lymphotropic virus (HTLV) • AIDS
Metabolic conditions
• Vitamin B12 deficiency • Copper deficiency • Mitochondrial disease • Leukodystrophies

Table 4. Continuation.

Vascular conditions
• Small vessel disease • Stroke • Susac's syndrome • CADASIL • Antiphospholipid antibody syndrome (APLAS)

1.1 Immunopathogenesis of multiple sclerosis

Immunopathogenesis, on a functional level, refers to the immune system's reaction throughout the disease's development. Despite debate regarding the immune system's particular function, the major hallmarks include an immunological inability to identify self from non-self, persistent CNS inflammation, and premature adaptive immunity alterations[25]. Generally, MS disease begins with a breakdown of peripheral T cell tolerance to myelin-associated antigens, resulting in the disease's hallmark demyelination and neurodegeneration[25,26]. Numerous ideas, however, have been suggested about the immunopathological processes that occur in MS. For example, it was stated that immune cells penetrate the CNS, destroying the myelin sheath and causing inflammatory damage. In contrast, additional studies suggest that primary CNS problems may result in inflammation and neuronal injury[27]. To begin with, because of their key involvement in inflammatory responses, humoral immunity components, glial cell function, and oxidative stress are the most critical aspects in the immunopathogenesis of MS. Biomarkers such as stimulatory molecules, inflammatory cytokine receptors, and microRNA changes may increase the activity of Th2 cells relative to Th1/Th17 cells, hence impairing regulatory T cell function and raising the likelihood of developing autoimmune disorders[28,29]. On the other side, the inefficiency of T-regulatory cells restricts B cells' peripheral tolerance and promotes the development of self-reactive B cell clones, which eventually results in myelin sheath destruction by reactive Th1/Th17 cells. Subsequently, these interactions may result in a breakdown of the blood-brain barrier (BBB) and its associated adverse effects (e.g., disruption and nerve damage)[30,31]. Furthermore, increased secretion of tumor necrosis factor-alpha (TNF- α), lymphotoxin, and interleukin (IL)-6, as well as decreased production of regulating cytokines, including IL-10 and IL-35, can all influence complement activation and T cell activity[32]. Other important pro-inflammatory substances are TGF-β and IL-21, which promote IL-23R production in Th cells[33,34].

1.1.1 Role of B cells and antibodies in multiple sclerosis

Despite the widespread belief that T cells are the primary contributors to inflammatory demyelination in MS, growing data reveals that B cells play a key role in disease pathogenesis. B-cell mediated CNS damage in MS is believed to be caused by both antibody-dependent and antibody-independent processes[35]. B-cell roles associated with the pathogenesis include (i) antibody secretion by plasmablasts and plasma cells; (ii) antigen presentation and the stimulation of brain-homing T cell auto-proliferation (perhaps by memory B cells); (iii) synthesis of pro-inflammatory cytokines and chemokines that propagate inflammation; (iv) generation of solubilized toxic substances leading to oligodendrocyte and neuronal damage; (v) contribution to the establishment of ectopic lymphoid aggregates in the meninges; and (vi) providing a reservoir for EBV infection[36]. Clinical trials demonstrating that anti-CD20 monoclonal antibodies are particularly effective in preventing new relapse disease activity highlight the significance of B cells in MS[37,38]. MS patients' peripheral B cells demonstrate abnormal pro-inflammatory cytokine responses, including increased lymphotoxin-α, TNF- α, IL-6 and granulocyte macrophage-colony stimulating factor (GM-CSF) production. When B cells are depleted, the pro-inflammatory responses of CD4+ and CD8+ T cells and myeloid cells are dramatically dampened as a consequence[32,39]. Anti-inflammatory cytokines like IL-10, IL-35 and transforming growth factor- $\beta 1$ (TGF) are also produced by B cells, which can combat inflammation in the body[35]. Data on MS patients reveal that their B cells produce less IL-10 than healthy controls, which may suggest that MS patients' B cells are less capable of downregulating immunological responses[40].

2 COVID-19 pandemic definition and clinical features

SARS-CoV-2, a novel RNA virus, belongs to the Coronaviridae family and causes COVID-19[30]. As the successor of the 2002–2004 SARS outbreak (SARS-CoV-1) and the Middle East respiratory disease (MERS) (since 2012), SARS-CoV2 shares 50–79% of its genomic sequence with the aforementioned coronaviruses[31,32].

CoVs have a diameter of around 65–125 nm and contain single strands of RNA[41]. CoV is distinguished by the club-shaped spike projections protruding from the virion's surface. These spikes are characteristic of the virion and give it the appearance of a solar corona, thus the name CoVs[41]. In terms of its structure, the SARS-CoV-2 virus includes four primary structural proteins, namely the spike (S) glycoprotein, the small envelope (E) glycoprotein, the membrane (M) glycoprotein, and the nucleocapsid (N) protein, in addition to a number of ancillary proteins[42]. On the surface of envelope viruses, a transmembrane protein known as

the "spike" (S) glycoprotein forms homo trimers, which enhances the attachment of envelope viruses to host cells by binding to angiotensin-converting enzyme 2 (ACE2)[42]. The CoV structural component that is structurally attached to the virus' nucleic acid material is the nucleocapsid known as N protein, which is found in the endoplasmic reticulum-Golgi compartment. As a result of its association with RNA, the protein is engaged in processes involving the viral genome, the viral replication cycle, and the biological response of host cells to viral infections[43]. An additional component of this virus is its membrane or M protein, the most structurally organized protein, which helps shape the viral envelope. This protein is capable of binding with all structural proteins. Assembling viral particles is facilitated by M protein binding to the nucleocapsids or N proteins, which helps to stabilize the N protein-RNA complex, inside the internal virion[44]. Lastly, the envelope or E protein is the smallest component of the SARS-CoV structure, which plays a function in the development and maturation of this virus[43] (Figure 1). SARS-CoV-2 binds to the ACE2 receptor, which is abundantly expressed in the lower respiratory tract, upper esophagus, absorptive enterocytes from the ileum and colon, cardiac cells, kidney proximal tubule cells and bladder urothelial cells[44].

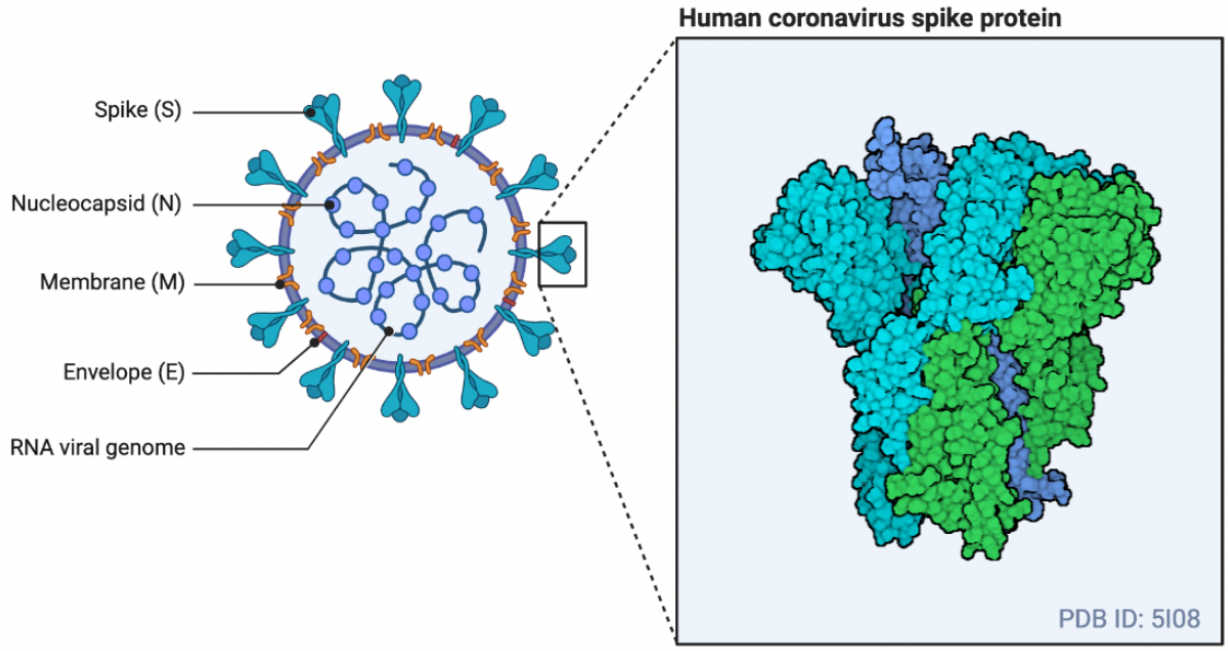

Figure 1. SARS-Cov-2 structure. According to: Astuti I, et al. (2020); (41). Created in BioRender.com

SARS-CoV2 is a member of the Nidovirus family, which means it may be transmitted to humans and animals alike. Based on genome sequencing, the receptor-binding domain of SARS-CoV-2 appears to be a modified form of its most closely related virus, RaTG13, isolated from bats (Rhinolophus affinis)[46]. Therefore, it is thought that the SARS-CoV-2 likewise started in bats and, after undergoing mutation, was able to infect other mammals[46].

Attachment of the S glycoprotein to the receptor ACE2 in a host cell (such as in type II pneumocytes) initiates the process of CoV entry into the host cell[45]. A subsequent fusion of the viral membrane with the host cell's membrane follows the viral entrance and binding activities[46]. After fusing, the host cell's TMPRSS2 (type II transmembrane serine protease) will remove the ACE2 and activate the receptor-attached spike-like S proteins[45]. Activation of the S proteins induces conformational changes that facilitate viral entry into cells. This virus's genetic material is mRNA that is ready to be translated into protein. This virus's genome has around 14 open reading frames (ORF), each of which encodes structural and non-structural proteins that contribute to its survival and pathogenicity[46]. In the next step, the sub-genomic proteins are translated into structural and accessory proteins such as M, S, and E proteins, which are then insulated in the endoplasmic reticulum and transported to the ER-Golgi intermediate compartment (ERGIC), meanwhile, the already duplicated genome program may immediately link the N protein to the nucleocapsid form and travel into the ERGIC. There, nucleocapsids and other structural proteins will combine to create wallet vesicles that can be exported from the cell by exocytosis[45,46]. (Figure 2)

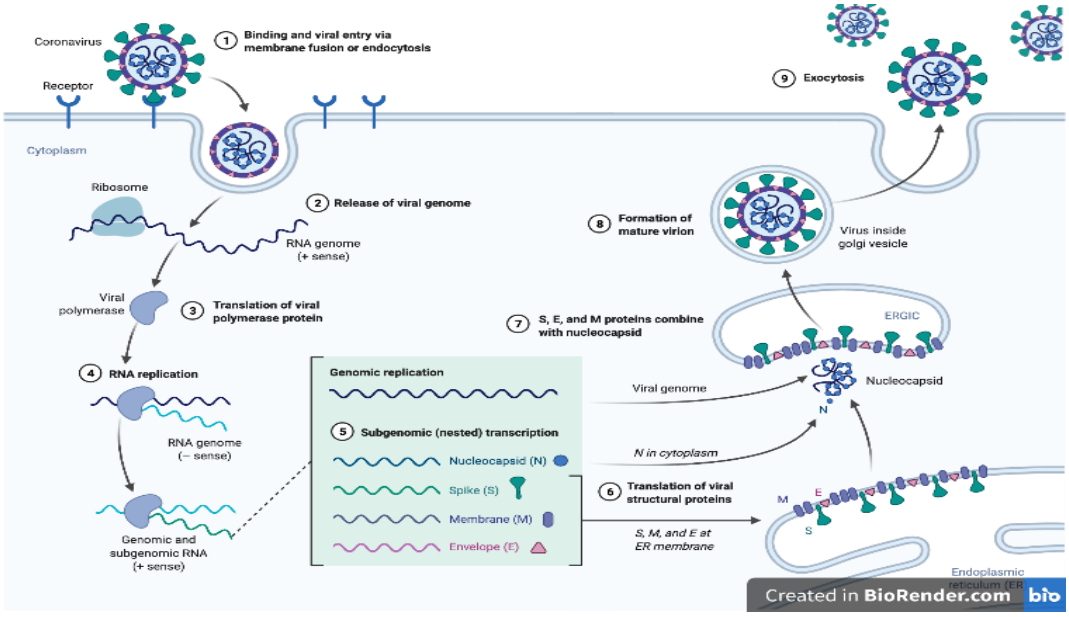

Figure 2. Viral entrance to CNS. According to: Lima M, et al. (2020); (58). Created in Biorender.com

SARS-CoV-2 is most frequently transmitted via two routes (i) direct exposure via cough, sneeze, and droplet inhalation within a range of roughly 2 meters (i.e., in small, crowded/poorly ventilated areas and during aerosol-generating processes); and (ii) contact transmission via contact with oral, nasal, and ocular mucous membranes (i.e., contaminated objects/surfaces)[47]. Although live viral testing is possible up to 61 days after the beginning of symptoms, virus shedding is expected to occur during the first eight days (particularly the first three days) and is most usually transmitted via the upper respiratory tract (URT)[48]. COVID-19 infection can present as either an asymptomatic or symptomatic disease. The most prevalent symptoms reported by individuals with symptoms were fever, sore throat, and fatigue/myalgia[49]. There were a few less frequent symptoms that were recorded as well, including congestion and rhinorrhea[50]. Diagnosis of a severe type of COVID-19 is based on symptoms such as shortness of breath, respiratory rate (RR) of more than 30 cycles per minute, and oxygen saturation below 93% at rest[51]. Acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulopathy were all more common in individuals with a serious form of COVID-19 disease than in those who weren't[51]. Other organ damages and even multiple organ failures were more common in patients with severe disease. Therefore, severe COVID-19 must be accurately predicted and diagnosed as soon as feasible[51,52].

The most often documented risk factors for a severe disease course and mortality include advanced age, cigarette smoking, and preexisting conditions (e.g., diabetes mellitus, heart disease, hypertension, chronic lung disease, and cancer). The most frequently found laboratory abnormalities include a decreased lymphocyte count, increased C-reactive protein level, and an increased lactate dehydrogenase level[52]. To confirm the diagnosis of COVID-19, serology testing for IgM and IgG, nucleic acid assays, and gene sequencing were all employed. Furthermore, computed tomography (CT) imaging is widely used to detect it; however, a chest CT scan may not be able to distinguish this disease from other viral causes of pneumonia[53,54]. (Figure 3)

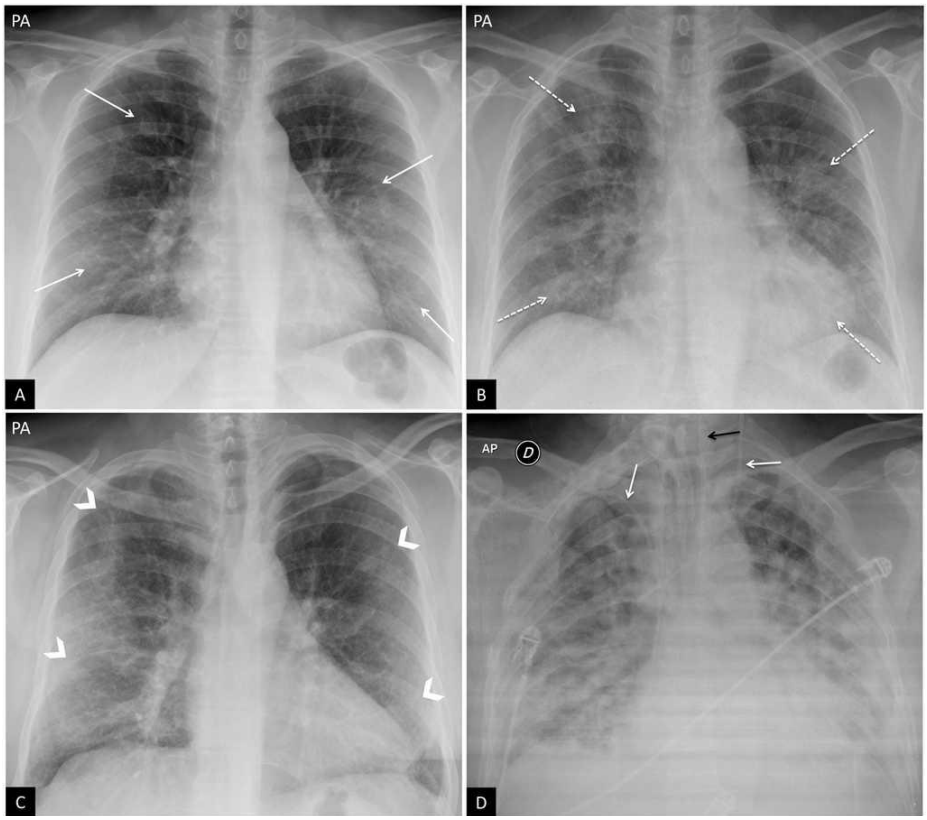

Figure 3. COVID-19 pneumonia is known for its typical findings. (A) Covid-19 is suspected in a 47-year-old female patient with signs and symptoms consistent with COVID-19. the preponderance in the reticular interstitial pattern (arrows). (B) Same patient from image A after three days later. SARS-CoV-2 was detected by PCR. The X-ray reveals small, spherical, bilateral peripheral alveolar opacities (dotted arrows). (C) SARS-CoV-2 positive PCR in a 57-year-old man with dyspnea. In the upper, middle, and lower fields, there are bilateral opacities (arrow tips). (D) Dyspnea and COVID-19 were found in a 45-year-old man by PCR in this case. Multiple bilateral diffuse confluent regions of consolidation are shown on the anteroposterior chest X-ray, with both lungs heavily affected. As you can see, the patient has two central lines, one left jugular and the other in her right subclavian (white arrows) and a gastrointestinal tube (black arrow). According to: Martinez Chamorro E, et al. (2021); 63:56-73 ;(56).

International efforts have been made to mitigate social viral transmission by implementing "physical distancing" strategies such as keeping at least two meters away from other people, avoiding group gatherings, considering delivery services, wearing a cloth face cover to protect the mouth and nose when around others or out in public, working from home whenever possible, avoiding public transportation, and

implementing digital/distance learning. "Quarantine" has been used to isolate someone who may have been exposed to COVID-19 from others, whereas "isolation" has been used to segregate ill persons from healthy people. These activities influenced the profile of viral transmission in nations that followed the "Centers for Disease Control and Prevention" guidelines[55].

Neurological symptoms associated with acute COVID-19 infection include dysgeusia and anosmia/hyposmia, headaches, stroke, delirium, and inflammation of the brain. Although the virus does not appear to induce widespread infection of brain cells, it is possible that immunological activation, neuroinflammation, and damage to brain blood vessels are the root causes of the neurological symptoms. Long-term consequences of acute COVID-19 infection have been labeled "Long Covid" and include a wide range of symptoms in the brain and nervous system, from loss of taste and smell to reduced concentration and memory, cough, shortness of breath, inability to exercise to prior levels, feeling unwell for a day or two after exercising (post-exertional malaise), and soreness in muscles, joints, and the chest, pain syndrome, sleep difficulties, nerve injury headache to psychiatric effects such as depression and psychosis. It's still unclear how the illness causes these lingering symptoms or why it affects some people but not others[57].

2.1 Immunopathogenesis of COVID-19

Host immune responses to COVID-19 have a significant role in the pathophysiology of the disease and its clinical symptoms. Like the inflammasome sensor NLRP3, pattern recognition receptors routinely identify viruses after infection and induce a local/systemic response to infection by releasing interferons (IFNs) and pro-inflammatory cytokines (e.g., TNF, IL-6, IL-1)[3]. This process involves the recruitment, activation, and differentiation of innate and adaptive immune cells, including inflammatory myeloid cells, $CD8^+$ T lymphocytes, neutrophils, and natural killer (NK) cells. Cytotoxic activity of $CD8^+$ T and NK cells is critical for infection resolution because it permits virus-infected cells to be eliminated. The inability to eliminate virus-infected cells may result in a hyperinflammatory condition known as macrophage activation syndrome (MAS) or "cytokine storm," which can cause lung damage (Figure 4)[3,59]. A detailed assessment of gene expression data from COVID-19 patients' blood, lungs, and airways showed that populations of myeloid-lineage cells power COVID-19 pathogenesis in each compartment with highly inflammatory states. Furthermore, the absence of cytotoxic cells in the lungs suggests a scenario in which the virus's delayed clearance increases myeloid cell activation to disease pathogenesis via the production of inflammatory mediators. Additionally, gene expression profiles might be used to identify potential therapeutic targets in order to alter therapy recommendations[60,61].

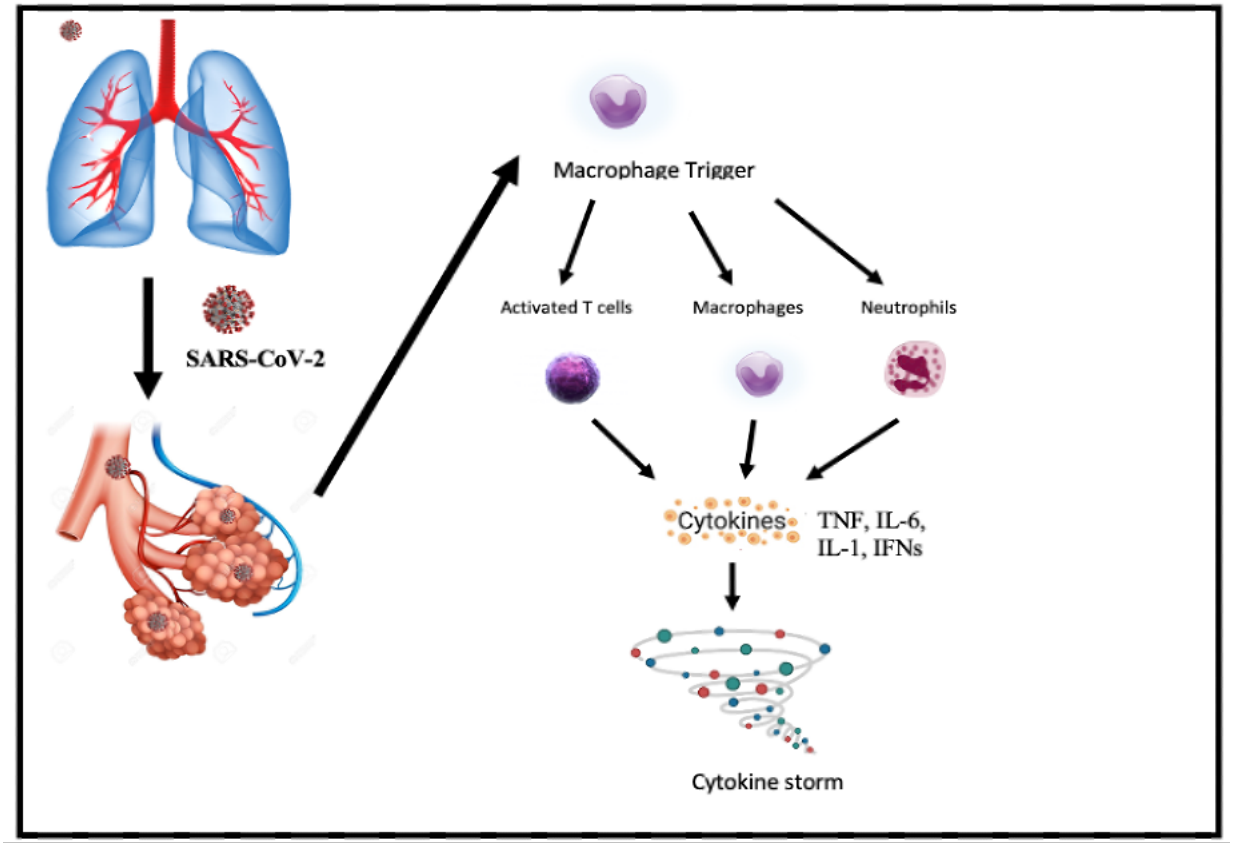

Figure 4. The immunopathogenesis of COVID-19. SARS-CoV-2 disrupts normal immune response leading to uncontrolled inflammatory response (cytokine storm). According to: Azimzadeh M, et al. Biomolecules (2021); (3).

The ACE2 receptor (a critical adsorption component during SARS-CoV-2 infection) is expressed in brain, lungs, kidney, bladder, heart, esophagus, ileum and colon cells. However, its degree of expression and distribution across brain regions appear to be restricted. There is mounting evidence that the viruses' direct impact may induce neurological issues alongside systemic inflammation and thrombosis/emboli. Dizziness and headache are the most prevalent neurological symptoms connected to COVID-19. However, neurological involvement tends to worsen in moderate and severe cases. Mutant viruses that spread swiftly dominate infectious diseases like COVID-19, which often involve a high percentage of asymptomatic individuals. The possibility of increased neurotoxicity due to the mutation cannot be ruled out; hence further scientific and clinical research is necessary[62,63].

B cells may be the key in the battle against the SARS-CoV-2 virus. A better understanding of B cells' defensive responses during infection might assist in developing therapeutic interventions. There are, however, some SARS-CoV2 clearance mechanisms that are not dependent on B cells, such as the activation of $CD8^+$ T cells or NK cells. Thus, a successful recovery from COVID-19 may not require the production of anti-SARS-CoV-2 antibodies[61,62]. SARS-CoV-2 impairs normal immune responses and results in a weakened immune system with an uncontrolled inflammatory response in severe cases of COVID-19. These patients have lymphocyte dysfunction, lymphopenia, granulocyte and monocyte abnormalities increased cytokine production, and elevated total antibodies count[3].

2.1.1 Lymphocyte dysfunction, lymphopenia

COVID-19 is characterized by lymphopenia, particularly in its severe manifestations. Lymphopenic patients are more prone to microbial infections, which can exacerbate disease progression/severity. For individuals with COVID-19, increasing data suggest that lymphopenia can be used as an indicator of disease severity and prognosis[46,65,66,67]. A decrease in T, B, and NK cells numbers were documented in this respect. Additionally, exhaustion and T-cell dysfunction are two more signs that may indicate severe COVID-19[68]. As a result, various pathways may be involved in the depletion and malfunctioning of lymphocytes:

- ACE2 receptors on lymphocytes, particularly T cells, may facilitate the entrance of SARS-CoV-2 into these cells[69,70].
- Increased cytokine levels (such as IL-6, IL-10, and TNF) may lead to T cell decrease and fatigue[71].
- SARS-CoV-2 has been shown to be capable of destroying lymphatic organs (e.g., spleen and lymph nodes)[72].
- Lactic acidemia, present in severe COVID-19, has been shown to impede lymphocyte proliferation[65,67].

2.1.2 Abnormalities of monocytes & granulocytes

In severe COVID-19 patients, the neutrophil/lymphocyte ratio is much greater. As such, it may be used as a critical indication of an unfavorable COVID-19 disease course. Additionally, the percentages of eosinophils, basophils, and monocytes are decreased during the severe phase of the disease. The most plausible explanation for the increased neutrophil count in COVID-19 is associated with lymphopenia, which predisposes to infection[73,74,75].

2.1.3 Increased production of cytokines

Another distinguishing feature of severe COVID-19 is the increased production of pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, GM-CSF, granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein 1 (MCP1), interferon-inducible protein-10 (IP10), macrophage inflammation protein-1a, IFN-γ and TNF-α[73,74,76]. This rapid rise in cytokine levels over a short period of time is referred to as a "cytokine storm"[64], with IL-1, IL-6, and IL-10 being the most significantly raised cytokines in severe instances[77,78]. The pertinent mechanisms are as follows:

- GM-CSF released by pathogenic T helper-1 cells after SARS-CoV-2 infection stimulates $CD14^+$ $CD16^+$ cells, resulting in increased inflammation (mostly the generation of IL-6)[79].
- Patients with COVID-19 have an increased subpopulation of CD14+ cells, which may stimulate the production of IL-1[80].
- It was shown that patients with COVID-19 had a Th17 response as well. Studies have revealed that Th17 cells stimulate the cytokine cascades (e.g., IL-1 and IL-6) by releasing IL-17, which attracts additional immune cells to the infection sites[81].
- Additionally, eosinophils directly combat RNA viruses by secreting a wide variety of cytokines, one of which, IL-6, is essential for the development of a cytokine storm in COVID-19[82].

Finally, the cytokine storm may result in viral sepsis, shock, respiratory failure, inflammatory-induced lung damage, ARDS, organ failure, and, in some cases, death[44]. Additionally, blood-cytokine levels can rise in non-severe COVID-19, albeit substantially less than in severe cases[73,83,51].

2.1.4 Increased antibodies

The detection of SARS-CoV-2-specific antibodies (IgM and IgG) in conjunction with nucleic acid assays (NAAT/PCR) is used to diagnose COVID-19. Researchers Zhang and colleagues demonstrated that a higher IgG level is related to disease severity[84]. As a result, the IgG level might serve as a straightforward marker for distinguishing between severe and non-severe cases. Furthermore, a poorer prognosis in COVID-19 was linked to a greater titer of total antibodies, which rises much faster than IgM or IgG levels[85]. Therefore, B cell proliferation/activation in COVID-19 patients, particularly in severe instances, has been shown to be associated with a poor prognosis[78,86]. This might be explained by the fact that viral infection is enhanced by antibodies in a virus-dependent manner. Antibody-dependent enhancement (ADE) of virus infection is a process in which preexisting sub-neutralizing antibodies facilitate viral entrance and multiplication, as seen with the Ebola, Dengue, and MERS viruses[64].

3 Multiple sclerosis and COVID-19

MS and COVID-19 share immune system dysfunction, characterized by the inappropriate activity of major immune cells, such as T lymphocytes, and their imbalance in the level of released anti- and pro-inflammatory cytokines[64]. PwMS receiving specific immunotherapy and those with a more severe disability and/or comorbidities are more vulnerable to infection and have a greater risk of morbidity and mortality[1,87,88]. However, MS alone is not considered a risk factor for symptomatic or severe COVID-19 infection[89,90]. According to data from ongoing studies, the majority of COVID-19 cases in pwMS are mild and consistent with general population clinical findings[91,92,93,94]. However, these findings should not be generalized to all pwMS since the risk of COVID-19 and COVID-19-related complications may vary substantially based on various factors, including, but not limited to, age, race, sex, comorbidities (such as history of hypertension, chronic lung disease, obesity, diabetes, and cardiovascular disease) and the local epidemiology of COVID-19[90]. Therefore, lengthy data collection is essential for gaining further understanding regarding the progression of COVID-19 in pwMS[95]. To help prevent the spread of SARS-CoV-2 infection, clinicians should give extensive counseling and follow national and local guidelines. These measures may include regular hand washing and/or disinfection, avoiding public transportation, social distancing, and wearing face masks in public[96].

Due to the growing number of pwMS who have recovered from COVID-19, it is critical to have a better understanding of the long-term implications of acute COVID-19 (also known as post-COVID-19 syndrome). Post-acute COVID-19 has been reported to include cognitive impairment, exhaustion, anxiety, and depression, all of which are typical in multiple sclerosis[97]. It is evident that treatment for patients infected with COVID-19 goes beyond the acute infection period. The goal must be to promote early diagnosis, investigation, meticulous documentation, and management of any COVID-19 sequelae that may impose a further burden on pwMS[95].

3.1 The risk of COVID-19 in patients with multiple sclerosis

According to various studies of COVID-19 hospitalizations and death worldwide, elderly individuals and those with considerable comorbidities have a greater chance of becoming symptomatic or having a reasonably severe clinical form of COVID-19[98,99,100]. In Italy, preliminary data revealed that, of the more than 1600 deaths, 87.88% occurred among people aged 70 and above and that the case fatality rate rose with age[98]. In a meta-analysis of 1567 individuals with COVID-19, the most prevalent comorbidities were hypertension (21.1%), diabetes (9.7%), cardiovascular diseases (8.4%), and respiratory disorders (1.5%)[99]. In many pwMS, these risk factors will necessarily coexist. According to Italian research of 232 pwMS, the

five patients who died in a group of ten people with severe COVID-19 were all older (age >60 years) and had substantial comorbidities, such as diabetes and/or cardiovascular disease[94]. Data from the Multiple Sclerosis and COVID-19 (MuSC-19) cohort demonstrated that age was a risk factor for severe COVID-19 in pwMS, as well as showed that mortality was greater among individuals with progressive MS than among the general population of Italy[101]. Additionally, the MS Global Data Sharing Initiative indicated that older age, progressing MS, more significant disability, and comorbidities were related to worse outcomes[102].

4 Multiple sclerosis disease-modifying therapies and COVID-19

In MS, the vast majority of DMTs are directed towards CD4 and Th17 T cells, as well as memory (CD19+ CD27+) and naïve (CD19+ CD27-) B cells[103,104]. Assuming that such immunotherapies would not significantly impair the ability to combat SARS-CoV-2 infection, it is essential to note that several MS treatments (such as alemtuzumab or autologous hematopoietic stem cell salvage therapy) are linked with widespread and severe immunosuppression[105]. In addition, SARS-CoV-2 medications have also been shown to have minimal collateral effects on the immunological processes implicated in response to the virus (such as a decrease in CD8+ memory T cells)[106]. It is reasonable to make some conclusions regarding the influence of MS treatment on COVID-19 using data from international registries of COVID-19 among pwMS and known pharmacology of DMTs[95].

4.1 First-generation DMTs

Interferons and glatiramer acetate are considered first-generation DMTs. Interferons are immunomodulatory (not immunosuppressive) drugs. Type I interferons exhibit powerful antiviral effects in vivo (e.g., reduced viral replication), which may also contribute to their effectiveness in MS[107]. When a cell is infected with a virus, it releases viral particles that can infect nearby cells. However, the infected cell can also protect nearby cells from possible infection by releasing interferons. Following this perspective, both Interferon-alpha and Interferon-beta have been evaluated as prospective therapies for coronavirus infection[108,109]. Aside from that, glatiramer acetate lacks systemic immunosuppressive qualities and does not raise the risk of viral infections in pwMS[110]. Due to that, a decreased risk of SARS-CoV-2 infection in pwMS has been linked to Interferon and glatiramer acetate[111].

4.2 Teriflunomide

Teriflunomide selectively inhibits dihydro-orotate dehydrogenase, a critical mitochondrial enzyme in de novo pyrimidine production required by rapidly proliferating lymphocytes[110]. The production of viral

protein and replication of the viral DNA/RNA genome require host resources for viral replication. Teriflunomide inhibits viral replication by inducing a G1/S phase arrest[112]. Therefore, teriflunomide may have a potential therapeutic function in COVID-19 due to its combined antiviral and immunomodulatory effects[113]. It has not been demonstrated that teriflunomide increases the incidence of severe COVID-19 [101,102,111]. Interferons, glatiramer acetate, and teriflunomide should not be stopped or delayed in pwMS during COVID-19 pandemic[95].

4.3 Immunomodulatory drugs with possible lymphopenic effects

Dimethyl fumarate (DMF) appears to block the NRF-2 protein, reducing inflammatory pathways, including macrophage activation[114,115]. When it comes to SARS-CoV-2 infection, the fact that lymphopenia is a well-known side effect of this drug is maybe the most critical consideration. It affects CD8 T cells and memory cells, occurring in at least 37% of patients (severe <500/mm3 in 8%)[89,114,116]. However, the infection incidence in MS patients treated with DMF is only marginally elevated[110]. In addition, research has shown that treatment with DMF can reduce the severity of lung fibrosis in patients who have pulmonary arterial hypertension[117]. When used in conjunction with COVID-19, the immune-modulating effects of DMF aren't expected to cause damage and may even be advantageous. As a result, it is not suggested to cease or postpone treatment with DMF during COVID-19 periods[101,102,111].

Fingolimod is a sphingosine-1-phosphate receptor (S1PR) modulator that inhibits autoimmune responses by preventing cells from exiting lymph nodes. The process of sequestering lymphocytes, rather than encouraging direct lymphocyte depletion, lowers the overall mean circulating lymphocyte count, which is typically above 200/mm^3 [103,110,118]. Despite this, there is a possibility that it might raise the risk of moderate infections, most often viral diseases such as the flu, herpes virus and potentially even SARS-CoV-2 infection[110,119,120,121]. S1PR modulators have been demonstrated to reduce cytokine storms, which are one of the pathways that contribute to severe COVID-19 in animal models. Consequently, fingolimod is currently being researched as a possible therapy for the ARDS linked with COVID-19 [89,120,122-125,127]. Despite the fact that certain case studies indicate that fingolimod may increase the incidence of severe COVID-19[126], this conclusion was not observed in larger cohorts[101,102,111]. Fingolimod medication should not be postponed during the COVID-19 period. Likewise, discontinuing fingolimod therapy should be avoided because of the risk of substantial rebound disease activity and worsening disability[110].

As a result, the danger of SARS-CoV-2 should be weighed against the possibility of MS relapse when S1P modulator medication is discontinued[103]. The presence of lymphopenia in individuals with COVID-19 has

been linked to worse outcomes[128]. For MS patients with significant lymphopenia due to DMF or fingolimod, it is advised to take special precautions to reduce the risk of SARS-CoV-2 infection[95].

4.4 Natalizumab

Natalizumab is a humanized monoclonal antibody that is directed against α4-integrin. Its mechanism of action involves inhibiting the migration of lymphocytes to the CNS[116]. Natalizumab inhibits lymphocyte migration across the blood-brain barrier without causing lymphopenia or systemic immunosuppression[110]. Natalizumab has been linked to a slightly greater risk of URT infections[129,130], although it is uncertain if this is relevant in regard to SARS-CoV-2 infection. Patients should be cautioned that discontinuing or postponing therapy with natalizumab for more than eight weeks carries the risk of rebound (e.g., a significant increase in relapse risk)[110]. Natalizumab does not raise the risk of severe COVID-19; therefore, discontinuing or postponing natalizumab medication during COVID-19 periods is not advised[101,102,111]. It is suggested that natalizumab should be administered at longer intervals (every 5–6 weeks) to allow patients to make fewer hospital visits and decrease their exposure risk as much as feasible[95,116].

4.5 Anti-CD20 monoclonal antibodies

Anti-CD20 monoclonal antibodies rituximab, ocrelizumab, and ofatumumab reduce B – lymphocytes via antibody-dependent cytotoxicity, antibody-dependent cell-mediated phagocytosis, complement-dependent cytotoxicity, and direct apoptosis, which effectively minimize MS relapses[105,110]. As a result, there is a 25 percent decrease in the total number of lymphocytes and a prolonged B lymphopenia due to their actions[116]. Long-term therapy and memory cell pool reduction both foretell an increased risk of hypogammaglobulinemia and thus, an increased risk of infection in comparison to other DMTs[101,103,131]. Anti-CD20 treatments have been linked to a higher incidence of SARS-CoV-2 infection in pwMS[89,111]. Therefore, several cases of COVID-19 in patients treated with anti-CD20 drugs have been documented and reported. Data from the MuSC-19 Italian cohort (n = 844 pwMS) demonstrated that pwMS who were treated with anti-CD20 drugs (ocrelizumab or rituximab) were more likely to develop a severe COVID-19 course than those treated with other DMTs[101]. New reports from the COVID-19 in MS Global Data Sharing Initiative and an extensive North American cohort with pwMS demonstrate that anti-CD20 agents are linked with poorer COVID-19 outcomes[102,132]. Although anti-CD20 monoclonal antibodies can be administered to pwMS with highly active or severe disease, in the era of COVID-19, an alternative highly effective DMT with a more favorable COVID-19 outcome profile may be considered[95]. Maintaining effectiveness while reducing the risk of infection and accompanying morbidity can be achieved by reducing the frequency of dosage or by tailoring it to the monitoring of B-cell repopulation kinetics in individual

patients[101]. People who are considered to have a high risk of severe COVID-19 disease may benefit from preventative treatment with neutralizing antibodies such as bamlanivimab/etesevimab or casirivimab/imdevimab[133]. However, it is not yet known if these neutralizing antibodies may reduce the likelihood of poor outcomes in pwMS who were treated with anti-CD20 either before or after they were exposed to SARS-CoV-2[95].

4.6 Immune reconstitution therapies

Immune reconstitution therapy (IRT) is a novel approach to the treatment of MS[134,135]. The purpose of IRTs is to eradicate a pathogenic immune repertoire through a short-term period of acute immunosuppression and then rebuild a new and healthy immune system with the goal of re-establishing durable immunological tolerance[136]. It is administered on an intermittent basis and has been shown to elicit long-term remission of MS that is maintained over subsequent treatment-free periods. Immune depletion does not correlate with clinical or radiological response, but the immune system experiences profound alterations in the lymphocyte repertoire and regains its ability to respond to infections when it is re-established[134,137,138]. Autologous hematopoietic stem cell transplantation (AHSCT), alemtuzumab, and cladribine tablets are all examples of IRT[134]. IRTs may put some pwMS at risk for a variety of infections[110]. Nevertheless, it is critical to distinguish between the depletion phase and the immunological reconstitution phase[95]. There is an increased risk of infection and infection-related consequences due to lymphopenia occurring during the depletion period. However, this risk is probably no more than that predicted for the general population[110].

4.6.1 Cladribine

Cladribine is a purine analog that inhibits DNA synthesis and repair, resulting in considerable myelosuppression through cell apoptosis in lymphocytes (mostly CD8+ and CD4+ T cells, but also B cells), without significantly affecting innate immune cells such as neutrophils, monocytes, and NK cells throughout the depletion period[103,110,118]. As a result, transient lymphopenia (typically mild to moderate) usually develops in the first six months[118]. This lymphopenia can have an elevated risk of infection following each treatment session[95,118]. However, existing data indicate that there is no greater risk of severe COVID-19 in pwMS who are treated with cladribine[101,139-141]. In patients with highly active disease and those for whom first-line DMTs have failed, treatment with cladribine is an option that can be explored during the COVID-19 periods[95]. According to Huang and Pranata's research from 2020, persons diagnosed with COVID-19 who have lymphopenia have a higher risk of experiencing poor outcomes[128]. As a result, it is recommended for pwMS who have severe lymphopenia following cladribine treatment to exercise caution regarding hygiene and social distance and refrain from engaging in high-risk travel[118].

4.6.2 Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a surface receptor on mature lymphocytes. It induces broad lymphopenia, especially of the major circulating T cells (CD3+, CD4+, and CD8+), analogous to an immunological reset, followed by immune reconstitution[110,116]. Typically, it induces durable disease remission after two or three treatment cycles, eliminating the need for long-term therapy. The innate immune system is also targeted (through activation of pro-apoptotic pathways on macrophages and dendritic cells) by CD52, which necessitates periodic follow-up[142]. The possible adverse effects are often at their peak during the initial six months following an infusion, when the risk of lymphopenia is highest[103]. As a result of the absence of both early and late immune responses, patients receiving alemtuzumab may be more susceptible to SARS-CoV-2 infection and re-infection[116]. Alemtuzumab has the potential to be an effective treatment for a broad range of pwMS, especially for patients with a very active form of the disease. However, there has been a link established between the use of alemtuzumab and an increased risk of infectious events, particularly opportunistic infections[110]. Although alemtuzumab may not result in a severe COVID-19 course[101,102,143,144], the number of pwMS treated with alemtuzumab and included in the COVID-19 series/registries has been judged insufficient to make significant conclusions[95]. During COVID-19 periods, DMTs with a better-established profile in terms of COVID-19 results may be utilized, as could temporarily postponing (between 6 and 12 months) alemtuzumab re-dosing depending on the local COVID-19 epidemiology[95,116].

4.6.3 Autologous hematopoietic stem cell transplantation

In recent years, AHSCT has been examined as a potential treatment option in several meta-analyses, systematic reviews, retrospective investigations, and clinical trials[145]. According to the findings of these investigations, AHSCT provides a therapeutic alternative for the treatment of highly active/aggressive MS that is both very effective and reasonably safe[145,146]. Compared to other DMTs, AHSCT is linked with more short-term risks, and it needs strong coordination between transplant physicians and neurologists. To mitigate these dangers, after-procedure monitoring and supportive treatment are essential[146,147]. AHSCT is a bone marrow transplantation procedure that uses immune ablative drugs to remove the self-reactive immune system and re-establish a healthy immune system. In some instances, this one-time procedure can considerably reduce or even eliminate disease activity[145]. As a result of the extreme immunosuppression caused by AHSCT, certain patients are at an increased risk of developing life-threatening infections[147]. The risk profile of AHSCT during the COVID-19 pandemic cannot be well defined in the context of MS due to the lack of sufficient data[101]. However, considering what has been learned from previous infections with respiratory viruses, it has been hypothesized that those who have undergone AHSCT might acquire severe

clinical disease[148]. In addition, new findings from research conducted at several centers that included 318 patients with hematologic malignancies or associated illnesses revealed that AHSCT recipients had a greater risk of mortality from COVID-19 than the general population[149]. As a result, initiating AHSCT during COVID- 19 periods is seen as a high-risk option, and other treatments with a more favorable COVID-19 outcome profile should be evaluated for MS treatment. Mitoxantrone, a cytotoxic drug with broad immunosuppressive effects, has received a similar recommendation[95]. Outlined DMTs recommendations for pwMS during COVID-19 pandemic are outlined in Table 5.

Table 5. Main attributes of licensed MS DMTs in relation to the COVID-19 pandemic. According to: Reyes S, et al. J Neuroimmunol (2021); (95).

DMTs	Class	Safe to start treatment?	Advice regarding treatment	In the event of COVID-19?
Interferon beta	Maintenance immunomodulatory	YES	Continue	Continue
Glatiramer acetate	Maintenance immunomodulatory	YES	Continue	Continue
Teriflunomide	Maintenance immunomodulatory	YES	Continue	Continue
Dimethyl fumarate	Maintenance immunosuppressive	YES	Continue	Continue
S1P modulators (fingolimod, siponimod or ozanimod)	Maintenance immunosuppressive	YES	Continue	Continue with lymphocyte monitoring
Anti-CD20 therapies (ocrelizumab, ofatumumab, rituximab)	Maintenance immunosuppressive	Probably	Risk assessment – continue or suspend dosing/EID	Temporary suspension of dosing depending on timing
Cladribine	IRT	YES	Continue. Temporary suspension of dosing if lymphopenic	Temporary suspension of dosing depending on timing

Table 5. continuation

DMTs	Class	Safe to start treatment?	Advice regarding treatment	In the event of COVID-19?
Natalizumab	Maintenance immunosuppressive	YES	Continue, but consider EID	Continue or delay the next infusion depending on timing
Alemtuzumab	IRT	Probably	Risk assessment – continue or suspend dosing	Temporary suspension of dosing depending on timing
AHSCT	IRT	NO	Suspend dosing	Suspend dosing
Mitoxantrone	IRT	NO	Suspend dosing	Suspend dosing

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; EID = extended interval dosing; AHSCT = autologous hematopoietic stem cell transplantation; IRT = immune reconstitution therapy; S1P = sphingosine-1-phosphate.

5 COVID-19 vaccine

Several COVID-19 vaccines are in use in various nations throughout the world, and many more are undergoing clinical testing. Currently, four distinct COVID-19 types of vaccines are in use or in research, each of which functions in a distinct manner[150,154]. Types of COVID-19 vaccine are outlined in Table 6. Although several medications have been shown to lessen disease duration and fatality in COVID-19 patients, there is presently no single therapy that is successful in all cases[151]. As a result, vaccination is the best strategy to combat the pandemic[95]. The rapid development of numerous vaccinations of a new generation was made possible by the completion of the genome sequencing of SARS-CoV-2 in January 2020[152]. A single-stranded RNA virus, SARS-CoV-2, is made up of four structural proteins: spike protein (S), an envelope protein (E), membrane protein (M), and nucleocapsid protein (N)[152]. The viral particle's S protein interacts with ACE2 on the cell surface, enabling receptor-mediated endocytosis of the virus[153]. Many vaccines employ protein S as an antigen since it is essential for viral entry into the cell[152].

Table 6. Types of COVID-19 vaccines. According to: Yamout BI, et al. (2021); (150).

Vaccine Type	MOA/effect	Examples
mRNA vaccines	Have the genetic code for the coronavirus 'spike' protein made as an "mRNA" and delivered in lipid nanoparticles	• Pfizer-BioNTech (Comirnaty) • Moderna (Spikevax)
Non-replicating viral vector vaccines	Have the spike protein genes in a non-replicating viral vector (commonly from an adenovirus)	• AstraZeneca/Oxford (Vaxzevria) • Gamaleya Research Institute (Gam-COVID-Vac or Sputnik V) • Janssen/Johnson & Johnson (Ad26.COV2-S) • Serum Institute of India (Covishield)
Inactivated virus vaccines	Use an inactivated form of the whole coronavirus	• Sinovac (CoronaVac) • Sinopharm (Sinopharm CNBG) • Bharat Biotech (Covaxin)
Protein vaccines	Contains the full-length spike glycoprotein of the virus plus an adjuvant delivered on the surface of synthetic lipid nanoparticles	•Novavax (NVXCoV2373) •Serum Institute of India (Covovax)

5.1 COVID-19 Vaccines and multiple sclerosis DMTs

It is now well documented that vaccinations against a variety of pathogens are both safe and effective when administered to pwMS[150]. Multiple investigations have found no difference in vaccination responses between pwMS and healthy participants[155]. In contrast, vaccine safety and effectiveness in MS patients using DMT must be carefully assessed[156].

- In terms of vaccination efficacy, some DMTs may reduce the vaccine's effectiveness, although they may still give some protection[131,155].
- Notably, the majority of research examining the impact of DMTs on vaccination effectiveness has used serum antibodies as their primary endpoints. T-cell immunity, on the other hand, may still be able to offer protection against COVID-19 infection, even though the antibody response to the vaccination may be diminished[150].
- For some DMTs, we may explore synchronizing the time of the vaccination with the DMT dosage in order to maximize vaccine effectiveness (Table 7)[150,157].

Table 7. Timing of COVID-19 vaccine in patients treated with DMTs. According to: Yamout BI, et al. (2021); (150).

Drug		Wait Prior To Initiating Treatment	Wait After Last Dose Given	Time Window to resume therapy after 2nd dose of vaccine
Interferons Glatiramer acetate Teriflunomide Dimethyl fumarate Natalizumab		Do not delay	Do not delay	Do not delay
S1P modulators		2–4 weeks	Do not delay	Do not delay
Cladribine		2–4 weeks	3 months	2–4 weeks
Anti-CD20	ocrelizumab, rituximab	2–4 weeks	3 months	4 weeks
	ofatumumab	2–4 weeks	No data available	2–4 weeks
Alemtuzumab		4 weeks	6 months	4 weeks

- As with any medical choice, a risk/benefit analysis should be performed, taking into account factors such as current pandemic activity in the region, as well as the patient's MS status, before a decision is made about when to provide the vaccination and whether or not to defer administration of the DMT dosage. Additionally, in certain countries, vaccinations are only available for a limited length of time based on the patient's level of risk[150,158].
- If there is a greater likelihood that the patient would experience a worsening of their MS rather than contracting COVID-19, then the DMT schedule should not be adjusted, and the patient should be given the vaccination as soon as it is available to them. On the other hand, if the patient's MS is stable and there is some leeway in terms of the availability of the vaccine, it may be worthwhile to consider making the following alterations to the patient's DMT administration to increase the efficiency of the vaccination[159,163]:
    i. Interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, and natalizumab: There is no need to delay therapy in order to receive immunization for patients who are going to begin

one of these DMTs. Patients who are already receiving one of these DMTs do not require any changes to the administration of their DMT[155].

ii. Fingolimod, siponimod, ozanimod: Before initiating therapy with fingolimod, siponimod, or ozanimod, it is suggested that patients have a complete immunization 2–4 weeks in advance[160]. Patients who are already receiving therapy should continue their medication as directed, and patients will be eligible to receive vaccinations as soon as the vaccine becomes available. However, according to new findings, patients on fingolimod had a considerably reduced humoral response to COVID-19 vaccinations[161].

iii. Alemtuzumab: Those scheduled to begin treatment with alemtuzumab should have a complete immunization four weeks before their first dose. Patients already receiving alemtuzumab should think about starting the vaccination process at least six months after their most recent dose of alemtuzumab[162]. Furthermore, it is recommended that alemtuzumab treatment be restarted at least four weeks following the completion of complete immunization. To acquire complete vaccination, it is permissible to delay the second cycle of alemtuzumab for up to two months[163].

iv. Cladribine[146]: Patients scheduled to begin cladribine treatment should have a complete immunization two to four weeks before the commencement of the course. Recent studies had shown that the effectiveness of COVID-19 vaccinations in cladribine-treated patients was comparable to that of healthy controls when vaccination was commenced 4.4 months following the last dose of cladribine, even in patients with Grade III lymphopenia[161]. On the other hand, consider administering the vaccination to cladribine-taking patients whenever possible, as the timing does not impair vaccine effectiveness. Patients scheduled for their second round of treatment should be given cladribine between two and four weeks after having their complete vaccine. It is permissible to postpone the second cycle of cladribine for up to two months in order to achieve full immunization.

v. Ocrelizumab, rituximab, ofatumumab [157,161,165]: Patients scheduled to begin treatment with B cell depleting therapy are advised to get full immunization at least two to four weeks before their first dose. Recent research demonstrates that individuals using ocrelizumab had a substantially diminished response to COVID-19 and other vaccines[157,161]. Typically, treatment with rituximab will result in a nearly complete reduction of B cells. This depletion will begin two weeks after the infusion and extend for six to twelve months. Therefore, it is suggested to provide SARS-CoV-2 vaccinations for at least three months (as in the VELOCE study[157]) following the last dose of rituximab/ocrelizumab or toward the end of the cycle of

therapy in order to maximize vaccine effectiveness. Ideally, you should restart ocrelizumab or rituximab treatment at least 3–4 weeks following the last dose of the vaccination[157].

- This proposed timetable is not always achievable. Therefore, it is best to take things one step at a time and look at each individual circumstance separately[150].

6 Telemedicine in multiple sclerosis during COVID-19

In the midst of the pandemic, the majority of health care systems redirected their resources to provide immediate COVID-19 treatment and established recommendations to reduce unnecessary hospital visits[95,166]. In addition, numerous patients have avoided healthcare settings[167,168], even in regions where outpatient services have not been interrupted, out of fear of contracting the virus. For the treatment of chronic conditions such as MS, telemedicine has replaced in-person appointments through direct video-link or telephone connection[169]. According to the American Academy of Neurology[170,171], telemedicine has been established to be a valid and suitable method for evaluating several aspects of MS care. There is a wide variety of software available, and the selection may be influenced by the preferences of the local organization[166]. Before engaging in telemedicine visits, physicians need to have a solid understanding of the local privacy rules as well as the necessity of obtaining patient consent[172]. One of the biggest obstacles to utilizing telemedicine to treat MS is the limited ability to conduct a distant neurological assessment, particularly when evaluating motor strength, tone, sensation, reflexes, and optic nerve function[166]. Implementing patient-reported outcome indicators, like the Patient Determined Disease Steps (PDDS), might overcome this limitation[173]. In pwMS, the PDDS has been validated and demonstrates a strong connection with the Expanded Disability Status Scale (EDSS)[173]. Clinicians can gain more insight into a patient's physical condition by having them fill out the PDDS prior to their telehealth consultations. While the PDDS can be a valuable tool to assess physical and mental health, completing a quality-of-life measure like the Multiple Sclerosis Impact Scale (MSIS-29) before a visit can give an additional assessment of mental well-being that might be used in conjunction with PDDS[174]. However, a face-to-face examination may still be required to evaluate relapses and acute modifications, especially when changing therapy is being considered[175].

7 Radiological monitoring

During the early stages of the COVID-19 pandemic, the majority of medical centers recommended that diagnostic testing be conducted only on individuals with life-threatening or acute medical issues[176]. Consequently, MRI scans for general disease monitoring and safety monitoring were postponed so that pwMS might avoid exposure to COVID-19[176]. When COVID-19-related restrictions began to lift across the world, a significant majority of MS centers began to resume their routine MRI scans for disease and safety monitoring[95]. When it comes to pwMS, the risk of COVID-19 and MS subclinical disease activity must be weighed against the potential for disability progression over time[177]. Because the danger of COVID-19 is constantly shifting and changing[178], it is imperative that all imaging centers comply with the recommendations made by the local public health and infection control agencies with regard to reducing the risk of SARS-CoV-2 exposure and transmission. All patients entering the facilities should undergo a preliminary screening for symptoms, recent travel to high-risk locales, or close contact with a confirmed case of COVID-19[178]. Additionally, individuals should be required to sanitize their hands before entering the facility, and if masks are given, they should wear them. Furthermore, it is crucial to have measures in place to maintain appropriate social distance in waiting rooms and to clean MRI equipment properly between patients[176]. Due to the frequency of COVID-19 outbreaks, imaging facilities may face capacity issues. And since the MRI has been declared to be clinically necessary, neurologists should emphasize to their patients the need to attend their scheduled MRI appointments, as it will be difficult to reschedule the procedure[95]. Lastly, neurologists should determine which MS patients require an MRI immediately and which patients may delay their MRI. Patients with moderately to highly active diseases and those who need to monitor their progress for Progressive multifocal leukoencephalopathy (PML) safety are examples of circumstances that may require an urgent MRI. MRIs can be postponed if the patient has had stable disease for several years and if the local conditions warrant it. Neurologists should additionally investigate patient-specific factors that may increase the likelihood of COVID-19 and COVID-19-related complications, such as the patient's advanced age, degree of impairment, and presence of comorbidities[95,176].

Conclusion

In conclusion, the key priority for MS neurologists during the pandemic was to guarantee continuity of therapy by decreasing the danger of infection and the severity of COVID-19. In this view, the treatment of MS patients should be tailored to the patient's lifestyle (job, social interactions, familial setting, etc.), the 'drug load' (administration burden and monitoring burden) and the DMT safety profile, and the overall risk of infection. Initially, immunosuppressive medications were of prime concern, and hence data collection on DMT safety was critical to aid in treatment decisions. Therefore, neurologists specializing in MS should carefully examine which treatment is appropriate for their patients, weighing the danger of infection against the risk of inadequate disease management. This approach may necessitate mixing face-to-face consultations with remote monitoring in order to early identify disease activity and/or progression, modify treatment schedules, and arrange the correct timing for vaccination against COVID-19.

A seasonal concern for immunocompromised patients such as MS patients is expected to arise when COVID-19 disease becomes endemic. Therefore, MS patients should receive the SARS-CoV-2 vaccine as soon as possible in order to lower their risk of infection and recurrence. MS patients should be able to safely receive the SARS-CoV-2 vaccinations now approved by the EMA, based on previous trials with non-live vaccines. However, vaccination may affect the immunological response of patients receiving certain DMTs, and evidence on the optimal time for vaccination, particularly in B cell-depleting therapy, is still limited. However, there are no constraints for MS patients on injectable or teriflunomide, fingolimod, natalizumab, siponimod and dimethyl fumarate, and exact scheduling should be arranged for patients on immunodepleting medications. In addition, in MS patients receiving ocrelizumab, cladribine, alemtuzumab, or ofatumumab, the timing of vaccination and medication delivery is critical to ensuring an adequate immunological response to the vaccine.

In addition, the utilization of modern technologies like telemedicine plays a vital role in the administration of patient care. For example, to preserve motor performance in pwMS, telerehabilitation in-home services were offered considering the pandemic's severe rehabilitation neglect.

In the long run, it is critical to keep MS patients well cared for while also ensuring their quality of life is not adversely affected by the pandemic's restrictions.

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Biography

Anna Safiulin was born in Lviv, Ukraine, on 7th of February, 1992. At the age of five, she immigrated with her family to Israel. During high school, her majors were Biotechnology. After completing her 2-year obligatory and 2- year reserves military service in the Israeli defense force (IDF) in the intelligence corps, she followed her dreams to become a medical doctor and study in English, so she started studying in the faculty of medicine, University of Zagreb, Croatia.