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REVIEW

SARS-CoV-2 infection in multiple sclerosis patients: interaction with treatments, adjuvant therapies, and vaccines against COVID-19

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Abstract

The SARS-CoV-2 pandemic has raised particular concern for people with Multiple Sclerosis, as these people are believed to be at increased risk of infection, especially those being treated with disease-modifying therapies. Therefore, the objective of this review was to describe how COVID-19 affects people who suffer from Multiple Sclerosis, evaluating the risk they have of suffering an infection by this virus, according to the therapy to which they are subjected as well as the immune response of these patients both to infection and vaccines and the neurological consequences that the virus can have in the long term. The results regarding the increased risk of infection due to treatment are contradictory. B-cell depletion therapies may cause patients to have a lower probability of generating a detectable neutralizing antibody titer. However, more studies are needed to help understand how this virus works, paying special attention to long COVID and the neurological symptoms that it causes.

Keywords SARS-CoV-2 · Multiple sclerosis · Disease-modifying therapies · Immunity · Adjuvant treatments · Neuro-COVID

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) as a pandemic, just 3 months after the appearance of the first cases in Wuhan (China) [1]. On May 26, 2022, the cases confirmed by the WHO are 524,339,768 and 6,281,260 deaths have been registered worldwide [2]. This pandemic has placed enormous pressure on medical resources and, in most countries, health care systems have had to reconfigure to manage the increase in severe COVID-19 cases and reduce the risk of vulnerable patients [3, 4].

The genome of the type 2 coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2) comprises 13 to

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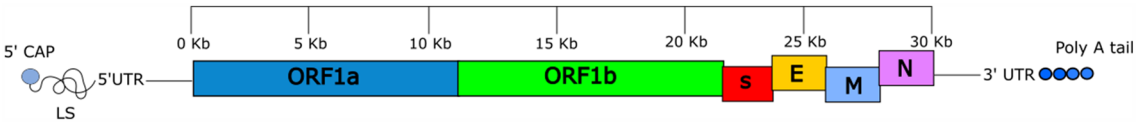

Fig. 1 SARS-CoV-2 genomic organization. Image made with Inkscape based on the article made by Dos Santos 2021 [5]

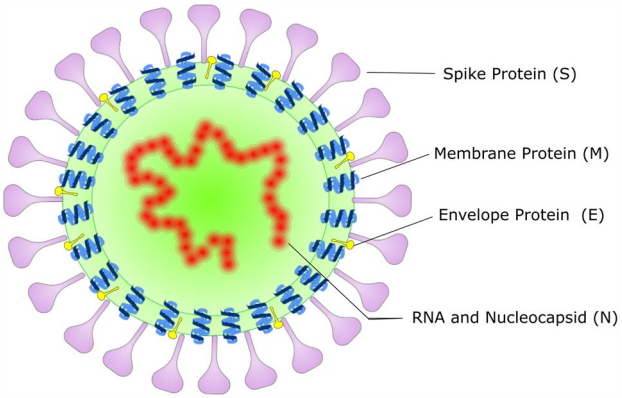

Fig. 2 Structure of SARS-CoV-2 with the main structural proteins. Image made with Inkscape based on the article made by Dos Santos 2021 [5]

15 open reading frames (ORF), of which 12 are fundamental, encompassing 11 genes that code for proteins (Fig. 1) [5, 6]. This virus consists of four main structural proteins [7]. The spike protein (S) enables the attachment and entry of SARS-CoV-2 to the host cells; The membrane protein (M) is a component of the viral membrane; the nucleocapsid protein (N) binds to viral RNA and supports the formation of the nucleocapsid and the envelope protein (E) that plays a role in viral assembly, release, and pathogenesis (Fig. 2) [8, 9]. When infection occurs, the first responders are alveolar macrophages [9]. This signal causes transcription factors such as IRF3/7 (interferon regulation factor) and NF-κB (nuclear factor kappa B) to be activated and the production of type I and III interferon (IFN) begins, as well as the secretion of interleukin 6 (IL-6) and interleukin 1β (IL-1β), which induces the recruitment of neutrophils and cytotoxic T cells [7, 10]. CD4 + T cells aid in the adaptive response, by stimulating CD8 + T cells and B cells [11]. In addition, they induce a Th1 response [12], which plays a dominant role in the adaptive immune response to viral infections [9, 11]. This response causes an increase in the secretion of pro-inflammatory cytokines, IFN-γ and Tumor Necrosis Factor alpha (TNF-α) [12]. Th17 cells produce IL-17, even more monocytes, macrophages, and neutrophils are recruited, and more cytokines are stimulated [9, 13, 14]. In certain cases, the levels of these cytokines are very high, due to a dysregulated immune response of the host, causing what is known as "Cytokine Storm".

SARS-CoV-2 has become a serious challenge for many areas of medicine, including neurology [15]. In this sense, since the beginning of the pandemic, there has been a special concern for those people suffering from Multiple Sclerosis (MS), especially those who are being treated with disease-modifying therapies (DMTs) [16], since it is believed that these patients may be at higher risk of infection or of having a more severe course of COVID-19 than the general population. This disease affects 2.5 million people in the world [17], being the most common cause of non-traumatic disability in young adults [18] between 20 and 30 years of age [19] (Fig. 3).

Therefore, the objective of this review is to describe how COVID-19 affects people who suffer from MS, evaluating the risk they have of suffering an infection by this virus, according to the therapy to which they are subjected, as well as the immune response of these patients to both the infection and the vaccines and the long-term neurological impact the virus may have.

Methodology

A literature search was performed in the PubMed and Scopus databases, without language limitations. The search was limited to articles published between 2020 and 2021. The keywords "COVID-19", "SARS-CoV-2", and "Multiple Sclerosis" were used. These terms were searched for alone or in combination, for example by combining "SARS-CoV-2 AND Multiple Sclerosis". In addition, the references of relevant studies, reviews, and editorials were also searched from the articles read. Specific references were also sought to write sections that were added throughout the writing of the manuscript, using keywords such as "disease-modifying therapies", "vaccines", and "adjuvant therapies". With these searches, a total of 257 articles were collected, including original articles, review articles, and abstracts. Articles dealing with the impact of home confinement on quality of life and muscle performance in patients with multiple sclerosis were excluded; therefore, 142 articles were included. After reading these manuscripts, 72 more articles were searched,

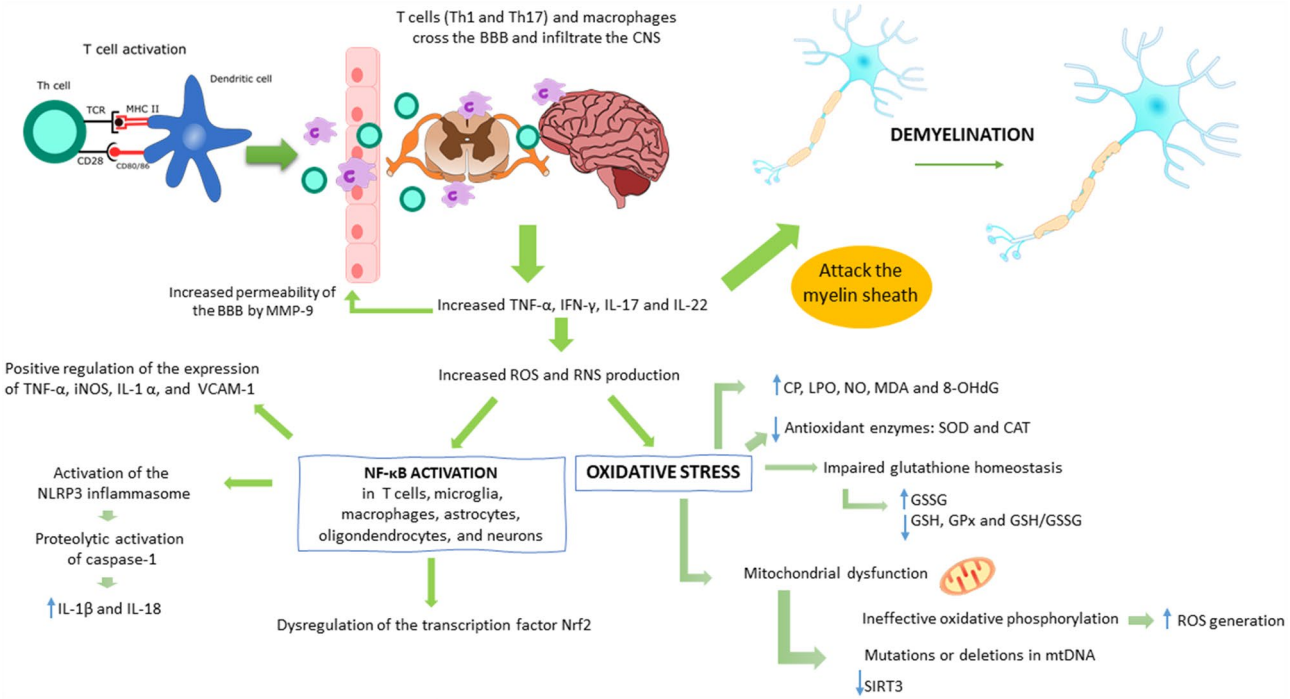

Fig. 3 Cellular and molecular mechanisms involved in multiple sclerosis. BBB blood–brain barrier, *CNS* central nervous system, *TCR* T-cell receptor, *MHC-II* major histocompatibility complex II, *VCAM-1* vascular cell adhesion molecule 1, *Th1,Th17* cells T helper 1, T helper 17, *IL-18* interleukin 18, *IL-10*: interleukin 10, *IL-17* interleukin 17, *IL-1β* interleukin 1 β, *IL-1α* Interleukin 1α, *TNF* tumor necrosis factor, *IFN* interferon, *MMP-9* matrix metalloproteinase-9, *iNOS* nitric oxide synthase, *CP* carbonylated proteins, *LPO* lipid peroxidation products, *NO* nitric oxide, *MDA* malondialdehyde, *GSSG* oxidized glutathione, *GPx* glutathione peroxidase, *GSH* reduced glutathione, *SIRT3* sirtuin 3, *NF-κB* factor nuclear kappa B, *mtDNA* mitochondrial DNA, *8-OHdG* 8-hydroxy-2′deoxyguanosine, *SOD* superoxide dismutase, *CAT* catalase, *ROS* reactive oxygen species, *RNS* reactive nitrogen species, *Nrf2* nuclear erythroid-related factor 2

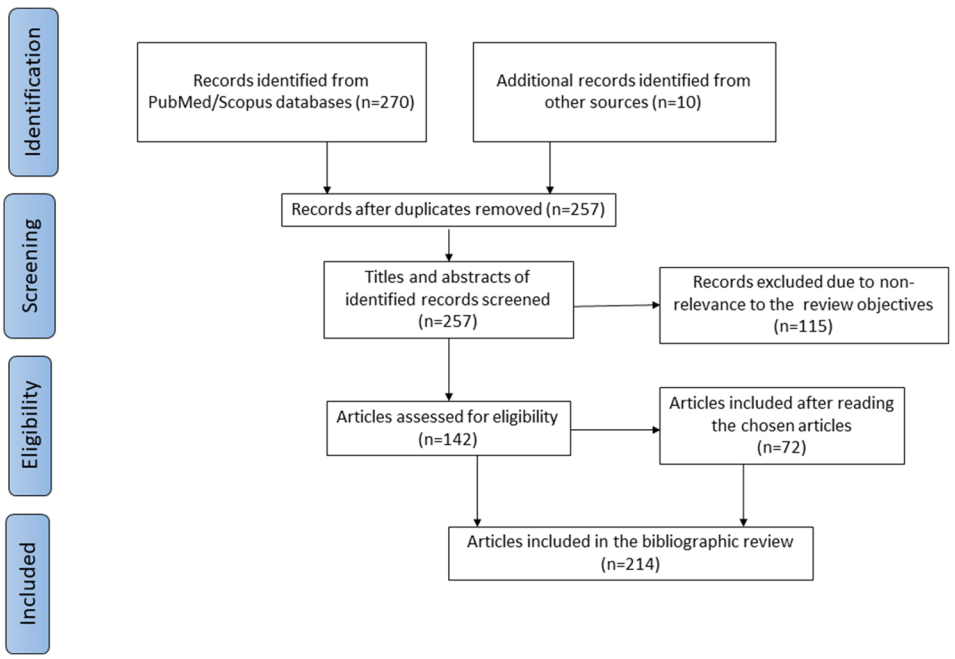

Fig. 4 Methodology for the literary search

so that, finally, 214 scientific productions were included in the review (Fig. 4).

Interaction COVID-19 and multiple sclerosis

PwMS, especially those with severe forms of the disease, are generally more prone to infections [16, 20]. The pandemic has also had a negative impact on the mental health of pwMS [21], since the fear of get the disease [22], home confinement [23], and social distancing have caused an increase in levels of anxiety and depression in these patients [21]. A study conducted by Ramezani et al., 2021 in 410 pwMS from Iran, reported that in the first wave, the prevalence of anxiety and depression in these patients was 31.2% and 39.3%, respectively [24]. The urgency to ensure the treatment of COVID-19 patients, left little leeway for the development and implementation of consistent strategies to continue the care of people with chronic diseases [25]. Despite the fact that during the pandemic, many diseases have been treated through the use of telemedicine, becoming a feasible tool to maintain patient care and reduce the risk of exposure to SARS-CoV-2 for both patients and workers of health [26, 27], the impact of COVID-19 on the health care system has been dramatic. The system had to undergo important changes, such as the postponement of surgeries and non-urgent medical care [28]. In patients with multiple sclerosis, regular physical activity is considered essential for disease management. These people usually require physiotherapists to carry out rehabilitation exercises, which, due to home confinement and social distancing rules, was unfeasible [29]. This has also led to an increase in fear of relapse in pwMS, due to the uncertainty about the management of the disease and access to health services [30]. Despite all benefits of telemedicine during the COVID-19 pandemic, the telemedical examination does not seem to be able to replace personal consultation fully [28].

COVID-19 in patients with multiple sclerosis

Role of DMTs in viral infection

Due to the higher rate of infection and mortality because of the COVID-19, among patients with chronic diseases, a concern has been raised with pwMS, since, normally, their treatment is based on DMTs [16]. In general, 70% of pwMS are treated with DMTs [31, 32]. DMTs are classified into two categories: Immunomodulators, are medications used to help regulate or normalize the immune system, and Immunosuppressants, which temporarily or permanently alter the functioning of the immune system [33]. Based on this, a safety problem has been raised with respect to the use of these treatments, since patients who use them could be more vulnerable to SARS-CoV-2 infection [20, 34]. Currently approved DMTs, to control autoimmunity in MS, affect multiple immune mechanisms, including the inhibition of immune cell trafficking, the depletion of subsets of these cells, as well as the alteration of their function and the inhibition of cell replication [35, 36]. Most of these DMTs are directed against CD4 + and Th17 T cells, memory (CD19 +, CD27 +), and naive B cells (CD19 +, CD27) [3, 37, 38].

DMTs are distinguished in two main categories, first-line DMTs (moderate effective; Oral administration or injection) (IFN-β, Glatiramer Acetate, Teriflunomide and Dimethyl fumarate) and second-line DMTs (high effective; Infusible or oral therapies) (Natalizumab, Fingolimod, Alemtuzumab, Cladribine and anti-CD20 treatment, Rituximab, Ocrelizumab, and Ofatumubab), as escalation therapy [39]. First-line therapies are moderately effective, but not immunosuppressive, and have excellent long-term safety profiles [40], while second-line therapies show greater efficacy, but cause immunosuppression and/or immunomodulation [41].

Considering the effects of these therapies, it is of special interest to study how they affect the risk of SARS-CoV-2 infection in people who are being treated with them. Since the beginning of the pandemic, numerous clinical cases, research, and reviews have been published in this regard.

Regarding the first-line DMTs, Glatiramer Acetate [3] causes blockage of MHC-II in immunological synapsis and shift from Th1 to Th2 immune responses [39]. This has been associated with a lower risk of SARS-CoV-2 infection in pwMS, like IFN-β, which has powerful antiviral effects in vivo [42] and reduces antigen presentation and Th1 expression [39]. In fact, in the study by Reder et al. (2021) obtained that those pwMS treated with therapies whose mechanism of action causes a reduction in Th1 responses and increase the anti-inflammatory response Th2, that is, IFN-β and Glatiramer Acetate, were less likely to develop COVID-19, compared with other DMTs [36].

Due to the potentially reduced risk of developing COVID-19 in pwMS treated with IFN-β or glatiramer acetate [43], the probability of death using either of these therapies is very low. This is confirmed in the systematic reviews by Sharifian-Dorche et al., 2021 and Zrzavy et al. 2021, in which they show that no patient treated with IFN-β and confirmed COVID-19, died [44, 45]. Zrzavy et al. 2021 in their review reports a fatal case of a pwMS treated with Glatiramer Acetate and Sharifian-Dorche et al., 2021 reported 2 deaths (1.4%) in pwMS of the 140 treated with Glatiramer Acetate infected by SARS-CoV-2 [32, 44, 46]. Some authors consider that IFN-β treatment can be started and continued in the case of a SARS-CoV-2 infection [47]. However, other authors state that IFN-β could be protective in the early stages of infection, but could become harmful in the stages of hyperinflammation, by facilitating the invasion of the lungs and other organs by macrophages [48, 49]. Despite

this, both therapies are being tested as possible treatments in cases of SARS-CoV-2 infection [50].

Teriflunomide is an agent that selectively and reversibly inhibits dihydroorotate dehydrogenase, and through this mechanism, teriflunomide reduces the level of immune activation without the major immunosuppression that occurs with several other MS DMTs [44, 51, 52]. Teriflunomide prevents viral replication, so it is believed that it may play a potential therapeutic role with COVID-19, by blocking de novo pyrimidine synthesis and exerting an antiviral effect. [3, 51–53]. In general, in patients who are treated with teriflunomide, diseases of the upper respiratory tract are more common [37]. A study conducted by Luetic et al., 2021, in 18 pwMS concluded that COVID-19 is mild in patients treated with teriflunomide and the continuation of this therapy during infection is safe and recommended [49]. A clinical case published by Yetkin et al., 2021, reported on pwMS being treated with teriflunomide and who was infected with SARS-CoV-2. Treatment was not interrupted during infection, which followed a mild course [53]. Another study carried out by Capone et al., 2021, in which they reported a clinical case of pwMS, treated with teriflunomide and that was infected by SARS-CoV-2, presented a self-limited infection and without relapse of MS. Patient continued treatment during infection [54]. The three reports cited agree that teriflunomide could have a beneficial effect against COVID-19, since it can prevent an excessive host immune response [53, 54]. Therefore, currently, the activities carried out by teriflunomide are under consideration to prevent the morbidity and mortality of COVID-19 [50].

Dimethyl fumarate (DMF) is a methyl ester of fumaric acid with anti-inflammatory and antioxidant properties, being a powerful activator of Nrf2 [55]. Likewise, DMF blocks the production of pro-inflammatory cytokines and can inhibit the action of macrophages [37, 44]. Thanks to these functions, DMF was proposed as a viable treatment option for the course of COVID-19, and can be rapidly implemented in the clinic to calm the cytokine storm that causes this disease [55]. However, it has been reported that DMF can cause severe prolonged lymphopenia in a small proportion of pwMS [3]. This lymphopenia can be grade 3 in 5–7% of patients [44]. Despite this, a few serious opportunistic infections have been reported in DMF-treated pwMS, so these patients would not have an increased risk of SARS-CoV-2 infection or suffer a more severe course of disease [3, 37, 44, 56]. Of 27 pwMS with positive PCR for SARS-CoV-2, reported in the review by Zrzavy et al. 2021, one of them passed away [45]. Similarly, Sharifian-Dorche et al., 2021 reported that of 314 pwMS infected by SARS-CoV-2, one (0.3%) died [32, 44]. Due to the activity of DMF, it has been proposed that this therapy could have a protective role against SARS-CoV-2, although the available data are insufficient to draw definitive conclusions [57].

With regard to second-line DMTs, it is known that Natalizumab can promote opportunistic infections [44, 56], as well as Fingolimod, which is associated with an increased risk of mild infections [44], but it is unknown if this is significant in SARS-CoV-2 infection [3]. Natalizumab is a humanized monoclonal antibody that recognizes the α4 chain of the VLA4 antigen, a component of the α4β1 integrin, an adhesion molecule expressed on the surface of lymphocytes and involved in transmigration across endothelia into the CNS [58, 59]. Inhibition of α4β1 causes reduced migration of lymphocytes through the BBB [3, 39]. Fingolimod is a sphingosine-1-phosphate receptor modulator that sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction by blocking trafficking to the target organ. It reduces the total mean circulating lymphocyte count by 73% from baseline and preferentially sequesters the naive and central memory lymphocytes rather than effector memory T cells [37, 39, 44, 59]. Natalizumab decreases immunosurveillance of the CNS and could increase the risk of encephalitis during a SARS-CoV-2 infection [60]. In the systematic review carried out by Sharifian-Dorche et al., 2021, they obtained that of 257 pwMS treated with Fingolimod, one (0.3%) died and of 233 pwMS treated with Natalizumab, 3 (1.2%) died [44, 61]. Likewise, Zrzavy et al. 2021 reported that of 24 and 10 patients with confirmed COVID-19, treated with Fingolimod and Natalizumab, respectively, one patient died with each treatment [45]. However, a study conducted by Mallucci et al., 2021 reported that, of 104 pwMS with COVID-19 and treatment with Natalizumab or Fingolimod, none required hospitalization, or had serious complications from the virus. Therefore, it could be assumed that these two treatments are safe, being a good therapeutic option for pwMS with active disease, during the pandemic [62].

Alemtuzumab is an anti-CD52 monoclonal antibody, which markedly depletes T and B lymphocytes [56], being one of the most widely used immunosuppressive drugs in MS [63] and Cladribine selectively depletes peripheral lymphocytes, being able to induce long-term memory B-cell depletion [56, 64, 65]. In relation to both treatments, it was reported that their use could suppose an increased risk of SARS-CoV-2 infection [66, 67]. This increased risk of infection was confirmed in the European prospective cohort study, RADAR-CNS, which compared the use of Alemtuzumab and Cladribine with injectable drugs [66]. Regarding the course of infection during the use of these drugs, a clinical case conducted by Iovino et al., 2021 reported on a 24-year-old woman with MS and COVID-19 treated with Alemtuzumab. Infection occurred 4 months after the last administration of the first cycle of Alemtuzumab. The course of the disease was mild, presenting only mild asthenia and low-grade fever [63]. Another study conducted by Jack et al., 2021, in which they evaluated a cohort of 261 pwMS

treated with Cladribine (160 had PCR-confirmed COVID-19 and 101 were suspected of COVID-19), concluded that patients treated with this drug, generally, do not have an increased risk of severe illness and/or a severe COVID-19 outcome compared to the general population [68]. Regarding the mortality rate, no fatal cases have been identified in patients treated with Alemtuzumab or Cladribine [44, 45].

Anti-CD20 treatments are one of the therapies that generate the most concern in the COVID-19 era. These therapies selectively deplete CD20 + B cells, which can cause hypogammaglobulinemia, if CD20 depletion occurs every 6 months [3]. The use of these agents has been associated with an increased risk of SARS-CoV-2 infection and with a more severe course of the disease in pwMS, compared to those patients who received other DMTs [3, 32, 36, 69]. Due to the mechanism of action of these therapies, different studies have been carried out to analyze the risk of suffering from COVID-19 in pwMS treated with them. In the observational study carried out by Wallach and Picone (2021), a higher incidence of SARS-CoV-2 infection was found in patients receiving treatment with anti-CD20 monoclonal antibodies [70].

Rituximab is a chimeric monoclonal antibody considered a selective immunosuppressant [71], widely used for the treatment of various diseases [72]. There are some discrepancies on whether the use of Rituximab is harmful or not, during the pandemic. There are studies which report that the use of this therapy causes an increased risk of SARS-CoV-2 infection, compared to other DMTs [73]. Rituximab may also decrease CD3 + and CD4 + T lymphocytes, which could justify this increased risk of viral infections, in patients treated with it [71, 74]. This is confirmed by the study conducted by Esmaeili et al., 2021, which further concludes that there is a greater possibility of severe disease and mortality in pwMS treated with Rituximab. To reduce this risk, the possibility of adopting a prolonged dosing interval of the treatment has been considered [75, 76]. However, other studies suggest that this agent does not cause an increased risk of infection and motivate its use [77, 78]. A study by Langer-Gould et al., 2021 in pwMS treated with Rituximab reports that these people are at higher risk of being hospitalized but not dying from COVID-19 [79]. These results coincide with those reported by Simpson-Yap et al., 2020, who state that with Rituximab, there is a significantly higher risk of hospitalization, ICU admission, and ventilation [80]. A clinical case published by Bose and Galetta 2021 reported a reactivation of SARS-CoV-2 in a 32-year-old woman with very active MS. She was positive for COVID-19 during Rituximab treatment and recovered. She was symptom free for 21 days before receiving Rituximab again, and 3 days after being treated, she developed respiratory symptoms again and required admission [81]. This could be because immunosuppression is a risk factor for recurrence in the appearance of symptoms, since it can decrease the ability to eliminate the virus [82]. Yarahmadi et al. 2021, in their review, they suggest the use of Rituximab with caution, since, although it seems that this therapy does not increase morbidity and mortality, more controlled studies are needed to reach a better conclusion [72].

Ocrelizumab is a humanized anti-CD20 antibody [33] that, like all other anti-CD20 therapies, has been associated with an increased risk of severe COVID-19 infection [83]. However, Fernandez-Diaz et al., 2021 evaluated the safety profile and effectiveness of Ocrelizumab treatment in 228 people with MS. Of these, only 3 get SARS-CoV-2 (1.3%). All 3 were men in an age range of 32 to 49 years and with scores on the Expanded Disability Status Scale (EDSS) of 0.6 and 7.5. Only the oldest and most disabled patient needed hospitalization and assisted ventilation [84]. Similarly, Louapre et al., 2020 in their cohort study, in which they used records of 347 pwMS, were able to verify that age, EDSS score, and obesity were independent risk factors for severe COVID-19, and there was no association between Ocrelizumab exposure and COVID-19 severity [84, 85]. The review carried out by Hughes et al., 2021 reported that people treated with Ocrelizumab and with SARS-CoV-2 infection, present a mild or moderate severity of the disease and most do not require hospitalization [86]. The mortality rate for pwMS with this treatment remains within the published ranges for the general population and other MS cohorts [61, 86]. On the other hand, there are authors who report a serious course of COVID-19, even being fatal in cases of Relapsing–Remitting Multiple Sclerosis (RRMS) treated with Ocrelizumab [69, 87–89]. Therefore, the possibility of prolonging the dosing intervals of Ocrelizumab was raised as a possible risk mitigation strategy in times of pandemic [89]. Studies that have investigated this possibility conclude that there are no clinical consequences for pwMS, by delaying the use of this drug [89, 90].

Likewise, the routes of administration of DMTs have been related to a different risk of SARS-CoV-2 infections. In this sense, DMTs administered by infusion have been associated with a higher risk of contagion, since, to receive this type of treatment, patients must go to the hospital, where they are more exposed to the virus. On the contrary, injectable and oral therapies are related to a lower risk of contagion, since they can be administered at home. For this reason, perhaps, alternative routes of administration should be investigated for some medications that currently require more frequent hospital care [91].

Despite everything described, most of the results obtained in relation to DMTs are contradictory, possibly explained by the different populations used and the bias in their selection [89] (Table 1). However, one thing most studies do agree on is that the risk of further MS

Table 1 Summary of the main studies on the influence of COVID-19 and DMTs on pwMS

Author (year)	Sex (number of patients)	Mean age (±SD)	Type of disease	DMT	Contribution
Ramezani et al. [24]	Female (386)/male (84)	38.60 (±10.35)	MS	Not specified	In this study they evaluate the prevalence of anxiety, depression and levels of fear of COVID-19 in pwMS during the pandemic. Among the patients who participated in the study the prevalence of anxiety and depression were 31.2% ($n=128$) and 39.3% ($n=161$), respectively
Luetic et al. [49]	Female (13)/male (5)	41.2 (±12.6)	MS and COVID-19	Teriflunomide	Teriflunomide therapy was evaluated for safety in pwMS with COVID-19. They concluded that COVID-19 presents a mild course in pwMS that receive this therapy. They also note that continuing treatment with teriflunomide during SARS-CoV-2 infection is safe for pwMS
Mallucci et al. [62]	Not specified (104)	Not specified	MS and COVID-19	Natalizumab or Fingolimod	No patient required hospitalization or showed severe complications from COVID-19. These findings indicate an absence of COVID-19 complications in pwMS treated with these DMTs and support the hypothesis that it is safe to maintain continuous treatment with these drugs in the current setting
Jack et al. [68]	Female (182)/male (57)/ not reported (22)	41	MS and COVID-19	Cladribine	Cladribine treated patients with MS are generally not at greater risk of serious disease and/or a severe outcome with COVID-19 compared with the general population
Esmaeili et al. [71]	Female (168)/male (90)	41.31	MS, NMOSD, and COVID-19	Rituximab	Rituximab seems not to be safe enough during the pandemic
Langer-Gould et al. [79]	Female (1364)/male (531)	44.5 (±12.3)	MS and COVID-19	Rituximab	Rituximab-treated pwMS should take extra precautions to avoid exposure to COVID-19 in the 5 months following each infusion. Using extended dosing intervals and lower doses could be considered
Fernandez-Diaz et al. [84]	Female (124)/male (104)	42.7 (±11.2)	RRMS, SPMS, and PPMS	Ocrelizumab	Of the patients who participated in the study, only 3 were infected with COVID-19. Confirm the effectiveness, tolerability, and short-term safety of Ocrelizumab

Table 1 (continued)

Author (year)	Sex (number of patients)	Mean age (±SD)	Type of disease	DMT	Contribution
Garjani et al. [104]	Female (307)/male (97)	50 (±11)	RRMS, SPMS, PPMS, and COVID-19	Beta interferons, Glatiramer acetate, Teriflunomide, Dimethyl fumarate, Fingolimod, Natalizumab, Ocrelizumab, Cladribine, Alemtuzumab	COVID-19 is associated with exacerbations of MS. Fewer people taking DMTs experience new neurological symptoms following COVID-19 and, therefore, it is important to consider carefully before altering or delaying treatment with DMTs because of concerns about their safety during the pandemic
Conte [111]	Female (21)/male (3)	46.1 (±12.49)	RRMS, SPMS, PPMS, and COVID-19	Ocrelizumab and other DMTs	Patients who received Ocrelizumab within the prior 6 months of COVID-19 infection had decreased odds of developing antibodies as compared with other DMTs. This suggests that Ocrelizumab may attenuate the antibody response to SARS-CoV-2
Iannetta et al. [115]	Female (1)/male (4)	33	RRMS	Ocrelizumab	The patients did not present anti-SARS-CoV-2 antibodies, or they presented them in a very low concentration. Despite this, a T-cell response was detectable in all the five MS patients
Habek et al. [118]	Female (47)/male (27)	39.7 (±9.2)	RRMS, SPMS, PPMS, and COVID-19	Natalizumab, Fingolimod, Alemtuzumab, Ocrelizumab, Cladribine, and Ublituximab	A significant proportion of convalescent COVID-19 pwMS on high-efficacy DMTs will not develop IgG SARS-CoV-2 antibodies. B-cell depleting therapies independently predict negative and low titer of IgG SARS-CoV-2 antibody

MS multiple sclerosis, *pwMS* patients with multiple sclerosis, *DMT* disease-modifying therapies, *NMOSD* neuromyelitis spectrum disorders, *RRMS*: relapsing–remitting multiple sclerosis, *SPMS* secondary-progressive multiple sclerosis, *PPMS* primary-progressive multiple sclerosis

progression due to treatment interruption possibly outweighs the risk of SARS-CoV-2 infection [33, 92]. In addition, it has been reported that the highest rates of hospitalization and mortality occur in pwMS that were not receiving any DMT [83]. Although this could be due to the fact that pwMS that do not receive treatment are elderly or are in terminal stages of the disease [93]. Therefore, there is a growing need for personalized medicine, which could play a key role in elucidating individual susceptibility to infection, as well as interindividual variability in the clinical course of the disease, prognosis, and response to treatment [94].

SARS-COV-2 infection in patients with multiple sclerosis

As described in the previous section, MS alone is not a risk factor for symptomatic SARS-CoV-2 infection [3]. However, there is a lack of information about the consequences that SARS-CoV-2 can have on pWMS, when the infection occurs [95]. Infections, in general, cause significant morbidity and contribute to exacerbation of the disease, in the form of relapses and/or worsening of neurological manifestations [34, 96]. Upper respiratory viral infection (URVi) are known to increase the risk of relapse in pwMS [95, 97]. 10–30% of these infections are caused by coronavirus [95, 98]. For these viruses, the host's aberrant immune response is responsible for severe respiratory failure, which can lead to 21% of pwMS to be hospitalized and 3.5% to die [83, 85, 99].

The effect of COVID-19 on the risk of MS exacerbation is still unknown, but some studies are already investigating it. Di Stadio et al., 2020 comment that a long-term neurologic sequela arising from COVID-19 infection in pwMS could be related both to the increase of cytokines and the activation of NLRP3 inflammasome by the SARS-CoV-2, which would cause a worsening of MS [100]. They also speculate that the intense immune stimulation and systemic stress produced by COVID-19 could be responsible for a higher frequency of relapses of pwMS [100, 101]. Barzegar et al., 2021 suggest that COVID-19 may trigger relapse in MS [95]. They support that there could be an association between COVID-19 and MS, due to the expression of pro-inflammatory mediators (IL-6, IL-7, IL-17, IFN-γ, and TNF-α) that causes SARS-CoV-2 infection. These mediators would cause an even greater dysfunction of the BBB and facilitate the migration of monocytes, macrophages and CD4 + and CD8 + T cells to the CNS, causing a neurological worsening and exacerbation of MS [95, 102, 103] (Fig. 5). In the prospective cohort study carried out by Garjani et al., 2021, in pwMS and SARS-CoV-2 infection, it was found that, of 404 participants, 57% had an exacerbation of MS. Of these, 207 experienced a worsening of pre-existing symptoms, 82 developed new MS symptoms, and 59 reported both events. They concluded that those with a higher EDSS score and a longer duration of MS were more likely to experience a worsening of their MS symptoms during COVID-19 [104]. In contrast, in the retrospective cohort study conducted by Etemadifar et al., 2021, they observed that the exacerbation rate was lower in RRMS patients who get SARS-CoV-2 than in patients who were not infected by the virus. They speculate that the lymphopenia associated with COVID-19 could, in part, prevent autoreactive memory cells from expanding and initiating relapses through the so-called "bystander

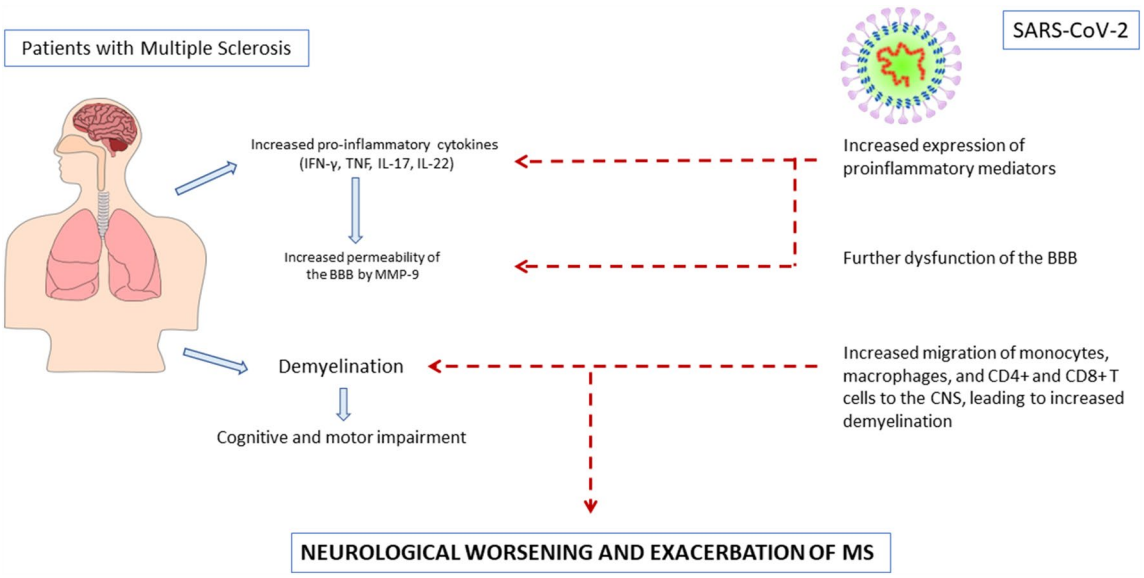

Fig. 5 Influence of SARS-CoV-2 viral infection in pwMS. *IFN-γ* interferon-γ, *TNF* tumor necrosis factor, *IL-17* interleukin 17, *IL-22* interleukin-22, *BBB* blood–brain barrier, *MMP-9* matrix metalloproteinase-9, *CNS* central nervous system, *MS* multiple sclerosis

effect of SARS-CoV-2 infection" [105]. Similarly, Nowak-Kiczmer et al., 2021 conclude in their study that SARS-CoV-2 infection was not related to worsening MS in most patients [15].

Immunity against SARS-CoV-2 in patients with multiple sclerosis

Generation of immunity after infection

After recovery from SARS-CoV-2 infection, the next question posed about pwMS is whether they will be able to generate a detectable neutralizing antibody titer, which can prevent reinfection [106]. There are already some reports, although limited, on certain DMTs affecting seroconversion after SARS-CoV-2 infection, in pwMS [106, 107]. In general, the administration of IFN-β has been significantly associated with the presence of antibodies against SARS-CoV-2, after infection with the virus [108]. In this sense, Bigaut et al. (2021) found that pwMS treated with IFN-β1a or Glatiramer Acetate had an anti-SARS-CoV-2 IgG index higher than that of patients treated with Fingolimod or anti-CD20 therapies [109]. Those patients who receive therapies that produce a reduction in B cells will present lower antibody titers and of short duration [108]. Thus, in the study by Bsteh et al. (2021), observed seropositivity rates were equal to or greater than 80% in pwMS treated with Dimethyl fumarate (80%), Teriflunomide (83%), IFN-β (88.9%), Glatiramer acetate (88.9%), or Natalizumab (90.9%). On the contrary, they obtain lower seropositivity rates in those pwMS treated with Ocrelizumab (50%), Alemtuzumab (50%), Rituximab (60%), Fingolimod (68.8%), and Cladribine (75%). Regarding anti-SARS-CoV-2 antibody titers, they were significantly lower with immunosuppressive treatments (84 BAU/ml) compared to immunomodulators (354 BAU/ml) [110]. Conte 2021 analyzed the probabilities of developing antibodies against SARS-CoV-2 in pwMS treated with Ocrelizumab compared to other DMTs. He concluded that those patients who had received Ocrelizumab were less likely to generate antibodies [111]. A clinical case published by this same author reported on the case of a 48-year-old woman under treatment with Ocrelizumab, with hypogammaglobulinemia and who had no detectable antibodies after recovery from COVID-19 [112]. Similarly, Lucchini et al., 2020 reported on a 60-year-old woman on Ocrelizumab treatment who developed COVID-19. After recovering from the disease, she underwent a serological test for SARS-CoV-2, demonstrating the presence of IgA while IgG was not detected [113]. Thornton and Harel 2020, reported 2 cases of pwMS treated with Ocrelizumab that developed COVID-19 and exhibited negative serology for specific antibodies against SARS-CoV-2 [114]. Another study carried out in 5 pwMS, who received treatment with Ocrelizumab for at least 1 year and who had recovered from COVID-19, reported that they did not present anti-SARS-CoV-2 antibodies or they presented them in very low concentration [115]. Therefore, they postulate that Ocrelizumab plays a role in reducing antibodies, damaging the humoral response of the immune system [114]. However, they were able to detect a T-cell response in these 5 patients [115]. This could suggest that the T-cell response is also involved in the recovery process from COVID-19 [115, 116]. Perhaps, a functional innate immune response, along with an antigen-specific T-cell response, could be sufficient to eliminate the virus, as most pwMS have a mild disease course and recover, even without evidence positive serological test [114].

A clinical case by Gelibter et al., 2021 reported a pwMS treated with Cladribine that, 1 month after recovering from COVID-19, had a negative result in the quantitative chemiluminescence immunoassay for IgM and IgG anti-SARS-CoV-2. This finding could indicate that patients recently treated with Cladribine have a reduced immunization [117]. A multicenter case–control study conducted by Habek et al., 2021, in which 64 pwMS diagnosed with COVID-19 and treated with different DMTs (Natalizumab, Fingolimod, Alemtuzumab, Ocrelizumab, Cladribina, and Ublituximab) participated, concluded that those patients taking B-cell depletion therapy, had a significantly higher chance of not developing seroconversion, compared to pwMS taking other DMTs or healthy controls [118]. They also highlight that 2 patients taking Fingolimob and another 2 with Cladribine, did not develop IgG antibodies against SARS-CoV-2 [118]. On the contrary, Flores-Gonzalez et al., 2021 reported a clinical case, about a pwMS with Ofatumumab that was infected by SARS-CoV-2 and that presented B-cell depletion. Despite this, he developed IgG antibodies and they remained positive after 3 months of recovery from COVID-19. They suggest that patients treated with this therapy could develop an effective humoral response against SARS-CoV-2 infection [119].

Generation of immunity after vaccination

Vaccination is the most efficient and cost-effective means to prevent and control the COVID-19 pandemic [7, 120]. Six vaccines have been approved by WHO against COVID-19, Pfizer/BioNTech, Moderna, AstraZeneca, Janssen, Sinopharm and Sinovac's CoronaVac. Of these, Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) are nucleoside-modified mRNA vaccines that encode the spike glycoprotein of SARS-CoV-2 [121]. With them, the genetic information of the antigen is administered, and subsequently, the antigen is expressed in the cells of the vaccinated individual [120]. AstraZeneca (ChAdOx1 nCoV-19) and Janssen (Ad26.COV2-S) are viral vector vaccines, using a chimpanzee and human adenovirus vector, respectively, designed to express

the spike protein of SARS-CoV-2 [120, 121]. Finally, Sinopharm (BB1BP-CorV) and Sinovac's CoronaVac are inactivated virus vaccines, where all the virus is presented to the immune system [120, 122].

Currently, 4.717.584.168 people (60.5% of the world population) have received the complete vaccination schedule against COVID-19 [123]. However, following the approval of these vaccines, concerns have been raised regarding their efficacy in pwMS [124], as the use of vaccines in these patients has been a controversial topic for decades, due in part to concerns about possible exacerbation of the illness [3, 120]. The responses to vaccination depend on the type of vaccine, the type of immune response they generate (humoral or cellular), and the impact of DMTs on immunity [120]. To date, there are limited data in large cohorts regarding the efficacy and safety of these vaccines in pwMS (Table 2) and new knowledge about it is urgently needed [120, 125]. An article published in April 2021 by Achiron et al., 2021 evaluated the safety of the BNT162b2 vaccine in adult pwMS. The results of this investigation showed that the relapse rate of the patients was 2.1% after the first dose and 1.6% after the second dose, being like the rate of unvaccinated patients. Therefore, they conclude that the Pfizer vaccine is safe in pwMS [126]. Another study carried out by this group investigated the humoral immune response to the BNT162b2 vaccine in pwMS treated with high-efficacy DMTs [127]. They found that 100% of the patients treated with Cladribine had protective humoral immunity. However, only 22.7% and 3.8% of patients treated with Ocrelizumab and Fingolimod, respectively, developed IgG antibodies. Therefore, they conclude that it is advisable to postpone treatment with Ocrelizumab in patients who are going to be vaccinated and not to vaccinate those people treated with Fingolimod, since they are not expected to develop a protective humoral response [127]. Drulovic et al., 2021 also investigated the immune response to vaccines in pwMS. Eleven pwMS treated with Cladribine participated in their study, of which 4 were vaccinated with the Pfizer vaccine and 7 with the Sinopharm vaccine and 4 pwMS treated with Alemtuzumab, of which 3 were vaccinated with Pfizer and 1 with Sinopharm. They found that 100% of the patients treated with Cladribine and vaccinated with Pfizer, as well as those treated with Alemtuzumab-developed antibodies. On the other hand, 42.9% of the patients treated with Cladribine and vaccinated with Sinopharm developed seroprotection [65]. In the study carried out by Maniscalco et al. (2022), they report that the humoral response to the BNT162b2 mRNA vaccine was increased in IFN-β-treated pwMS. In addition, they found a direct correlation between the IgG titer and the B-cell count in pwMS treated with Dimethyl fumarate and between the IgG titer and the lymphocyte count in pwMS treated with Glatiramer Acetate, both therapies maintaining an efficient humoral response [125]. Similarly, Mariottini et al. (2022) obtained that 100% of the patients who were receiving first-line treatments or Natalizumab developed detectable antibody levels after vaccination [128]. In the study by Disanto et al. (2021) in which 120 pwMS participated, obtained that, after vaccination against SARS-CoV-2, all patients treated with Teriflunomide were seropositive. In contrast, the humoral immunity of patients treated with fingolimod or anti-CD20 therapy was markedly reduced, with 33% and 48.2% remaining seronegative, respectively [129]. Likewise, Jakimovski et al. (2022) conducted a study that included 757 pwMS and other neuroinflammatory disorders, obtaining a significant difference in seroconversion according to the DMT used at the time of vaccination. Successful seroconversion was observed in 85% of patients treated with IFN-β, 88.9% with Glatiramer Acetate, 87% with fumarates, 73.7% with Teriflunomide, 98.3% with Natalizumab, and 61.5% with Cladribine. Again, lower seroconversion rates were seen in fingolimod and anti-CD20 patients (30.8% and 23.2%, respectively) [130]. Even after administration of the third dose in pwMS, the immune response to the vaccine was weak in patients treated with anti-CD20 therapy or Fingolimod [131].

Regarding the possibility of relapse, only one case of acute relapse has been described in a woman after vaccination [125]. The patient developed paresthesia and weakness in the left extremities 48 h after receiving the BNT162b2 vaccine. In addition, after conducting an Magnetic Resonance Imaging (MRI), 3 new lesions could be observed [125]. It is important to keep in mind that any vaccine can cause side effects, among which fever stands out. Fever can make MS symptoms temporarily worse, but they return to previous levels when the fever goes away [132]. Studies carried out to date have reported that the side effects caused by vaccines against SARS-CoV-2 in pwMS are the same as in the general population, regardless of the clinical course of MS and the DMT used, characterizing, in mostly because they are mild and short-lived [133]. In the study by Mariottini et al. (2022), they find that approximately one-third of patients reported common adverse events, such as injection site pain, fever, and asthenia [128]. Similarly, Capone et al. (2021) obtained that the side effects reported by pwMS after vaccination were pain at the injection site (57.1%), fatigue (37.9%), myalgia (27.1%), fever (23.6%), and headache (15.7%) [134]. Likewise, Briggs et al. 2022 that of 719 pwMS, 64% reported experiencing a reaction after the first dose of the vaccine. As in the other reports described above, the most common reactions were injection site pain (54%), fatigue (34%), headache (28%), and malaise (21%). Lower odds of reactions were seen in pwMS treated with an alpha4 integrin blocker (Natalizumab) or a sphingosine-1-phosphate receptor modulator (Fingolimod). After the second dose of the vaccine of 442 pwMS, 74% experienced an adverse reaction [135].

Table 2 Summary of major studies on COVID-19 vaccines at pwMS

Author (year)	Sex (number of patients)	Mean age (±SD)	Type of disease	DMT	Vaccine	Contribution
Achiron et al. [126]	Female (72)/male (53)	47,9	RRMS, SPMS, and PPMS	Cladribine, Ocrelizumab, and Fingolimod	BNT162b2	Cladribine treatment does not impair humoral response to COVID-19 vaccination. We recommend postponing Ocrelizumab treatment in MS patients willing to be vaccinated as a protective humoral response can be expected only in some. We do not recommend vaccinating MS patients treated with Fingolimod as a protective humoral response is not expected
Achiron et al. [127]	Female (364)/male (191)* Female (284)/male (151)**	> 18	MS	Beta interferons, Glatiramer acetate, Teriflunomide, Dimethyl fumarate, Fingolimod, Natalizumab, Ocrelizumab, Cladribine, Alemtuzumab, Rituximab and IVIg	BNT162b2	COVID-19 BNT162b2 vaccine proved safe for pwMS. No increased risk of relapse activity was noted
Drulovic et al. [65]	Female (17)/male (5)	42.4 (±9.4)[a] 34.8 (±13.6)[b]	RRMS	Cladribine and Alemtuzumab	BNT162b2 and Sinopharm	All four (100%) patients under cladribine who were vaccinated with Pfizer-BioNTech vaccine, and three out of seven (42.9%) vaccinated with Sinopharm, developed antibodies. All 4 patients under alemtuzumab developed antibodies after vaccination. In all cases, seroprotection occurred, irrespective of timing of vaccination and absolute lymphocyte count

MS multiple sclerosis, *pwMS* patients with multiple sclerosis, *RRMS* relapsing–remitting multiple sclerosis, *SPMS*: secondary-progressive multiple sclerosis, *PPMS* primary-progressive multiple sclerosis

*First dose of the vaccine; **second dose of the vaccine

[a]Cladribine-treated patients

[b]Alemtuzumab-treated patients

To date, there are not much data about the possible interference of DMTs on the immune response to COVID-19 vaccines and many of the vaccination strategies that are being followed are based on previous evidence with other vaccines, such as the seasonal influenza vaccine. Since the administration times of these must be adjusted to guarantee security and optimize responses [136], the National Multiple Sclerosis Society (NMSS) published specific guidelines for the timing of the vaccine, in relation to the dosage of DMTs [121]. The main guidelines recommend full vaccination 2–4 weeks before starting anti-CD20 therapy, S1P modulators, and Cladribine and 4 weeks before starting Alemtuzumab therapy. For those patients already receiving a DMT, they recommend vaccinating 24 weeks or more, after the last dose of Alemtuzumab, 12 weeks after the last dose of Ocrelizumab or Rituximab [41, 137], and between 3 and 6 months after the last administration of Cladribine, at which time the absolute lymphocyte count is reconstituted [124, 138]. Likewise, there is evidence, although very limited, of the possible protective effect of some drugs for MS against immune-mediated adverse events generated by vaccines, but more studies are needed in this regard [132].

In general, more immunological studies are needed to monitor responses, both humoral and cellular to COVID-19 vaccines in pwMS [47], since, although these are likely to be safe and effective, mRNA and viral vector vaccines are the first of its kind in clinical use, so it is essential to have representative data on its application in these patients [67]. Likewise, it would also be necessary to evaluate the effect of the booster dose of the vaccines, recently approved, in pwMS that have presented an insufficient immune response after receiving the complete vaccination schedule [47].

Role of adjuvant therapies in SARS-CoV-2 in pwMS

The use of adjuvant therapies, such as vitamin D or melatonin, can be an effective strategy to treat those pwMS who have contracted SARS-CoV-2 infection. However, although there are already studies on the effect that both therapies could have on COVID-19 in the general population, we found a lack of studies evaluating the effect of vitamin D or melatonin in pwMS infected with SAR-CoV-2.

Vitamin D

For the treatment of COVID-19, different active therapies are used, but nutritional supplements with antimicrobial and immunomodulatory activities are postulated as promising therapeutic adjuvants in the fight against SARS-CoV-2 [139].

Vitamin D (VD) is a steroid hormone that has a multitude of regulatory effects [140]. It is a powerful modulator of the immune system [141], with antimicrobial functions [139, 142]. VD exerts its functions through interaction with a nuclear vitamin D receptor (VDR) [143], in the VD/VDR signaling pathway [144]. This receptor is expressed in a wide variety of immune cells, influencing the secretion of cytokines and the function of different populations of lymphocytes [139, 145].

Vitamin D deficiency is a risk factor for MS and has been inversely correlated with disease severity [146]. Furthermore, serum concentrations of 25-hydroxyvitamin D (25 (OH) D) or calcifediol are lower during relapse phases than during remissions in pwMS [140, 147–149]. Specific micronutrient deficiencies have been shown to manifest adverse effects in immunity and thereby cause poor prognosis in viral infections [150, 151]. Some studies have shown that there is an association between VD deficiency and SARS-CoV-2 infection (Table 3) [151, 152]. Low levels of 25(OH) D at the time of hospital admission have been shown to be associated with the severity and mortality of COVID-19 [152–154]. Based on this, it has been proposed that VD supplementation could be a safe and beneficial treatment for treating COVID-19 patients [144, 155].

One of the most serious symptoms produced by SARS-CoV-2 infection is ARDS, which involves two main pathophysiological mechanisms: cytokine storm and aberrant activation of the Renin–Angiotensin System (RAS) [144, 156]. VD acts as a RAS inhibitor [151, 157, 158] and reduces the production of immunoglobulins, as well as the Th1 and Th17 response, decreasing the release of pro-inflammatory cytokines and promoting the proliferation of Treg cells and the development of a Th2 response [139, 159, 160]. It also produces antimicrobial peptides such as cathelicidins and defensins [139, 161, 162], and improves endothelial dysfunction by reducing oxidative stress and suppressing the NF-κB pathway [162].

A randomized clinical trial, conducted by Elamir et al., 2021 reported that the administration of 0.5 µg of calcitriol, improved oxygenation and reduced hospital stay in patients with COVID-19, compared to the group that received no treatment [163]. Castillo et al., 2020 conducted a pilot clinical trial in which they used calcifediol, to treat hospitalized patients with SARS-CoV-2 infection. They found that the need for admission to the ICU was much lower in the group treated with VD (2%) compared to standard treatment (50%) [164]. The retrospective study carried out by Loucera et al., 2021, which concluded that patients who had adjusted their serum levels of 25(OH)D, for other health objectives, within the 15–30 days prior to hospitalization, presented better response to COVID-19 and increased survival [165]. Another cross-sectional study in 508 patients, conducted by Vasheghani et al., 2021, reported that mortality from COVID-19 had a negative correlation with the serum level of 25(OH)D and in those patients who were hospitalized, low levels of 25(OH)D, were associated with more severe

Table 3 Summary of major studies on the role of adjuvant therapies against COVID-19

Author (year)	Sex (number of patients)	Mean age (±SD)	Type of disease	Adjuvant therapy (dosage and administration)	Contribution
Elamir et al. [163]	Female (17)/male (5)	64 (±16)[a] 69 (±18)[b]	COVID-19	Calcitriol (0.5 µg daily)	Calcitriol treatment improved oxygenation among hospitalized patients with COVID-19
Castillo et al. [164]	Female (31)/male (45)	52.77 (±9.35)[a] 53.14 (±10.77)[c]	COVID-19	Calcifediol (0.532 and 0.266 mg orally)	Administration of a high dose of Calcifediol or 25-hydroxyvitamin D, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19
Loucera et al. [165]	Not specified (16,401)	Not specified	COVID-19	Cholecalciferol, Calcifediol and Calcitriol	A significant reduction in mortality in patients hospitalized with COVID-19 is associated with the prescription of vitamin D, especially calcifediol, within 15–30 days prior to hospitalization
Vasheghani et al. [162]	Female (244)/male (264)	56 (±17)	COVID-19	Adjuvant treatment was not administered[#]	Disease mortality had a positive correlation with age and had a negative correlation with the serum level of 25(OH)D. In hospitalized patients with COVID-19, low 25(OH)D was associated with severe disease and increased ICU admission and mortality rate

Due to the absence of studies analyzing the effect of vitamin D or melatonin in pwMS infected with SAR-CoV-2, only studies conducted in the general population have been included

25(OH)D 25-hydroxyvitamin D, *ICU* intensive care units

[#]25(OH)D levels were measured

[a]Control group

[b]Calcitriol group

[c]Calcifediol group

disease and increased ICU admissions [162]. However, the results obtained by Murai et al., 2021 show that a single dose of cholecalciferol does not cause any clinical benefit [166].

There is more and more research, stating that VD supplementation, especially an analog of this vitamin approved by the Food and Drug Administration (FDA), paricalcitol, has beneficial effects during SARS-CoV-2 infection [144]. However, the evidence regarding VD and the preventive or curative mechanisms against SARS-CoV-2 is limited and presents some controversies [151, 167–169]. In fact, a Lancet editorial is skeptical of the findings of the benefits of VD supplementation in COVID-19 patients, until more robust data are available [151, 170].

Melatonin

Melatonin (MLT) is an indolamide produced and secreted by the pineal gland in a circadian rhythm [171, 172]. It can also be secreted by extrapineal sources, such as cells of the immune system, brain, skin, and gastrointestinal tract [171]. It is a multifunctional molecule, which acts on the immune responses, oxidative process, apoptosis, and mitochondrial homeostasis [171, 173], exerting its effects through receptor-dependent and receptor-independent pathways [174]. In pwMS, it has been proven that there is a decrease in melatonin levels, a fact that has been correlated with the severity of the disease and some of the symptoms such as fatigue, insomnia, or depression [175].

MLT has been shown to have a great antioxidant and anti-inflammatory capacity [172]. These properties are of great importance in the preservation of bodily functions and homeostasis [176]. The combination of both properties has caused MLT to attract attention as a possible adjunctive treatment during SARS-CoV-2 infection [176].

Thanks to its anti-inflammatory and immunomodulatory effect, MLT regulates the levels of effector and regulatory T cells [177] and pro-inflammatory cytokines [172]. MLT has been shown to decrease Th1 and Th17 responses and improve levels of Tr1 regulatory cells [177]. It also has the ability to reduce the production of pro-inflammatory cytokines, especially TNF, IL-1β, and IFN [175, 177–180], as well as to increase the levels of anti-inflammatory cytokines, such as IL-10 and IL-4. This effect would make it possible to combat the cytokine storm caused by SARS-CoV-2. Likewise, MLT has the capacity to inhibit the inflammasomes activated by SARS-CoV-2, which are responsible for the triggering of the cytokine storm [181].

The SARS-CoV-2 infection induces, like MS, an increase in oxidative stress, with the consequent increase in ROS [100]. MLT could also combat this effect of COVID-19 since this hormone is characterized by having a powerful antioxidant function. It has the ability to reduce oxidative stress, being able to eliminate toxic free radicals [172] and reduce the toxicity induced by lipid peroxidation [182]. It also reduces the main biomarkers of oxidative stress [carbonylated proteins (CP), lipid peroxidation products (LPO), nitric oxide (NO), and malondialdehyde (MDA)] [17, 183–188] and oxidative damage to nuclear DNA both in vivo and in vitro [183], and has the ability to enhance sirtuins [189].

In addition to these properties, MLT has also been shown to have an antiviral effect, being able to decrease the viral titer and reduce the production of new progeny by inhibiting the replication of the virus [189–191]. Likewise, it has neuroprotective actions, reducing the damage to the CNS that SARS-CoV-2 infection can produce, restoring BBB homeostasis through the activation of its MT2 receptor [189, 192] and attenuating the activation of astrocytes and microglia [193].

For all that has been described, MLT could be a beneficial adjuvant treatment against COVID-19, both in pwMS and in the general population [194]. It is a hormone with a high safety profile, which has been shown to be a good adjuvant in respiratory diseases, while improving cardiac function in pulmonary arterial hypertension [176, 194, 195]. However, despite this, its efficacy against SARS-CoV-2 has not been demonstrated in clinical trials [176].

Chronic neurological consequences after infection by SARS-CoV-2

It is speculated that SARS-CoV-2, like other human coronaviruses, presents neurotropism, being able to invade the CNS and cause neurological symptoms and signs [53, 96]. On some occasions, neurological symptoms may precede the typical symptoms of the disease [196]. These symptoms have been termed NEURO-COVID [197], and can be divided into CNS manifestations, including headache, dizziness, stroke, altered consciousness, encephalitis, meningitis, and seizures, and Peripheral Nervous System (PNS) manifestations, including hyposmia, hypogeusia, Guillen-Barré syndrome, and myalgia [198]. Of all these symptoms, the most prevalent in European patients are hyposmia, detected in 85.6% of patients, and hypogeusia, detected in 88% of patients [199–201]. However, the mechanism through which SARS-CoV-2 accesses the CNS is not fully understood [53]. It has been proposed that SARS-CoV-2 can take a direct transynaptic route through the olfactory bulb [7, 202], only part of the CNS that is not protected by the dura mater [60], and invade neural tissue. After this, the virus can cause reactive astrogliosis and activation of the microglia, and produce a systemic inflammation that compromises the BBB and induces an alteration of homeostasis and death of neuronal cells [7, 202]. Another possibility is that SARS-CoV-2 can cross the BBB through vascular endothelial cells

and directly access the brain [198, 203]. However, other authors state that the mechanism responsible for the development of NEURO-COVID is an immunological mechanism rather than a direct neuroinvasion [107, 204]. We have already described that SARS-CoV-2 can interfere with the clinical course of MS, also exhibiting a long-term latency potential [96, 205], which could trigger disease exacerbations in pwMS that have recovered from COVID-19 [96]. However, there is another concern about the consequences that SARS-CoV-2 can have, due to its neurotropic characteristics. Although it is not known for sure what triggers MS, the pathology of this disease implies a possible viral etiology [206]. Thanks to experimental evidence, certain viruses are known to be associated with MS [206, 207]. The Epstein–Barr virus is one of the most important risk factors for this disease [208], but also infection by Human Herpesvirus 6 [180, 209] and by certain members of the coronavirus family [210]. With regard to human coronaviruses (HCoV), it has been proven that there is an association with the pathogenesis of MS [206]. Murray et al., 1992 revealed that murine coronavirus infection, in susceptible mice, led to an inflammatory demyelination similar to MS and detected coronavirus RNA and its antigens in demyelinating lesions [211]. One of the four endemic coronaviruses, OC43-CoV, has been detected in human brain samples from patients with neurological diseases such as Alzheimer's, Parkinson's and MS [210]. In addition, HCoV RNA has been found in the cerebrospinal fluid (CSF) of MS patients [212]. In relation to SARS-CoV-2, so far, 2 cases of MS have been described after recovery from COVID-19. Palao et al., 2020, reported the case of a 29-year-old woman who was infected by SARS-CoV-2 after which she experienced a reduction in visual acuity [1]. Laboratory results showed the presence of oligoclonal bands in the CSF, as well as periventricular lesions, making the diagnosis compatible with MS. They conclude that in this case, the virus could act as a precipitating factor, rather than MS being a direct consequence of the infection [1]. Another case, published by Fragoso et al., 2021, reported on a 27-year-old woman who suffered from COVID-19 and 6 months after virus infection, she developed dysesthesia, hypoesthesia, and hyperreflexia. Her MRI showed demyelinating lesions, of which 2 were enhanced by gadolinium and her CSF was positive for oligoclonal bands. They speculate that SARS-CoV-2, in this case, caused an autoimmune disease through a neuroimmunopathological condition induced by it [213].

In general, the proportion of patients with severe neurological symptoms is small compared to respiratory symptoms [60]. Although more research is needed to evaluate and monitor these symptoms, since their prevalence varies from one study to another [197]. This would be of great importance, given that there is concern about the possible increase in the worldwide incidence of MS and other autoimmune neurological disorders as a consequence of SARS-CoV-2, in the next 10 years [206]. In addition, another aspect that is going to be a major study objective is the so-called Long COVID, which causes sequelae and persistent symptoms [214]. A recently published systematic review estimated that 80% of SARS-CoV-2 infected patients developed one or more long-term symptoms [215]. Long COVID does not have a fixed pattern in all patients [216], although the most common symptoms are usually fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) [215]. Although this alteration is reported mainly in people who have had a severe course of the disease, it can also occur in individuals with a mild infection, who have not required hospitalization [215, 217]. Therefore, more studies are needed to define Long COVID [215] and identify the possible factors associated with these sequelae, which could be useful to optimize preventive follow-up strategies in primary care [214].

Conclusions

Since the beginning of the pandemic, it was thought that pwMS had a higher risk of SARS-CoV-2 infection than the general population, due in part, to the type of DMT they were using, especially if it was an anti-CD20 therapy. In general, the results on DMTs, reported to date, are contradictory. However, stopping treatment poses an even greater risk than SARS-CoV-2 infection, as it could lead to further progression of MS. Once infection has occurred, it is suspected that COVID-19 could cause a worsening of MS symptoms, as URVi are known to increase the risk of relapse in pwMS. Nevertheless, although studies are beginning on this topic, a definitive conclusion has not yet been reached and the effect of COVID-19 on the risk of exacerbation of MS is unknown.

In relation to the generation of immunity, it seems that those patients who have overcome COVID-19 and who are being treated with a B-cell depletion therapy and more specifically, with Ocrelizumab, are less likely to generate a detectable neutralizing antibody titer, which can prevent reinfection. Regarding vaccines, those that have been approved so far, seem to be safe in terms of the possibility of causing a relapse of MS. However, the humoral immune response can be affected by DMTs; therefore, the NMSS published specific guidelines for the time of the vaccine, in relation to the dosage of DMTs. In general, more immunological studies are needed to monitor responses, both humoral and cellular, to infection and to COVID-19 vaccines in pwMS.

To combat this disease, different active therapies are being used, but nutritional supplements with antioxidant,

antimicrobial, and immunomodulatory activities, such as vitamin D and melatonin, are postulated as promising therapeutic adjuvants. Both have properties that could be beneficial, both for pwMS and for the general population. Even so, more studies are needed to confirm its clinical efficacy against SARS-CoV-2.

Finally, it has been found that SARS-CoV-2 causes a series of neurological symptoms that affect a significant part of infected people, confirming the neurotropism of the virus. For this reason, it is of special importance to study the prevalence and to follow up those people who have presented these symptoms, since it is thought that this could cause an increase in neurological diseases in the coming years, including MS.

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Declarations

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