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REVIEW

Multiple Sclerosis, COVID-19 and Vaccines: Making the Point

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ABSTRACT

On 11 March 2020, the World Health Organization declared the coronavirus disease 19 (COVID-19) outbreak a pandemic. In this context, several studies and clinical trials have been conducted since then, and many are currently ongoing, leading to the development of several COVID-19 vaccines with different mechanisms of action. People affected by multiple sclerosis (MS) have been considered high-risk subjects in most countries and prioritized for COVID-19 vaccination. However, the management of MS during the COVID-19 pandemic has represented a new challenge for MS specialists, particularly because of the initial lack of guidelines and differing recommendations. Despite an initial hesitation in prescribing disease-modifying drugs (DMDs) in naïve and already treated patients with MS, most national neurology associations and organizations agree on not stopping treatment. However, care is needed especially for patients treated with immune-depleting drugs, which also require some attentions in programming vaccine administration. Many discoveries and new research results have accumulated in a short time on COVID-19, resulting in a need for summarizing the existing evidence on this topic. In this review, we describe the latest research results on the immunological aspects of SARS-CoV-2 infection speculating about their impact on COVID-19 vaccines' mechanisms of action and focused on the management of MS during the COVID pandemic according to the most recent guidelines and recommendations. Finally, the efficacy of COVID-19 and other well-known vaccines against infectious disease in patients with MS on DMDs is discussed.

Keywords: Multiple sclerosis; COVID-19; Disease-modifying treatment; Vaccines; Recommendations

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Key Summary Points

In patients with multiple sclerosis (MS), older age, male sex, comorbidities, higher Expanded Disability Status Scale and treatment with anti-CD20^{+} monoclonal antibodies are risk factors for a severe coronavirus disease 19 (COVID-19) course.

Interferon beta (IFNβ) has been associated with a decreased risk for COVID-19, and defects in IFN immunity could be a risk factor for a severe COVID-19 course.

Most of the international and national recommendations agree on not stopping disease-modifying drugs in already treated patients with MS, but risks and benefits of starting a treatment with a particular drug should be considered in naïve patients.

Patients with MS should vaccinate as soon as possible against SARS-CoV-2. For patients treated with ocrelizumab, rituximab and alemtuzumab, timing should be discussed with the MS specialist to maximize the effectiveness of the COVID-19 vaccine.

There is no currently evidence that the currently available COVID-19 vaccines may lead to clinical relapses in patients with MS.

Patients with MS should vaccinate against SARS-CoV-2 as soon as possible with the available vaccines, which are safe and effective in protecting against COVID-19.

INTRODUCTION

The coronavirus disease 19 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has completely dominated the social, political, economic and health scenario since it was declared by the World Health Organization (WHO) on 11 March 2020 [1]. By the end of 2020, WHO had already confirmed more than 82.8 million cases and about 1.9 million deaths worldwide [2], and the first COVID-19 vaccine had received conditional marketing authorization by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [3, 4].

Most people, particularly young and healthy subjects, experienced only the first phase of COVID-19, characterized by no symptoms or mild flu-like ones. However, SARS-CoV-2 infection can lead to the development of a bilateral interstitial pneumonia with respiratory failure and, in the most severe cases, to a hyper-inflammatory state driven by a cytokine storm, possibly presenting with sepsis, disseminated intravascular coagulation and multiorgan failure [5, 6].

Different vaccination strategies have been adopted by almost all countries in the world. Almost everywhere priority has been given to the most vulnerable subjects, at high risk for complications associated with COVID-19 due to older age or significant comorbidities.

Among them, people affected by multiple sclerosis (pwMS) have been officially regarded as high-risk subjects in several countries and have been generally prioritized for COVID-19 vaccination [7]. Since most pwMS are on disease-modifying treatments (DMTs) and 15 vaccines are currently used in at least one country among 115 vaccine candidates [8], some questions have arisen: which vaccines should be recommended and how should DMTs be managed in pwMS in the COVID-19 era?

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

IMMUNOLOGICAL CONSIDERATIONS ABOUT COVID-19

SARS-CoV-2 belongs to a group of enveloped single-strand RNA viruses, called coronaviruses, as well as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). They are

characterized by four structural proteins, including envelope, membrane, nucleocapsid (N) and spike (S) proteins [9]. In recent months, several virus variants have spread worldwide, some of them characterized by an increase in transmissibility and a reduced response to the currently available vaccines [10].

The infection by SARS-CoV-2 initially and mainly involves the respiratory tracts through interaction between the angiotensin-converting enzyme 2 (ACE2) receptor expressed in the bronchial and alveolar epitelium and viral S protein [11]. The virus seems to suppress the attempt of the innate immune system to control the infection, leading to a protracted presymptomatic period (2–12 days) with uncontrolled viral replication, particularly observed when the activation of $CD8^+$ T cells is delayed. In vulnerable subjects, this may favor a dysregulated inflammatory response leading to acute respiratory distress syndrome and potentially life-threatening cytokine release syndrome with consequent heart failure and multiorgan failure [12].

Humoral response, mainly against S and N protein in natural adaptive immunity, develops after 1–2 weeks and seems to be higher and more sustained in symptomatic compared with asymptomatic subjects [13]. The neutralizing antibody titer that can be sufficient to protect against SARS-CoV-2 infection is not known, nor is the lifetime of the humoral response [11].

It seems that T cell-mediated immunity is crucial, as is the humoral immune response, in protecting against SARS-CoV-2, leading to major implications in COVID-19 vaccination design and development [14]. In a study involving 78 patients who recovered from SARS-CoV-2 infection, a comparable T cell immune response was quantified through interferon-γ ELISpot in both patients with high and undetectable IgG against S protein [15]. The same technique was used in another study, reporting a significantly higher T cell immune response in convalescent patients compared with healthy donors, with the additional observation of a trend toward an increased frequency of NK cells in follow-up patients compared with newly discharged ones [16]. T cell receptor-dependent activation-induced marker assays were used in another study to detect functional circulating SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells in patients who recovered from COVID-19, which were identified respectively in about 70% and 100% of patients [17].

Among T cell-mediated immunity, the role of T regulatory cells (Tregs), a subset of $CD4^+$ T cells, is emerging as particularly crucial. Tregs exert a protective role in controlling tissue damage due to the immune response to viral infections, as pointed out in other studies focusing on respiratory syncytial virus infection [18], herpes simplex virus [19], coronavirus-induced encephalitis [20] and HCV-induced liver injury [21]. Indeed, Tregs can shift the balance between the effector and the regulatory functions toward a downregulation of antiviral T cell responses, preventing the hyperactivation of the immune system and the consequent lung injury and cytokine storm [22]. Several recent studies reported a lower level of circulating Treg in patients who developed severe COVID-19 compared with patients exhibiting a mild or moderate course [22]. Moreover, COVID-19 patients exhibited higher levels of Treg compared with healthy controls [23, 24], but no differences were observed in COVID-19 patients before and after the age of 45 years [25]. It could be speculated that the efficacy of currently available vaccines against COVID-19 may be partly related to the expansion of Tregs and to the generation of a memory pool of this subset of $CD4^+$ T cells [26]. Indeed, Tregs may prevent a severe COVID-19 course in vaccinated patients in the event of a successive infection by SARS-CoV-2 (Fig. 1).

MULTIPLE SCLEROSIS AND COVID-19

Risk of SARS-CoV-2 infection and COVID-19 course in MS

MS has been associated with a generally higher infection risk and a two-fold higher rate of hospitalized infections, especially urinary tract, pulmonary, skin and opportunistic infections [27–29]. As for other autoimmune diseases [30], the increased risk could be related to both a

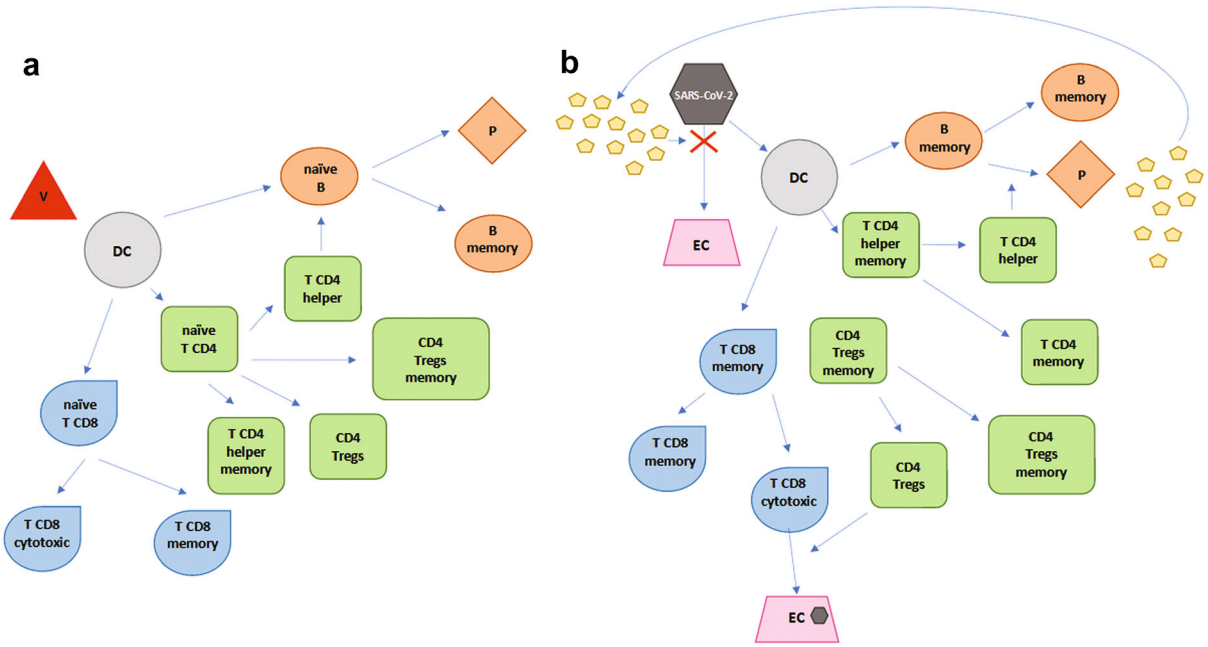

Fig. 1 Development of T-cell and B-cell response after vaccination against SARS-CoV-2 and subsequent activation of the immune system in case of infection. The administration of vaccines against SARS-CoV-2 (V) determines the activation of dendritic cells (DC), with subsequent antigen processing and presentation to naïve B, T CD4+ and T CD8+ lymphocytes (**a**). Naïve B cells differentiate into plasma cells (P), leading to antibody production, and B memory cells. Naïve T CD8+ cells differentiate into memory and cytotoxic cells. Naïve T CD4+ cells, including a subset of Tregs, differentiate into memory and effector T cells (T CD4+ helper and Tregs). T CD4+ helpers support the differentiation of B cells into plasma cells, favoring the humoral immune response. When SARS-CoV-2 infection occurs in a vaccinated subject, the virus initially enters the upper airway epithelial cells (ECs) (**b**). Memory B cells are able to differentiate into plasma cells (P) with the support of T CD4+ helper cells, leading to antibody production and to regeneration of the pool of memory B cells. Memory T CD8+ cells differentiate into T cytotoxic cells, able to destroy infected cells, and regenerate the pool of memory T CD8+ cells. Tregs modulate the immune response by downregulating antiviral T cell responses, preventing the hyperactivation of the immune system and the consequent tissue damage and cytokine storm driven by T cells, leading to severe COVID-19

disease-related dysregulation of the immune system and the use of immunomodulatory or immunosuppressive drugs [31].

Several studies and data from clinical trials have confirmed an increased infection risk over time only for some DMTs, including natalizumab (NTZ), fingolimod (FTY), ocrelizumab (OCR), alemtuzumab (ALM) and cladribine (CDA) as well as for immunosuppressive drugs and rituximab (RTX), used off-label for MS treatment [32, 33]. In addition, some recent registry- and population-based retrospective studies attributed the lowest infection risk to injectable DMTs (interferon beta, IFNβ, and glatiramer acetate, GA) [34, 35] and the highest risk to RTX [34], with some controversies over NTZ and FTY [34, 35].

Nevertheless, several studies investigating SARS-CoV-2 infection in pwMS have not detected an increased risk of infection in these patients [36–38], nor in those suffering from other systemic autoimmune diseases [39], but a higher risk of hospitalization has been reported [36].

In a retrospective study involving 758 subjects, pwMS exhibited similar incidence, outcomes and risk factors for COVID-19 compared to the general population [38]. In the MS

cohort, age, contact with a confirmed case, MS duration and time exposure to an anti-CD20$^+$ treatment were independent risk factors for COVID-19. Among them, only age was associated with a severe course of COVID-19.

An international study involving > 30,000 pwMS identified obesity, Black/African ancestry and comorbidities as risk factors for SARS-CoV-2 infection, without any differences between patients and the general population [31].

In a French multicenter, retrospective, observational study involving 347 pwMS infected with SARS-CoV-2, a higher risk of severe COVID-19 was associated with older age, obesity, male sex and higher EDSS [40]. Noticeably, cardiovascular and pulmonary comorbidities, as well as diabetes and obesity, were reported with high frequency in subjects with severe COVID-19, while no association between severe COVID-19 and any DMTs emerged in this study. However, in a successive pooled analysis including two large cohorts of patients from Italy and France (1066 and 721 patients, respectively), treatment with anti-CD20$^+$ mAbs was associated with a two-fold increased risk of a severe COVID-19 course, while a protective role of IFNβ emerged [41].

In this regard, a role of auto-antibodies (auto-Abs) against type I IFN or monogenic defects at loci involved in type I IFN immunity has been recently claimed as a risk factor for a life-threatening COVID-19 course [42, 43]. This has called into question the potential beneficial effect of treatment with IFNβ in pwMS.

Management of MS during the COVID-19 pandemic

So far, results from several studies on the impact of DMTs on the COVID-19 disease course have varied, and the debate is still open. On the one hand, the involvement of an exaggerated immune response in severe COVID-19 cases has emerged, raising doubts about the effective risk attributable to DMTs [44]. On the other hand, data are limited, and the benefit-risk ratio of stopping treatment possibly causing a rebound disease activity has to be taken into account [45].

In this context, a change in the frequency of DMT prescription during the SARS-CoV-2 pandemic was expected in clinical practice and has been observed. The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) conducted an online survey between March and July 2020, completed by 360 neurologists from 52 countries [46]. Changes in DMT management were reported by 70%, with 23% preferring to avoid immune-depleting drugs in naïve pwMS during the pandemic and 43% considering postponing further administrations of anti-CD20$^+$ mAbs in patients already treated with these DMTs. No particular concerns were declared about the use of IFNβ and GA nor of DMF, TFM and FTY in patients who did not exhibit moderate-to-severe lymphopenia. Noticeably, the activation ex novo of new strategies, specifically telemedicine, to manage and follow-up pwMS despite COVID-19 restrictions was reported by 73% and implemented by 17% of neurologists.

In another survey administered to 243 US and Canadian neuroimmunology-focused neurologists, 54% considered some DMTs as safer than others, particularly GA (95%), IFNβ (80%) and TFM (50%) [47]. Conversely, several neurologists reported avoiding the prescription of certain DMTs, especially ALM (61%), CDA (47%), OCR (38%), RTX (35%) and NTZ (34%), while 4% considered not starting any DMTs.

Similar results were reported by another nationwide survey involving 41 neurologists, who reported the interruption of treatment with ALM (21.4%), CDA (11.9%), OCR and RTX (16.7%) among their pwMS, while 38.1% considered the adoption of extended dosing intervals for NTZ [48].

A Dutch study involving 86 pwMS confirmed no associations between DMT and COVID-19 disease course nor between lymphocyte count and disease severity [49]. Furthermore, a community-based prospective observational study, developed as part of the UK MS Register, confirmed no differences in DMT use among pwMS with COVID-19 [37], while the use of IFNβ has been even associated with a decreased risk of COVID-19 in several studies [31, 41, 50–52].

Similarly, the North American Registry of MS reported a minor risk of admission to intensive

care units (ICUs) in pwMS on DMF and NTZ treatment compared with untreated subjects [53]. Differently, in this MS cohort, the use of steroid treatment in the prior 2 months emerged as a risk factor for hospitalization and fatal course.

Whereas an acceptable safety profile emerged for the majority of DMTs toward COVID-19 in several studies, the use of anti-$CD20^+$ monoclonal antibodies (mAbs) has recently emerged as a risk factor for severe COVID-19. In a large retrospective register-based study conducted by the Multiple Sclerosis and COVID-19 (MuSC-19) group, treatment with RTX or OCR was significantly associated with an increased risk of severe COVID-19, and a worse outcome was also related to high-dose steroid treatment occurring in the previous month [50]. Other studies reported the use of anti-$CD20^+$ mAbs, especially after long treatment exposure, as an independent risk factor for COVID-19 [31, 36, 38, 41, 54] and hospitalization [53].

Among pwMS treated with OCR in ten ongoing Roche/Genentech clinical trials up to 31 July 2020, 51 of 4000 patients were identified as confirmed or suspected cases of COVID-19 [55]. Of them, 31.4% were hospitalized, 19.6% had a severe course, and 5.9% died, while 68.6% had mild or moderate disease, independent from the period of DMT exposure. Additionally, from the OPTUM ® database, among an estimated 97,502 subjects treated with OCR in the US, 48 pwMS were confirmed to have COVID-19, with an incidence rate of 0.05% [55].

Differently, no severe COVID-19 cases have been observed in subjects treated with ALM, despite concerns being raised for pwMS treated with this DMT due to the related prominent lymphopenia [56, 57].

Comprehensively, these findings led national neurology associations and organizations to produce guidelines on the management of MS during the COVID-19 pandemic, based on expert consensus statements [58] (Table 1). At first, considering the mechanisms of action and long-lasting effects, most of them advised neurologists to reconsider the use of immunodepleting DMTs in newly diagnosed pwMS and to postpone the redosing between 6 and 12 months [59–62], but these considerations were not univocal [63].

Most of the international and national recommendations agreed on not stopping other DMTs in already treated pwMS, even during active COVID-19 infection, and on favoring the choice of IFNβ, GA and NTZ in naïve pwMS, but always discussing risks and benefits of DMTs for each patient [58].

Opinions about the use of dimethyl fumarate (DMF), teriflunomide (TFM) and FTY in newly diagnosed pwMS have varied, since recommendations by the MS International Federation, the European Multiple Sclerosis Platform and the MS Society of the UK raised some doubts about starting a new treatment with these DMTs during the pandemic [60, 61, 64].

Particular consideration should be made for patients planning to undergo autologous hematopoietic stem cell transplantation (HSCT), often after failure of highly active DMDs [65]. As recommended by the European Society for Blood and Marrow Transplantation (EBMT), all prevention practices implemented during the COVID-19 pandemic should be strictly applied to patients and health care staff and alternative treatments should be considered, since HSCT recipients are at high risk for SARS-CoV-2 infection regardless of the conditioning regimen used [66, 67]. Accordingly, only patients with a clear risk/benefit ratio, not diagnosed with COVID-19 and with no severe comorbidities should undergo HSCT during the current pandemic [67]. In a recent retrospective study conducted by Sharma and colleagues, among 318 HSCT recipients (134 autologous, 184 allogenic) diagnosed with COVID-19, 14% of patients required mechanical ventilation and 21% died, with an overall survival probability at 30 days after COVID-19 diagnosis of 67% [68].

DMTS AND VACCINES

Considering the scarce availability of data on the response of pwMS to COVID-19 vaccines, previous results from clinical trials and real-world experience exploring the response to other vaccines provided a basis for estimating their safety and efficacy profile (Table 2).

Table 1 Recommendations from main national neurology associations and organizations for the management of MS during COVID-19 pandemic

DMDs	Recommendations
IFNβ	Any adjustments required in newly diagnosed pwMS, in those who currently take the drug or in patients with COVID-19 [59–61, 132–135]
GA	Any adjustments required in newly diagnosed pwMS, in those who currently take the drug or in patients with COVID-19 [59–61, 132–135]
DMF	Any adjustments required in newly diagnosed pwMS, in those who currently take the drug or in patients with COVID-19 [59, 60, 134, 135]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59]
	Patients currently taking this treatment should continue, considering more frequent monitoring of immune cell counts [132, 133]
TFM	Any adjustments required in newly diagnosed pwMS, in those who currently take the drug or in patients with COVID-19 [59, 60, 134, 135]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59]
	Patients currently taking this treatment should continue, considering more frequent monitoring of immune cell counts [132, 133]
	Consider the risk/benefit ratio of starting a new treatment with this drug [59]
FTY	Patients currently taking this treatment should continue [134], considering more frequent monitoring of immune cell counts [132, 133], and vaccinate as soon as possible [61]
	Any adjustments required in pwMS currently taking the drug [59]
	Consider initiating treatment after the patient is fully vaccinated [61]
	Consider the risk/benefit ratio of starting a new treatment with this drug [59]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59]
NTZ	Any adjustments required in newly diagnosed pwMS, in those who currently take the drug or in patients with COVID-19 [59, 60, 134, 135]
	Patients currently taking this treatment should continue, considering more frequent monitoring of immune cell counts [132, 133]
	Consider home infusion in regions with high COVID-19 incidence [136]
	Extended interval dosing could be considered [135]
OCR	Consider delaying treatment initiation in older patients and in those with comorbidities [132, 133, 135, 136]
	Consider on a case-by-case basis the risk/benefit profile in pwMS with additional risk factors for worse outcomes from COVID-19 (age > 60 years, male gender, comorbidities, higher levels of disability) [59, 132, 134]
	Retreatments should be administered if clinical indication is met [134]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59, 132, 133]
	Consider the risk/benefit in PPMS patients [135]
	Consider starting treatment after full vaccination [61]

Table 1 continued

DMDs	Recommendations
	Consider home infusion in regions with high COVID-19 incidence [136]
RTX	Consider delaying treatment initiation in older patients and in those with comorbidities [132, 133, 136]
	Consider on a case-by-case basis the risk/benefit profile in pwMS with additional risk factors for worse outcomes from COVID-19 (age > 60 years, male gender, comorbidities, higher levels of disability) [59, 132, 134]
	Retreatments should be administered if clinical indication is met [134]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59, 132, 133]
	Consider home infusion in regions with high COVID-19 incidence [136]
ALM	Consider delaying treatment initiation in older patients and in those with comorbidities [132, 133, 136]
	Consider to initiate treatment after the patient is fully vaccinated [61]
	Consider on a case-by-case basis the risk/benefit profile in pwMS. Retreatments should be administered if clinical indication is met [59, 134, 135]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59, 132, 133]
	Consider home infusion in regions with high COVID-19 incidence [136]
CDA	Consider delaying treatment initiation in older patients and in those with comorbidities if disease activity allows it [133, 136]
	Consider initiating treatment after the patient is fully vaccinated [61]
	Consider on a case-by-case basis the risk/benefit profile in pwMS. Retreatments should be administered if clinical indication is met [59, 134, 135]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59, 132, 133]
BAF	Consider the risk/benefit ratio of starting a new treatment with this drug [59]
	More restrictive protection measures should be considered for pwMS treated with this DMT [59]
	Consider initiating treatment after the patient is fully vaccinated [61]
	Patients currently taking this treatment should continue, considering more frequent monitoring of immune cell counts [59, 132, 133]

DMT disease-modifying treatment, *pwMS* patients with multiple sclerosis, *IFNβ* interferon beta, *GA* glatiramer acetate, *DMF* dimethyl fumarate, *TFM* teriflunomide, *FTY* fingolimod, *NTZ* natalizumab, *OCR* ocrelizumab, *RTX* rituximab, *ALM* alemtuzumab, *CDA* cladribine, *BAF* siponimod

In this regard, IFNβ and GA were not expected to decrease the humoral immune response after COVID-19 vaccination, based on the comparable rate of immunization developed by treated patients and controls after vaccinations against influenza viruses [32, 69–72]. Similar considerations have been assumed for pwMS on TFM and DMF, who generally did not exhibit a decreased serological response to vaccines compared with IFNβ-treated patients [73, 74].

Although live-attenuated vaccines should not be administered to pwMS on FTY, inactivated ones do not raise particular safety concerns but may be less effective when administered during FTY and within 2 months from the last administration [70, 72, 75, 76]. Differently, the effectiveness of influenza

vaccines in pwMS treated with CDA does not seem to be reduced [77, 78].

Some evidence exists about a decreased serological immune response to vaccines in pwMS treated with NTZ compared with healthy controls [70, 79, 80]. Although a loss of effectiveness is expected when vaccines are administered during treatment with ALM and within 6 months from the last dosing, a pilot case-control study reported comparable humoral immune responses after the administration of several vaccines in pwMS treated with ALM and controls [81, 82]. PwMS treated with ALM should not receive live-attenuated vaccines during and within the 6 weeks from the last infusion, and similar safety recommendations are provided for treatment with the anti-$CD20^+$ mAbs OCR and RTX, which also affect the development of an adequate humoral immune response toward several vaccines [75, 83–85].

According to EBMT recommendations [86], patients should be preferably vaccinated against preventable infections before undergoing HSCT; in any event, a precise timing of immunization should be considered. Several studies confirmed that antibody titers reduce after HSCT and in the following years [87, 88] and that revaccination or additional vaccine doses should be considered after HSCT [89], particularly against some infections which are more frequent and severe in transplanted patients (pneumococcus, *Haemophilus influenzae* type b, influenza, varicella-zoster virus) [86]. As a general rule, the humoral response to vaccines is low during the first 6 months after HSCT and increases from 25 to 60% when immunization occurs after at least 2 years from immunosuppression [86]. Moreover, live-attenuated vaccines should not be administered except in special conditions.

MULTIPLE SCLEROSIS AND COVID-19 VACCINES

COVID-19 Vaccines

Since the end of 2020, more than a billion COVID-19 vaccine doses have been administered worldwide, with different national policies and vaccination strategies. A huge number of molecules with different mechanisms of action has been explored, and > 20 vaccines were approved by at least one country in the first half of 2021, including inactivated, non-replicating viral vector, protein subunit and messenger RNA (mRNA) vaccines [8]. All the approved vaccines require parenteral administration and target the development of neutralizing antibodies against S protein among the four structural viral proteins, since they are only able to confer protection against SARS-CoV infections [90]. Differently, while viral vector and live-attenuated vaccines seem suitable to trigger an adequate $CD8^+$ T cell-mediated immune response, inactivated, protein subunit and virus-like particle vaccines do not. Nucleic acid-based vaccines may also trigger a moderate T cell-mediated response, as reported for the so far approved mRNA vaccines, depending on the chosen adjuvant and formulation [11]. This is a focal point since the currently available recommendations for MS patients only consider the humoral immune response to COVID-19 vaccines, although vaccination may protect patients under B-cell-depleting treatments with no humoral response by inducing a memory pool of T cells against SARS-CoV-2.

mRNA vaccines encoding S protein have been developed by Pfizer/BioNTech (BNT162b2, Comirnaty®) and Moderna (mRNA-1273, Spikevax®). These vaccines do not contain any live materials, consisting of lipid nanoparticles delivering mRNA into host cells, where it guides the synthesis of SARS-CoV-2 S antigen, to trigger the cellular and serological immune response [57, 91]. Both received conditional marketing authorization from the Commission of EMA in December 2020 and January 2021 [3, 92], respectively, and by FDA in the US in December 2020 [4, 93]. A very high efficacy rate in preventing COVID-19 infection of 94% and 95% has been reported in phase 3 trials for the two-dose regimen of mRNA-1273® and Comirnaty®, respectively, whose adverse events mostly include headache, mild-to-moderate pain at the injection site and fatigue [94, 95] (Table 3).

FDA and EMA also approved the COVID-19 viral vector vaccine Ad26.COV2.S developed by

Table 2 Immune response to vaccines in patients treated with DMDs

IFNβ	An adequate humoral response (hemagglutination titer ≥ 40) to influenza A virus subtypes H1N1 and H3N2 vaccines and influenza B vaccine was detected in a similar proportion of patients on IFNβ-1a and controls [69]
	High seroprotection rates (> 84%) after trivalent seasonal influenza vaccination (H1N1, H3N2 and influenza B) in IFNβ-treated patients [70]
	IFNβ did not decrease seroprotection toward pandemic H1N1 (swine flu) and seasonal influenza vaccination compared with controls (44.4% vs 43.5%) [71]
	No significant differences in rates of protection against H1N1 for patients treated with IFNβ-1a/1b compared with controls at 3, 6 and 12 months [72]
GA	No significant differences in rates of protection against H1N1 for patients treated with GA compared with controls at 3, 6 and 12 months [72]
	High seroprotection rates against influenza A subtype H3N2 (73.1%) and influenza B (80.8%), comparable to patients on IFNβ [70]
	Reduced seroprotection to seasonal influenza and swine flu was reported in patients on GA compared with controls (21.6% vs 43.5%) [71]
DMF	In DMF compared with IFNβ-treated patients, responder rates (≥ twofold rise) to tetanus-diphtheria toxoid, pneumococcal polyvalent and meningococcal tetravalent oligosaccharide vaccines were comparable [74]
TFM	Seroprotection rates after influenza vaccination type H1N1 were comparable for TFM- and IFNβ-treated patients [73]
	For H3N2, fewer patients in the TFM group exhibited seroprotection to H3N2 compared with IFN-β-1 group (61% vs 82%) [73]
FTY	The responder rates (seroconversion or increase ≥ fourfold in antibody titers) for influenza vaccine in FTY and placebo groups were 54% vs 85% at 3 weeks and 43% vs 75% at 6 weeks post-vaccination [76]
	The responder rates (seroconversion or increase ≥ fourfold in antibody titers) for tetanus toxoid booster vaccine in FTY and placebo groups were 40% vs 61% at 3 weeks and 38% vs 49% at 6 weeks post-vaccination [76]
	Decreased seroprotection against H1N1 in NTZ-treated patients compared with IFNβ, GA and untreated patients at 3, 6 and 12 months [72]
	Decreased seroprotection against influenza A subtype H3N2 (33.3%) and influenza B (66.7%) was reported compared with patients on IFNβ and GA [70]
NTZ	Decreased seroprotection against influenza A subtype H3N2 (28.6%) and influenza B (57.1%) was reported compared with patients on IFNβ and GA [70]
	Decreased seroprotection against H1N1 in NTZ-treated patients compared with IFNβ, GA and untreated patients at 3 and 6 months, not at 12 months [72]
	Humoral responses against influenza B and influenza A vaccines were not different between NTZ-treated patients and healthy controls [79]
	A reduced seroprotection to seasonal influenza and swine flu was reported in patients on GA compared with controls (23.5% vs 43.5%) [71]
	NTZ-treated patients exhibited similar levels of anti-tetanus toxoid IgG antibodies compared with untreated patients [80]

Table 2 continued

OCR	Humoral response to tetanus toxoid vaccine at 8 weeks was decreased in OCR-treated patients compared with untreated or IFNβ-treated patients (23.9% vs 54.5%), with vaccine administered 12 weeks after the last administration [83]
	Positive response rate to ≥ 5 serotypes in 23 PPV at 4 weeks was observed in 71.6% in OCR-treated patients and 100% in the control group, with vaccine administered 12 weeks after the last administration [83]
	Seroprotection rates at 4 weeks against 5 influenza strains ranged from 55.6% to 80.0% in OCR-treated group and 75.0% to 97.0% in the control group, with vaccine administered 12 weeks after the last administration [83]
RTX	RTX-treated patients did not exhibit a significant increase of IgM and IgG H1N1- and H3N2-specific antibodies compared with healthy controls. In patients treated with RTX 6–10 months before vaccination, IgG response to vaccination was restored, but not IgM response [84]
ALM	Vaccine responses in ALM-treated patients, within 6 months of treatment, were normal toward tetanus, diphtheria and polio vaccines, meningococcus C, pneumococcal antigens [82]
CDA	Adequate antibody titers developed when vaccination against influenza occurred early (1.5–6 months of the first year of treatment or 1–4.5 of the second year) or late (months 8.5–10.5 of year 1) [77, 78]

IFNβ interferon beta, *GA* glatiramer acetate, *DMF* dimethyl fumarate, *TFM* teriflunomide, *FTY* fingolimod, *NTZ* natalizumab, *OCR* ocrelizumab, *RTX* rituximab, *ALM* alemtuzumab, *CDA* cladribine

Janssen Pharmaceutica NV (in February and March 2021, respectively), while only EMA approved ChAdOx1-S recombinant viral vector vaccine by AstraZeneca, now known as Vaxzevria, in January 2021 [96–98]. Non-replicating adenoviruses act as a carrier for the S gene of SARS-CoV-2, needed to ultimately synthetize S protein and stimulate both the innate and the adaptive immune responses [99]. ChAdOx1-S recombinant vaccine exhibited an efficacy of 62.1% after two standard doses [100], while Ad26.COV2.S had efficacy of 66.9% against symptomatic moderate and severe SARS-CoV-2 infection [101] (Table 3).

EMA also started rolling review of COVID-19 vaccines from Novavax (protein-based), Curevac AG (mRNA) and Gamaleya's Sputnik V (viral vector, approved in Russia in August 2020) for formal marketing authorization application [102, 103].

Currently, 41 vaccines are under assessment in phase 3 clinical trials, 56 in phase 2 and 36 in phase 1, while trials on 5 vaccines have been interrupted. Among them, further mechanisms of action have been tested, such as replicating viral vector, DNA and virus-like particle (VLP) vaccines [8].

Safety and efficacy considerations on COVID-19 vaccines and MS

Actually, no particular safety concerns have arisen related to the use of the currently approved COVID-19 vaccines in pwMS on DMT, also considering that no live-attenuated COVID-19 vaccines have been approved so far. Moreover, in a recent study involving 555 pwMS who underwent vaccination with BNT162b2 vaccine, no increase of relapse activity emerged [104]. As further confirmation, a recent prospective study including 324 patients with MS who received BNT162b2 vaccine did not detect an increased risk of clinical relapses during the 2-month short-term follow-up after the first vaccine dose [105].

The concurrent use of DMTs, though, may lead to a decrease in the effectiveness of COVID-19 vaccines. Comprehensively, risks related to SARS-CoV-2 infection, including COVID-19-related complications and MS exacerbations, led to the unanimously accepted recommendation to not stop current DMT and to vaccinate as early as possible with the available COVID-19 vaccines [106].

Table 3 Characteristics of currently approved vaccines against SARS-CoV-2 by the EMA and FDA

Vaccine	Type	Age	Efficacy	Doses	Approval	FDA/EMA warnings
Comirnaty (Pfizer-BionTech)	mRNA	≥ 12	95% against severe disease in phase 3 trials [94]	2 (21 days apart)	EMA: December 2020 [3]	Myocarditis, pericarditis [141]
			84.3% against hospitalization (real-world evidence) [137]	Fully effective after 2 weeks from the 2nd shot	FDA: December 2020 [4]	
			88% against symptomatic disease (Delta variant) [138]			
			42% against symptomatic disease (Delta variant) [139]			
			96% against hospitalization (Delta variant) [140]			
Spikevax (ex COVID-19 vaccine Moderna)	mRNA	≥ 12	94% against symptomatic disease (86% in ≥ 65 years) [95]	2 (28 days apart)	EMA: January 2021 [92]	Myocarditis, pericarditis [141]
			90% against symptomatic disease (real-world evidence) [137]	Fully effective after 2 weeks from the 2nd shot	FDA: December 2020 [93]	
			76% against symptomatic disease (Delta variant) [139]			
Vaxzevria (ex COVID-19 vaccine AstraZeneca)	NRVV	≥ 18	62–76% against symptomatic disease (85% in ≥ 65 years) [100, 142]	2 (4–12 weeks apart)	EMA: January 2021 [97]	Blood clotting disorders [144]
			100% against severe disease [142]		FDA: Not approved	
			62–67% against symptomatic disease (Delta variant) [138, 143]			
			90% against hospitalization (Delta variant) [140]			

Table 3 continued

Vaccine	Type	Age	Efficacy	Doses	Approval	FDA/EMA warnings
Janssen (Johnson&Johnson)	NNVV	≥ 18	67% against symptomatic disease [101]	1 Fully effective after 2 weeks	EMA: March 2021 [96]	Blood clotting disorders [148]
			85% against severe disease (Beta variant; included a subset of Delta variants) [145, 146]		FDA: February 2021 [98]	Guillain-Barré syndrome [149]
			72% against symptomatic disease [147]			
			86% against severe disease [147]			

NNRV non-replicating viral vector, *EMA* European Medicine Agency, *FDA* Food and Drug Administration

Evidence about the effectiveness of COVID-19 vaccination in pwMS on different DMTs is sparse. Based on their mechanisms of action and results from previous studies, major doubts could involve cell-depleting therapies (anti-CD20$^+$ mAbs, ALM and CDA) and FTY. Accordingly, among US and Canadian neurologists participating in an online survey, 80% agreed that some DMTs may not allow patients to develop an adequate serological immune response after COVID-19 vaccination, particularly referring to anti-CD20$^+$ mAbs ocrelizumab and rituximab (84% and 83% respectively), alemtuzumab (78%), cladribine (60%) and steroid treatment (53%) [47].

In this regard, previous studies detected reduced antibody titers and frequent seroconversion after vaccination in pwMS treated with anti-CD20$^+$ mAbs [107], but other considerations are needed. OCR and RTX selectively target CD20$^+$ antigen expressed on pre-B cells, mature and memory B cells, leading to their depletion, not affecting innate immunity, T cells, pre-existing humoral immunity and B cell reconstitution [107, 108]. The effects of anti-CD20$^+$ mAb-related hypogammaglobulinemia on prior immunization are not known [107, 109]. However, in patients with autoimmune diseases treated with RTX, an adequate recall immune response to influenza vaccines was observed after CD19$^+$ cell recovery, despite a lack of influenza-specific memory B lymphocytes [110].

In this context, a recent international cohort study, conducted as part of the Italian Multiple Sclerosis and COVID-19 (MuSC-19) project on 423 patients, reported a significant association between anti-CD20$^+$ treatment and a reduced probability of developing a humoral immune response to SARS-CoV-2 after infection [111], confirming previous evidence from single observations [112] and the results of a case-control study involving 24 pwMS treated with OCR in the 6 months preceding SARS-CoV-2 infection [113]. Differently, treatment with other DMDs did not affect the development of antibodies after COVID-19 in the same study [111]. Additionally, preliminary evidence of a decreased humoral response in patients treated with OCR compared with healthy controls after vaccination with BNT162b2 vaccine has recently emerged [114].

Nevertheless, two recent studies showed promising results related to the development of

an adequate T-cell response in more than 96% of patients treated with anti-CD20^{+} mAbs, regardless of the low humoral response exhibited after SARS-CoV-2 infection or COVID-19 vaccination [115, 116].

As for FTY, a reduced immune response to other vaccines has already been reported [117] as well as evidence of an altered cellular and humoral immune response after SARS-CoV-2 vaccination in a patient treated with this DMT [118]. Despite some concerns about the development of an adequate response after COVID-19 vaccines in such patients [119], these should be administered to patients, possibly encouraging the evaluation of the immunization state after at least 2 weeks from the last dose.

Differently, no differences in the development of a robust humoral response were detected between patients treated with NTZ and healthy controls 7 days after the second dose of BNT162b2 mRNA vaccine [120].

Confirming these preliminary considerations, a recent study explored the development of a protective humoral response in 125 pwMS on different DMTs and in 47 healthy controls within 4.5–6.5 weeks following the second dose of BNT162b2-COVID-19 vaccine [121]. PwMS treated with CDA, untreated ones and healthy controls exhibited comparable SARS-CoV-2 IgG against S protein, while 22.7% of those on OCR and only 3.8% of patients on FTY developed a protective humoral response.

Robust evidence is still lacking on the durability of protection induced by COVID-19 vaccines. A recent study involving 27 healthy participants revealed a substantial reduction of neutralizing SARS-CoV-2 IgG at 3 months post-vaccination with mRNA vaccines against all variants [122]. In this regard, Pfizer/BioNTech disclosed data coming from more than 44,000 enrolled volunteers, detecting a decrease from 96 to 84% in BNT162b2 vaccine efficacy over 6 months, with an average drop of 6% every 2 months after vaccination [123]. Similarly, mRNA-1273 vaccine developed by Moderna showed only a slight wane in efficacy over 6 months (from 100 to 96% against Alpha and Delta variants) [124].

However, a third (booster) dose is supposed to be required and was already authorized by FDA on 12 August 2021 and recommended by US Centers for Disease Control and Prevention and the Joint Committee on Vaccination and Immunisation in the UK for immunocompromised individuals needing further protection from COVID-19 [125–127]. Many other countries have already announced the decision to offer booster doses to vulnerable subjects and the elderly in the coming months, while other are already administering third doses, e.g., Israel and Serbia [128].

Recommendations on COVID-19 vaccination in patients on DMTs

Currently, the administration of vaccines against SARS-CoV-2 is strongly recommended to all patients with MS and is considered safe, since preliminary evidence has confirmed no increased risk of relapses after vaccination [104]. PwMS have been prioritized for COVID-19 vaccination in many countries as vulnerable subjects and should vaccinate against SARS-CoV-2 as early as possible, with the vaccines available in their countries. All approved vaccines have been demonstrated to be effective in reducing the risk of severe COVID-19 and hospitalization, leaving no doubts about the risk/benefit ratio of vaccination in the current pandemic.

Wherever practicable, to maximize the effectiveness of COVID-19 vaccines, optimizing times for starting new DMTs or administering immune-depleting therapies has been suggested by several national neurology associations and MS organizations [59, 60].

Based on what was already known about vaccines and DMTs, it has been assumed that IFNβ, GA, DMF, TFM and NTZ do not require any adjustments in view of vaccination [60].

No adjustments have been advised for pwMS already taking FTY, ozanimod or siponimod [59]. However, if a new treatment with these drugs has to be started, neurologists could suggest completing COVID-19 vaccination at least 4 weeks before starting therapy [60].

The vaccination strategy for pwMS treated with CDA could rely on very few data until recently. PwMS and neurologists have been advised to consider COVID-19 vaccination at

least 4 weeks before starting treatment or to delay it at least 12 weeks after the last administration of CDA [59, 60] as well as for ALM [60, 129]. However, based on the recent data from the MS-magnify study [78], it seems that COVID-19 vaccines could be administered 4 weeks after the last intake of cladribine without penalizing effectiveness and safety [57].

Differently, time adjustments are required for patients treated with anti-CD20$^+$ mAbs willing to be vaccinated. Particularly, some national guidelines addressed the need to delay vaccination at least 12 weeks after the last administration of OCR (or RTX) or to anticipate vaccination at least 4 weeks before [57, 59, 60, 130, 131].

Steroid treatment in pwMS with evidence of disease activity should be temporally outdistanced from the timing of vaccination. Some national organizations such as the Italian Society of Neurology (SIN) suggested administering COVID-19 or any other vaccines to pwMS whose disease has been stable during the last 30 days, not requiring any steroid treatments in the same period. However, if steroids are needed because of MS exacerbations, COVID-19 vaccination should be postponed at least 4 weeks [59]. Differently, the MS International Federation advised considering COVID-19 vaccination after at least 3–5 days from high-dose steroids [60].

There is still no evidence of COVID-19 vaccine efficacy in patients who were subjected to HSCT. However, it is suggested to avoid live-attenuated and replicating viral-vector vaccines and to consider vaccination at least 3 months from HSCT for other vaccine types. Revaccination could be required in patients who were administered COVID-19 vaccines before autologous transplantation [67].

CONCLUSION

In over a year, the COVID-19 pandemic has claimed more than 3 million victims, particularly among the most vulnerable. Only with the recent start of the vaccination campaign among the general population does achieving control of the current pandemic seem a little closer. However, many questions are still unanswered. The durability of the adaptive immune response to COVID-19 vaccines is not known, and the effectiveness of the vaccine administration to pwMS on DMTs is currently under evaluation. Moreover, the approved COVID-19 vaccines mainly target the development of the humoral immune response, but the prominent role of the T cell-mediated immunity in protecting from SARS-CoV-2 infection is emerging.

Among DMTs for the management of MS, anti-CD20$^+$ mAbs still cause concerns, since they may both negatively affect the COVID-19 course and preclude the development of an adequate immune response to vaccines. However, much has been done in a short time, and clinical research is very active on this topic.

At present, and until proven otherwise, all pwMS should be advised on COVID-19 risks and preventive measures and all should be recommended to vaccinate as soon as possible with the available vaccines. Moreover, the individual benefit/risk ratio should always be evaluated by physicians in the management of pwMS, particularly for those treated with immune-depleting DMTs.

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