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Anti-SARS-CoV-2 vaccination in people with multiple sclerosis: Lessons learnt a year in

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It has been over a year since people with multiple sclerosis (pwMS) have been receiving vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With a negligible number of cases in which vaccination led to a relapse or new onset MS, experts around the world agree that the potential consequences of COVID-19 in pwMS by far outweigh the risks of vaccination. This article reviews the currently available types of anti-SARS-CoV-2 vaccines and the immune responses they elicit in pwMS treated with different DMTs. Findings to date highlight the importance of vaccine timing in relation to DMT dosing to maximize protection, and of encouraging pwMS to get booster doses when offered.

KEYWORDS

COVID-19, vaccines, SARS-CoV-2, multiple sclerosis, disease modifying therapies, immune response, adverse events

Introduction

Since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan China on 31 December 2019, it has caused over 6 million deaths (1).

The development of vaccines against SARS-CoV-2 started as soon as the genetic sequence of the virus was made publicly available in January 2020 and has progressed at lightning speed thanks to previous knowledge of other coronaviruses, advances in vaccine design and unprecedented global funding.

SARS-CoV-2 is a single-stranded positive-sense RNA virus (Figure 1). Spike (S) proteins on the virion membrane mediate entry into host cells by binding to angiotensin-converting enzyme 2 (ACE2) and triggering membrane fusion (2, 3). S proteins have been the main target of vaccines since antibodies against this protein block virus entry to host cells and inhibit viral replication (4).

As of September 2022, six anti-SARS-CoV-2 vaccines have been authorized for use in the European Union by the European Medicines Agency (EMA) (5). These vaccines reduce the risk of severe disease by activating humoral and cellular immune responses against SARS-CoV-2 (6, 7).

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS) that causes significant and irreversible neurological disability. People with MS (pwMS) are not at greater risk of SARS-CoV-2 infection than the general population (8). However older age, male sex, comorbidities, a high Expanded Disability Status Scale score, and treatment with anti-CD20 monoclonal antibodies or high dose glucocorticosteroids, are risk factors for a severe SARS-CoV-2-related disease (COVID-19) course (9–12), defined by acute respiratory distress syndrome, intensive care unit admission and death.

Some disease modifying therapies (DMTs) for MS exert their effects on humoral and cellular immune activity and, thus, may affect the response to anti-SARS-CoV-2 vaccines. This review examines the effects of different DMTs on the response to anti-SARS-CoV-2 vaccines in pwMS and the recommended timing of vaccination relative to DMT dosing to achieve maximum vaccine efficacy.
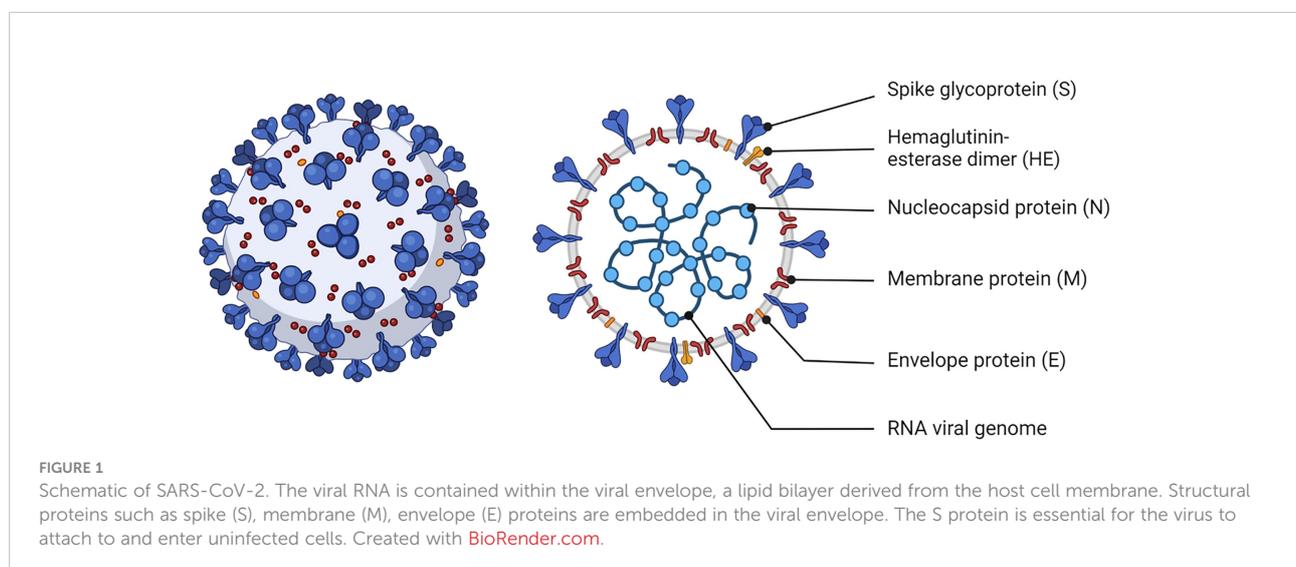
Vaccination in pwMS: General considerations

Systemic infections can worsen MS, thus, vaccination will lower the risk of relapses by reducing the risk of infections (13). Nevertheless, there are still some concerns about the safety and efficacy of vaccines in pwMS.

There is no significant evidence of a causal relationship between the onset or deterioration of MS and vaccination against hepatitis B virus, human papillomavirus, seasonal influenza, measles-mumps-rubella, variola, tetanus, Bacillus Calmette–Guérin (BCG), polio, typhoid fever, or diphtheria (14, 15). One study suggested there may be an increased relapse rate in travelers with MS following vaccination with live-attenuated yellow fever vaccines (16).

Live attenuated vaccines are contraindicated in pwMS on immunosuppressive treatments because of the risk of infection. Inactive vaccines may be less effective in pwMS on immunosuppressive treatments as they can inhibit the development of a protective immune response.

Because the safety and efficacy of anti-SARS-CoV-2 vaccines in pwMS is still being assessed, vaccination guidance should take into consideration the effects of any MS therapy on the immune system, the type of vaccine, disease burden and risk of infection.

FIGURE 1
Schematic of SARS-CoV-2. The viral RNA is contained within the viral envelope, a lipid bilayer derived from the host cell membrane. Structural proteins such as spike (S), membrane (M), envelope (E) proteins are embedded in the viral envelope. The S protein is essential for the virus to attach to and enter uninfected cells. Created with BioRender.com.

Types of anti-SARS-CoV-2 vaccines

Currently approved vaccines in the EU are either RNA vaccines (Moderna and Pfizer/BioNTech vaccine), viral vector vaccines (Oxford/AstraZeneca and Janssen), protein vaccines (Novavax) or whole virus, inactivated, adjuvanted (Valneva).

RNA vaccines deliver the mRNA of the SARS-CoV-2 virus S protein, so that it is endogenously expressed on cell surfaces (17). The immune system recognizes the protein as foreign triggering both cellular and humoral immunity. With this approach there is no risk of reversion to virulence or anti-vector immunity. RNA vaccines can be manufactured quickly and inexpensively so they can be rapidly deployed during emergencies, but they require storage at specific low temperatures (18). RNA vaccine candidates against Ebola and Zika are undergoing preclinical and clinical testing (19, 20).

The Pfizer/BioNTech vaccine (BNT162b2) and the Moderna vaccine (mRNA-1273) are administered intramuscularly, two doses are required at least 21 or 28 days apart, respectively (21, 22).

Viral vector vaccines use an unrelated harmless adenovirus (the viral vector) to deliver the SARS-CoV-2 S protein gene. Host cells use the genetic material to produce the specific viral protein, which triggers a cellular and humoral immune response.

The Oxford/AstraZeneca vaccine (ChAdOx1 nCoV-19) requires two intramuscular injections given 4-12 weeks apart (23). The Janssen COVID-19 vaccine (Ad26.COV2-S) requires only one dose, and a booster can be given at least 2 months after the primary dose (24).

Novavax is a protein vaccine that contains the full-length SARS-CoV-2 S protein and a Matrix-M1 adjuvant to boost the immune response (25). Two doses should be administered intramuscularly with an interval of 3-4 weeks.

The latest vaccine to be approved by the EMA in June 2022, Valneva, contains whole particles of the original strain of SARS-CoV-2 that have been inactivated and cannot cause the disease. Two intramuscular injections 4 weeks apart are required for protection.

At the time of writing, over 85 vaccine candidates are in Phase 3 clinical trials (26). These include inactivated vaccines (Sinopharm, Sinovac), live-attenuated vaccines (Meissa) and DNA-based vaccines (Inovio) (27–30). Inactivated and live-attenuated anti-SARS-CoV-2 vaccines are unlikely to be used in pwMS.

Because most published data in pwMS are with the mRNA-1273, BNT162b2 vaccine and ChAdOx1 nCoV-19 vaccines, this article will focus on these.

Most studies to date indicate that these vaccines do not increase the risk of relapse activity or prevent DMTs from being fully effective (31–33). There have been a series of clinical cases in which a temporal association between vaccine administration and MS relapses have been reported (34–37). Although this association is rare, it might be an adverse event of anti-SARS-CoV-2 vaccination that will need to be examined further (see 'Vaccination and adverse events' section for more details).

Anti-SARS-CoV-2 vaccination, DMTs and immune response

Most national neurology associations and organizations agree on not discontinuing MS treatment with DMTs during the pandemic, even during active infection (38–41). However, to maximize the effectiveness of anti-SARS-CoV-2 vaccines the mode of action of DMTs and the timing of immunization should be considered (Table 1).

Based on previous results from clinical trials and real-world experience exploring the response to other vaccines, as well as emerging data with anti-SARS-CoV-2 vaccines, no adjustments to vaccine administration are required in pwMS taking interferon-beta, glatiramer acetate, dimethyl fumarate, teriflunomide or natalizumab (42–47). These DMTs do not affect the response to vaccinations in general, although in some cases they can cause lymphopenia which could interfere with immune response. To date, there are no reports that these DMTs impair the immune response to the mRNA-1273, BNT162b2 vaccine and ChAdOx1 nCoV-19 vaccines (48).

Similarly, no adjustments are required for pwMS already under treatment with fingolimod, ozanimod, ponesimod or siponimod. It has consistently been shown that most patients treated with S1P1 modulators exhibit low humoral and cellular immune responses to anti-SARS-CoV-2 vaccines, yet the likelihood of COVID-19 breakthrough disease with hospitalization is not increased (45, 49). These findings suggest that the mechanism of action of S1P1 modulators may offer protection against COVID-19 (for example, by reducing cytokine release in the CNS) (50, 51) and are driving further research into the contribution of T and B cell responses towards protection against SARS-CoV-2 (47). Ideally, in patients that are about to start treatment with sphingosine 1-phosphate receptor modulators, anti-SARS-CoV-2 vaccination should be completed at least 4 weeks before.

Because anti-CD20 based treatments can reduce the humoral immune response to some vaccines (52), patients about to start treatment with ocrelizumab and rituximab, are advised to complete anti-SARS-CoV-2 vaccination at least 6 weeks before infusion. If vaccination is not possible prior to treatment initiation, vaccine administration should be carefully planned to take place after B-cell repopulation. This could be achieved by administering the vaccine 5-6 months after the last anti-CD20 treatment (53).

Several studies have reported decreased humoral responses in patients treated with ocrelizumab or rituximab compared with healthy controls after anti-SARS-CoV-2 vaccination (46,

TABLE 1   DMT, vaccination response and timing recommendations.

DMT	Vaccine	Timing	Response	Other
Beta interferons Glatiramer acetate Dimethyl fumarate Teriflunomide Natalizumab	mRNA-1273 BNT162b2 vaccine ChAdOx1 nCoV-19	No adjustment required	Comparable to untreated MS patients and healthy controls	Less likely to experience short term reactogenicity to vaccine
Sphingosine 1-phosphate receptor modulators		No adjustment required	Low humoral response in many patients	In new starters anti-SARS-CoV-2 vaccination should be completed at least 4 weeks before Less likely to experience short term reactogenicity to vaccine
Anti-CD20 based treatments		Vaccination should take place 5–6 months after the last anti-CD20 treatment	Low humoral response	In new starters anti-SARS-CoV-2 vaccination should be completed at least 6 weeks before
Cladribine		Vaccination should take place 2-4 weeks before course of therapy	Mostly comparable to healthy controls	In cases of lymphopenia, it is advisable to wait until recovery of lymphocyte count
Alemtuzumab		Vaccination should take place at least 3 months after the last course of therapy	Mostly comparable to healthy controls	In new starters anti-SARS-CoV-2 vaccination should be completed 4-6 weeks before.

47, 49, 54–56). However, most MS patients treated with anti-CD20 monoclonal antibodies develop a cellular response after anti-SARS-CoV-2 vaccination, regardless of the low humoral response (57–60). Further studies are required to determine whether this translates into full protection against infection.

Most studies show that pwMS treated with cladribine or alemtuzumab develop a humoral response against S protein that is comparable to healthy controls (45, 49, 61, 62). Because cladribine tablets cause a rapid depletion of peripherally circulating B and T lymphocytes with a mean nadir at 13–24 weeks, it is advisable to complete vaccination against COVID-19 2-4 weeks before starting a course of treatment (63, 64). However, no adverse effects associated with vaccination have been found after treatment, so experts suggest that these patients should get the anti-SARS-CoV-2 vaccine when offered, unless they have a contraindication (65). In pwMS treated with alemtuzumab, it is recommended to complete vaccinations at least 6 weeks before starting treatment (63). If therapy has already started, patients should wait 3-6 months after the last dose for B cells to return to basal levels.

In patients taking high-dose steroids or who experience a clinical relapse, vaccination should be postponed by 4 weeks so that the response is more effective (31).

To develop protective immunity from anti-SARS-CoV-2 vaccines, pwMS receiving haematopoietic stem cell transplantation (HSCT) should wait at least 3 months after treatment before vaccination (66). Revaccination may be required in patients who were administered vaccines before autologous transplantation.

Continuous surveillance of vaccine effectiveness in pwMS taking immunomodulatory and immunosuppressive drugs is vital to inform future treatment strategies and vaccination

protocols. At the time of writing there is consensus that a reduced response (cellular and/or humoral) to anti-SARS-CoV-2 vaccines is better than none and that the risks of COVID-19 by far outweigh any potential risks from the vaccine. Assessing patients' serological status in post-vaccination check-ups will help to determine whether booster doses are required.

There are limited data about differences in effectiveness and safety between approved vaccines in pwMS. However, the CDC (Centers for Disease Control and Prevention) in the US, recommends using mRNA vaccines (mRNA-1273 and BNT162b2) over the Janssen vaccine Ad26.COV2-S in pwMS (67). One study showed that vaccination with mRNA-1273 resulted in a systematically 3·25-fold higher antibody level than with BNT162b2 vaccine (49), and another found a higher humoral response rate with the BNT162b2 vaccine compared to the inactivated vaccine, Sinovac, in MS patient cohorts (62).

Vaccination and adverse events

The short-term COVID-19 vaccine reactions experienced by pwMS are similar to those reported in trials in the general population (31, 33, 68). The most common reactions being pain at injection site, fatigue, headache, and malaise (a general feeling of discomfort). Younger age, female sex and prior SARS-CoV-2 infection were associated with greater odds of experiencing adverse effects after vaccination. Interestingly, individuals treated with specific classes of DMT, such as sphingosine-1-phosphate receptor modulators or dimethyl fumarate, were less likely to experience short-term reactogenicity (33).

In July 2021, the EMA declared that myocarditis and pericarditis can occur in very rare cases after vaccination with anti-SARS-CoV-2 mRNA vaccines and recommended listing them as new side effects in the product information (69). A US study showed that the risk of myocarditis was highest after the second vaccination dose in adolescent males and young men (70). There are no reports on the incidence of myocarditis and pericarditis after vaccination in pwMS.

Oxford/AstraZeneca's viral vector vaccines have similar common side effects to the mRNA ones (feeling unwell, fatigue, fever, headache). In April 2021, the EMA reported a possible link between the Oxford/AstraZeneca vaccine and a very rare side effect of unusual blood clots in the brain (cerebral venous sinus thrombosis), the abdomen (splanchnic vein thrombosis) and in arteries combined with low levels of blood platelets (71), which led to updated guidance for healthcare professionals on how to minimise risks, as well as further advice on symptoms for vaccine recipients to look out for after vaccination. There is no indication that pwMS have a higher risk of blood clotting following vaccination.

It is still unclear whether anti-SARS-CoV-2 vaccination might induce an immunological response that could activate MS. Fever caused by vaccination can temporarily worsen MS symptoms, but there have been reports of longer-term disease worsening in some MS patients and a few cases of acute demyelinating disease onset.

For example, a 31-year-old Italian woman with stable MS (after a second cycle of cladribine) experienced a severe relapse 48 hours after receiving the 1st dose of the Pfizer/BioNTech vaccine (37). She made a full recovery after 5 days of treatment with methylprednisolone.

Four individuals aged 24 to 48 years experienced active demyelination in the optic nerve, brain, and/or spinal cord within 1-21 days of Moderna or Pfizer/BioNTech (1st or 2nd dose administration) (36).

There have also been reports of new onset of relapsing-remitting (RR) MS and new onset neuromyelitis optica (NMO) after vaccination (36). A 26-year-old white Hispanic woman showed optic neuritis, and new lesions in the brain and spinal cord 14 days after the 2nd dose of Moderna vaccine, and a 33-year-old Caucasian man showed optic neuritis and new MRI lesions 1 day after the 2nd dose of the Pfizer/BioNTech vaccine. Both recovered after treatment with methylprednisolone.

Described cases of new onset NMO include a 64-year-old Caucasian man who showed spinal syndrome 18 days after the 1st dose of the Pfizer/BioNTech vaccine as well as extensive new MRI spinal cord lesions (36), and a 32-year-old male who presented with a 2-week history of acute confusional state and imbalance 1 week after receiving the 2nd dose of the Sputnik vaccine (viral vector vaccine) (72). Both made a partial recovery after treatment.

Overall, the number of individuals who experience active CNS demyelinating disease is very small given the large number of pwMS who have received vaccination. Data to date suggest that a causal relationship between anti-SARS-CoV-2 vaccines and acute CNS demyelination is unlikely.

ParadigMS Foundation experts' consensus

Immunization against COVID-19 is highly recommended for all MS patients regardless of age and comorbidities. The vaccination course should be completed even if the first dose was associated with a temporary flaring of symptoms.

Family members should also be vaccinated in order to reduce risk and impact of infection in MS patients.

Because it takes up to 28 days after the first dose of the Pfizer-BioNTech vaccine and up to 22 days after the Oxford-AstraZeneca vaccine to reach some level of immunity, it is crucial to maintain precautions after initial vaccination.

Evidence of waning immunity 4-6 months after vaccination (73, 74), and the emergence of novel variants of concern that have the potential to cause increased disease severity and to decrease COVID-19 vaccine effectiveness, has led to several countries offering third vaccine doses or vaccine boosters, not just to the highest risk groups (including older and immunocompromised people) but to the general population by the end of 2021.

A third dose of the Pfizer-BioNTech or the Moderna vaccine has been shown to be safe and to significantly increase SARS-CoV-2 antibody levels in the general population (75, 76) and in pwMS (77, 78). Breakthrough infections in pwMS during the delta and omicron wave have been associated with low SARS-CoV-2 antibody levels, and a third vaccine dose significantly reduced the risk of infection during the Omicron wave (79).

At the time of writing several countries are offering fourth COVID-19 vaccine doses to people who are immunocompromised and care home residents as they have been shown to boost antibody levels and prevent severe omicron COVID-19 (80, 81).

Despite the recommendation that MS patients should take the offered vaccines, up to 20% are hesitant, mainly due to safety concerns (82–84). Factors such as younger age, low education level, lower perceived risk for COVID-19 infection, and higher functional disability have been independently associated with reduced vaccine willingness (83, 84). Consistent and context-specific vaccination counselling for pwMS will help tackle vaccine hesitancy and improve vaccine roll out in the most hesitant patient subgroups.

Conclusions

The potential consequences of SARS-CoV-2 infection in MS patients outweigh the risks of vaccination.

Currently EU-approved anti-SARS-CoV-2 vaccines produce high immunogenicity associated with favorable safety profile in the MS population. Emerging data support not delaying vaccination or stopping MS treatment during the SARS-CoV-2 pandemic.

Clinicians should discuss anti-SARS-CoV-2 vaccination timing with pwMS to maximize the effectiveness of the vaccine, taking into consideration their risk of infection, the type of DMT they are taking, their current immune status, their general health and the coexistence of other diseases.

These recommendations will need to be regularly updated as knowledge of how pwMS respond to SARS-CoV-2 vaccines (and the extent to which they protect against new virus variants) is evolving very rapidly (85).

Author contributions

TB, MP, H-PH led the conceptual framework of the manuscript and critically reviewed all versions of the article, read and approved the final manuscript, and agree to be responsible for all aspects of the work. CO-G, CP, LA, MA, NG, MM, BV, MZ, RL, AC, PV contributed to the conceptual development of the article, critically reviewed it, read and approved the final manuscript, and agree to be responsible for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

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