COVID-19 Vaccines in Multiple Sclerosis

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Understanding the risks of COVID-19 in patients with Multiple Sclerosis (MS) receiving disease-modifying therapies (DMTs) and their immune reactions is vital to analyze vaccine response dynamics. A systematic review on COVID-19 course and outcomes in patients receiving different DMTs was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Emerging data on SARS-CoV-2 vaccines was used to elaborate recommendations.

COVID-19 vaccines multiple sclerosis immunosuppression multiple sclerosis/therapy

1. Introduction

After SARS-CoV-2 infection, the innate immune system (macrophages, dendritic cells, natural killer (NK) cells) triggers signalizing cascades leading to an increase of pro-inflammatory cytokines. Simultaneously, significant T lymphocyte subside, limiting the establishment of adaptative immunity and the host ability to solve the infection [1]. Later, to establish a prolonged immunity and reduce the risk of re-infection, plasmacytes and memory B and T cells take place to produce neutralizing antibodies. Since the outbreak of the pandemic, in addition to the well-known COVID-19 symptoms, including neurological ones [2], there has been a concern with populations facing a higher risk of infection [3]. Multiple sclerosis (MS) patients are usually under disease modifying therapies (DMTs) and have been identified as a high-risk population, both because inflammation is an integral part of MS pathogenesis, and infections are well known exacerbation triggers of MS-related disease activity [4].

While many immunotherapies, including DMTs used for MS, have been pointed as COVID-19 candidate therapies [5], the development of SARS-CoV-2 vaccines was early assumed to be the turning point for the still expanding pandemic, and a high priority research topic. Now that many vaccines have been developed and approved by the regulatory agencies, the vaccination campaigns are speeding up all over the world. Notwithstanding, besides the susceptibility and clearance of SARS-CoV-2 infection in patients under different DMTs, the question is now turning to understanding the vaccine response in MS patients. This will be the key to define the best vaccination strategy and a guarantee of effective immune response after vaccination.

2. COVID-19 Vaccine in MS Patients on DMTs

The COVID-19 vaccination has been heralded as a key step to overcome this pandemic. As the virus uses its outer spike protein (S protein) to bind to angiotensin-converting enzyme-related carboxypeptidase 2 (ACE2) on the host cell surface [6], many vaccines use this protein as their target antigen [7][8]. Despite their distinct mechanisms of

action, they all intend to mimic the natural process of infection. In December 2020, the lipid nanoparticle-formulated Pfizer-BioNTech® (New York, USA/ Mainz, Germany) (BNT162b2) COVID-19 vaccine [9] was the first to receive conditional emergency approval worldwide, followed by the mRNA-1273 vaccine from Moderna® (Cambridge, MA, USA) [10] in January 2021. Both feature viral genetic material and are based on nucleoside-modified mRNA vectors encoding the spike glycoprotein of SARS-CoV-2. These vaccines have proven an efficacy superior to 90% in preventing severe and mild forms of COVID-19, independently of age, race and certain comorbidities including asthma, COPD, diabetes, hypertension and obesity (BMI ≥ 30 kg/m^2) [9][10]. COVID-19 Vaccine AstraZeneca® (Cambridge, UK) (Vaxzevria) is an adenoviral vector-based vaccine in which the DNA encoding the coronavirus spike protein antigen is cloned into a viral vector that lacks the ability to reproduce and cause disease itself. The vaccine has demonstrated an efficacy ranging from 60–94% at protecting people from the extremely serious risks of COVID-19, including death, hospitalization and severe disease in clinical trials, including in aged people over 65 years old [11][12]. The most common side effects with AstraZeneca® (Cambridge, UK) vaccine were usually mild or moderate and typically short-limited. Similarly, another adenovirus-based vaccine from Janssen® (Beerse, Belgium) led to 67% reduction in the number of symptomatic COVID-19 cases weeks after immunization, also with mild or moderate side effects which mostly consisted of pain at injection site, headache, tiredness, muscle pain and nausea. New very rare side effects have been recognized such as embolic and thrombotic events with a focus on thrombosis in combination with thrombocytopenia for both the Janssen® (Beerse, Belgium) and Vaxzevria COVID-19 vaccines. With any of these vaccines, the goal is to activate the immune system, namely B and T cells to produce neutralizing antibodies (equivalent to the titer found in convalescent patients) and prevent a future infection. While vaccines from Pfizer-BioNTech® (New York, NY, USA/Mainz, Germany) and Moderna® are administered intramuscularly in two administrations 21 days or 28 days apart, respectively, AstraZeneca® (Cambridge, UK) vaccine requires two intramuscular injections administered 4–12 weeks apart. Other new generation vaccines are under study and include recombinant protein vaccine, bacterial vector-based vaccine, plasmid DNA vaccine and trained immunity-based vaccine.

While vaccine supplies are still limited, priority is being given to healthcare workers and others at higher risk of exposure or complications such as older and immunosuppressed patients. As live and attenuated viruses' vaccines are contraindicated in MS patients, these new DNA-RNA vaccines are well welcomed in patients on DMTs [13]. Yet, common concerns of the population and medical community are vaccine safety and effectiveness. Recent studies have focused on the willingness of MS patients to get the COVID-19 vaccine. 80.9% of European MS patients were willing to receive the vaccine, however 54.1% would prefer to postpone vaccination until they seek advice of their physician. Interestingly, older patients and those with comorbidities were the ones with the biggest interest in getting the protection of the vaccine [14]. In the US, the acceptability was slightly inferior, but 66% of the participants were still willing to get a COVID-19 vaccine. The information sources most highly trusted were healthcare providers and the National MS Society, confirming the importance of review studies and expert recommendations [15]. Several studies have shown that there is no difference in vaccine responses between MS patients and healthy individuals [16] but, given the variable immune responses and the absence of clinical trials in this population, the safety and efficacy of approved SARS-CoV-2 vaccines in MS patients is still unknown to us, [17][18][19][20][13][16]. A recent study conducted in Israel, a country where vaccination has been a keen priority, evaluated the adverse

event profile and immediate risk of acute relapses in 555 MS patients who received the COVID-19 BNT162b2 vaccine [21]. No events of anaphylaxis or life-threatening responses were registered. Between the two doses, three patients (0.5%) were infected by SARS-CoV-2, all being asymptomatic or with mild disease. A pseudo-relapse with flu-like symptomatology was reported in 2% and 4.8% of patients after the first and second vaccination doses, respectively. Acute relapses shortly after vaccination corresponded to the expected relapse rate and so the vaccine was not associated with increased disease activity.

Several questions regarding the timing of the vaccine and drug administration need to be addressed [16]. Despite one study found a negative impact of GA on immune response to Influenza vaccine, it was not replicated in subsequent studies, and so it seems safe to administer a vaccine against SARS-CoV-2 in MS patients treated with both IFN or GA [16][22] Similarly, based on previous observations from Influenza vaccine responses in MS patients treated with teriflunomide [23] and confirmed seroconversion after COVID-19 [17], a successful vaccination can be anticipated in patients treated with teriflunomide [24]. Regarding fumarates and natalizumab, previous response to other vaccines suggest that patients can mount an adequate seroprotective response to inactivated or protein-based vaccines, probably because they retain functional T and B cells and stable serum immunoglobulins [16][25]. Given its mechanism of action and reduced immunoglobulin responses to SARS-CoV-2, concerns might be anticipated about the impact of fingolimod on vaccination [17]. As so, serology status should be tested after vaccination, to ensure serological protection. Nonetheless, MS patients with lymphopenia still mounted anti-SARS-CoV-2 humoral responses suggesting that COVID-19 vaccination might hold out an attenuated but still protective response in this vulnerable population. For IFN, GA, DMF, teriflunomide and fingolimod, therapeutic withdrawal as a mean to increase vaccination efficacy is not encouraged.

On the other hand, for anti-CD20 monoclonal antibodies, a blunted seroconversion might be anticipated in the 6–10 months after the last infusion, allowing for a time-window vaccination that might be programmed based on the kinetics of repopulation of the naive cell pool with immature B cells. Memory B cell repletion can take up to 18 months after discontinuation of ocrelizumab, and up to 11–12 months for rituximab and ofatumumab [13]. Additionally, the presence of worsening hypogammaglobinemia with repeated infusions may contribute to suboptimal serological responses. In a patient series, less than 20% of MS patients treated with ocrelizumab generated an antibody response when naturally infected by COVID-19 [26]. Further, attenuated humoral responses to tetanus, seasonal flu and pneumococcus vaccines were detected in B-cell-depleted ocrelizumab MS patients in the VELOCE study (a randomized, open-label, Phase III trial) [27]. Recently, real-world data on COVID-19 vaccination and ocrelizumab were revealed. While a 64-year-old female patient, treated with ocrelizumab and vaccinated 3 months after the last infusion, was able to produce a protective antibody response against COVID-19, another 46-year-old female patient treated with ocrelizumab, who received the vaccine 2 months after the last infusion, did not produce a serological response [28]. Both had similar low CD19 counts. The same was observed in a patient who received the second dose of COVID-19 vaccination nine days after last ocrelizumab infusion [29]. Further, vaccination failure was described for a 52-year-old male MS patient on ocrelizumab who developed his first symptoms of SARS-CoV-2 infection 19 days after receiving the last dose of the COVID-19 vaccine [30]. The role of genetic discordance of the different SARS-CoV-2 strains to these observations remains a significant but unanswered question [31]. As for COVID-19 outcomes, the dose and treatment duration may have a significant

impact on vaccination efficacy, especially in ocrelizumab patients previously treated with rituximab [13]. Importantly, as ocrelizumab does not appear to modify pre-existing humoral immunity, MS patients might safely resume ocrelizumab 4–6 weeks after receiving SARS-CoV-2 vaccine. For those already taking anti-CD20 therapies, administered on a 6-month interval schedule, vaccination should be deferred toward the end of the cycle, at least 12 weeks after the last drug dose [27]. For the newer monthly administered subcutaneous B cell–depleting therapy ofatumumab, vaccination might be delivered toward the end of the monthly cycle, and the next two ofatumumab doses skipped to allow for the booster vaccine to take effect.

Finally, for the two long-term immune-depleters, cladribine allows CD19 naive B cells to recover in approximately 30 weeks [32], while for alemtuzumab there is usually a rapid repopulation of naive B cells, despite a marked memory B cells depletion. For both DMTs, a reduction in cellular and humoral responses to COVID-19 vaccines is expected during maximal lymphocyte depletion, so that vaccination timeline is dependent on immune reconstitution. In clinical trials, patients under cladribine mounted immune response to influenza vaccine four weeks after vaccination, without additional adverse events [32], while a blunted antibody response to vaccination has been observed in the first six months after alemtuzumab treatment [33]. For alemtuzumab, delaying vaccination for at least six months after the last treatment cycle and adjust the second cycle to ensure an optimal vaccination response is highly advisable [34][35][13][16]. Similarly, for cladribine we recommend a three-month gap after the treatment cycle until vaccination (or until the recovery of lymphocyte count) [36]. In line with it, real-world data show that the first two patients under cladribine receiving the adenoviral vector-based vaccine (AstraZeneca® (Cambridge, UK) and the Pfizer-BioNTech® (New York, NY, USA/ Mainz, Germany) mRNA vaccine three months after the second cycle of treatment exhibited a protective antibody response despite an incomplete reconstitution of the absolute values of circulating lymphocytes [28]. As for other DMTs, checking serological status after vaccination is encouraged, especially during the lymphocyte depletion phase. Additional booster vaccinations for patients demonstrating insufficient responses might be amenable.

Apart from B cell responses, the role of T cell-induced responses (as it occurs for herpes zoster vaccine) remains to be studied but an ongoing pioneer prospective study analyzing this aspect confirms that ocrelizumab-treated patients who get COVID-19 have good robust T-cell responses, suggesting persistent T-cell immune memory to SARS-CoV-2 up to 10 months following infection, even in B-cell depleted MS patients [37]. The question of whether patients fail to respond to the vaccine at both an antibody and T-cell level remains to be solved. Further, for patients who have received high-dose steroids in the last month, it is likely favorable to postpone vaccination [38], despite the lack of data on vaccine efficacy in people treated with high doses of corticosteroids (≥20 mg prednisone equivalents for ≥14 days) [16]. Finally, given their more advanced age and greater disability, patients with progressive MS face an increased risk of severe COVID-19 and frequently do not receive DMTs (unless in early and active phases). Vaccination benefits seem to clearly outweigh any potential risk associated with vaccine administration in this group.

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