Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Insight in booster COVID-19 vaccine and disease modifying therapy in multiple sclerosis

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1. Introduction

Since early December 2019, the Coronavirus Disease 19 (COVID-19), the disease caused by the virus Sars-Cov-2, has devastated communities on a global scale, infected over 200 million people, and caused over 4.3 million deaths worldwide [1]. In December 2020, the FDA approved two mRNA vaccines for Sars-Cov-2. After tiresome effort by healthcare workers around the world, over 4.7 billion doses of the vaccine have been administered as of August 2021 [1].

Multiple Sclerosis (MS) is a chronic inflammatory disease characterized by demyelinating and neurodegenerative changes of the Central Nervous System. Viral infections have been shown to trigger severe relapse and increase progression of the disease. Initial recommendations for patients with MS were to receive the COVID-19 vaccine if possible. There was some concern over vaccination itself inducing relapse of disease, but the risks of severe disease due to COVID-19 greatly outweigh the potential risks of the vaccine [2].

Current guidelines for MS therapy indicate the use of Disease Modifying Therapies (DMTs). The question remains as to whether patients on these therapies, especially newer DMTs such as ofatumumab, ozanimod, cladribine, siponimod, ocrelizumab, and fingolimod, will mount adequate responses from the COVID-19 vaccine, given that immunocompromised patients were excluded from early trials. It has been well documented that immunosuppressive therapies significantly diminish the normal immune response to vaccinations [3].

Furthermore, with lack of longitudinal studies surrounding the COVID-19 vaccine and the pandemic in general, we are severely lacking in data that could provide a threshold antibody level to determine whether a patient is sufficiently immunized. It has been suggested that any patient with MS requiring DMT will likely require booster vaccinations [4].

On August 12, 2021, the FDA announced the authorization of a third dose of the COVID-19 vaccine to 'certain immunocompromised individuals.' In this literature review, we aim to make a recommendation on whether patients with MS taking DMTs should receive the third dose of the COVID-19 vaccination, and establish goals for future studies on immune responses to vaccination in these patients.

2. Discussion

The greatest limitation of our study is the lack of existing data on humoral responses of MS patients that have been fully vaccinated against COVID-19. Despite this, it is important to formulate guidelines for our patients with MS who are treated with various medications that affect their immune system. We aim to make recommendations based on current data regarding COVID-19 vaccinations, immunological knowledge, and historical data from other vaccination trials.

2.1. For patients on Anti-CD20 therapy (Ocrelizumab, Ofatumumab and Rituximab)

Anti-B-Cell Therapies, such as Ocrelizumab and Rituximab, are monoclonal antibodies directed against CD-20, a B-cell marker. Historically, patients receiving anti-CD20 therapies have demonstrated reduced or absent numbers of B cells, and diminished responses to vaccinations. Pre-existing antibody titers seem to be unaffected [5].

In response to Pfizer, J&J, or Moderna first and second doses, patients receiving these infusions, demonstrated diminished humoral responses [4,6]. Importantly, this deficit decreased as time since last infusion increased. Some patients on anti-CD20 therapies did mount a humoral response to the vaccine. However, these patients were vaccinated long after their last infusion. There is a strong positive correlation

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between B-cell count at the time of vaccination and humoral response [4].

Although we are lacking in concrete evidence on how beneficial a third dose would be, based on immunological principals and the known effects of Anti-CD20 therapies, we would strongly recommend a third vaccine to boost the weak antibody-responses to all patients receiving anti-CD20 therapies. Preferentially, a third vaccine dose would given 12 weeks, or more, after their last infusion to allow B cells to repopulate prior to vaccination; Thereby, increasing the chances of a favorable humoral response. The National MS Society has made the same recommendation (see Table 1) [7].

Of note, patients taking anti-CD20 therapies remained capable of generating antigen specific CD-4 T cell responses. Patients with a more robust CD-4 & CD-8 response have demonstrated better outcomes from COVID-19 infections [8] and likewise, patients taking anti-CD20 therapies have not encountered increased severity of disease or increased mortality due to COVID-19 [4].

Table 1
National MS society Guidelines on Timing for MS medication with COVID-19 vaccines.

DMT	Time to Immune Reconstitution	Adjustment of Therapy with Vaccination	Adjustment of Therapy with Booster
Anti-B-Cell (Ocrelizumab, Ofatumumab, and Rituximab)	72 weeks, on average, to B-cell repletion since last infusion	Fully vaccinate 2–4 weeks prior to starting therapy If already on therapy consider vaccination 12 weeks or more after the last dose (insufficient data for Ofatumumab)	Receive booster 3 months after last dose (insufficient data for Ofatumumab)[a]
Cladribine	30 weeks to B-cell and lymphocyte repletion to threshold values	Fully Vaccinate 2–4 weeks prior to starting therapy Insufficient date on scheduling vaccination if already on therapy	Receive booster 3 months after last dose[a]
S1P Receptor Modulators (Fingolimod, Ozanimod, Siponimod)	1–2 months to lymphocyte repletion This may be extended in drug use >1 year	Fully Vaccinate 2–4 weeks prior to starting medication If already on therapy, continue therapy as is and get vaccinated	May receive booster at least 28 days after most recent vaccination dose[a]
Alemtuzumab	8 months to B cell repletion Up to 3 years to T cell repletion This is despite elimination half-life of 2 weeks	Fully Vaccinate 4 or more weeks prior to starting therapy If already taking therapy vaccinate 24 or more weeks after last dose	May receive booster at least 28 days after most recent vaccination dose[a]
High dose steroids	NA	Start vaccination 1–5 days after the last dose of steroids	May receive booster at least 28 days after most recent vaccination dose[a]
Interferons	Effects last 5 times the elimination half-life (range up to 390 h)	Do not delay therapy	May receive booster at least 28 days after most recent vaccination dose[a]
Glatiramer Acetate	Effects last 5 times elimination half-life (3−12*h*)	No adjustment required if already on therapy	May receive booster at least 28 days after most recent vaccination dose[a]

Abbreviation: MS, Multiple Sclerosis; COVID-19, Coronavirus Disease 2019.

[a] These recommendations are for patients who received Pfizer or Moderna vaccines. Boosters for Johnson&Johnson are not available yet, and a recommendation for these have not yet been made by the National MS guidelines.

2.2. For patients on Cladribine

Cladribine is a deoxyadenosine analog that preferentially depletes lymphocytes. In theory, this treatment would diminish humoral response to vaccination, but this was not reported. Instead, Achiron et al. showed that every MS patient taking Cladribine demonstrated a healthy immune response to the COVID-19 vaccine comparable to healthy controls [6]. Additionally, infected patients showed milder disease course and adequate production of antibodies following infection [9]. For this reason, we recommend the third dose be encouraged 12 weeks after the last dose of Cladribine. Allowing lymphocytes to repopulate before vaccination is key to inducing adequate immune responses in these patients.

2.3. For patients on Sphingosine-1-phosphate receptor modulators (Fingolimod, Ozanimod, Siponimod)

S1P receptor modulators bind S1P receptors on lymphocytes directly, preventing their migration from the lymph nodes to the CNS, and reducing peripheral lymphocyte counts. Fingolimod is known to hamper both cellular and humoral immune responses to vaccination [7,10]. As expected, Fingolimod was associated with concerningly low rates of protective antibody levels in response to COVID-19 vaccination. Achiron et al. suggested that failure of adequate response to vaccination may be the result of low absolute lymphocyte count in these patients [6]. Yet, even patients with adequate lymphocyte counts did not respond to vaccination [9]. Before vaccination, we would, ideally, extend the time from last dose to allow lymphocytes to repopulate and elicit protective immunity. However, halting Fingolimod therapy is associated with severe relapses in MS patients [9]. If vaccination before Fingolimod therapy is not achievable, it would be advisable to determine levels of COVID-19 antibodies. Practitioners may then assess the need for a booster dose, before considering a carefully monitored switch to another DMT to gain adequate immunity to SARS-COV-2.

2.4. For patients on Alemtuzumab

Alemtuzumab binds CD52 on lymphocytes and monocytes, depleting B and T cell populations. Alemtuzumab could diminish humoral responses, similar to other immunosuppressants, but, as of yet, we have no documented record of this. Historically, patients taking Alemtuzumab are considered to be at higher risk of infections [9]. For this reason, we and the National MS Society, suggest the third vaccine dose be strongly encouraged [7].

2.5. For patients taking high dose steroids

The current recommendation for MS patients taking high dose steroids is to be vaccinated 3 to 5 days after last dose [3]. A literature search produced no data on the humoral response to COVID-19 vaccine in patients receiving high dose steroids. We recommend the booster dose be given once the steroids have been stopped.

2.6. For patients taking Interferons and Glatiramer acetate

Interferons and Glatiramer acetate do not seem to reduce the immune response to vaccination. Vaccination does not need to be delayed in patients taking these medications [3,10]; therefore, a third dose may be administered down the line.

There is always concern that vaccination could induce relapse or progression of MS. In patients who have been vaccinated, there has been no observed increase in risk of acute relapse following either dose [10].

Rates of relapse are comparable to pre-vaccination status [10]. As more vaccines are administered, this risk could change. However, the outcomes of COVID-19 have been severe in patients with MS, and therefore, a third dose of the vaccine is a safe option that has potential to build immunity in these patients.

The efficacy of a third dose has not been established due to the emergent nature of the pandemic. Booster doses have proven to be useful in diseases well known for waning immunity, Hepatitis B and Tetanus being two notable examples of this. Several studies have documented booster vaccination to be sufficient for seroconversion in both diseases [11–13]. However, an exact comparison to the COVID-19 booster cannot be drawn. For one, the Pfizer and Moderna vaccines are mRNA vaccines, in which booster vaccination and subsequent immune responses have not been studied. Other mRNA vaccines for Rabies and Influenza have largely been tested in animal models, not in large clinical trials. It has not been determined if there would be a need or even a benefit from booster doses. Furthermore, the emergence of the alpha-variant, and now the delta-variant, are more comparable to influenza, whose virologic behavior necessitates annual novel vaccination, not only a booster. Finally, a trend in waning immune responses, especially associated with breakthrough cases of COVID-19, is already being observed in fully vaccinated individuals [14]. While this creates greater urgency to explore the utility of a booster dose, it also makes COVID-19 vaccination even less comparable to Hepatitis B, Tetanus, or any other well immunized disease, that we as a human population have encountered.

AstraZeneca, the modified adenovirus SARS-COV-2 vaccine, has been studied as a two-dose regimen with a booster in other countries. The third dose of AstraZeneca has been documented to increase immunity in those cases [15]. This is the best evidence we possess that a booster dose may be of value, especially to immunocompromised patients, such as those with MS on DMTs.

For these reasons, we believe it is of utmost importance for our clinicians and researchers to continue collecting data on titers in vaccinated patients with MS on DMTs. In order to learn more about the value of the third vaccine, it would be useful to collect levels of COVID-antibodies before and after the third dose administration; this would aid future decision making for possible re-vaccinations, or switching medications.

As more vaccine types, such as AstraZeneca and Novavax, become available in the US, it will be crucial to obtain data on immune responses for different DMT therapies to make the best recommendation for our patients in the future as we continue to sail the uncharted waters of the COVID-19 pandemic.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Code availability

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Availability of data and materials

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Author contributions

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Declaration of competing interest

None of the authors have any conflict of interest to disclose.

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