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Key points to keep in mind related to COVID-19 vaccines in people with multiple sclerosis

Lorna Galleguillos [a,*], Ricardo Alonso [b]

[b] Neurology Department, Hospital Ramos Mejías, Buenos Aires, Argentina
[a] Neurology and Psychiatry Department, Clínica alemana, Neurology and Neurosurgery Department, Clínica Dávila, Santiago, Chile

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ABSTRACT

Vaccinations are often the most effective tool against certain diseases known to mankind, and their interaction with multiple sclerosis (MS) has been discussed for decades. With rapidly accumulating numbers of cases and deaths due to COVID-19, there is a global effort to respond to this pandemic in terms of scale and speed. Different platforms are currently being used around the world for the development of best COVID-19 vaccine. While some COVID-19 vaccines have already been approved by different regulatory agencies, there is scarce data in large cohorts regarding the efficacy and security of COVID-19 vaccines in people with MS. In this short review we aimed the most important information to keep in mind regarding this topic.

1. Introduction

It has been a little over a year since we heard of the first case of COVID-19 in China. It spread quickly and was declared a pandemic in March 2020. (Krammer, 2020, Chung, Beiss, Fiering, and Steinmetz, 2020) Since then, significant research effort has been mobilized to develop a vaccine to halt the disease. Prior to this era, vaccines were not pursued against coronavirus because the four common strains (2 alpha coronavirus NL63 and 229E and 2 betacoronaviruses HKU1 and 229E) that affect people cause a mild flu and the impact of the vaccine would be minimal against the wide range of viruses that cause the common cold. (Krammer, 2020) Today, we are running against the clock, and there are currently more than 30 vaccines in clinical trials with over 200 in various stages of development. It is important to note that only very few vaccines are currently approved. (Sharma, Sultan, Ding, and Triggle, 2020) There has been great interest in the new COVID-19 vaccines and how they might affect people with multiple sclerosis (MS). In this brief review we consider four key points to keep in mind related to COVID-19 vaccines in people with MS.

2. Key Point 1: Immune response to SARS COV 2 and vaccine

The immune system plays a crucial role in the pathogenesis of COVID-19. To develop an understanding of the immune response and the underlying mechanism is relevant to develop an effective vaccine. A study published by Grifoni A et al., showed that infected individuals have a strong T cell response to the virus: helper T cells recognize the spike protein on SARSCoV-2, stimulate B cells to further release antibodies and stimulate cytotoxic T cells. (Grifoni et al., 2020) These helper T cells may be triggered from a previous coronavirus infection since there is some similarity in S proteins between the different coronaviruses (Sharma, Sultan, Ding, and Triggle, 2020). Furthermore, patients who have recovered from COVID-19 have CD4+ and CD8+ T cells against nucleocapsid protein (NP) of SARS-CoV-2 (Le Bert et al., 2021), supporting the theory that the T cell immune response can be stimulated following exposure to other beta coronaviruses. (Le Bert et al., 2021) On other hand, levels of SARSCoV-2-specific neutralizing antibodies (NAbs) have shown to be varied between different groups of populations (elderly patients develop high levels of SARS-CoV-2 specific NAbs compared to younger patients). (Wu et al., 2021) Therefore, T cell response plays an important role and may suggest a strong cellular immune response. However, whether high levels of Nabs protect such patients from contracting a severe disease requires further evaluation. (Le Bert et al., 2021) Regarding B cells, plasma cells and memory B cells that emerge in response to the primary infection are involved in long-term protection against a reinfection (Vabret et al., 2020). The IgG titers increase during the first 3 weeks following symptom onset and then decline by the second month, always maintaining levels above the

* Corresponding author at: Neurology and Psychiatry Department, Clínica alemana, Neurology and Neurosurgery Department, Clínica Dávila, Santiago, Chile Avenida Vitacura 5951, 10th floor, Vitacura, Santiago, Chile
E-mail addresses: lgalleguillos@alemana.cl (L. Galleguillos), ricardoalonsohrm@gmail.com (R. Alonso).

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detectable threshold; this may indicate of protection against a reinfection in the short term (Adams et al., 2020)

Protection achieved by vaccines depends on three factors: period of incubation, quality of the immune response, and levels of antibodies produced by memory B cells. Memory response may be sufficient to protect against disease if there is an extensive incubation period between pathogen exposure and the onset of symptoms to allow for the 3 to 4 days required for memory B cells to generate antibody titers above the protective threshold. (Pollard and Bijker, 2020) An important concept arises here, one that may improve vaccination strategies, known as 'original antigenic sin.' This phenomenon occurs when the immune system fails to generate an immune response against a strain of a pathogen if the host had previously been exposed to a closely related strain (as demonstrated in a number of infections, including dengue and influenza). (Vatti et al., 2017) This could have important implications for vaccine development if only a single pathogen strain or pathogen antigen is included in a vaccine, as vaccine recipients might demonstrate impaired immune responses if later exposed to different strains of the same pathogen, potentially putting them at increased risk of infection or more severe disease. (Pollard and Bijker, 2020, Vatti et al., 2017) Strategies to overcome this include the use of adjuvants that stimulate innate immune responses, which can induce sufficiently cross-reactive B cells and T cells that recognize different strains of the same pathogen, or the inclusion of many strains in a vaccine as possible (now that new strains of COVID-19 are appearing). (WHO)

Biologically speaking it is important to understand the disease process and to keep in mind the immune dysregulation in MS in order to make a recommendation regarding vaccination against COVID-19. (Li and Patterson, 2018) The immune response triggered by vaccination is blunted in patients under immunosuppressive treatments (see Key Point 2). Accordingly, more information concerning COVID-19 vaccines is needed to make responsible recommendations to our patients in an era of fast track approval and the scarce available information from large cohort regarding effectiveness and adverse events in our patients.

2.1. Key Point 2: Well-known vaccine responses from therapies used in MS

Several studies have evaluated the impact of MS disease-modifying therapies (DMT) on immune response to vaccines. Responses to any vaccination depend on the vaccine type, the type of response (humoral and/ or cellular response), and the impact of the DMT on immunity in response to that vaccine type. Regarding teriflunomide, 97% of patients achieved post-vaccination antibody for H1N1 vaccine and B strain, and 77% for H3N2. (Bar-Or et al., 2013) In this study, patients treated with interferon B1 achieved post-vaccination antibody titers of more than 90% for H1N1, H3N2 and B strain. (Bar-Or et al., 2013) Dimethyl fumarate and interferon beta response to specific pneumococcal strain, tetanus-diphtheria toxoid and meningococcal vaccines were analyzed with no meaningful differences between the drugs in proportion to responders. (von Hehn et al., 2017)

For fingolimod, a trial showed that 54% of MS patients and 85% of patients on placebo mounted a protective antibody response 3 weeks after the vaccine and 6 weeks post-vaccination only a 43% of MS patients had a response (Kappos et al., 2015). Flu and pneumococcal vaccine response in patients treated with siponimod was studied prior to and during treatment and after drug interruption. For Influenza "A/California strain", protective antibody levels occurred in 86.7% of subjects on placebo, in 92.9% of those vaccinated preceding, 74.1% during, and 71.4% with interrupted treatment. For Influenza "B/Massachusetts strain", response rates were 50% preceding, 25.9% during and 28.6% on interrupted treatment. It is noteworthy that 100% of subjects immunized with pneumococcal vaccination prior or during siponimod treatment mounted protective antibody levels. (Ufer et al., 2017)

A small trial with alemtuzumab showed that immunologic memory to common viruses (in the form of IgG titers) and responses to T-cell–dependent recall antigens (tetanus, diphtheria, and polio), a T-cell–dependent novel antigen (meningococcus C), and T-cell–independent antigens (pneumococcal) vaccinations appear normal. (McCarthy et al., 2013) In this trial, the only patient vaccinated within 2 months of alemtuzumab treatment had a poor response to several vaccines, suggesting that immunization very early after alemtuzumab may not be effective (McCarthy et al., 2013). We should vaccinate before alemtuzumab or after 2 months of receiving the infusion. Cladribine depletes B cells more than T cells and this is considered key in its efficacy to control MS but lymphopenia brings also risk of viral infections. Even though the lymphopenia is usually mild to moderate with cladribine, a small group of patients can develop severe lymphopenia (Mateo-Casas et al., 2020). Today there are no large cohorts that show whether patients can mount an effective immune response during lymphocyte depletion in the cladribine treatment (including inactivated vaccines), so it should not be initiated within four weeks after vaccination with an attenuated live vaccine and should not receive live vaccines until their white blood count and total lymphocyte count have returned to within their normal reference ranges (Furer et al., 2020).

Anti-CD20 therapies can blunt the optimal immune responses to certain vaccines (Eisenberg et al., 2013, Baker et al., 2020) because they target the B cell population that expresses CD20, which includes memory B cells that are responsible for the humoral response of vaccines. As an example of this we know that rituximab decreases the humoral response to the influenza and pneumococcal vaccine. (Eisenberg et al., 2013) The VELOCE trial (Bar-Or et al., 2020) showed that in MS patients, flu-virus antibody responses were 56%-80% on ocrelizumab compared to 75-90% on placebo or interferon. In addition, antibody response rates for pneumococcal vaccination was reduced. Therefor we can presume that vaccination responses are blunted until naive B cells repopulate (Baker et al., 2020).

2.2. Key Point 3: COVID-19 vaccine mechanism of action and main candidates

Vaccines that induce large quantities of high affinity virus-neutralizing antibodies may optimally prevent infection and avoid unfavorable effects. Vaccination trials require precise clinical management complemented with detailed evaluation of safety and immune responses. (Krammer, 2020, Chung, Beiss, Fiering, and Steinmetz, 2020, Sharma, Sultan, Ding, and Triggle, 2020) Different platforms are currently being used around the world for the development of vaccine candidates: a) inactivated vaccines, where the entire virus is presented to the immune system; therefore, the immune responses are likely to target not only the spike protein of SARS-CoV-2 but also the matrix, envelope and nucleoprotein (Xia et al., 2020) b) recombinant protein vaccines that can be divided into recombinant spike-protein-based vaccines, recombinant receptor-binding domain (RBD)-based vaccines, and virus-like particle (VLP)-based vaccines. These recombinant proteins can be expressed in different expression systems. One advantage of this is that they can be produced without handling live viruses. However, spike protein is relatively difficult to express, and this is likely to have an effect on production yields and on how many doses can be produced. The RBD is easier to express, but it is a relatively small protein when expressed alone and, although potent neutralizing antibodies bind to the RBD, it lacks other neutralizing epitopes that are present on the full-length spike (Nascimento and Leite, 2012); c) replication-incompetent vectors are typically based on another virus that has been engineered to express the spike protein and has been disabled from replication in vivo by the deletion of parts of its genome. The majority of these approaches are based on adenovirus (AdV) vectors. Delivered intramuscularly, they enter the cells of the vaccinated individual and then express the spike protein, to which the host immune system responds. Advantages of this platform are that it is not necessary to handle live SARS-CoV-2 during production and that the vectors show

good stimulation of both B cell and T cell responses. The disadvantage is that some of these vectors are affected and are partially neutralized by pre-existing vector immunity. In addition, vector immunity can be problematic when prime–boost regimens are used, although this can be circumvented by priming with one vector and boosting with a different vector (Zhu et al., 2020, Zhu et al., 2020) d) with RNA vaccines, the genetic information for the antigen is delivered instead of the antigen itself, and the antigen is then expressed in the cells of the vaccinated individual. Either mRNA (with modifications) or a self-replicating RNA can be used. Higher doses are required for mRNA than for self-replicating RNA, which amplifies itself, and the RNA is usually delivered via lipid nanoparticles (LNPs). The advantage here is that the vaccine can be produced completely in vitro. The disadvantage is that the technology is new and, required frozen storage so it can be challenging with large-scale production and long-term storage stability. Also, it is important to remember that these vaccines are administered by injection and are unlikely to induce strong mucosal immunity. (Corbett et al., 2020)

No more than 20 vaccines have reached the final stages of testing in clinical trials on humans, and very few have been approved in different countries around the world. Sputnik vaccine, a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (rAd26-S and rAd5-S) (Logunov et al., 2020), enrolled healthy adult volunteers aged 18-60 years. All participants produced antibodies to SARS-CoV-2 glycoprotein. At day 42 the seroconversion rate was 100% (receptor binding domain-specific IgG and neutralizing antibodies), and cell-mediated responses were detected in all participants at day 28 with a good safety profile. The controversy arises from the percentage of outcome results, which may have been influenced by other factors not discussed. (Balakrishnan, 2020) Recently, Astrazeneca / Oxford University published the interim analysis of the trial where they used a deficient chimpanzee adenoviral vector ChAdOx1 containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene. In this trial, healthy volunteers aged 18–70 years were enrolled, but in some sites people with pre-existing conditions such as cardiovascular, respiratory and diabetes mellitus were included (AVS, Gilbert, Pollard, and Group, 2020). Vaccine efficacy was 62.1% in the ChAdOx1 nCoV-19 group vs 71% in the control group. From 21 days after the first dose, there were ten cases hospitalized for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74,341 person-months of safety follow-up, 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. (AVS, Gilbert, Pollard, and Group, 2020) Regarding the mRNA vaccines, the BNT162b2 mRNA COVID-19 vaccine (Pfizer/Biontech) (Polack et al., 2020) enrolled volunteers of 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection. Results show that the vaccine is 95% effective in preventing COVID-19. The safety profile was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups. The mRNA-1273 SARS-CoV-2 vaccine (Moderna) (Baden et al., 2020) included eligible participants of 18 years of age or older with no known history of SARS-CoV-2 infection and with locations or circumstances that put them at an appreciable risk of SARS-CoV-2 infection, a high risk of severe COVID-19 or both. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2 vaccine. Efficacy was 94.1%.

2.3. Key Point 4: COVID-19 vaccine safety and immune response in MS patients

The first data on safety and immune response to the COVID-19 vaccine in patients with MS was recently published. (Achiron et al., 2021) Safety profile was studied in 555 patients who received the first BNT162b2 vaccine dose and 435 patients vaccinated with two doses. Safety profile of BNT162b2 vaccine in MS patients was characterized by mild symptoms (mainly, pain at the injection site, fatigue and headache) (Achiron et al., 2021). Multiple sclerosis patients had similar rates of adverse reactions to what has been reported in the general population (Polack et al., 2020). Moreover, no increased risk of relapse activity was noted during the follow-up. (Achiron et al., 2021) The immune response to BNT162b2-COVID-19 vaccine was studied in 125 MS patients either being untreated of with high efficacy DMT (ocrelizumab, cladribine or fingolimod). The anti-spike protein-based serology was measured 1 month after the second vaccine dose (Achiron et al., 2021). Protective SARS-CoV-2 antibody titers were detected in 100% of untreated MS patients and patients treated with cladribine. Otherwise MS patient treated with ocrelizumab and fingolimod showed lowest rates of protective humoral immunity 22.7%, and 3.8% respectively.

3. Conclusion

Since the first publications on COVID-19 vaccines, the MS community (patients, caregivers, neurologists and stakeholders) have had several questions. Biology of the infective disease and of the demyelinating disorders has raised a red alert: are all the COVID-19 vaccines safe and/or effective for these patients? Can patients under immunosuppressive treatment mount an appropriate immune response? Will they trigger a relapse or another autoimmune phenomenon after vaccination? Which vaccine should we recommend? We believe that these questions are partially answered. Despite having information on the safety and immune responses for one of the COVID-19 vaccines, it should be noted that both data came from a single center and only BNT162b2 mRNA COVID-19 vaccine was investigated (Pfizer / Biontech). (Achiron et al., 2021, Achiron et al., 2021)

Even though we need more information regarding the other vaccines in use, it is thought that the approved ones use a technology that appears to be safe in our patients. (Krammer, 2020, Chung, Beiss, Fiering, and Steinmetz, 2020, Sharma, Sultan, Ding, and Triggle, 2020) The only vaccine type red-flagged for immunosuppressed patients is the live attenuated virus due to a report related to the yellow fever vaccine (not replicated) that showed an increased risk of relapse in MS. (Farez and Correale, 2011) Currently, there are 3 COVID-19 vaccine candidates in the preclinical evaluation stage that have been developed using this platform (Sharma, Sultan, Ding, and Triggle, 2020), so we must be aware when they reach the final approval stage. It is worth recalling that the Astrazeneca/ Oxford University or the Sputnik use an incompetent vector. Immunologically speaking, these two vaccines will generate a more robust immune response and probably stimulate immunological memory, especially if the immune response is blunted, but this is only a theory right now. On the other hand, mRNA vaccines will elicit an important humoral response against S protein, but what will happen with the other strains of COVID-19 if this protein changes too much? Will we have humoral response, how long will it last, can we still recommend it to our patients that are B cells depleted? As discussed above, mRNA vaccines had impaired humoral response in MS patients treated with ocrelizumab but also with fingolimod. We need to remember that fingolimod diminishes circulating CD4 T cells (no impact on effector T cells) that are crucial to the immune memory due to vaccination. Moreover, the authors found that even in patients with absolute lymphocyte count> 1000 cells/mm3, failed to mount an immune response. (Achiron et al., 2021) The data shown in this cohort should be replicated in other cohorts abroad with other COVID-19 vaccines so we can start to answer the questions raised in this review.

Before this publication, our preferences on the different COVID-19 vaccines were different and the importance was centered on getting the patients vaccinated. Today we can hypothesize that anti CD20 therapies and fingolimod may benefit from repeated inactivated vaccines (more than 2 doses?) or maybe combination of 2 different vaccine platform (for example inactivated and inactivated vectors?) but these requires further study. All the other treatments should benefit just from the regular dosage of any COVID-19 vaccine that does not use live virus between its components.

Scarce data are currently available to establish vaccine safety, efficacy and the potential for reduced immune responses in persons under immunosuppressive therapies. (Achiron et al., 2021, Achiron et al., 2021) Persons with stable HIV infection have been included in mRNA COVID-19 vaccine clinical trials, though data remain limited. (CDC COVID-19 VACCINES) Nevertheless, no imbalances were observed in the occurrence of symptoms consistent with autoimmune conditions or inflammatory disorders in clinical trial participants who received a COVID-19 vaccine compared to placebo. (Xia et al., 2020, Nascimento and Leite, 2012, Zhu et al., 2020, Zhu et al., 2020, Corbett et al., 2020, Logunov et al., 2020, Balakrishnan, 2020, AVS, Gilbert, Pollard, and Group, 2020, Polack et al., 2020)

The vaccines seem to be effective in preventing severe COVID-19, and data showed in this review can be extrapolated to confirm our recommendation that our patients should get vaccinated against COVID-19 except with live attenuated viruses. All of this information is dynamic and changes every day. In the near future perhaps we will recommend a boost using a ddifferent vaccine in order to induce perdurable immunological memory and to obtain the most from B and T cells.

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Lorna Galleguillos: Conceptualization, review, writing-original, draft preparation

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