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The Efficacy and Safety of SARS-CoV-2 Vaccinations in People with Multiple Sclerosis

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Interview Summary

While people with multiple sclerosis (MS) are not more likely to contract COVID-19, the incidences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19-related complications may be higher for people with MS who have comorbidities or who are taking certain disease modifying therapies (DMT). Robert Shin, Professor of Neurology at MedStar Georgetown University Hospital, Washington, D.C., USA, and Deborah Fuller, Department of Microbiology, University of Washington School of Medicine, and Associate Director of the Washington National Primate Research Center, Seattle, Washington, USA, first discussed why vaccinations against SARS-CoV-2 should be recommended to people with MS. They then discussed evidence that suggests that the antibody response following vaccination may be dampened in people taking some DMTs, especially those that deplete CD20+ B cells; however, T cell responses to vaccinations may also provide protection. There is also evidence that messenger RNA (mRNA) SARS-CoV-2 vaccines, as opposed to viral vector or recombinant protein subunit vaccines, and boosters may lead to a better antibody response. Vaccine responses vary between patients taking different sphinogosine-1-phosphate (S1P) receptor modulators, being low for fingolimod and high for next generation S1P receptor modulators. Overall, more studies of vaccine response and timing are needed to best update the guidelines for people with MS.

INTRODUCTION

The autoimmune disease MS likely affects more than 2.8 million people globally.[1,2] MS is characterised neuropathologically by lesions/plaques, caused by infiltrating CD8+ T cells, B cells, and plasma cells, alongside brain resident microglia and astrocytes.[2]

For people with MS, the COVID-19 pandemic has raised questions regarding how vulnerable they are to the disease and whether they should be vaccinated against SARS-CoV-2 infection. To discuss these issues, EMJ talked to Robert Shin and Deborah Fuller. These experts provided important insights into SARS-CoV-2 vaccine responses in people with MS and highlighted the need for further research to help update current guidelines.

INFECTION WITH COVID-19 AND SARS-COV-2 VACCINATIONS IN PEOPLE WITH MULTIPLE SCLEROSIS

It is known that infections can exacerbate MS;[3,4] therefore, there was concern at the beginning of the COVID-19 pandemic that people with MS might be more vulnerable if they were infected with SARS-CoV-2. Although studies of people with MS have found that the susceptibility to SARS-CoV-2 infection and the outcomes of such are comparable to those in the general population,[5,6] there is some evidence that certain MS treatments may be associated with a higher incidence of COVID-19[7,8] and that comorbidities may be associated with more severe disease.[9,10]

There have also been concerns regarding the risks of SARS-CoV-2 vaccines in people with MS, as discussed by Shin and Fuller. "Before the pandemic," reported Shin, "people would ask things like, 'should I even get vaccinated if I have MS?', and there was this idea that as MS is an immune system disease, the immune system is too active and it's attacking the brain and spinal cord, vaccines are stimulating the immune system, so maybe we shouldn't vaccinate people." However, according to Shin, it subsequently became clear that the benefits of vaccination outweighed any potential or hypothetical risk and that people with MS should be encouraged to get vaccinated, for instance, against influenza.[11]

"Then we moved into the [COVID-19] pandemic," Shin continued, "and nobody really knew what to do. There was a lot of fear initially because we have been using medicines that are, to one degree or another, immunomodulatory or immunosuppressive, and there was concern that, maybe inadvertently, we were exposing our patients with MS to greater risk or that something intrinsically about MS might prove to be a risk factor the way age and obesity proved to be. But it seems as though people living with MS are not at greater risk of getting the infection or of having a bad outcome."[5,6]

According to Fuller, "studies have conclusively shown that the vaccines, particularly mRNA vaccines, are very safe" for people with MS.[12-14] Fuller explained that the risk of exacerbating MS or having severe disease as a result of SARS-CoV-2 infection is much higher than any risk associated with the vaccine. Fuller continued: "Even if we don't fully understand the response in different demographics, how durable it is, and when to get boosters, vaccination is a safe thing to do."[15]

While discussing studies of SARS-CoV-2 vaccination in general, Shin said: "It is important to emphasise that there was an effort to address vulnerable populations, I would say populations much more vulnerable than people living with MS, meaning people who are, frankly, immunosuppressed for other reasons, or in older or younger age groups seem to also benefit from the vaccine. The challenge depends on where you're starting from. If your hypothesis is that people with MS are very different from people without MS with regards to defence, then people may question the state of the data and say you haven't done an MS-specific trial of each and every vaccine. I think that's unreasonable because my starting point would be that, as best we can tell, we're all the same in this regard, and so the beneficial effects of vaccines that have been demonstrated in our general populations do apply to my patients living with MS."

IMMUNE RESPONSES TO SARS-COV-2 VACCINES IN PEOPLE WITH MULTIPLE SCLEROSIS

There are currently over 15 SARS-CoV-2 mRNA, viral vector or recombinant protein subunit vaccines.[16] "Seroconversion demonstrating an antibody response against the spike protein is the standard way of evaluating whether or not a vaccine is immunogenic,"[17] said Fuller. A number of studies have demonstrated humoral responses to SARS-CoV-2 vaccines in people with MS.[18-22]

Fuller also highlighted that antibody levels increase with subsequent booster immunisations in people with MS.[14,17,23] "That's an important consideration," continued Fuller, "especially when we're entering into an era where we still have a pandemic, but we are now able to manage and control the disease better through regular vaccination. With multiple booster immunisations, the differences between people with MS and people without in response to vaccination is going to be smaller."

Fuller discussed how vaccine studies in people with MS indicate that "mRNA vaccines have been very promising in terms of responsiveness."[18,20-22] She explained that "mRNA vaccines are not really a live viral vector vaccine, but they mimic their activity by expressing the immunogen within the patient's own cells, and this can leverage important arms of immunity such as the T cell response. With mRNA vaccines," continued Fuller, "there's a lot that needs to be studied in terms of why they might work better than other types of vaccines, but I think it relates very closely to the T cell response; even as the antibody wanes, a T cell response can persist much longer and facilitate the development and persistence of the antibody response." Fuller added: "We know that if the antibody doesn't fully protect somebody from infection and the virus gets in, the T cell response can help accelerate the clearance."[24] Shin agreed, saying that, "at the very beginning of the pandemic, because it was a novel coronavirus, we were all relying on innate immunity. What we have learned is that it appears that each of us mount different kinds of responses to [SARS-CoV-2] vaccination or boosting; there are some who rely more heavily on B cell antibody responses and not as heavily on T cell responses, and there are others who do the opposite."

Fuller stated that if people with MS are "able to generate and sustain a decent T cell response, then we can be optimistic that, even in the face of newly emerging variants, we can expect ongoing protection from severe disease and hospitalisation. What we've seen when new SARS-CoV-2 variants emerge," Fuller continued, "are increases in infection rate, but not necessarily increases in hospitalisation or severe disease.[25]

Adverse events experienced by people with MS after SARS-CoV-2 vaccination include short-term fatigue, headache, febrile symptoms, and injection site pain.[18] Larger studies including people with MS have not shown increased rates of new MS symptoms or symptom worsening following vaccination against SARS-CoV-2.[12,13] Data suggest similar safety profiles for vaccine boosters.[14]

COVID-19 INFECTION, SARS-COV-2 VACCINATIONS, AND DISEASE MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS

DMTs for MS include immune modulators such as β-interferons, glatiramer acetate, teriflunomide, cladribine, natalizumab, and dimethyl fumarate; S1P receptor modulators, including fingolimod, ozanimod, siponimod, and ponesimod; and agents that deplete CD20+ B cells, including ocrelizumab and ofatumumab.[26]

"Early on [in the pandemic]," explained Shin, "there was a concern that patients with MS might be extra vulnerable and that DMTs could increase vulnerability to COVID-19, particularly the categories of medicines that are perceived to be more immunosuppressive." This, Shin discussed, led to some prescribers delaying certain treatments at the start of the pandemic, although, in general, Shin reported that this is no longer occurring.

In regard to the vaccine response, some studies have found that, compared to healthy controls, SARS-CoV-2 IgG levels were similar and/or deemed adequate in people with MS treated with natalizumab, dimethyl fumarate, glatiramer acetate, cladribine, β-interferon, or teriflunomide, but impaired in people receiving ocrelizumab or fingolimod.[18,20-22,27-30]

Another concern mentioned by Fuller was that immune modulating drugs might have a detrimental effect on the vaccine response. Shin agreed, saying: "We knew pre-pandemic that responses to vaccinations like the flu shot might be somewhat diminished by some agents, but we just said, go ahead, get vaccinated."[31] Indeed, several studies have reported a reduced humoral response to SARS-CoV-2 vaccination in people with MS taking ocrelizumab as compared with other agents.[11,20,21,28-30,32-34] Conversely, a T cell response to vaccination has been shown in people on ocrelizumab, as indicated by high levels of CD8+ T cells and type 1 helper T cells.[35] Similar results have been described for patients with MS taking ofatumumab.[36]

Some studies of people with MS taking a DMT have shown that the administration of booster injections results in notable increases in IgG titres.[14,37] For instance, studies in people with MS administered ocrelizumab have shown that antibody and T cell responses increase with subsequent SARS-CoV-2 vaccinations, although the antibody level was typically lower than that achieved in those not taking ocrelizumab.[38,39] These findings may account for why, in a study of 19,641 vaccinated people with MS, breakthrough COVID-19 infections were limited in number but occurred at a higher rate in those on ocrelizumab.[40]

According to Fuller, however, what is unclear is whether or not these studies investigated timings between when treatment was administered and when the vaccine was given, which is of relevance for DMTs that are given periodically as opposed to being taken every day. "This could lead to confusion among clinicians about what they should recommend to the patient in terms of when to take the vaccine," said Fuller. "We've seen some evidence that if vaccination is close to when a person is getting their immune modulators, it could potentially dampen the antibody response to the vaccine." Indeed, a recent study of people on B cell depleting treatment found that while the antibody response to SARS-CoV-2 vaccination increased with a longer interval between the last therapy cycle and vaccination, the T cell responses were higher when vaccination occurred soon after the cycle.[41] Fuller called for more studies regarding vaccinations and DMT timing.

"I don't think any of us know the correct timing of boosters," said Shin. "We should be careful about over-recommending special timing schedules and whether to avoid or not avoid certain times when we really don't know. Timing considerations are always going to be debatable," Shin continued, "but if you do have the luxury of non-urgency, let's say you've been vaccinated, you've been boosted, you're thinking about another set of boosters, or you've had COVID-19 in the past few months, then [you might want] to try to vaccinate later on in the cycle if you're doing a once every 6 months infused treatment, for example. However," Shin stated, "my general message is to get vaccinated and get boosted; to me, timing considerations are secondary because we have so little data to guide us."

SPHINOGOSINE-1-PHOSPHATE RECEPTOR MODULATORS AND THE RESPONSE TO SARS-COV-2 VACCINES

"[Regarding] S1P receptor modulators, based on how they work, I don't know if I would have anticipated that they would have affected SARS-CoV-2 antibody titres, but it was observed," said Shin. However, it is known that fingolimod may be associated with a lower antibody response to the influenza vaccine[31] and a higher rate of breakthrough COVID-19 infection.[40]

Several studies have included patients taking fingolimod, a number of which have found a lower antibody response compared to other DMTs. These studies included the array of SARS-Cov-2 vaccine types (with a higher response rate with mRNA vaccines)[42] at a number of timepoints following vaccination, up to 6 months.[18,20-22,27-30,32,43] A study of booster vaccination showed increased IgG levels in patients taking fingolimod, but only two out of 29 patients had 'assumed protective humoral immunity' (IgG: >70 AU).[37] IgG levels were also not increased after a booster vaccine in a study involving 24 patients.[28] Another small study (n=15) demonstrated seroconversion (seven out of 15 patients tested) but no T cell response after a booster injection (0/6 patients tested).[23] This latter finding was also reported by a study involving 12 patients receiving fingolimod.[39]

Similar findings of a lowered antibody response to vaccination were found in a small study of patients treated with siponimod.[44] Another study showed that the development of antibodies was lower in patients treated with siponimod than in those treated with other DMTs, but, overall, the response was deemed adequate (56.3% of 17 patients had seroconverted at 1 month following vaccination). However, the T cell response was low after 1 month.[45] A further study (n=10) found that just over half of those receiving two vaccine doses (four out of seven) and all receiving three doses (three out of three) showed an adequate immune response to an mRNA vaccine,[46] with a study with four people receiving siponimod also showing adequate response,[28] and one including eight patients taking siponimod found that seven out of eight had a positive antibody status.[29]

There are a limited number of studies including ozanimod. One such, including three patients, showed all mounted an antibody response following vaccination.[29] Another, in an open-label extension trial, showed that all patients receiving an mRNA (80 out of 80) vaccine and 62% receiving a non-mRNA vaccine (18 out of 29) mounted an antibody response.[47] An observational study found that all of 30 people treated with ozanimod mounted an antibody and T cell response.[48]

A long-term extension study of people with MS receiving ponesimod[49] has enabled an in-depth analysis to be carried out for this S1P receptor modulator. The analysis included 49 patients who had received at least one vaccine regimen and had both pre- and post-vaccination antibody levels available. The majority received an mRNA vaccine (68.0%), with 16.5% receiving a viral vector vaccine and 8.7% an inactivated virus vaccine. Pre-vaccination lymphocyte count was <500 mm^3 in 31.1% of patients, ≥500/mm^3 in 64.1% of patients, and unknown in 4.9% of patients. Among these patients, 85.3% developed a measurable humoral response to vaccination. This was higher for the mRNA vaccine (90.6%) than the viral vector (71.4%) or inactivated virus (33.3%) vaccine, with 93.8% of those with a pre-vaccination lymphocyte count ≥500/mm^3 meeting response definition compared to 56.3% of those with a lymphocyte count <500/mm^3.[50]

Fuller remarked how the above data for ponesimod and ozanimod indicate that "people who are receiving this treatment do still respond to the vaccination. Seeing seroconversion in nearly all of the subjects is really promising," Fuller continued, "but on the other hand, there are other variables that have to be considered such as the level of response compared to people not receiving S1P modulators." In regard to the spread in study results for S1P modulators and SARS-CoV-2 vaccines, Fuller stated that, "when there's hugely contrasting results from different medications, one has to look at why that might be. Were there differences in how the studies were done, or differences in the population or in the medication itself? Those are the unknowns that need to be acknowledged when you see such contrasting differences in results."

RECOMMENDATIONS FROM GUIDELINES FOR PEOPLE WITH MULTIPLE SCLEROSIS REGARDING VACCINATION

"In terms of recommendations, there's not one single body," said Shin. "The National MS Society relatively early on convened a working group that generated a list of consensus statements on recommendations surrounding the COVID-19 vaccines, by medication action and by class, and they tried their best to incorporate consensus thoughts on timing of vaccinations. Some of the recommendations were later revised based on data as they came out. Now if you look at the recommendations, the bottom line is, always get vaccinated."[15]

A European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)/ European Academy of Neurology (EAN) statement confirmed data reporting that there was no higher risk for people with MS to be infected with SARS-Cov-2, except for those with comorbidities, and that "all the currently available vaccines can be administered to patients with MS, including patients receiving immunosuppressant DMTs."[51] Similarly, the MS International Federation advice is that "all people with MS should get vaccinated against COVID-19," and that "the COVID-19 vaccines are safe for people with MS, including those who are pregnant, and young people." They advise to talk to a healthcare provider regarding vaccine timing for those receiving DMTs.[52]

HOW THE SARS-COV-2 PANDEMIC MAY EVOLVE AND WHAT IT COULD MEAN FOR PEOPLE WITH MULTIPLE SCLEROSIS

"I don't think there's going to be a day that the world will declare 'the pandemic is over, let's celebrate,'" said Shin. "It's simply that it will become incorporated into the fabric of our daily lives." Fuller explained that as COVID-19 converts from a pandemic to an endemic, "we can prepare by increasing immunity in the population through booster immunisations just prior to the surge that's typically expected in the winter months. We have not entered that period yet for SARS-CoV-2, but as expected whenever a virus has an opportunity to replicate worldwide, we are going to see the emergence of new variants." Fuller continued: "What we see is the emergence of mutations that make [the virus] more resistant to our antibody response; that doesn't mean the virus is completely escaping the immune response or that our vaccines are not working against it, but they are less potent so vaccines will still protect from severe disease and vaccinated people will recover much faster from the infection."

Fuller went on to explain that if people with MS exhibit a lower antibody response to the vaccines, the antibodies they have are going to be less effective against new variants that emerge. "The waning of an antibody response to the vaccine is an important consideration," said Fuller, "particularly when we're anticipating an uptick in SARS-CoV-2 infection rates. That influences, in turn, recommendations for timing of vaccinations to make sure that those are timed ideally prior to a potential surge, like when we see a new variant emerging or in the winter months when respiratory infections in general increase." Fuller suggested that "immune compromised people, like the aged, people with transplants, and people taking drugs for MS, may need to have additional recommendations for more frequent booster doses or updated vaccines to keep their immunity at a level needed to protect them from COVID-19 to the best degree possible."

THE IMPACT OF SARS-COV-2 VACCINE STUDIES ON VACCINES FOR OTHER INFECTIONS

Fuller discussed how "mRNA vaccines are new for COVID-19; there's no other infectious disease that we currently have an mRNA vaccine for. We do see some dampening of the response to mRNA vaccines in older people," Fuller continued, "but it's not as dramatic as, for example, the response in the elderly to the flu vaccine,[53] which is an inactivated vaccine, so there's something promising there regarding mRNA vaccines for other infections." Fuller went on to say that "there are clinical trials [of mRNA vaccines] going on for influenza[54,55] that might eventually replace our current vaccines that have not worked as well in the immune compromised or elderly."

CONCLUSION

While there were concerns at the beginning of the COVID-19 pandemic regarding both infection with and vaccines for SARS-CoV-2, Fuller and Shin are assured that the risk of exacerbating MS is far greater by getting COVID-19 than from receiving the vaccine. Further work is needed to understand the relationship between vaccinations, including specific types and DMTs in people with MS, but the data on people who have received booster injections indicates that sufficient immunity against SARS-CoV-2 infection can be mounted in many cases.

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