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Calibrating COVID-19: The Interplay of Disease Modifying Therapy and Vaccination in Patients with Multiple Sclerosis

Dr. Subei:
Welcome to CME on ReachMD. This activity entitled "*Calibrating COVID: The Interplay of Disease-Modifying Therapy and Vaccination in Patients with Multiple Sclerosis*" is jointly provided by Efficient and Postgraduate Institute for Medicine. Before starting this activity, please be sure to review the disclosure statements as well as the learning objectives.

My name is Dr. Adnan Subei and I'm the Director of the MS Program at Memorial Healthcare Systems, Neuroscience Institute in Hollywood, Florida and I'll be your moderator. I'm joined today by Dr. Robert Bermel, neurologist and Director for the Mellen Center for MS Treatment and Research at Cleveland Clinic and Dr. Claire Riley, Medical Director of the Multiple Sclerosis Center and Assistant Professor of Neurology at Columbia University.

As we know, COVID-19 introduced a multitude of considerations into MS management for which there is little historical experience to pull from. Much like the virus, itself, guidance on these issues seems to evolve every day as we continue to learn more. In particular, the introduction of a new class of vaccines has left many to wonder how, if at all, COVID vaccines may interact with immune-modulating medications and whether providers can be assured that patients using these agents can achieve adequate protection from the virus.

Here to help answer these questions, I'd like to introduce Drs. Bermel and Riley. Dr. Bermel, Dr. Riley, it's a pleasure to have you on this program.

Dr. Riley:
Looking forward to a lively discussion, this evening.

Dr. Bermel:
Thanks for having me, today. I'm looking forward to a great discussion, too.

Dr. Subei:
Before we get into the specifics of individual disease-modifying therapies and vaccines, I wanna start by addressing exactly what it is that these agents do to the immune system and how that compares to immune response generated by COVID-19 vaccines. We now have twenty approved disease-modifying therapies for MS. And they all have their impact on the immune system in various ways.

My question to you, Dr. Riley, is what intact immune functions do the available COVID-19 vaccines require in order to properly work and generate sufficient response?

Dr. Riley:
That's a question that really gives us an opportunity to walk through, you know, how the immune system really works. So, first you have to be able to present antigen, right? So, antigen-presenting cells are our friends, here. Whereas, in MS, it's a more questionable role but here, you know, when an mRNA vaccine particularly is given, that protein is made and then APC is needed to pick it up and really generate the immune response. And then you get activation of lymphocytes and then you get T-cell mediated and b-cell mediated pathways, right. So, then you see the development ideally of both types of vaccine response.

Dr. Subei:
So, Rob, maybe now is a good time to review the, sort of, mechanism of action of the mRNA vaccines.

Dr. Bermel:
Sure, Adnan. So, the mRNA vaccine is a new type of vaccine, it's the most common type that's administered in the U.S. against COVID-19 or SARS-CoV-2. And the way it works is that mRNA is incapsulated in lipid microcapsules within the vaccine itself. Then the mRNA gets taken up by antigen-presenting cells within the muscle and the mRNA gets translated into a portion of the spike protein. And this spike protein for SARS-CoV-2 then generates an immune response.

Dr. Subei:
And how about the viral vector vaccines, how are those different?

Dr. Bermel:
Yeah, the viral vector vaccine such as the Astra Zeneca vaccine or others that are used internationally, the Johnson and Johnson vaccine in the U.S. utilize a little bit of a different way to get the RNA into the cell. It uses and adenovirus vector. But similar principal, whereby the transfection of this actually makes it into antigen-presenting cells, becomes, uh, spike proteins that gets expressed by the body's cells, very temporarily, probably for a couple of days, and then leads to both humoral and cell mediated immune responses in the body.

Dr. Subei:
So, the National MS Society put out a statement on vaccines and MS. What they mention is that vaccination against COVID-19 is critical for public safety, safe in people with MS and not likely to trigger a relapse or impact the disease in the long-term. 'Get the vaccine as soon as it's available to you', was their message to their patients. So, Dr. Riley, do you agree with this statement.

Dr. Riley:
Well, first I just wanna say how tremendously difficult a task this was. And I really appreciate the MS Society putting together a really thoughtful task force to make a recommendation and a guideline. And also, I think one of the big challenges is just what a moving target COVID has been. So, I think the guideline that may have been most appropriate when developed, you know, we may think differently about it even a few months down the road.

So, do I think that these statements are reasonable? I think they're reasonable. It's not entirely in line with all of my practice. So, for example, getting the vaccine as soon as it's available to you, I think, I don't necessarily practice that. I think timing becomes important. Or patients depending on what disease-modifying therapy they're on. Or if they're not on a disease-modifying therapy. And so, now I'm certainly tailoring timing of vaccination to the individual patient situation in a way that's not encapsulated in that overall society statement. So, I think there's some nuance there.

Dr. Subei:
So, now they made specific guidelines to DMTs depending on the mechanism of the DMT. And this first category focuses on interferon beta, glatiramer acetate, teriflunomide, the fumarates, and natalizumab. And their recommendation was that the medications are not delayed for a vaccine injection. And if the patient is already on the DMT, then no adjustments needs to be made.

So, Dr. Riley, do you agree with this statement and is this what you would practice?

Dr. Riley:
I think that I basically agree that these therapies are unlikely to have a major impact on the vaccine efficacy and so I haven't specifically targeted these for modification.

Dr. Bermel:
Yeah, I certainly also agree. And just overall thoughts, as well, that this is definitely an evolving area to understand. The MS Society, as Dr. Riley said, has really done a commendable job of bringing together experts to try to give best guidance. But we have to recognize that this is something where we literally week by week and month by month are learning more. And the practice may be evolving. But certainly, with patients on this class of medications, I think, these classes of medications are the least likely to impact immune response to a vaccine. And so, I would not alter dosing of the medications for sure, around the timing of a vaccine.

Dr. Subei:
We've certainly seen them in previous trials on other vaccinations and they don't seem to suppress the immune response.

Dr. Bermel:
That's right. You know, the data are definitely emerging about this, and you'll see that there are papers and posters emerging with dozens of patients on each of these, if that, but as the numbers start to grow, I think we'll get more information.

Dr. Subei:
Absolutely.

I am curious to ask you about natalizumab, that it's been placed in the same category as the traditional platform therapies, the fumarates and teriflunomide. Some studies don't show significant impact on the immune response, but others suggest that there may be. And so, do you think this is reasonable to have natalizumab in the same category?

Dr. Riley:
We love to think about how these drugs work, right? So, we know that natalizumab functions by blocking adhesion of lymphocytes to the vascular endothelium and transit into the central nervous system. If anything, in the periphery we see an escalation or often times a rise in the peripheral white blood cell count. So, we think that this kind of mechanism shouldn't impact a vaccine response. And what we can see here is individuals on natalizumab that had been on it for at least six months were dosed with tetanus toxoid or KLH and they all achieved what's considered to be protective against tetanus. Now, there's no real disease that's related to KLH, so there's no protective bar. But essentially the responders to these antigens or KLH, which is really an neoantigen were similar in people who were on natalizumab or not.

And then conversely, in a second study pictured here, we see that individuals with influenza response, there was some difference in that antibody response to the H3N2 strain of the seasonal flu that was low compared to response to H1N1 in b-strain. So, you know, I think that there's obviously more to this story, but kind of, on first order, we believe mechanistically that natalizumab should not be so problematic, even though it's a high efficacy agent, because of its mechanism of action, shouldn't really give you so much problem in the periphery.

Dr. Subei:
So, our next category of medications are the S1P receptor modulators, specifically fingolimod, siponimod, ozanimod and ponesimod. The National MS Society guidance recommends that initiating an S1P receptor modulator be delayed if the patient is vaccinated but it's not recommended that the vaccine be delayed if the patient is already on the S1P medication. Why is that?

Dr. Bermel:
So, I think there's some special issues with the S1P receptor modulators. In general, if someone has active MS, I want to get them on disease-modifying therapy as soon as possible. And if we're going to select an S1P receptor modulator for them, we may try to get them vaccinated before they begin, but I'll often not want to delay starting disease-modifying therapy in order to do that. And so, if logistically, like for right now, for instance, the availability of vaccine in the U.S. is quite good and so, maybe we could get someone a complete vaccination quickly, with say, a single-step Johnson and Johnson vaccine while we're getting the paperwork going and getting the startup process running. And in that case, maybe I would do it, but if I was in a situation where vaccine supply was short and a patient had active relapsing or mitigating MS, I would often prioritize getting them on disease-modifying therapy.

S1P receptor modulators, because they're self-trafficking agent, have a separate effect of, uh, potential for rebound disease activity after stopping and S1P receptor modulator. And so, this is one class of agents that we tend not to interrupt for the purposes of vaccination, alone, because we don't want to lead to reactivation. And there's really no data on, kind of, a treatment interruption followed by vaccination and then try to resume therapy. There's no data on what that would do to the patient's MS or the immune response. And so, I tend to start disease-modifying therapy, especially S1Ps when I need to and then continue them. And this is gonna be a common theme throughout a lot of my management, as really it's our job I think to manage a patient's MS and in the setting of active MS, especially, it's possible that vaccination kind of takes a little bit of a backseat relative to how important it is for any individual patient to control their MS disease activity.

Dr. Riley:
I agree. I think that it depends on, sort of, the level of activity of the disease, which I think we're in agreement on. But if somebody who has very active disease, I would not be interested in vaccinating that person at that time because a) I wanna prioritize getting them on MS immunotherapy, and b) I don't want to further stimulate their immune system, at that time. I think that it's probably unwise.

Dr. Subei:
How 'bout with the newer S1P agents and so do you believe that there would be any difference with regards to the vaccination having an impact?

Dr. Riley:
I don't have as much clinical experience with the newer agents. I guess none of us does, compared to 11 years of open market. And I think I have been a bit trepidatious about starting people recently on S1Ps and you know to Rob's point, I really don't like to discontinue them. And not knowing, kind of, what's over the next hill in terms of vaccination. Whether or not rebound relapse will be a class effect or

unique to fingolimod, I don't think has been yet determined. I haven't taken enough people off of siponimod, ozanimod, or ponesimod to really say from my individual experience, yet. But I think we can look at some specific data. We have some data on pneumococcal vaccination with siponimod, we've seen I guess influenza and pneumococcal vaccine response looks pretty steady with pneumococcal and modestly diminishes, so about 70% response to H1N1 and H3N2, but that's within the criteria and that was defined as a response. So, as in many booster-type more recall response, we've seen adequate but diminished response, but these are known antigens, right?

Dr. Bermel:
I agree with that, Claire, I don't have substantial reason to believe that each of these is different from another. But that being said, we tend to over-simplify this when we think about the immune system and so I remain open-minded and wait for more data to emerge.

Dr. Subei:
Moving on to the anti-CD20 therapies. The society recommends that if a patient is about to start an anti-CD20 therapy, they should consider getting fully vaccinated two to four weeks more prior to starting therapy, similar to the S1P receptor modulators. However, if the patients are already taking ocrelizumab or rituximab, they should consider getting vaccinated twelve weeks or more after the last DMT dosage. When possible, patients should resume therapy four weeks or more after getting fully vaccinated. With regards to ofatumumab, there's no data currently to guide the timing of the vaccine in relation to the last DMT injection, since it is a monthly injection.

So, Dr. Bermel, what could happen, if anything, should the patient receive a vaccine prior to the end of a post-therapy waiting period, suggested by the society?

Dr. Bermel:
So, this issue of how to time vaccination around and infrequently-dosed anti-CD20 therapy has been a really complicated one to unravel. And again, we still don't have all the answers, but there's some data from the rheumatology experience with rituximab suggesting that patients who received vaccination further out from their last infusion or rituximab, in this case, more than three months out, actually mounted a little bit better humoral response, that means you could measure antibody titers that were a little bit higher in their blood. But as Dr. Riley already said, that's only one component of immunity. And it was not to an mRNA or an adenovirus vector SARS-CoV-2 vaccine. And so, I think extrapolating data is a little bit dangerous. Of course, we'll use any data that we have to try to understand this as we await better information. But the most recent information I think suggests that vaccination is certainly safe, especially with the mRNA vaccines and the adenovirus vector vaccines. But maybe less effective in protecting people who are on anti-CD20 therapies. Then we do not right now have a good way to predict exactly who might mount a good immune response to a vaccine on an anti-CD20 and who might not.

Dr. Riley:
And there are even, you know, other things to consider, as well. How long has the individual been on this immunotherapy? What's the age of the patient? Did they have COVID also? I mean, there are lots of other features. I mean, a lot of people out there already had COVID (laughter), right?

Dr. Subei:
But, for the time being, what would you tell our learners? How do you practice right now?

Dr. Bermel:
So, we have a very large MS practice and we have received just an absolute onslaught of patient inquiries about what people should be doing. And as easy (laughter), you know, as it would be to provide a uniform guidance of you know this is our policy, this is what we're doing across the board, we have not been able to do that because we really feel as though each individual patient situation is a little bit different. The National MS Society guidance is really good, but it still needs to be applied individually, at least that's what we've found so far in trying to manage a complex set of patients.

Dr. Subei:
Moving on to our next medication, and that would be cladribine. The society recommends that if a patient is about to start cladribine that they should consider getting fully vaccinated two to four weeks, as with the prior therapies, prior to starting cladribine. If a patient is already taking cladribine, the current available data doesn't suggest the timing of the vaccine in relation to cladribine dosing, is it gonna make a significant impact. If a patient is due for their next treatment course, when possible, they should resume cladribine two to four weeks after getting fully vaccinated.

So, Dr. Riley, have you come across any conflict with cladribine and vaccine in your practice?

Dr. Riley:
I haven't. I have not a huge number of cladribine patients in my practice, but in all of those, we were past the first year and I was encouraged to actually see some concrete data with cladribine and one of the mRNA-based COVID vaccines showing that there really

seemed to be an excellent humoral immune response, similar to what we see in people who are not treated. And I think that that gave me a lot of comfort. And in fact, you know, I think I'm somebody who likes to make a lot of, sort of, contingency plans and talk with my patients about this contingency plan. So, I have quite a few patients that I've spoken with recently who are concerned about being on a B-cell therapy and if they're not getting fully-protected by a vaccination, we've discussed cladribine as an alternative to allow us to control their MS, let the B-cells return with impunity and then vaccinate. And so, I think that it's a good option for our patients in this situation.

Dr. Bermel:
I agree.

Dr. Subei:
And our next medication is alemtuzumab. So, the National MS Society recommends that if a patient is about to start alemtuzumab, they should consider getting fully vaccinated four weeks or more after starting. The emphasis here is it's not two to four weeks, but it's more weeks. And so, my first question to you is, why is that, is that related to the mechanism of action of alemtuzumab as to why that distinction was made?

Dr. Bermel:
Yeah, I think this is a situation where we're really basing it off of the mechanism of action. We're basing it off empiric, kind of, assumptions about how things work and trying to err on the side of safety. And I would like to stress that yes, you know, vaccine response or timing of SARS-CoV-2 vaccination is one factor that we consider, but generally I would say that I'm choosing medications like alemtuzumab, cladribine, I'm using them in select circumstances, where the patient's MS and their situation and their individual health circumstances demand it. And we'll work vaccination around the patient's MS treatment in those situations. So, I, sort of, let the MS be the primary driver of which medication I'm selecting, and the patient situation and then usually SARS-CoV-2 vaccination is a secondary factor.

Dr. Subei:
So, the National MS Society also recommends that if a patient is already on alemtuzumab that they should consider getting vaccinated twenty-four weeks or more after the last dose. so, Dr. Riley, what is your take on this?

Dr. Riley:
Well, again, I think this speaks to the mechanism of action of the drug. With alemtuzumab, it's action against CD52, we see a dip in both T-cells and B-cells and then around six months or so, those B-cells start returning. And so, as we talked at the top of this program, right, in order to respond to a vaccine, you'll have B-cell and T-cell pathways. I think we want at least one working well (laughter). And so, I think with alemtuzumab where you have both of those populations dipping, I think it makes a lot of sense to wait about six months until those B-cells start to return.

Dr. Subei:
And Dr. Bermel, would you monitor patient's lymphocytes counts or just follow the six month after alemtuzumab dosing?

Dr. Bermel:
Yeah, I wouldn't have sufficient rationale to base the decision off of lymphocytes counts. I think I would probably follow this guidance. And I think that honestly, I've in general, erred on the side of trying to get my patients vaccination sooner rather than later. And so, I think I would probably wait the six months and that's it.

Dr. Subei:
And in this era of COVID-19 and COVID-19 vaccinations, would you opt out of considering alemtuzumab as a treatment option for patients?

Dr. Bermel:
No, I think that we still leave all of our treatment options on the table. I mean, we still have patients undergoing autologous hematopoietic stem-cell transplantation for very severe active MS that's refractory to other therapies. And so, I would include alemtuzumab on the list of medications that I would consider.

Dr. Subei:
Now, we do have one study that was published recently on one of the COVID-19 vaccinations. And it was a population of 125 MS patients with 47 controls. And these patients were on fingolimod, cladribine, or ocrelizumab, 32 were untreated. And what's interesting to see here is that humoral response to the vaccine, as cladribine had 100%, ocrelizumab had 22%, and fingolimod had a 3.8%. Dr. Bermel, do you find this data surprising?

Dr. Bermel:
So, I think that the most surprising part for me were the fingolimod data. I think it definitely segregates some of our therapies into a category where we're less certain that there's a protective response to the vaccine and I would for sure put anti-CD20s and S1P receptor modulators in that group. It doesn't mean there will not be a response to the vaccine. I think looking at the antibody or the humoral response alone is only part of the issue, it may be an important part for, you know, novel viruses like this, but it's not the only response and so, looking at cell mediated immunity is more challenging. It's not as easy to measure or quantify, but it does provide an important mechanism of support for our immune system. So, I think this is a really great first step and it raises a lot more questions.

Dr. Subei:
For this last section, I'd like to take a minute to discuss how the things we've discussed are actually playing out in clinical practice, so, I have a case for you.

So, let's say you have a patient whose last ocrelizumab infusion was administered two weeks ago, informs you that she just received the first does of an mRNA COVID-19 vaccine without your consultation. And so, Dr. Riley, should this patient worry about potential affects? And should she received the second dose as scheduled or delay her next ocrelizumab?

Dr. Riley:
If this is somebody that's been on B-cell modulation for some time, I guess to segment out the questions, should the patient be worried about direct ill effects from the vaccine? I think not. I think that the vaccine is safe in this person. If she had been on B-cell therapy and was already quite suppressed and actually two weeks after an ocrelizumab infusion, probably her B-cells are quite suppressed, even if it's her first dose. So, my concern for her is that this is unlikely to be a particularly effective vaccination, in my opinion. So, as to whether she should receive the second vaccine dose as scheduled, I guess my inclination would be to say, why don't you delay and maybe even push it out three months. We're seeing some data coming from international sources that have spaced out, for example, the Pfizer vaccine three month interval showing a better effect or a higher antibody titer level rise in elderly people and that's coming out of Britain. So, I think I might tend to follow something like that with this patient. I think I would probably delay the second dose. But there's not a right answer, here, I don't think. And I'd be interested, actually, Rob to hear what would you do? Or what have you done in this case?

Dr. Bermel:
This sort of thing has come up quite often, actually, because, you know, like you mentioned, Claire, there's been a mentality of when you get the opportunity to get vaccinated you should take it and it was a competitive environment for vaccination for a while. And so, I tend to stick to the recommended timing of the vaccine and would probably let the patient get their second step of the vaccine as scheduled. And then I would probably dose their ocrelizumab on schedule, as well, cautioning the patient that yes, they have their card, yes they got their two shots, and they should remain cautious in their activities and protect themselves because they may not be fully protected based on what we know about anti-CD20s and the timing of his or her vaccine.

Dr. Subei:
Dr. Riley, would you check antibody titers to the vaccine in such situations to verify that there was an immune response?

Dr. Riley:
There is very little benefit to checking an antibody titer in this situation. I've acquiesced to quite a few patients who've wanted to be tested for anti-spike antibody now that it's commercially available, and my experience is those on B-cell therapy, even those in whom I've held doses out six and nine months from their last dose, are not developing detectable anti-spike antibodies. And so, I think that I could send it, but I don't think it's probably valuable and I think it's probably negative. But when it's negative, we don't exactly know what it means, right? Some people who have a response to a vaccine will not mount this detectable antibody response. So, again, it leaves out the whole picture of the T-cell pathway. What do you think, Rob?

Dr. Bermel:
We've not been widely using, we've actually been recommending against getting antibody tests for all the reasons that you brought up. I don't think that right now an antibody titer helps in individual management.

Dr. Subei:
And finally, I'd like to ask if any of you have any interesting cases or other examples that you'd like to share with relation to DMTs and the COVID-19 vaccinations?

Dr. Bermel:
Thankfully, the most common situation I've encountered, even in patients on anti-CD20s or S1P receptor modulators has been smooth, clinical course with their MS and, uh, uneventful course, if someone were to contract COVID-19. I also try to strike a generally reassuring tone with people and in the absence of data showing that there's a substantial advantage to a different plan, I tend to

recommend vaccination even if they're on a medication whereby the vaccination might be less effective. And if we can make small adjustments in their treatment plan, delaying doses by weeks, for instance, or delaying start by a couple of weeks, we'll do that. But, in general, we sort of stick to the plan.

Dr. Riley:
I agree. I think I try to give patients similarly a positive and, sort of, upbeat view and I tell patients though who are uncertain about vaccination or fearful or hesitant, whatever you wanna say, yes, of course, a vaccine stimulates your immune system and that's something that I've been telling you to avoid, right? Ever since I've been caring for you, I've been telling you to try to avoid unduly stimulating your immune system. But, you know, something that's extremely immuno-stimulatory? COVID-19. So, a COVID-19 infection revs up your immune system tremendously. I've seen bad post-infectious inflammatory events more than in my experience, yet I've seen some cases of potentially linked vaccine inflammatory events. But I think the infection that is COVID is such a driver of the immune system that we need to educate our patients to avoid that in the best way that they can, which is vaccination.

Dr. Subei:
Well, Dr. Bermel, Dr. Riley, thank you so much. I appreciate you joining us in our program this evening and sharing your expertise and your experience to all of our listeners. Thank you.

Dr. Riley:
My pleasure. It was great to talk with you both.

Dr. Bermel:
Thank you, so much.

Dr. Subei:
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