Dr. Doghramji: The spread of the COVID-19 pandemic has caused us to reconsider how we treat and manage our patients with multiple sclerosis, or MS for short. Healthcare professionals have been questioning the role of immunosuppression in autoimmunity resulting in delays and even discontinuations in immunotherapy treatments. How do we decide what the best course of action is, and what does limited research available tell us about making the right treatment decision? These are the questions we'll be considering today.

Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is Medical Breakthroughs from Penn Medicine. I'm Dr. Paul Doghramji, and joining me on this episode is Dr. Amit Bar-Or, Chief of the Multiple Sclerosis Division and Director of the Center for Neuroinflammation and Neurotherapeutics at Penn Medicine.

Dr. Bar-Or, welcome to the program.

Dr. Bar-Or: Hi, Paul, great to be here.

Dr. Doghramji: Great. So, Dr. Bar-Or, to start us off, can you tell us how the COVID-19 pandemic has impacted your patients with MS?

Dr. Bar-Or: So, when the pandemic started, we were, of course, quite concerned, not knowing how the pandemic may influence people living with MS being treated with immune-directed therapies that can take the edge away from the immune system. And we, like many other places, transitioned to video telemedicine as opposed to face-to-face visits to enable people to remain relatively isolated and safe and tracked the hotspots of COVID so that we could learn as more individuals with MS were living through the pandemic in other regions, even prior to reaching North America. And overall, we became increasingly reassured. The first was that people with MS are at no greater risk of contracting the virus or its complications just by virtue of having MS. We also were able to learn that there is no particularly increased risk overall, nothing obvious in terms of increased risk for people living with MS on the different immune therapies.

And in parallel to this, we were learning more and more about the virus and the serious complications because, in fact, what one would be particularly concerned about is not so much whether you had some symptoms of the SARS-CoV-2 virus but whether you developed the severe complications referred to as COVID-19 complications. And it turns out that the serious complications are not actually because of the virus going rampant in the face of an incompletely functional immune system; rather the serious complications are now thought to be a result of the person's immune system responding to the virus. So, in fact, a vigorous response to the virus is associated with serious complications, and, in fact, some of the MS therapies have been used in the last months in clinical trials to treat and try to prevent COVID-19 serious complications with some degree of success, so overall, it's been reassuring.

Dr. Doghramji: And how has the way you've treated patients with MS evolved from the beginning of the pandemic?

Dr. Bar-Or: So, from the get-go, we remained very vigilant to what was happening and, as I mentioned, what we learned from other places. The decision had been, to avoid using the particularly aggressive immune therapy, such as bone marrow transplantation for the most part to stay the course, recognizing that, as we got more information, the risk appeared to be very low, if there at all, and the importance of maintaining people on a treatment that will control their MS was viewed as overweighing the potential risks associated with the treatments. We continued to monitor closely and really changed essentially nothing about the regimen of the different therapies with the

exception again of the particularly aggressive approaches to treatment, which are used really in less than 1–2% of people with MS.

Dr. Doghramji: So, looking at the treatment options available for patients with MS, how do immunotherapy agents positively affect the course of this disease?

Dr. Bar-Or: Well, we know that the immune therapies affect the course of MS in an important way in limiting new injury. There's nothing at the moment to suggest or at least compellingly point to medications that improve the outcome of COVID; although, as I mentioned, some early successes suggest that MS therapies, particularly first-line therapies, may in some ways be protective. We're certainly not recommending that as a treatment for COVID-19. And perhaps most importantly, by virtue of being treated, maintaining your treatment for your MS, you're avoiding MS disease activity, which should limit your need to be exposed to the healthcare system, and hence the benefit of the treatments is essentially keeping you away from the doctor.

Dr. Doghramji : For those just tuning in, you're listening to Medical Breakthroughs from Penn Medicine on ReachMD. I'm speaking to Dr Amit Bar-Or, Chief of the Multiple Sclerosis Division and Director of the Center for Neuroinflammation and Neurotherapeutics at Penn Medicine.

Dr. Bar-Or, we spoke a bit earlier about the role of immunotherapy agents. So, switching gears, let's talk about a topic that's been creating some controversy in the MS community.

It's been suggested that MS patients might be at higher risk of contracting severe COVID-19 if they are being treated with anti-B-cell drugs. What can you tell us about this?

Dr. Bar-Or: Well again, the question that's important is not so much whether you become symptomatic or not as much as whether you develop the severe complications. And the reason that we've been paying particular attention to this treatment is a study that has come out of Italy where people with MS followed on multiple different treatments, including anti-CD20, were considered in terms of the potential association of different treatments with severe COVID complications. And this study suggested that there may be a small but real increase in the risk of developing severe COVID-19 complications on anti-CD20. Now, importantly, several other studies from other countries, including the French cohort, the Dutch cohort and the relatively early United States cohort do not replicate this observation, and they together have pretty decent numbers of individuals exposed to the different therapies, including anti-CD20.

What does this mean? Well, it likely means that if there is an increased risk, it is small. It depends very much on what population of patients is treated with different therapies. We do know that risk factors of developing serious complications in anyone, whether you have MS or not, include increased age, comorbidities, such as high blood pressure, and a variety of other conditions that can increase in frequency overage. And in certain populations of MS where anti-CD20 was reserved for people with more progressive MS forms, the observation of increased risk of serious complications may in fact relate to these other features of the individuals, their age and comorbidities, rather than the actual treatment that they were on.

So we do need more information, but this at the moment is an area that's being followed closely without us changing our approach to either the initiation or the spacing out of the anti-CD20 treatments.

Dr. Doghramji: And coming back to the pandemic, we are all eagerly awaiting a vaccine against COVID-19. Given that vaccination responses are predicted to be blunted until naive B-cells

repopulate, can you talk to us about the potential risks of vaccination for patients with MS who are taking these drugs?

Dr. Bar-Or: So the question is not so much about the risk of complications from the vaccination in people with MS but whether the vaccine response will be mounted by the patient when they are on a treatment such as anti-CD20. And there is no question that there's a blunted antibody response in that context.

Now, it's important to note that while measuring antibodies to mark the response to vaccines is easy, it is actually not the only way by which the immune system mounts an effective vaccine response.

In fact, the cellular limb of the immune system's response to the vaccine in many cases is just as important, if not more important, than the antibodies, and it is not surprising in the context of anti-CD20 therapy where you remove B-cells as precursors to making antibodies that you would diminish the antibody response when that's used as the measurement for the vaccine.

So, while we still need to learn more about whether the SARS-CoV-2 virus is effectively dealt with by the cellular immune response as by the vaccine antibody-mediated response, at the moment the likelihood is that vaccine responses will still be worthwhile. One of the interesting questions comes up whether there may be value in delaying infusions to allow a little bit more B-cell reconstitution to have a stronger vaccine response. The good news there is that unlike some of the medicines in the world of MS where stopping the medicine can be associated with return of MS disease activity, return with a vengeance, this is not the case with anti-CD20 therapies, and there are studies now that are considering whether increasing the dose interval may help mount an even more vigorous and protective vaccine response.

Dr. Doghramji: Lastly, Dr. Bar-Or, based on what you've learned throughout this pandemic response so far, what are some takeaways or lessons you'd like to pass on to our listeners?

Dr. Bar-Or: Well, I think that we continue to learn. There's more information that we're collecting, and now several registries and different prospective studies are being set up internationally and nationally to get more good-quality information that will help us have a better sense of what risks there may or may not be in association with different treatments, including the question about anti-CD20, and of course we need to learn more as the field rolls out different vaccine opportunities for individuals with and without MS.

We have been overall reassured. We recognize that the immune therapies for the most part are not associated with increased risk and in some cases may be protective, although the bottom line is that we're certainly not suggesting to people with MS on therapies to be any less vigilant than the general population, which means social distancing, masking, frequent handwashing, avoiding touching your face and so on, so being just as careful as everybody else.

Dr. Doghramji: Well, I'd like to thank my guest, Dr. Amit Bar-Or, for sharing his insights on the role of immunotherapy agents and impacts of the COVID-19 pandemic on our patients with multiple sclerosis. It was a pleasure speaking with you, Dr. Bar-Or.

Dr. Bar-Or: The pleasure was mine, Paul. Thank you.

Dr. Doghramji: I'm Dr. Paul Doghramji with ReachMD. To find other episodes in this series, visit ReachMD.com/Penn. Thank you for listening.