Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/neurofrontiers/b-cell-therapy-for-ms-what-we-need-to-know/13378/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

B-Cell Therapy for MS: What We Need to Know

Announcer:
You're listening to *NeuroFrontiers* on ReachMD, and this episode is sponsored by Novartis. Here's your host, Dr. Charles Turck.

Dr. Turk:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turk, and joining me to discuss B-cell therapy for multiple sclerosis, or MS, is Dr. Francesca Gilli, Associate Professor of Neurology and Co-Director of the Graduate Program in Integrative Neuroscience at Dartmouth. Dr. Gilli, thanks for being here today.

Dr. Gilli:
Thank you for having me.

Dr. Turk:
So, Dr. Gilli, let's begin by taking a look at the types of B-cell therapies. Would you tell us what's currently available for patients with MS?

Dr. Gilli:
Sure. Currently, there are two categories of B-cell therapies available for patients with multiple sclerosis: B-cell depletion therapies and the Bruton's tyrosine kinase inhibitors, or BTKs. B-cell depletion therapies involve the administration of monoclonal antibody that bind receptors expressed on the surface of the B cells to induce cell death by activating different mechanisms of cytotoxicity. The most common B-cell antigen to be targeted are CD20 and CD19. Both express on a wide range of developing B cells, although CD19 is expressed in a broader range of B cells, including late B cells. Another possible target antigen for monoclonal antibody therapy is CD38, a surface protein expressed on plasma cells. However, the wide expression of CD38 on other immune cells, including regulatory B cells, could discourage its potential use in multiple sclerosis. More recently, the second category of the therapies has been developed. Bruton's tyrosine kinase inhibitors, or BTKs, which encompass a new class of therapeutics currently being evaluated to treat MS, these are treatments that are not approved for the treatment yet. Therapeutic inhibitions of this enzyme, BTK, involves B cells and myeloid cells activation and function is regarded as the next generation approach that aims to attenuate both innate and adaptive immune functions. Moreover, brain penetrant BTK inhibitors may impact the neural inflammation, so the inflammation in the central nervous system – in the brain – and the following neurodegeneration, which normally that's something that we cannot obtain specifically with added treatments that are not that able to cross the blood-brain barrier and enter into the brain.

Dr. Turk:
Now I'd like to zero in on two of those therapies in particular: the anti-CD20 monoclonal antibodies, or MABs, and the BTK inhibitors. Starting with the anti-CD20 MABs, what do we need to know about them?

Dr. Gilli:
So anti-CD20 therapies are the first and most used B-cell therapies to treat patients with multiple sclerosis. Among these therapies, we have two that are actually approved by both the FDA and AMEA for the treatment of multiple sclerosis – different forms of the disease. CD20 is a transmembrane iron channel protein expressed in B cells across different stages of maturation, ranging from very early cells like pre-B cells in the bone marrow to short-lived plasma blasts, which are later and more mature cells. Its spare CD20 negative and long-lived plasma cells, which produce antibodies directed against previously encountered pathogens and vaccines, might explain the favorable safety profiles of these treatments. The B cell degrading effect of anti-CD20 therapies is mediated through apoptosis, that is cell death. The two different mechanisms of cytotoxicity is the antibody dependent cellular toxicity, or ADCC, and the complement dependent cytotoxicity, or CDC. A single treatment normally leads to a rapid depletion of CD20-positive B cells and circulating B cells,

which represent only about 2% of the total B-cell pool, are the compartment most efficiently depleted by CD20-targeting agents. In contrast, B-cell depletion in lymphoid organs and other tissues, including the central nervous system, is quite limited. Of the anti-CD20 antibodies, we have rituximab, ocrelizumab, ofatumumab, and ublituximab – it's really weird names – and all these different treatments have been developed specifically to treat multiple sclerosis.

Dr. Turk:
Now you'd spoken a little bit about them before, but what else can you tell us about the BTK inhibitors?

Dr. Gilli:
Sure. BTK inhibitors have recently been developed as a multiple sclerosis treatment, and as I said before, it is still not an approved treatment for multiple sclerosis. It is still under investigation, but it's a very promising treatment. BTK is a cytoplasmic tyrosine kinase. Is an enzyme expressed by B cells and myeloid cells, like microphages or microglia cells. And these are both types of cells that are critical in the development of multiple sclerosis. So various BTK inhibitors are being developed to treat multiple sclerosis. Right now, we are at four inhibitor treatments that are still either in phase 2 or phase 3 trials. Tolebrutinib, evobrutinib, oral ibrutinib, and fenebrutinib, so again, very difficult names to pronounce. All these molecules are selective, covalent, oral inhibitors of BTK that block B-cell activation and cytokine release. They have been shown to inhibit the activation, the differentiation, and the polarization of proinflammatory cells, like M1 microphages or M1 microglia, and the following release of proinflammatory cytokines, reducing, in general, the inflammatory environment. BTK inhibitors may be less likely than monoclonal antibody to trigger an antibody response, allergic reactions, or neutralize their therapeutic action.

Dr. Turk:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turk and I'm speaking with Dr. Francesca Gilli about B-cell therapies for multiple sclerosis. Switching gears here a bit, Dr. Gilli, let's examine the use of these medications in the context of the COVID-19 pandemic. For patients undergoing B-cell therapy, what else can you tell us about the increased risk of infection?

Dr. Gilli:
So treatment with B-cell therapies, both B-cell depletion therapy and the BTK inhibitors, may adversely affect the immune responses to SARS-CoV-2 infection, mainly because of a significant reduced production of specific antivirus antibodies because of the B-cell depletion and/or the disruption of the B-cell receptor signaling pathway. People with progressive MS, those who are older, those who have a higher level of physical disability, those with certain medical conditions – for example, diabetes, high blood pressure, or basically heart and lung disease – and also some specific ethnical higher risk population, like black and Hispanic population, these are all groups with a high risk of hospitalization and worse COVID outcome due to this preexisting condition. B-cell therapy might further increase the likelihood of developing complications from a COVID-19 infection in all these categories of patients. Still, this risk needs to be balanced with the risk of stopping or delaying treatment, and the recommendation is for people with multiple sclerosis currently taking B-cell therapies to continue their treatment unless advised to stop by their treating clinician. Before starting on any new B-cell therapy, people with MS should discuss with their healthcare professional which therapy is the best choice for their circumstances. The decision should consider MS disease course and activity, the risk of and benefits generally associated with different treatment options, and additional risks related to COVID-19, such as the presence of other factors for a more severe case of COVID-19 like we discussed before. The COVID-19 risk in the local area, risk of exposure to COVID due to lifestyles, for example, whether they are working in a high-risk environment, and also emerging evidence on the potential interaction between some treatments.

Dr. Turk:
And when it comes to the COVID-19 vaccines, is there any interaction with B-cell therapies?

Dr. Gilli:
So first, let me start by saying that vaccinations, both for flu and COVID-19, are highly recommended, even for patients treated with B-cell therapies. Yes, indeed the ability of the immune system to generate appropriate antibody responses to the SARS-CoV-2 virus or the vaccine is reduced by such B-cell therapies, especially B-cell depletion therapy. And the extent of protection that the SARS-CoV-2 vaccine provides to individuals with low or absent humoral responses after vaccination is significantly lowered. However, the immune response against the virus and the vaccine are not completely absent in these patients, and I'd like to stress two main biological and immunological features characterizing B-cell therapies that need to be kept in mind. The first thing is that B-cell depletion therapies spare CD20-negative, long-lived plasma cells, which normally produce antibodies directed against previously encountered pathogens and vaccines. Preexisting specific immunity is not affected by the B-cell depletion therapies. It is suggested to vaccinate patients starting B-cell depletion therapies four to six weeks before the first dose. If the patient has already begun treatment, the findings strongly argue for the use of extended interval dosing to obtain the best window for vaccination. So the best vaccination time is around four to six

months after the last infusion. In this way, the effect of the B-cell depletion therapy is significantly reduced, and we have, again, cells that can be instructed and start a specific immune response against the vaccine, and therefore be maintained during the actual treatment.

Dr. Turk:
Before we come to a close, Dr. Gilli, let's take a look at this on a broader scale. From your vantage point, what sort of impact have B-cell therapies had on our approach to treating MS?

Dr. Gilli:
So definitely a really important impact. The FDA has approved, so far, two different B-cell therapy drugs for treating MS: ocrelizumab and ofatumumab. These may be used for different types of multiple sclerosis, which is very interesting, and this includes a relapsing remitting MS, of course, which is the type and the form of the disease that has more actually approved treatment right now. But these therapies are also approved for progressive forms of the disease like secondary progressive and primary progressive MS like ocrelizumab, as we discussed before. They are also approved for the treatment of clinical isolated syndrome as these treatments have been shown to reduce the risk of progression to defined multiple sclerosis. It would be a bit an overstatement to say that everyone with multiple sclerosis can be treated with B-cell therapies, but these drugs are appropriate for a majority of patients with this disease, and at the same time, there is a nuance to using these drugs because not everyone will respond well to them. So you may think the patient is a good candidate, but it turns out a different therapy would be better, so I think we really need to balance this, and definitely these are very good treatments and very effective in the treatment of multiple sclerosis. But on the other side, we also need to keep in mind that there are other drugs that might be more effective for that specific patient.

Dr. Turk:
Well this has been a very informative look at the use of B-cell therapies for MS, both in the context of the COVID-19 pandemic and beyond it. And I want to thank my guest, Dr. Francesca Gilli, for joining me to share her insights. Dr. Gilli, it was great having you on the program.

Dr. Gilli:
Thank you for having me.

Announcer:
This episode of *NeuroFrontiers* was sponsored by Novartis. To access other episodes in this series, visit reachmd.com/neurofrontiers, where you can Be Part of the Knowledge. Thanks for listening!