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B-Cell Therapy: When Is It Right for Our MS Patients?

Dr. Turck:
Increasing evidence indicates the involvement of B-cells in the pathogenesis of multiple sclerosis, but their exact role is unclear. Despite that uncertainty, B-cell depletion therapies have shown to ease symptoms, prevent relapses, and even slow the course of the disease. So how exactly do B-cell therapies work? And how do we know if they're right for our patients?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck. And joining me to talk about B-cell therapies for multiple sclerosis is Dr. Andrew Chan, Professor of Neurology and Head of the Medical Division Neuro at Inselspital University Hospital at Bern in Switzerland.

Dr. Chan, welcome to the program.

Dr. Chan:
Thank you very much for having me today.

Dr. Turck:
Let's start with some background, Dr. Chan. Can you give us an overview of B-cells and how they contribute to multiple sclerosis?

Dr. Chan:
Yeah. Well, thank you very much for this almost $1 million question. So if you had asked me 20 years ago, I would have said, "Why do you ask at all?" because at that time we were really T-cell driven. Meanwhile, we have understood that really B-cells obviously contribute to the disease, not only in a biomarker fashion or so but really are intimately involved in pathogenesis. During the early 2000s or so, we really understood that B-cells do not only secrete antibodies which may, per se, be pathogenic, but this is really a controversial field, but they may also secrete other soluble factors, like cytotoxic cytokines. They do contribute to antigen presentation for T-cells, and all over we find them in peculiar locations within the CNS, meaning in the meninges, and there B-cells really appear to contribute to what we call lymphoid-like follicles, meaning that we believe that the B-cells really there have a perfect ecosystem to foster the autoimmune reaction within the CNS.

Dr. Turck:
With that in mind, let's zero in on B-cell depletion therapy. Would you mind giving us some details on how that works?

Dr. Chan:
We know that several also older agents really target B-cells, not preferentially, not selectively, but we know, for example, azathioprine in myasthenia gravis does of course target B-cells or also older substances, such as mitoxantrone. So B-cell depletion treatments are very selective in that they target a specific cell surface molecule on the surface of specific B-cell maturation stages. Normally, what we are talking about here would be the CD20 molecule, which is expressed by specific B-cell maturation stages, meaning not the very early stages but also not the late plasmablasts that really secrete the autoantibodies are targeted but those stages in between. And here we

believe that they more or less selectively really deplete these cells. However, one has to acknowledge that a small proportion also of T-cells carry this CD20 marker, and therefore, they are also attacked.

When it comes to the actual depletion, probably in vivo there are two major mechanisms. One would be the complement-dependent mechanism, and the other would be the antibody-dependent cellular cytotoxicity. And probably, all the substances which are available use both pathways in vivo—however, to a different sort of extent, and the different sort of mechanisms and the different cell-depleting potency really may have implications, for example, for dosing.

Dr. Turck:
And what types of B-cell therapies are available?

Dr. Chan:
So in general, what we are talking about in multiple sclerosis is monoclonal antibodies that target, as I mentioned, CD20. The oldest one still off-label would be rituximab, , which is a quite old chimeric antibody, meaning partly mouse, partly human sequences. That was followed by ocrelizumab, a humanized antibody, which is now also added by ofatumumab, a fully human antibody. And there's a new kid on the block, an antibody, which we have seen phase III data during last ECTRIMS in autumn 2021, ublituximab, which is also a chimeric antibody.

Dr. Turck:
And as a quick follow-up to that, Dr. Chan, how do you decide which B-cell therapy is right for a patient?

Dr. Chan:
Although these antibodies do target CD20 there are differences in that really there are different binding epitopes. So rituximab and ocrelizumab are very similar target epitopes, whereas ofatumumab and ublituximab have distant epitopes. In as much as this really translates into something clinically palpable is still controversial. However, in practical terms, all these antibodies that I have mentioned can be differentiated by, for example, the application route, meaning that rituximab, ocrelizumab, and ublituximab are IV, whereas ofatumumab will be administered subcutaneously. The dosing is entirely different, and also, the dosing intervals are different in that with the IV forms we rather give boluses every half a year approximately, whereas with ofatumumab, we have a more frequent sub-q injection. And that already explains a lot of those differentiating factors, which are important for individual patients, meaning what is the patient more comfortable with—infusions, which are like half yearly, or regular home-based sub-q injections. With the IV substances, there's a premedication necessary, usually steroids and antihistamines. That is a differentiating factor. So a lot of aspects really level in in here, which in the end tell me there's no one-size-fits-all approach, but really, even with those anti-CD20 agents, we have different means to individualize our treatment.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Andrew Chan about B-cell therapies for multiple sclerosis. Now if we circle back to the therapies you just mentioned, Dr. Chan, are there any adverse effects that both clinicians and patients should be aware of?

Dr. Chan:
I think this sort of benefit-risk profile is really key in modern MS treatment, especially also when we try to level in the COVID-19 pandemia. So one aspect which is mostly a tolerability aspect but can sometimes rarely be more severe are infusion-related reactions or injection-related reactions, so we're talking about typical systemic reactions, even down to true allergic anaphylactic reactions but more so in reactions that we believe are associated with the actual depletion of cells, meaning release of also cytokines. That is one aspect which appears to be quite pronounced also with the IV preparations, and this is why usually we give premedication, as I mentioned before, anti-allergic and steroids. It is noteworthy that those injection-related reactions mostly occur during the first injection or infusion and then level off when necessary.

Also in the light of COVID-19, there is, of course, the infection risk. We do have a certain risk of different infections: viral, but we also do

see some bacterial infections for these patients. Do we have any biomarker for that? One has to be aware of the rare, very rare neutropenia, which can be early on or also somewhat later. And what we also do see as a class effect would be an IgM reduction, mostly in the first year of treatment, and some substances also carry the risk of an ongoing IgG reduction, which may also be associated with an increasing risk for infections; although, one has to admit that not all studies really show that, however, the experience sometimes is limited with limited patient years.

Dr. Turck:
And if we look toward the future, is there additional research needed to better understand these agents' safety and efficacy?

Dr. Chan:
Yeah, I think so. As a translational scientist, certainly I would love to understand as much the modification of these molecules with sort of targeted design of more sort of maybe complement-dependant cytotoxicity or other pathways, and also different epitopes, that are bound, how that really translates into clinically palpable effects, meaning dosing, application scheme, side effects even. For some substances we see a more pronounced IgG reduction. As for others, issues like that. We would love to understand what we really do within the body because we understand we deplete B-cells. We do not fully understand to which extent this B-cell depletion is really, how can I say, needed, so we talk about a deep depletion, meaning probably we not only deplete the B-cells from the circulation but also from several tissues versus some maybe lighter level of B-cell depletion and, of course, then also a repletion. But how this is associated with other aspects of risk for infections or response to vaccinations, that is currently quite unclear, and where new data and novel data is really urgently needed.

Dr. Turck:
Well, this has been a very insightful look at B-cell therapies and how they may benefit our patients with multiple sclerosis. And I want to thank my guest, Dr. Andrew Chan, for shedding light on the topic. Dr. Chan, it was great speaking with you today.

Dr. Chan:
Thank you very much. Looking forward to speaking with you again.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.