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### Innovations in MS: Mechanisms of Disease Progression and Immune Reconstitution

Announcer:

Welcome to CME on ReachMD. This activity, titled *Innovations in MS: Mechanisms of Disease Progression and Immune Reconstitution*, is provided by TOPEC Global and The Global Neurology Academy, and supported by an independent medical educational grant from Merck KGaA, Darmstadt, Germany.

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Your host is Dr. Matt Birnholz. Dr. Birnholz will speak with Prof. Andrew Chan of Bern University Hospital in Bern, Switzerland; Prof. Tobias Derfuss of University Clinic, Basel in Basel, Switzerland; and Dr. Gavin Giovannoni, of the London School of Medicine and Dentistry in London, UK.

Here's Dr. Matt Birnholz.

Dr. Birnholz:

Coming to you from Baveno, Italy, from McCann Complete Medical's special meeting on multiple sclerosis, this is CME on ReachMD, and I'm Dr. Matt Birnholz. Joining me to discuss recent advances in our understanding of MS disease progression and treatment are Professors Andrew Chan and Tobias Derfuss. Doctors, welcome to you.

Prof. Chan:

Thank you very much.

Prof. Derfuss:

Thanks for the invitation.

Dr. Birnholz:

So, to start, I'd like to get a background, a primer if you will, on the immune system's role in multiple sclerosis, and I want to focus particularly on B cells because, although they have always been around, our perspectives on them, what we've seen them contributing to MS, seems to have changed over the last ten years. So, Dr. Derfuss, let me focus on you for a second. Help us understand a little bit about the role of B cells in MS disease progression.

Dr. Derfuss:

So, that's true. When we look back, I think, from the animal model, it was clear maybe 20 years ago that T cells play a role, and this comes from the finding that you can transfer the disease by transferring the T cells. So, if you have antiangiogenic T cells and you inject it into a naïve animal, the T cells alone can induce disease, and from this it was concluded that T cells are the main players also in human MS. We know from the clinics for a long time that B cells seem to be relevant because we have these oligoclonal bands in the CSF and the intrathecal immunoglobulin production in the CSF, indicating there is an activation of B cells and an influx of B cells into the brain and the CSF. So this was clear for a long time, and it's used still in diagnosis, and, in fact, the new McDonald criteria that will be published soon, they again emphasize the role of oligoclonal bands in the diagnosis of MS, but still, when looking at therapeutics, all the

therapeutics on the market so far they were designed to somehow modify or inhibit the T cells, but, in fact, if you then look back now, all the drugs still have also an impact on B cells. They were not designed for this, but they still like blocks, of course, the migration of T cells but also blocks the migration of B cells into the brain, and I think the breakthrough, of course, was the B cell depleting therapies, the CD20 antibodies like rituximab, ocrelizumab, ofatumumab that all showed a very effective treatment in multiple sclerosis, and this was the point when everybody thought, "Okay, these B cells must really play an important role."

Dr. Birnholz:

Interesting. So, we almost discovered the role of B cells by proxy to some of the treatments that happened to be also affecting B cells.

Prof. Derfuss:

Yeah, and, I mean, also the hypothesis with which a B cell depleting therapy was started, it was, like, reducing autoantibodies. That was, I think, the main idea in the beginning, but when you look at the reduction of disease activity or the timing, it's very fast. So, within a few weeks of the B cell depletion, you see already a decrease of gad-enhancing lesions. So, it acts very fast, and an effect on the antibodies is seen after a very long time, so it cannot be the antibodies that are reduced.

Dr. Birnholz:

That actually provides a nice segue into another area which is the advances in imaging that have come lockstep with some of the advances in the molecular pathophysiology. What can you tell us about where we are with imaging right now in terms of being able to assess disease progression, and what advances have been made?

Prof. Chan:

I think this is a very important question because really when you think about the one single methodological progress which has been made, then it's really MRI, which has really not only changed the way we diagnose MS as you've mentioned earlier but also the way we manage MS. So, early on we used MRI as a paraclinical means to sort of objectify a dissemination of lesions in space and time. Then, a couple of years later when we noticed it's so much more sensitive, we also used it as an outcome parameter in early clinical trials, based on two trials especially, and now we've come to an era where we really actively sort of combine clinical and paraclinical readouts, MRI readouts. For example, in this paradigm, no evidence of disease activity (NEDA) to really manage our patient and manage the treatment of our patients.

Dr. Birnholz:

And yet, when you mentioned NEDA (No Evidence of Disease Activity), I imagine our perspective on that from an imaging standpoint is constantly evolving.

Prof. Chan:

There's still a gap to translate that into clinical practice. So, one concrete example. So, with more sensitive-like MRI analysis we're now able to assess brain atrophy quite accurately, it may, you know, have implications for therapy because when we look at a large matter analysis it's been shown that the effect, the treatment effect, of anti-inflammatory agents is, on disability, is also associated on the treatment and effect on brain atrophy. So, there may be some interplay really between these mechanisms. The problem really starts when you go back to, you know, like concrete terms and clinical practice. So, brain atrophy in daily clinical routine is very difficult to assess, and only very few centers really routinely do it. I don't know whether you routinely have it?

Prof. Derfuss:

I mean, I completely agree. I think brain atrophy in clinical trials is a very good measure of neurodegeneration and if a drug can prevent neurodegeneration, but in clinical practice it's very hard. but, I mean, there might be other biomarkers like neurofilaments that could substitute for brain atrophy, and I'm more optimistic that these neurofilaments can be used really in clinical practice.

Dr. Matt Birnholz:

For those who are just joining us, this is CME on ReachMD. I'm Dr. Matt Birnholz, and joining me to help me understand better the advanced understandings of disease progression and treatment for MS are Drs. Andrew Chan and Tobias Derfuss.

Doctors, I had also a chance to talk with and catch up with Dr. Gavin Giovannoni, and on this therapeutic area that I'd like to shift over to, his focus was on immune reconstitution therapy, and why don't we take our audience to that right now so they can see what we discussed.

So, Dr. Giovannoni, help us understand some of the essentials around immune reconstitution therapy, or IRT. I'm particularly interested in for whom it's indicated, what place you think it has in the treatment armamentarium going forward?

Dr. Giovannoni:

So, we kind of invented the term immune reconstitution therapy to differentiate it from other treatments that are given continuously, and

the risk/benefit profile of these two treatments is, these two classes of therapy, is very different, and the immune reconstitution by definition includes two phases to the treatment that includes a depletion phase, and the depletion phase can be selective and unselective depending on what cells are removed, and then it allows the repopulation or reconstitution phase where the immune system recovers, and the reconstitution really refers to the normal function of the immune system so when it comes back it's competent so it can find off infections, you can mount an immune response to vaccines, you can deal with exotic viruses you've never seen before, and you can have immune surveillance, in other words, look for malignancies. So, when it comes back, it's normalized, and so the immune suppression that's linked to the immune depletion is usually very short-lived while the cells are down, and so the side effect profile is limited and frontloaded, whereas in the maintenance treatments the immune suppression happens continuously, and what happens is the risks go up with time because it's got to do with exposures to opportunistic infections, and immune surveillance is down continuously so that the risk of getting malignancies or secondary malignancies will increase with time. So, we talk about accumulative risk going up versus the frontloading.

Dr. Birnholz:

Although, I imagine even with the frontloading approach there's still a sizable risk given that it is effectively an immune reset.

Dr. Giovannoni:

Well, it depends which one you look at, and so we used, I used to have a term called pulsed immune reconstitution therapy that refers to the therapies that are given in multiple pulses, but we also included in that hematopoietic stem cell transplantation which is just usually given as a single treatment upfront, and so I agree, but it also depends on how selective it is, and so with hematopoietic stem cell transplantation and the other one in the class at the moment, alemtuzumab, it not only takes down the depths of T and B cells but it also depletes your innate immune system. So, you have a leukopenia. Your neutrophils are down, your monocytes are down, and that puts you at a lot of risk upfront for bacterial and fungal and viral infections. With the cladribine, for example, it leaves the innate immune system intact so your neutrophils, your NK cells, your monocytes don't get affected by cladribine. So, we don't see the same upfront risk of listeriosis, nocardiosis, pneumocystis carinii. There isn't a problem with it. What we do see is that also the T cell depletion is much less than the B cell depletion. So, I think oral cladribine is working as a B cell depletor because the T cells only come down about 40-60% depending on which subsets and what dosing you'll get, and that doesn't bring the cells down to a level that is associated with opportunistic infections. So, we haven't seen opportunistic infections with cladribine, so it's quite a smart drug because it leaves the T cells relatively intact, brings down the B cells, and has very high efficacy, and so it's quite a smart, I think it's like an anti-CD20. That's a small molecule anti-CD20 because it's taking out a specific range of B cells and leaving the rest of the immune system relatively intact. I mean, the only infectious complication we saw in the trials with cladribine was a high risk of herpetic infections, particularly herpes zoster.

Almost all the immune suppressive drugs have a zoster signal, and we're kind of de-risking that because if you're waiting until grade 3 or 4 lymphopenia, you had a higher risk of getting zoster, and so we have a dosing schedule now that allows re-dosing if your counts go above 800, and by doing that, we should bring the risk of getting, you know, a severe lymphopenia grade 4 well below 1%. So, we think the way we are all going to be using the cladribine in clinical practice will de-risk the zoster signal quite a lot.

Dr. Birnholz:

So, would you say as an overall viewpoint this is a game changer in the entry to MS treatments or is it something that's part of the armamentarium?

Dr. Giovannoni:

I think it's a game changer because of the easy use, the posology, the way we use the drug in terms of its dosing is remarkable. I mean, you just give ten days of treatment, you know, five days in month one, five days in month two, and you repeat that in year two, and, you know, no other treatment, and also the monitoring requirements, and we haven't seen an opportunistic infection signal, we haven't seen a secondary malignancy signal, we haven't seen a secondary autoimmunity. So, all those worries that come with some of the other therapies are not there. So, you know, in terms of easy to use, it's going to make it a lot better for MS services to use. I mean, another thing I haven't mentioned is the depletion rate is much slower than with the other immune reconstitution therapies.

Dr. Birnholz:

That's an excellent point. Well, it's been really insightful. Thank you for your time, Dr. Giovannoni.

So, Dr. Derfuss, why I don't I come back to you then after what our audience just saw on this topic of IRT. What do you think is the most likely place for this therapy to have in MS treatment for neurologists?

Prof. Derfuss:

I think there's a lot of controversy about this kind of therapy. I mean, it's really different from center to center and also different from countries to country. I mean, like, the alemtuzumab treatment, for example, is very in fashion and in UK. It was invented there, and

neurologists really like to use it there, and I think in, like, from a Swiss perspective, it's registered in Switzerland, but for us, alemtuzumab is like rather a third or fourth line treatment if the other treatments didn't work, and this is mainly due to our feeling of the safety of the drug.

Prof. Derfuss:

We have cladribine coming on the market or already on the market in the EU, which and uses also a depletion of immune sets but not as strong as alemtuzumab, and on the other end of the spectrum, we have the stem cell transplantation. So, I think, but with these three options, I think we can see which patient fits to which option.

Dr. Birnholz:

I give you both credit for being able to look at it and say this could be practice-changing, but it's not ready for primetime yet.

Dr. Birnholz:

Well, with that, I very much want to thank my guests, Dr. Andrew Chan and Dr. Tobias Derfuss, for helping discuss some of the recent advances in MS disease progression and treatment. Doctors, it was great having you on the program.

Prof. Chan:

Thank you very much for having us.

Announcer:

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