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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; and Prof. Tobias Derfuss of University Clinic in Basel, Switzerland. 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. I am Dr. Matt Birnholz, and joining me today to talk about
the evolving treatment landscape and ushering in a personalized medicine for MS are Drs. Andrew Chan and Tobias Derfuss. Welcome to you both doctors.

Dr. Chan: Thank you very much.

Dr. Derfuss: Thanks for having me.

Dr. Birnholz: So, Dr. Chan, let me start with you. Maybe before we look forward, as this entire piece is devoted to, we can take a quick look back, because we have an evolved understanding of MS that has a story behind it. It helped us open doors to new treatment approaches, but how has that evolved understanding or the changing understanding over time given us that opportunity?

Dr. Chan: It is a very interesting question and very interesting story also, because at least to my understanding, the initial progress that was made was not really, you know, like a clear hypothesis and then you follow it up and then you have a translational success or something; but, it really came the other way around, so like the story with interferon beta or also glatiramer acetate really evolved from a different point, one has to say, so interferon beta was introduced into the clinical development program, once it was understood that interferon gamma, the natural counterpart, just failed. So, it is just not, you know, like a hypothesis-driven something, but it is just like trial and error and similarly glatiramer acetate. Still, you know, then we had some major progress with also very good study designs, new techniques like MRI really helped us to make better studies and then we came up with some newer histopathological data that indicated that we have, quite early on during the disease, axonal damage, which is potentially irreversible in MS, so in the early 2000s we started with the paradigm of very early treatment of MS. A couple of years later, we came up with even potentially more efficacious but also more aggressive substances such as natalizumab, which was one of the first agents in that sort of category. This is really where we are now, so we have a plethora of newer treatment modalities which sort of cover different phenotypes and different needs of the patients. We have certain understanding of the potential modes of action, but then there are some downsides in terms of unanticipated and adverse drug reactions.

Dr. Birnholz: Excellent. So, Dr. Derfuss, with that context in mind, I am interested in getting your thoughts on this looking back, but also to help take us forward to what some of the novel therapies are both in Europe and the U.S. Maybe you can walk us through that.

Dr. Derfuss: So, I think these therapies also provided some answers or some insight into the pathogenesis of a mass and for example, it was long thought that MS and rheumatoid arthritis were related diseases; they have common immunological backgrounds and, therefore, TNF blockade was also tried in multiple sclerosis but in the end, it increased the disease activity, so it had an opposite
effect in multiple sclerosis. Another example is B-cell depletion. B-cell depletion works very good and it was thought that mainly the plasma cells should be targeted because they produce the antibodies and the idea was that all antibodies are important in MS, so not only was CD20 depleting antibodies used, because it does not deplete the plasma cells and another treatment was tried called atacicept and that is also a biological that blocks survival factor of B-cells and the difference to a CD20 depleting therapy is that with this treatment you also get the plasma cells depleted and you get a reduction in immunoglobulins, but this study showed that MS also gets worse if you give this treatment, so it is, again, an opposite effect. I think this highlights how complicated the immune system is, and you can target B-cells, but you have to target the right B-cells and maybe the plasma cells are regulatory B-cells.

Dr. Birnholz: So, with that in mind, it brings up the question of trying to get the right medication or the right therapy to the right patient at the right time, a very complex maneuver. What are the overall factors that you look at to try to hone in on making more personalized decisions?

Dr. Chan: So, certainly it is like the sort of normal medical approach, you know, like you have a certain disease phenotype; you have a certain level of activity; you have some prognostic factors like age; we have paraclinical markers such as MRI activity so that really helps you a bit. Luckily we have now almost a dozen substances approved, so obviously other factors also play a role and then we come down to issues, for example, patient-related aspects, adherence, and monitoring burden for the patient.

Dr. Birnholz: If you are just joining us, this is CME on ReachMD. I am Dr. Matt Birnholz. Joining me to discuss recent innovations in our treatment landscape as well as personalized medicine approaches for MS, are Professors Andrew Chan and Tobias Derfuss. In the absence of reliable biomarkers, is the ability to start targeting treatments with a measure of confidence that the side effects will be minimal for that particular patient and the benefit will be highest – it is not necessarily compromised, but does it make it a little bit more tenuous in terms of being able to predict how a patient will react to one medication or therapy versus another?

Dr. Chan: Well, when it comes to benefit/risks, at least for the risks, we do have some single markers which may aid in treatment selection there. Well, the way you phrase the question is sort of leading into one direction. I would rather see it from a different side. You know, because it comes back to an issue where really the communication with the patient; the mutual trust; the understanding of the patient’s needs are equally important, sometimes even more important, and that is really back to being a physician, isn’t it? So, you know, yes we have the choice. For me, it is a luxury. I am very happy that I can choose among broad therapeutic armamentarium, and it really helps me to try to include the patient’s needs in terms of trying to act as a doctor.
Dr. Derfuss: I completely agree. I think we being neurologists are always very humble and we say we cannot predict the future (of course we cannot predict it), but I agree that our gut feeling is not as bad as we might think. I mean, we integrate a lot of information. We look at how strong was the relapse? How was the recovery of the steroid? Where are the lesions on the MRI located? What do they look like? So, these different data are integrated and they will influence our treatment decisions.

Dr. Birnholz: That brings up a thought here, because what I am gathering here from the two of you is that even the very concept of NEDA or no evidence of disease activity, is highly variable to how the patient defines that with you as the clinician. Maybe the two of you can remark on that a little bit, as that helps us segue into the concept of personalizing medicine.

Dr. Chan: You raise a very important point, so current NEDA definitions meaning we do not have relapses, we just do not have disability progression and we do not have new MRI activity is certainly one step forward, but we are not there yet. So, why should, you know, is it plausible that a new lesion counts as much as a relapse, as a severe relapse, probably not. Then, you know, there are other domains. Right now, we only focus on several MRI lesions. We just leave out the assessment of spinal cord MRI. We leave out the impact of brain atrophy. We leave out the impact, for example, neurocognitive or neuropsychological dysfunction, fatigue, employment, and, you know, these are all very old studies and also all the parameters that we are focusing on as physicians may not be the parameters which are really relevant to the patient or at least, you know, which are not the parameters which are important for the patients in terms of quality of life and daily activities of living.

Dr. Birnholz: Dr. Derfuss, what are your thoughts on that?

Dr. Derfuss: I mean, the concept of NEDA, I think, you also have to see it in the context of where the patient is with regard to his disease course and his previous treatments. It is quite easy if you have a patient on interferon or Copaxone and it is an early-stage patient that has continuous disease activity, then you escalate them. It gets harder once you are in this high-efficacy treatment and you get an MRI lesion, would this then be enough to escalate to something else or is there something left or what about the side effects. Is it really well-balanced? I think this will be a problem, especially when we count with his new therapies for progressive MS, especially the B-cell depleting therapies. I mean, they have been registered in Switzerland and also in the EU. The label in Switzerland is quite open, so we can treat everyone with primary MS without any limits, so no age limit; no EDSS; no disability limit; and I think that might be a problem in the end. I think the efficacy of the drug is shown in clinical trials, or I think I believe in this, but, of course, they are probably long-term risks and you really have to think if it makes sense to start this treatment in every patient. There are data from subgroup analysis that show that younger patients respond better. Of course, if your disability level is lower, you probably also have a
better chance of responding to this treatment, and this we have to also always incorporate in our
treatment decisions. I think the European label in this respect is better, because it takes into account
also the disability level of the patient and the age of the patient.

Dr. Birnholz: You know, we cannot really say the term personalized medicine without moving on certain
concepts that have become almost synonymous with it. I mean, the ideas of pharmacogenomics, the
idea of having unique combination therapies to every patient that are tailor-made so that the patient will
have the least risk of developing, let’s say, malignancies or other characteristic severe side effects that
can emerge with some of these treatments. Are we there yet in practice, realistically, is it down the
road?

Dr. Chan: Well, again, you are touching upon a difficult issue. You know, when you want to develop
biomarkers, maybe even surrogate markers, especially on a pharmacogenomics background, for me
there is like sort of three stages – two stages of development and, you know, in the end, at the third
stage, you come up with a profile from a blot from CSF, from whatever, body fluid or tissue that, you
know, informs you on treatment selection; however, of course, we are not there yet. I think we are
beyond the first step that we have identified several potential molecular markers to name a few most
recently highly-discussed was a blot maker that is not a pharmacogenomic marker, but a blot protein
that would be in neurofilaments, which could be interesting. Then again, you know, the second step
after this biomarker, sort of, identification is really the validation. Is it true in independent cohorts? Is it
true for different phenotypes? Would it, you know, hold up for treatment monitoring? These are the
aspects, and the majority of identified biomarkers really fail during that stage, one has to say.

Dr. Birnholz: Well, with that plethora of insights, I very much want to thank my guests, Dr. Andrew Chan
and Dr. Tobias Derfuss for helping to look back and look forward, as Dr. Chan said, “Two steps
forward, one step back,” but at least we are moving forward in the field. Doctors, thanks so much for
your time.

Dr. Chan: Thank you very much.

Dr. Derfuss: Thank you very much.

Announcer: This has been CME on ReachMD. The preceding activity was brought to you by TOPEC
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