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Disease Modifying Therapies in MS: Highlights from ACTRIMS 2018

Narrator:
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ReachMD Host:
We recently caught up with the attendees of the 2018 Americas Committee for the Treatment and Research in Multiple Sclerosis Forum held in San Diego, California. The ACTRIMS Forum covered New and Emerging Concepts in the Field of Multiple Sclerosis. Here to discuss their takeaways from the ACTRIMS Forum are Dr. Thomas Leist, from the Comprehensive Multiple Sclerosis Center at Jefferson University, and Dr. Clyde Markowitz, from the Perelman School of Medicine at the University of Pennsylvania.

Dr. Markowitz:
So Tom, we had a very nice meeting in San Diego, ACTRIMS 2018, which is actually a breakaway from the traditional way ACTRIMS has been done for the last several years, and this is now a stand-alone meeting and I think it was phenomenal. What's really nice about the meeting is that it targets kind of like a topic and really focuses on really like one general line of thought. And I think we saw a lot of interesting presentations related to mechanisms of action, mechanisms of the disease, the populations of cells that are involved in the pathophysiology, and really understanding that maybe there's a lot more to this disease than just what's happening in the adaptive immune system, but maybe what's happening in the innate immune system, and what's happening in the resident microglia and astrocytes. So I think there was a really nice mix of presentations that were discussed there.

Dr. Leist:
Yes, Clyde. I mean, to see it was obviously focused towards the glial cells and we have re-visited the blood-brain barrier. We have re-visited the contribution of all the cell types, for example, also the astrocyte. From that point of view this was really a focused meeting. It tried to also link what we observe structurally, what we observe from an immunological response point of view, to the disease process. We have a first-time kind of a marrying of genetics and the astrocyte, for example. The Yale group presented some data on a single nucleotide polymorphism in the regulatory sequence that actually affects how astrocytes produce cytokines. Many of us didn't really think a lot about astrocytes with the introduction of the NMO antibodies. We know that they play an intricate role. We know the three-dimensional structures, that being the pericyte, astrocytes, and the nerve cells, as well as the oligodendrocytes, and this has been very important. What has also been very important is linking of these different cell types. This, the disease process, and then, obviously in a next step, base the mode of actions that we think our agents work.

Dr. Markowitz:
I think about how the field has evolved. We started out essentially thinking of MS as primarily a T-cell-driven disease. Then more recently, we've seen that B cells have a very large part and treatments have demonstrated quite a robust effect when you hit that. So I just wonder, as we think about some of these evolving treatments that we have, and maybe even to understand that these microglia are playing important roles in this disease, we're going to have to think about targeting that population; where we really have not spent any time, at least over the last 25 years, looking at this disease, looking at that population. So you have the adaptive immune system we talk about. We have the innate immune system now that we're really particularly interested in. And there's some very exciting things coming

up about the idea that maybe these astrocytes, microglia, they can present antigen, they can actually function at some level as an immune stimulator or antigen presentation. So I think it's going to become a very, very exciting area. Now let's talk a little bit about some of the drugs that we currently have and how the mechanisms of that might play into this. So you think about T cells. We've had so much conversation over the last 20 years-plus about the effect of these drugs on T cells.

Dr. Leist:
I think it has become clear that B cells, particularly CD20-expressing B cells, play a significant role. We have obviously agents that don't just affect T cells, but also affect B cells, so we have agents such as alemtuzumab, or in other jurisdictions other than the United States, at this point, I think cladribine, that affect both T cells and B cells. We also learned that many of these agents indirectly affect the microglia or the migration of microglia. So we see that all components within, of the immune system, and within the central nervous system play a significant role. And so one of the things, obviously, is that we are all aware of is the fact that we have different modes of action of MS medications. And a lot has been done to think about oral versus injectable or parenterally administered medications. How do you divide, in your mind, medications? How do you think of mechanisms of actions?

Dr. Markowitz:
So, I think that we started out with interferons and they seemed to have a variety of effects, whether it be, you know, we called it immune modulatory, so maybe it reduces some proliferation of immune cells to some degree, maybe it even reduces migration of lymphocytes across the blood-brain barrier. Glatiramer has a slightly different mechanism. Maybe has effects on which populations of immune cells may be preferentially reducing cytokine productions, or things like that. But what's, I think, happened with the newer medications, or even a medication like natalizumab, you really look at targeting a particular molecule. And in the case of natalizumab where you are blocking the receptor that would allow these lymphocytes to traverse the blood-brain barrier, you get very robust effects. So I think that we went from more of a pleomorphic effect to more targeted effects. And then with the newer agents, even particular cell-depleting agents like alemtuzumab or rituximab, or even ocrelizumab and also cladribine, they tend to have more specific effects. The question ultimately is going to be: Is that good? We think it's good because it might allow us to administer the medication at a reduced frequency, potentially. At least some of the medications now are administered either maybe once a month or once every 6 months, once a year.

Dr. Leist:
So if we have a treatment that is given at two annual cycles, and then has a long forward-looking stability of the patient, then we obviously would like to have data that really evaluates how long this effect is present, because we are changing our approach from an agent that is given every day, or twice a day, or every month, so agents that are ongoing treatments rather than agents that are given in short treatment courses.

That's the question surrounding disease remission in absence of presence of that actual agent so that you have a treatment when the agent is present, then the agent is eliminated, but the biologic effect persists. The prototypical approach for this will be probably autologous stem cell transplant where we do this. We have now other agents, for example alemtuzumab; certainly cladribine can fall into this, and dependent on infusion schemes that are used, so we have this transition to agents that may have a long biologic effect without necessarily presence of that medication.

Dr. Markowitz:
If you are giving an agent that, let's say, depletes a whole population of cells, what happens to the population of cells that come back after some period of time? There's some emerging data that suggests that the populations that come back seem to be a little bit more naïve and maybe, therefore, the cytokine profile of those cells, maybe their activation state, may not be as inflammatory, and being able to have a population that comes back that doesn't require chronic treatment all the time, and could really give you a lasting effect, kind of makes sense biologically.

Dr Markowitz
And, you know, of course, you have the question about: Is it safe? Because you don't know whether or not wiping out a population for a long period of time is ultimately going to create a new safety concern. So I think there's some data, unfortunately you don't have the ability to do this in the extension trials because the patients who were originally started on, let's say the placebo group who then transition over to the active treatment, and then you follow these people over time, you don't have a good comparison any longer as you go down that path. But real-world studies have been able to show stability of patients.

Dr. Leist:
So our first generation of agents that we have had, we have now had them almost for a generation, and we have learned significantly about their side effects. We have been able to follow patients over a long period of time with these agents. Over recent years we have

introduced medications that may lead to secondary autoimmunity in a subset of patients. We have agents that lead to long-term reduction of lymphocyte counts in individuals. Interestingly, if we look at the anti-CD20's, if we look at cladribine where we have reduction of lymphocyte counts, we generally, and this is also true for alemtuzumab once we are beyond the acute reduction of lymphocytes, we have generally a relative resilience with respect to the infection risk. And that has probably to do that most of these agents do not affect the neutrophil host defense. All of this, obviously, needs to be monitored in patients and each one of these agents has a monitoring scheme that needs to be adhered to. Some of these long-term data come from safety registries. So for example, safety registries where the total population that has been exposed to a given agent is followed for many years, and where we can also start to understand what the risk factors are or what the risk proposal is in these patients. But just to give an example also with respect to long-term data or how we can even learn, after many years, about new things about an agent, I was very pleased to see for the first time at ACTRIMS, data from the TOUCH Program in the United States with natalizumab regarding potential safety issues surrounding the extended dosing of the medication. That obviously didn't inform us about the efficacy, but it at least informed us about the fact that perhaps an agent may be able to be used more safely if we learn from the post-marketing experience.

Dr. Markowitz:
. There's a potential signal that came up with possibility of some malignancies, maybe some breast cancers at a higher rate. It's a small number and needs to be really assessed. But do we need to start worrying about malignancies for these stronger medications? And I think that patients come into the office these days and they always have this in the back of their mind: What is the concern on safety? What is the long-term issue of taking this medication? I try and make a real concerted effort to let them know about, is that not only is there safety concerns with the medication, but there's also concern about the risk of the disease. And I think that's a big, big piece we need to impart to patients when they come into the office.

Dr. Leist:
And I think you bring up a very important point and that's the point that there is a dual risk. There is the risk of the disease and there are the risks that we introduce by treating the patients, and obviously we would like to have a balance between these risks. There is also the other thing that is important in multiple sclerosis and that is that there may be an early window where the disease is much more amenable to treatment than later on.

Dr. Markowitz:
Well, I think that it's 2018, it's a pretty exciting time in the field of MS and I look forward to many more meetings about the treatment and how we manage MS. So thank you, Tom.

Dr. Leist:
Thanks, Clyde.

Narrator:
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