Emerging Concepts in the Management of MS: A Focus on T and B-Cell Targeting

Narrator:
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Dr. Birnholz:
Welcome to On the Frontlines of Multiple Sclerosis. I’m your host, Dr. Matt Birnholz. Joining me today is Dr. Andrew Chan, who is the Chief Physician, Deputy Clinical Director, Head of the Outpatient Neuro Center, and Head of the Neurological Polyclinic at the University Hospital of Bern, in Bern, Switzerland. He and I are going to discuss the role of T and B cells in treating patients with multiple sclerosis. Dr. Chan, welcome to the program.

Dr. Chan:
Good morning, or good afternoon, to you, from Switzerland.

Dr. Birnholz:
Great to have you with us. So, why don’t we start with a review of T-cell roles in the pathogenesis of MS, since this understanding seems to go back a long ways, is that true?

Dr. Chan:
Yes, indeed, the discovery of T cells in the pathogenesis of multiple sclerosis is really one of the major cornerstones on which we still build our hypothesis and also therapeutic hypothesis. Actually, there was one landmark paper in the early ‘80s where a German and an Israeli neuro-immunologist, or immunologist at that time, really did the pivotal experiment in that they injected auto antigen-specific T cells into naïve animals, by that fulfilling Koch’s postulates for autoimmunity. And they could elicit a passive version of, what we call, adoptive transfer autoimmune encephalomyelitis. So, by that, they really highlighted the role, the essential pathogenic role, of T cells in EAE and, of course, many of our hypotheses in multiple sclerosis are built on animal experiments.

Dr. Birnholz:
When did B cells start to enter the picture of MS pathogenesis?

Dr. Chan:
So, actually, B cells and their products, especially antibodies, have always been around. So, we know when we do diagnostic CSF taps that we will find plasma cells. We know we will find antibodies. And, indeed, like oligoclonal bands are one of the hallmarks in CSF analysis which gives us a good indication for multiple sclerosis, right? So, diagnostically, B cells have been around for decades, since the early ‘70s, or even earlier than that. However, really, the discussion about B cells as a major driver of pathogenesis is not that old. I’d say rather like 10 years, or so, 5 to 10 years. And it was a combination, really, of histopathological data, CSF data, the detection of clone leaks pondered memory B cells, for example, in the CSF. And then, also, some early clinical trials with B-cell-directed therapies which really then paved the way for B cells and the B-cell hype that we are having right now, in a way.

Dr. Birnholz:
And regarding that hype that you talked about, so, a number of our audience are aware of this 2-stage hypothesis that was originally put out there for MS development, but now we have T-cell and B-cell interactions that might be factoring into it, or even reshaping that hypothesis. What can you tell us about that?

Dr. Chan:
I find that a very, very difficult question, to be honest. So, first of all, this 2-stage hypothesis is really a hypothetical construct based on some experimental data and some epidemiological data. So, what we tend to believe is that really B cells may fit in, especially during the chronic phases of the disease, and really may be one of the drivers, also, of chronic progressive MS. And now that we’re having first clinical trials with success in primary progressive MS, really this paradigm and this hypothesis of this 2-stage theory that you’re mentioning, is also questioned, isn’t it? Because one fundamental hypothesis there is, that you have a sort of window of opportunity for antiinflammatory agents. And now what we
are seeing is that even when you try to hit a chronic-progressive disease, the primary chronic-progressive MS's phenotype with an antiinflammatory B-cell-directed treatment, then you do have some success. So, really, what I'm trying to say is that these clinical data question, rather question also many of these hypotheses.

Dr. Birnholz:
Thank you, Dr. Chan. I know it's a difficult question. Why don't we focus then on the B-cell targeted therapies, in particular, since we’re moving in that direction? And you mentioned a few that are in development already. But, can you reiterate what the rationale was in targeting B cells, specifically for MS?

Dr. Chan:
So, basically, as I mentioned before, we had a lot of histopathological data, we had some experimental data from the animal models, and we also had some cellular immunology data from the CSF which all pinpointed to a potential role of B cells in the pathogenesis. And especially one finding, by an Italian group, which demonstrated that there may be a specialized compartment for the maturation of B cells in the CNS in the meninges. By that time, they called it lymphoid-like follicles; you know, gave the whole topic a tremendous boost. So, that was really the background behind and the rationale behind developing B-cell-directed therapies. But now we’ve come to an age that we understand many substances touch upon B cells, but not necessarily all of them will have clinical efficacy, or not necessarily all of them will have positive results in clinical trials.

Dr. Birnholz:
And does that understanding right there inform practitioners as to whether B-cell-targeted therapies, in today's practice, should be employed early or later throughout the disease course?

Dr. Chan:
So, the preference in MS therapy is always to use immunologically active agents early during the disease, because regardless of whether it’s T-cell-directed, B-cell-directed, or pleiotropic, we tend to believe that we have tissue damage with accruing disability and we want, if anything at all, we want to treat early. When it comes to B cells, then it appears that they may have a pathogenic role early during the disease, but also later during sort of chronic stages, they may also have some pivotal roles. And, indeed, it appears that experimental and histopathological data supports this, and especially also the clinical trials. I mean, you know, we had clinical trials focusing specifically on B cells with, for example, monoclonal antibodies, but also with other substances which also touch B cells, which were very successful, especially relatively early on during the disease, but may also show some efficacy, and that is really what the clinical study data tells us, at other disease stages. So, it’s not an either or, but again,
if we treat, we treat early. But maybe we may sort of have a longer window of opportunity, a wider
window of opportunity, to treat with B-cell-directed treatments.

Dr. Birnholz:
And on those clinical trials and the efficacy data that’s come from them, are we clear that there is an
established benefit for patients in the long-term with these therapies, or is it still too early to tell?

Dr. Chan:
I guess, as with all novel agents, that’s far too early to tell. The clinical development has started only a
couple of years ago, and so, we are still waiting for longterm data, not only on efficacy, but also
especially on safety. How often do we have to apply these agents? How safe is it to apply them
repetitively? So, these are all open questions. So, you know, we can’t really forecast.

Dr. Birnholz:
What about the prominent risks in these early studies to date? Are there risks that have really come
out associated with this line of treatments?

Dr. Chan:
So, the clinical studies which were just recently published indicate maybe some slight signals in terms
of malignancy. So, we saw in one of the three clinical trials, with a novel CD20 antibody, we saw a
slight increase of malignancies in the treated group in comparison to the placebo. However, when we
talk about a population level and when we talk about other controlled groups, then it’s relatively
uncertain whether this is a true signal or not. So, we really have to see what will happen in the long-
term, also in the post-marketing setting.

Dr. Birnholz:
Well, before we wrap up our interview, I always like to look ahead and in this case, I’d like to get your
impression as to where you see T and B cell research and therapies evolving. Is it a promising direction
or is there more work to be done?

Dr. Chan:
Well, very difficult question, again. I see certainly hope, but I also see questions and problems, as
always, in research and in medicine, I guess. So, we’ve been talking about T-cell-directed therapies for
decades almost now, and due to different aspects, methodological aspects, this has not been
translated into any clinical program or even, you know, like clinical use. So rather, what I believe will be
fruitful is the research, which is highly active right now, on biomarkers: molecular markers, cellular
markers, which may, sort of, predict the treatment response to a specific mechanism of action, for
example, B-cell-directed therapy. I guess that’s a very promising field of research which would also
meet a high medical need, really.

Dr. Birnholz:
Well with that, Dr. Chan, I very much want to thank you for joining us to share your expertise in MS research with our ReachMD listeners and viewers. It was great having you on the program.

Dr. Chan:
Thank you very much.

Narrator:
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