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Exploring the Evolving Landscape in Managing Multiple Sclerosis

Dr. Weisman:
For the nearly one million people in the United States with MS, living with the debilitating symptoms like vision and mobility problems can be challenging. But the good news is that we, as clinicians have access to treatment options that can help with these symptoms. Which is why, today, we're gonna take a look at the current landscape and what we may be able to use in clinical practice in the future. Welcome the *NeuroFrontiers* on ReachMD. I'm Dr. David Weisman and joining me to discuss the disease state of multiple sclerosis as well as key management strategies is Dr. Adil Javed, a board-certified neurologist and an Associate Professor of Neurology at the University of Chicago. Dr. Javed, welcome to the program.

Dr. Javed:
Thank you so much for having me, David.

Dr. Weisman:
So, you worked hard and after residency you went off and you did MS and that has become your absolute passion. Every time I talk to you, I learn something new. Why has MS been so successful? There are tons of medications; why is this?

Dr. Javed:
So, I think it's all the research that has gone into multiple sclerosis. I remember as you recall, looking at MS patients when we were residents and that was in 2000 to 2004 and we only had a handful of medications at that time. But since 2004, after graduation and that decade afterwards there was a lot of research done in terms of the mechanism responsible for inflammation and the mechanisms responsible for neurodegeneration. And we are very good at looking at the inflammation, the early multiple sclerosis where the inflammation is more predominant. And there were a lot of drugs that came out from that research looking at the early inflammation and looking at the targets and those targets were, they basically the mono-clonal antibodies, the b-cells and the and some of their products and also some of the adhesion molecules how the immune cells went into the brain across the blood-brain barrier and caused some damage. And again, I'd like to stress that this was all inflammatory damage so with those targets in mind and with the drugs that looked at those targets and, sort of modified their response.

And I think that's where the plethora of medicines came out, in the ensuing decade from 2004, onwards into well into 2015 and then even now. So, I think it's a research, knowing targets, and funding from pharmaceuticals so the agencies, and that really led the way to having almost fifteen drugs for multiple sclerosis.

We are very good at treating early MS. And also the clinical trials just about every other year we have a clinical trial that is unfolding its results early on in the disease process these trials are highly successful but we still struggle with the neurodegenerative part of multiple sclerosis that is a progressive MS. So, I think it's just the research and knowing the targets that has led to the plethora of medicines in MS and it's very good for the patients.

Dr. Weisman:
And your role in this has been, you're an imaging person, but also a clinician and tell me more about your role within this MS research.

Dr. Javed:
So, after residency, you know, and I was interested in multiple sclerosis so I did a fellowship, for two years at the University of Chicago and my fellowship was funded by the National Multiple Sclerosis Society, specifically a grant called the Sylvia Lawry Fellowship which is essentially a fellowship that takes young physicians and educates them into how clinical trials are done, essentially. And at the end of

those two years, I was hired by the University of Chicago to lead their clinical trials program, so in addition to being a clinician having that training of what MS is doing purely multiple sclerosis for two years, day in and day out, looking at the clinical trials, looking at research papers and my job was to, you know, broaden that clinical trial program at the University of Chicago.

And then I also had research interest. So, you know, in specifically translational research interest, meaning that you have patients, and is there something we can learn from those patients? So, I figured that one of the unmet needs was looking at the imaging in terms of brain atrophy and also microstructural damage that can be picked up by unconventional MRI techniques, called diffusion tensor imaging. And so, I took that upon as a unmet area that needs to be investigated. And so we published some papers later on that. So, really, my role is clinician, first and foremost, looking at patients and helping them through their disease. My role as a clinical trialist, to enroll them into appropriate clinical trials and a investigator into unmet needs in terms of imaging and translational research to see where I can contribute to on-point knowledge and further it.

Dr. Weisman:
So the field has exploded and we're dealing with like an abundance of riches here. We have so many medications, so when you're sitting down with a patient, you know, a patient facing, how does that go? What is your general approach to dealing with any MS situation?

Dr. Javed:
I think, every patient is unique in terms of multiple sclerosis. Multiple sclerosis is very variable among case-to-case are patients that walks in your door, and you think you've seen that also in your practice and patient comes in with various, sort of, ailments, symptoms, and so each I would like to stress that each case is very individual. So, you know, based on where the lesions are, in the brain or spine, patients have different set of symptomology, so there's a heterogeneity in presentation and also, how patients, perceive that, sort of, symptomology. So, when I see a patient, you know, I categorize them into risk, where they are, how much disease burden in terms of MRI they have and their neuroaxis, brain and spine, what their physical disability is, what their cognitive disability is. And based on that, there are two, sort of sets of, you know, treatment plans. One is obviously for the multiple sclerosis, the autoimmune disease and that autoimmune disease, what I do, realize that it's different along the continuum of progression. Early patients with multiple sclerosis have inflammatory disease. Later patients have progressive disease, so one shoe doesn't fit, all sort of, sizes in terms of progression of the disease over time. So, you have to decide, which therapy to choose in terms of, controlling their multiple sclerosis. Has the MS been ongoing for 20 years, is the patient in a wheelchair or is the patient walking in and has very, low disability?

And the other set is the set of symptomology: bowel, bladder spasticity, pain, cognition and those are the set of medications and rehab things we talk about. So, it's a long visit nonetheless. And it takes quite a bit of effort to address on multiple visits, several of the dynamics of the MS disease.

Dr. Weisman:
What do you think are the unmet needs, here? You, sort of, alluded to the progressive folks, how can we help those people better?

Dr. Javed:
So, that is the main problem we have at the progressive multiple sclerosis patients that there are no good treatments, in terms of medications. We know that the immune system changes over time. You have mostly the inflammatory macrophage, and b-cells and t-cell adaptive immunity plays a very important role early on. I would say in first five to ten years of multiple sclerosis and after that you have the progressive multiple sclerosis, which the immune milieu has changed from adaptive and macrophagic inflammation to actually microglial and astrocytic inflammation and we don't have good targets. We've looked at the medication we have currently for our inflammatory stage of the multiple sclerosis and it just simply doesn't work and many trials have failed in progressive multiple sclerosis. So, in the unmet need is to identify the immune milieu and targets in the progressive stage of multiple sclerosis, number one. Number two, to see what type of medications would work.

Clinically, I think, what we do with patients, in terms of addressing progressive needs are mostly rehab and management of their various symptoms in terms of spasticity, pain, cognition, and bowel/bladder issues. So, clinical management is mostly symptomatic treatment, more so than I can think of any specific drug that would significantly help them.

Dr. Weisman:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. David Weisman and I'm speaking with Dr. Adil Javed about multiple sclerosis. In ten years, do you think we're going to have better disease modifying therapies for progressive disease based on these targets in the secondary progressive phase?

Dr. Javed:
I really think so, David, I think from the research we have seen and the clinical trials we're doing, and there are couple of drugs that are

in phase 3 trials. And the reason they go into phase 3 is because phase 2 was somewhat successful. So, I think in the next ten years, we are, sort of, edging towards some more and more and from phase 1 to phase 2 and phase 3. So, there are several trials that are in phase 2 going onto phase 3 and that is a comfort because I know that, when you see a phase 3 trial in progressive MS that has some inkling or some decent idea from phase 2 that the there is some success.

Dr. Weisman:
Do you think MS will ever have a cure as defined by a single therapy that will arrest the disease?

Dr. Javed:
So, the issue is that the cause of MS is still largely unknown, and the target of multiple sclerosis is largely unknown. There are diseases that have specific targets like NMO, neuromyelitis optica, the aquaporin 4, and as you know that they are great advances in, sort of, basically you know, curtailing the relapses and, i.e.: getting closer to the cure. But a cure is, you know, in my opinion, maybe a target or two or three and that's the problem in multiple sclerosis because we don't know how the disease starts.

The diseases are in the bag, it's already started by the time the person walks into the room. Because when a person walks into the room with an ailment, say optic neuritis, or transitionalitis, you look at the MRI and there's about 50 lesions. So, the disease has been ongoing for years and quite a few of these patients and there's brain atrophy even after the first attack of multiple sclerosis, you can see evidence of brain atrophy.

So, the problem is, we don't know the target, we don't know when the disease really starts and hence the problem. So in the targets are a multitude and the targets change in early MS versus progressive MS, so and here lies the problem. So, I think that as we gain understanding of these targets that are involved in progressive MS, and I think we will edge towards better management and hopefully cure in the future but I don't see in the ten years ahead I think we'll be better at treating progressive MS but I'm not sure if "cure" is something I would use.

Dr. Weisman:
Well, this has been an intriguing look at MS and what we can expect to see in terms of future treatment options. I want to thank my guest, Dr. Adil Javed for joining me in discussion. Dr. Javed, it was great having you on the program.

Dr. Javed:
Thank you.

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