As Treatment Options Expand, Researchers Continue to Explore the Basis of MS

New treatments have emerged and others are expected. What have changes meant for patient care?

A Q&A WITH MOSES RODRIGUEZ, MD

What were the biggest stories in MS care this year?

Moses Rodriguez, MD: From the standpoint of research and therapeutic development I guess the biggest story was Tecfidera (Dimethyl fumarate), which was approved by the FDA. It's a new oral medication, found kind of by serendipity. It's a drug derived from the Krebs cycle, which is part of the cycle that is important in our maintenance of energy metabolism in every cell. It was found to have very significant effects on decreasing MS attacks and decreasing MRI lesions, even more effective than some of the interferons. It is extremely well-tolerated. The side effect profile is relatively small: some patients developed diarrhea, some patients developed paresthesias, but there are no major side effects compared to the other drugs that are available, especially the other oral medicines for multiple sclerosis.

So, Tecfidera was a big story in 2014, and it's going to be an even bigger story in 2015. Especially when people get used to prescribing it and really get used to the side effect profile that the patients will be dealing with, I think it could turn out to be the drug of choice for patients early on in the disease course of MS. One concern, though, is the recent report of a patient that developed Progressive Multifocal Leukoencephalopathy (PML). More information will be needed to determine how often this severe complication is seen. It remains a single case report and it appears that the lymphopenia that developed is this patient lasted years.

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But the big story for MS continues to be how to prevent progression. There is still not a single drug that prevents progression. So, even though we can stop the attacks pretty dramatically with drugs like Tysabri, which shuts down the blood/brain barrier completely and shuts down pretty much all the attacks of MS, the patients continue to progress. There is something uniquely different about progression compared to exacerbations, as we have none from epidemiologic studies in the Olmsted County population.

I think the pharmaceutical companies are beginning to focus more and more on progression but they have focused almost exclusively on an experimental model called experimental autoimmune encephalomyelitis, EAE, which is an immune model that is very good for predicting drugs that prevent attacks. It's not a perfect model by any means and it doesn't really help from the standpoint of the progressive disease.

The model that is probably more effective for understanding progression is Theiler's virus induced demyelination, which is

a viral disease in mice that can be induced experimentally. In that disease there is demyelination for the life of the animal. They develop large areas of demyelination that are associated with secondary axonal injury and progression throughout the life of the animal, meaning it's a lifelong disease just like MS. Some companies are beginning to switch to this model. It's still a very, very minor model compared to EAE from the standpoint of its usage, but, for example, we use it extensively at the Mayo Clinic and a number of drug companies are approaching us because we are able to test their drugs to see if it prevents progression or it promotes remyelination.

The other big story is remyelination. It was thought that remyelination was impossible, it was not possible to promote repair; and we have shown here at Mayo that remyelination can be enhanced and we have a drug called Antibody-22 which just completed Phase I clinical trials in 72 patients and the side effect profile was basically nil—no side effects.

This is a natural autoantibody that binds to oligodendrocytes. The goal is to see if it promotes remyelination. It was a double-blind, placebo-controlled trial, so the code has not been broken from the standpoint of efficacy. And that will be interesting when the code is broken sometime in the middle of 2015. This is being done by Acorda Therapeutics, and that will be a very big story in 2015 to see if there is any evidence of remyelination by imaging or clinical improvement in patients

The other drug that is now being used for remyelination is another antibody called Nogo. Nogo is an inhibitory compound that inhibits the promotion of remyelination and the idea is to block this compound in an effort to see if by blocking this compound you can enhance the reparative process. That drug is also in Phase I/Phase II clinical trials. It looks like it may have a little bit more of a side effect problem than Antibody-22, though it's still early in the game, so it's hard to know. And it's difficult to know whether blocking this one molecule will be sufficient to promote repair.

The two drugs are very different. They're both antibodies but one is blocking a protein and the other one is stimulating oligodendrocytes to proliferate and repair the lesion. They're very different approaches to enhance repair.

If either one of these drugs is found to be effective, it's really going to change the playing field dramatically in MS because at the present time we don't have anything to try to promote repair, try to improve the function of patients that have fixed neurological deficits. I hate to use the word curative, but, it could be something where you are actually repairing the nervous system, which in a sense is a curative type therapy.

What were some of the important overlooked stories?

Dr. Rodriguez: A very new paper has claimed that myelination in the central nervous system is really a segmental process.[1] It is a very controversial paper and I think one of the most interesting papers I've ever read on myelin. It is a basic science paper, which examined myelination using electronmicroscopy but using serial sections. They were able to provide a computer montage of an axon starting from the very heart of the cerebral cortex (cell body) all the way down to the brainstem and thus could follow that individual axon.

We have always assumed that if an axon is myelinated, that it's myelinated all the way through. They found in normal rodents that when they actually looked at the myelination profile, it was segmental. There were areas that were myelinated, but there were areas that were not myelinated at all. This whole idea of conduction velocity and the important roles Nodes of Ranvier is now in complete flux because of this one study. I don't know whether the study has been confirmed yet or not, but it was one of the most fascinating papers I've ever read on myelin. If true it will change how we view myelination and ultimately demyelinating conditions in humans.

What do you think 2015 has in store for MS care? Are there any studies you're looking forward to?

Dr. Rodriguez: I think that the big shift that you are seeing in MS is going from this issue of relapses to this issue of progression. All of the companies are now focused on preventing progression, because they see that the market is completely clogged up from the standpoint of relapses. We already have 12 drugs; it's beginning to look like the epilepsy field where we have 12 drugs for epilepsy and none of them may work any better than any of the others. Basically, we're just generating new drugs and new derivatives of the same drug, but there are very few new drugs or new concepts.

That's why I mention Tecfidera. That's because it's completely outside the realm of how most people have been thinking about drugs for MS. Most people have been thinking about the immune system and targeting different parts of the immune system, and what that has done is resulted in new drugs, targeting the different aspects of the immune system, and none of them are any better. I think that the better approach is to prevent progression and develop ways to enhance repair. Those are the things that are going to be the big buzzwords for the future. ■

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1. Tomassy GS, Berger DR, Chen HH, Kasthuri N, Hayworth KJ, Vercelli A, Seung HS, Lichtman JW, Arlotta P. Distinct profiles of myelin distribution along single axons of pyramidal neurons in the neocortex. Science. 2014 Apr 18;344(6181):319-24.