



**MS Learn Online
Feature Presentation
Research News
Peter Calabresi, MD**

Tom>> Welcome to MS Learn Online I'm Tom Kimball.

Tracey>> And I'm Tracey Kimball. Those of us with MS are always on the lookout for new developments in the treatment of, and ultimately for the cure of MS. In this program, Dr. Peter Calabresi, a neurologist from Johns Hopkins, shares some of the recent findings in the world of MS.

Tom>> Yes, Dr Calabresi will answer correspondent Rick Sommer's questions on a wide range of topics, from the latest in genetics research to stopping MS progression. He begins with the popular topic of oral treatments.

>>Rick Sommers: You're well entrenched in research, and a lot of the research lately, a lot of the research that's got people interested is about oral medication. Talk to us about that.

>>Dr. Calabresi: Right. So, there's not a week that goes by where my patients don't ask, "When will you have a pill for MS?" We're fortunate to have the injectable therapies, but, of course, there are side effects.

And so the good news is that there are five pills in Phase III testing. That's the final stage of FDA mandated clinical trial testing for agents before they get approved to be sold on the market. And all these have shown promise in Phase II, meaning that they have been shown to be effective and reasonably safe. And now they're going into typically what are two-year Phase III trials, and some of these are actually finishing. So that the two that are really the closest are Cladribine and FTY720, or a drug called Fingolimod, and those have data that suggest that they're really quite effective in reducing relapses. And hopefully over the two-year trials we'll know more about their effects on disability progression and understand a little bit better their safety profile. I think that's going to be the key as we move forward, because I think some people have the impression that pills are safe, just like an aspirin. But, of course, we know that everything has potential for side effects. And so obviously we need to get more experience.

>> **Rick Sommers:** Typically, when you have a patient who is newly diagnosed, are they deferring treatment to wait for an oral?

>>**Dr. Calabresi:** Everyone is different. I think some people really have a certain anxiety about the diagnosis and want to get on treatment as soon as possible. And, of course, the data support early treatment. But other people prefer to wait. They recover fully from a relapse, and in some situations we actually recommend waiting, because there is maybe -- if there has been 20 years between exacerbations, perhaps they have benign MS.

>> **Rick Sommers:** Research on T cell migration that you're doing, talk to me about that.

>>**Dr. Calabresi:** So, understanding how these T cells, or white blood cells that circulate in our blood get into the brain and spinal cord is, of course, really important to treating MS. Because normally those cells move around the body trying to fight off infection in the skin or different organs. But, normally they're not supposed to be

going to the brain, spinal cord and chewing up the myelin. So, understanding how that process happens could lead to better therapy.

Of course, this is how natalizumab or Tysabri works. It blocks what we call an adhesion molecule, that allows these cells to stick to the blood vessel walls and get into the brain. The problem with Tysabri is that it's almost too effective and sort of renders the brain susceptible to infections. So, if we could understand more specifically how to target the bad cells without compromising the good ones, maybe we could prevent MS without making people susceptible to infections.

>> **Rick Sommers:** So, you're upbeat -- I mean, are we far along on the path?

>> **Dr. Calabresi:** I think we're getting there. We understand a lot more every year about what characterizes an MS cell. One of the challenges is that it seems to be different in different people, so I don't think it's going to be one size fits all.

>> **Rick Sommers:** What's the latest research in stopping MS progression, the march forward?

>> **Dr. Calabresi:** There is a lot of research aimed at understanding the later stages of MS. So, of course, early on we think of MS as being a predominantly inflammatory disease where there are a lot of relapses. But later on there is more progression and understanding how that happens will be critical to treating progressive MS.

And so their major breakthrough, I think, in the last decade has been understanding that the nerve wires that we call axons break up, and they can break up for two reasons: one is that immune cells can go in and make them snap or become transected. And the other seems to be that just the loss of myelin, chronic demyelination renders those axons susceptible to this process that we call degeneration.

So, it's like a tree trunk without the bark around it. The trunk becomes susceptible to the weather and the elements, and they start to not process the nutrients from the soil up to the leaves. And that may be the same kind of thing that happens in MS. And so we're now understanding it at a molecular level exactly how those nerve wires dysfunction and are developing whole new strategies to intervene that are very different from the ones that we've been using in MS over the past 20 years.

>> Rick Sommers: When I was diagnosed, as many people are, you go through the MRI and you go through a spinal tap. There's new technology, or tell me about mass spec. First of all, what that stands for and what it means.

>>Dr. Calabresi: Right. So, mass spec is a technique that's designed to quantify different proteins in fluids. And for years we've known that there are abnormal proteins in MS spinal fluid, but we've been very fixed on the immunoglobulins. And it turns out that there are many other proteins in the spinal fluid that could be used both for diagnosis and prognosis, determining how people are going to do.

And so our group, as well as several others around the world, have identified some new proteins that we hadn't seen before in the spinal fluid. And we think that this is exciting because we might recognize a pattern or a footprint, if you will, of the disease that could help us distinguish early on, is this MS or is this a cousin of MS, like lupus or Sjogren's syndrome. And then if it is MS, if you saw protein markers that said the nerves were degenerating, maybe it would tell you if it was a worse form or not, and it might help to tailor therapies.

>> Rick Sommers: A lot of people always ask me is it genetic? That is a question we could spend the whole hour on.

>>Dr. Calabresi: Right.

>> **Rick Sommers:** People always ask, "What's the genetic link to MS? Mom and Dad have MS; Mom or Dad has MS. Am I going to be susceptible?" Or, moving forward, "If I have kids, am I going to pass the gene on to them?" What can you shine some light on that about for us?

>>**Dr. Calabresi:** Well, there has been a lot of research on the role of genes and MS, and what we know is that there seems to be a genetic predisposition, but it's not the whole story. So, if you have an identical twin with MS, your chances of getting MS are 30% or 40%, which is higher than a sibling or a nonidentical twin, where it's 3% or 4%. But it's, of course, not the whole story, so you could have the exact same genes and still more often than not you won't get MS. So, that suggests to us that there's an environmental component or trigger that then brings it out.

The genetic research, though, has been very helpful. We've now found three changes in genes that increase the likelihood of getting MS, and these are all immune-related genes. So this does lend credence to the research that's being done on understanding the immune system and how those genes work, and hopefully will lead to more targeted therapies.

>> **Rick Sommers:** People have been talking about a molecule 4-AP, which I guess has a brand name by now, and that it may soon be available to those of us who are dealing with MS?

>>**Dr. Calabresi:** 4-aminopyridine, which will probably be marketed as a drug called Fampridine. It's very exciting. It's a pill. It blocks a potassium channel. It's involved in how nerves conduct impulses. And it was actually shown almost 30 years ago that by blocking this channel you can improve the conduction along a demyelinated nerve. I think one of the things that's held up its movement towards the market is that it's been associated with seizures.

So, if one enhances the conduction of the nerves, it's not always specific for the location we'd like it to be, the demyelinated area, and you can enhance conduction in other parts of the brain and elicit seizures.

Fortunately, now there's a slow release or extended release formulation where we control the levels that the drug reaches in the blood and really limit the risk for seizures with still deriving some of the benefit. And so this is something that could be used for people with progressive MS, walking problems, who might improve walking times.

One caveat is that it doesn't work for everyone. It seems to be a subset of patients with MS benefit from this, but in my opinion it's something that one would try and if it didn't work you'd stop it, but if it did and it was tolerated well, of course, it would be nice to have.

>> Rick Sommers: Is there a correlation amongst the group that it hasn't worked with, men, women, young, old, anything like that?

>>Dr. Calabresi: There has been a suggestion in studies that people who are particularly heat sensitive may benefit the most, and so that's something that's been looked at, but I think we need to get more experience with it.

Tom>> There's so much happening in research today.

Tracey>> In fact, there's so much going on, we couldn't fit it all in one program. Please join us as Dr. Calabresi continues his discussion with Rick in the second installment of Research News.

Tom>> See you then.