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Studying the Safety of Discontinuing DMTs in MS Older Adults

Dr. Wilner:
Disease-modifying therapies, or DMTs, reduce disease activity and reliably slow progression of disability in multiple sclerosis. However, it's unclear whether they are effective in older adults with MS as their relapses become less common. So the question comes up, when is it safe for older adults to discontinue DMTs?

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Andrew Wilner. With me today is Dr. John Corboy, the lead investigator of a recent multicenter study that aimed to determine whether stopping therapy in older patients with MS allowed disease activity to increase. Dr. Corboy is a Professor of Neurology and the Director of the Rocky Mountain MS Center at the University of Colorado.

Dr. Corboy, welcome to the program.

Dr. Corboy:
Dr. Wilner, thank you very much for having me. I'm happy to be here today.

Dr. Wilner:
Well, so am I because I'm really interested to hear what you found in your study, so let's start with some background, Dr. Corboy. What happens to a patient's MS when he or she gets older? And before you answer that, please define older.

Dr. Corboy:
For the purposes of our study, we used the age cutoff of 55, and there were many different reasons for that, not the least of which was that many of the studies, the phase III studies that gained approval for many of these medications, had a maximum age of 55 during their use. And so we also know that the natural history of the disease changes. Now this gets at your primary question. MS, like many conditions throughout the body, changes over time. We know that when people are younger they have many acute relapses and many MRI scan changes that presumably represent acute inflammatory events, autoimmune disruption, affecting their brain, spine, and optic nerve, but these acute relapses and scan changes diminish as people age, and many people either become stable or go into a slow progressive phase independent of relapses, and during that phase, the medicines that are presently available are less effective. Many studies have shown that they are less effective, so consequently, the question arose—and many patients would ask in the office—"Do I need to really continue to take this? Am I having any benefit?"

And then on the other side, we also know that there's potential for risks that may increase with aging. As we age, we're more prone to get infections, and many of the medications that we use are potentially immunosuppressive, and they may be associated with enhanced risk of infection, so the risk-benefit dynamic may change over time with age. But what really prompted us to do this study was that patients who come into the office frequently after years of stability and say, "I have no idea if this drug is doing anything for me or not, and it's really expensive, and I don't know if I really need to continue to take it."

Dr. Wilner:
Yeah, so very legitimate question. So can you walk us through how your study was designed and what you found?

Dr. Corboy:
Sure. The population that we were interested in looking at was people who actually had continued to use their medications and had become stable, at least with regard to having a relapse or recent MRI scan activity who are asking the question, "Would you deliberately make a choice to go off of your disease-modifying therapy?" And there were really no studies that looked at that population in that fashion, and there were no randomized controlled trials with blinded observers that had been done. And so we started enrolling in 2017

at our place and 19 other centers in the United States, and what we did was we did a randomized, controlled, investigator-blinded study.

And we enrolled individuals who were 55 and older who had not had a relapse for at least five years and who had not had a new MRI scan lesion for at least three years and who had been continuously taking a disease-modifying therapy, a DMT, for at least five years. The whole time of that five-year time that they would not have a relapse, and they were on their same DMT for at least two years. We had eventually 259 individuals who enrolled, 128 who were randomized to stay on their medication, and 131 who were randomized to go off their medication.

And the primary outcome measure that we used was the question of whether or not there was new disease activity as measured by either a new relapse of disease activity or any MRI scan change on the brain over that two-year period of time compared to baseline. We checked the scans at six, 12, and 24 months after they were randomized to go to whatever treatment assignment.

In addition, we had a number of other outcome measures, including the Expanded Disability Status Scale, or EDSS, which measures confirmed disability over the course of the time in the study, as well as a variety of other outcome measures, such as patient-reported outcomes with regard to symptoms, quality of life. We also did the Symbol Digit Modalities Test, the SDMT, a cognitive processing speed test, and a patient satisfaction with how satisfied people were on their disease-modifying therapy or off their disease-modifying therapy in the case of those who discontinued.

The primary outcome measure was looked at with a noninferiority approach, which was relatively unusual. When a new drug comes on the market, they might compare either to a placebo or they might compare it to another drug on the market, and they try and prove that they're superior. We tried to prove, in fact, that something was not inferior to the present model, the present model being on medication. So we expected about two percent of people over two years who remained on drug to continue to have new disease activity, and we would accept up to 10 percent in the discontinued group and still call that noninferior, and this allowed us the greatest degree of statistical significance, feasibility.

So the primary results of that then, we followed people for up to two years, and in the group that continued on their therapy, six out of 128 individuals had new disease activity, either a relapse or a scan change, and in the discontinued group, 16 out of 131 had new disease activity, either relapse or scan change. There were very few relapses and most of these changes that were seen between the two groups were just one to two new lesions on the brain MRI scan. But when they did the statistical analysis, we had three potential outcomes. We could show that going off drug was inferior, we could show that going off drug was not inferior, or we could find something in between. That is, it's not clear if it's inferior or not inferior, but we could not demonstrate noninferiority. And in fact, it's the latter that we found. With the statistical model that we had, we could not show that going off drug was noninferior. Similarly, it was also not inferior, so it was sort of a mixed result.

And when we, furthermore, looked at the secondary outcomes, that baseline, the same level of disability on average and over time, 11 to 12 percent of people had confirmed disability progression and was pretty much the same in both groups, no different statistically. And when we looked at the symptom scores, the SDMT, the cognitive processing speed test, there was really no difference, quality of life and other things, no difference between the groups at baseline and no differences in the changes over time between them.

Dr. Wilner:
Thanks for that very clear explanation, Dr. Corboy. For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. John Corboy about discontinuing disease-modifying therapy in older adults with MS.

So given everything we've discussed so far, Dr. Corboy, what are the benefits and challenges to discontinuing DMTs in this patient population?

Dr. Corboy:
The greatest challenge for these patients is that we still have only short-term data. Our study was only two years in duration, and for many patients, the biggest concern is, "What happens to me five years from now, 10 years from now, if I discontinue my disease-modifying therapy? Or even if I, perhaps, deescalate it, don't use it as frequently, or perhaps use a less risky medication that may not work as well?" It's the same kinds of questions. And so only having a study for two years' duration is a limitation of this study.

Another limitation of the study is that we really focused primarily on individuals who were using some of the older disease-modifying therapies that have relatively lower efficacy, but very low risk. We had about 75 percent who were using old injectable medications, like glatiramer acetate and interferons, and we didn't have a large proportion of individuals who were using more highly effective newer therapies, and that's important because a couple of those are associated with potential rebound of disease activity if they go off the medication, especially natalizumab and fingolimod, but then also, some of the risks are greater in those individuals if they remain on the drug. So the biggest challenge for patients is balancing this potential recurrence of disease activity that is still not perfectly understood in

terms of certainty against the risks of the medication and the cost of the medications and other things like that. So the biggest challenge is balancing all of these risks and benefits and having imperfect data, and then trying to make a complex decision that could affect them with disability for the rest of their life.

Dr. Wilner:
I just wanted to comment also that your population is really very, very selected. These were adherent patients, right? These were patients whose MS was not very active, so it's not just anybody over 55. I think that's important to emphasize.

And I'm just going to ask you one last question is that there has been a tendency, I think, for physicians to start disease-modifying therapy earlier because of this parallel concept in MS that, yes, there are relapses, and it's important to stop them. But there may also be some other progressive neurodegenerative process, like atrophy or something that's either linked to or almost independent of the relapses, and that's a reason to continue treating even if the MRI looks great. What do you think about that in context of these patients?

Dr. Corboy:
Yes, I have a couple comments. One, you're exactly correct. This is a limited population. And we did this explicitly with that population because we wanted to ask the question in a maybe broader sense, and that is if we can't show in this population that it is reasonable to consider a trial off disease-modifying therapy, then this may actually end the question completely because you're not going to be able to show this in younger patients.

And then in addition, the second part of that would be that there's a concept now in our world, called progression independent of relapse activity, PIRA, and although, it's certainly true and multiple studies have shown that having progression in this EDSS that I mentioned previously is much greater in older individuals than younger individuals, but when you have progression of disability, even in younger individuals, most of it is independent of relapse activity—in one large study, 83 percent. In our study in an older population, that number was even higher. It was 93 percent. And so you are correct, absolutely, that there is an underlying neurodegenerative process that's ongoing, and the very earliest MRI scans of patients even before they have had symptoms related to their MS, they already have diminished brain volume compared to age and sex-matched controls. So what this really gets at is that there's this risk that is independent of these relapses and new scan changes, and it is ongoing from the very beginning of disease process, and our present medications don't appear to do much for this.

And in fact, in our study, on and off drug in this population, there was really no difference between those on and off drugs having progression disability.

So you pointed out an important limitation of all of these medications, and the important thing for us is really not the relapses. Relapses are the bright, shiny object that everybody can see. The reality is the biggest thing to care about is progression of disability over time, and that remains a major unmet need in our area.

Dr. Wilner:
Well, thanks for that. This has certainly been an insightful look at the recent research on discontinuing disease-modifying therapy in older patients with MS. I'd like to thank my guest, Dr. John Corboy, for joining me today to discuss his research and insights. Dr. Corboy, it was a pleasure speaking with you.

Dr. Corboy:
Thank you, Dr. Wilner. Thanks for listening.

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