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MS Perspectives™

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Practical Insights on Multiple Sclerosis

In This Issue

What Your Neurology Team Has Learned Recently

News from the American Academy of Neurology Meeting

Page 10

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The International Organization of Multiple Sclerosis Nurses

> And Spring arose on the garden fair,
> Like the Spirit of Love felt everywhere;
> And each flower and herb on Earth's dark breast
> rose from the dreams of its wintry rest.

—"The Sensitive Plant" by Percy Bysshe Shelley

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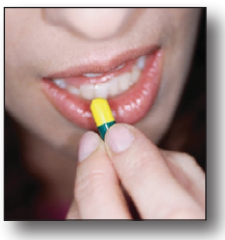

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UPDATE ON MS Oral Medications

The treatment of multiple sclerosis (MS) is undergoing a revolution—there are now three, count them, *three* oral medications that have the potential to modify the disease, and others are being tested. Part of our mission at *MS Perspectives* is to keep our readers up-to-date on new advances in MS, so we've compiled the latest information on these three drugs for you. (Also be sure to read the "Ask the Clinician" column later in this issue, where we discuss the reasons you may or may not consider switching to one of these drugs if you're currently on an injectable or infusible disease-modifying therapy.)

Gilenya™

Gilenya™ (fingolimod) was the first oral drug approved for MS back in 2010. You take it in capsule form at a dose of 0.5 mg once a day with or without food. Gilenya™ works in a different way than the injectables and infusibles to calm the overactive immune system by decreasing the number of lymphocytes (white blood cells) that can attack the central nervous system. It may also protect the brain. It is approved for the treatment of relapsing forms of MS to reduce the frequency of relapses and

to delay the accumulation of physical disability. On-going studies are continuing to evaluate the safety and effectiveness of the drug in people with MS, including progressive forms.

Over 63,000 people worldwide have taken Gilenya™ in clinical trials and over the past 3 years. Since its approval, the prescribing information for the drug has been updated to reflect data from two large trials—called FREEDOMS and TRANSFORMS—that showed Gilenya™ reduced the number of new or enlarging lesions seen in the brain. The prescribing information has also been updated based on safety analyses and reports of several deaths among people taking the drug (although it is unclear if the deaths were actually related to Gilenya™).

FYI

Did you know that...

- ***There are now three oral disease-modifying medications for relapsing forms of MS: Aubagio®, Gilenya™, and Tecfidera™.***
- ***The three drugs work in different ways from one other.***
- ***Other oral agents are being investigated.***

Before you start Gilenya™, you will need to have an electrocardiogram to test your heart function. People who have had recent heart problems or strokes should not use the drug. Since Gilenya™ can increase your risk of developing serious infections, you need to be tested for the chicken pox virus and if you haven't had that infection, you need to be vaccinated. You can't start treatment if you have other active or chronic infections (such as hepatitis). Your MS clinician will also want to check your liver function via a blood test, and have your eyes examined, since Gilenya™ can affect the liver and the eyes.

When you take the first dose, plan to stay in your doctor's office for 6 hours so your heart rate and blood pressure can be monitored hourly. That's because the drug has been shown to slow the heart rate and lower blood pressure during the first few doses. If you're okay during the first 6 hours, you're unlikely to have a cardiovascular event related to the drug after that. The side effect usually diminishes with a month of

starting the drug. By the way, if you stop taking Gilenya™, do not restart it without talking to your healthcare provider. You may need to repeat the 6 hours of monitoring in case of a heart event.

Aubagio®

The second oral drug to be approved by the US Food and Drug Administration (FDA), just last year, was Aubagio® (teriflunomide). Aubagio® works by inhibiting the action of an enzyme that promotes the production of T cells and B cells in the immune system that are thought to prompt damage in the central nervous system. It is taken once a day in tablet form with or without food at a dose of 7 mg or 14 mg.

The drug was approved based on the results of two trials. The TEMSO study was a 2-year trial of two doses of teriflunomide in 1,088 patients between 18 and 55 years of age. It showed that at doses of both 7 mg and 14 mg once daily, Aubagio® significantly reduced relapses compared with a placebo. The 14-mg dose also significantly reduced the accumulation of disability, and both doses reduced the number of active and new lesions seen on magnetic resonance imaging (MRI) scans.

The TOWER study, an 18-month trial with 1,169 patients between 18 and 55 years of age who received either 7 mg or 14 mg of teriflunomide or a placebo daily, also showed significant reductions in the relapse rate for both doses. The higher 14-mg dose reduced the

progression of disability. Post-marketing research is continuing to monitor the safety and effectiveness of Aubagio®. For instance, the just-reported results of the 2-year TOPIC trial show that people who took Aubagio® after a clinically isolated syndrome were significantly less likely to go on to develop MS (which was defined in the trial as a second attack of clinical symptoms).

The most common side effects of Aubagio® experienced by patients in clinical trials include diarrhea, nausea, hair thinning (which is reversible), and liver problems. Rarely, Aubagio® may cause numbness and/or pain in the hands or feet.

Before you start using the drug, you should have blood tests for liver function; these tests should be repeated monthly for 6 months. You should also have a screening test for tuberculosis and your

blood pressure should be checked. Importantly, due to the results of animal studies showing the potential for harm to an unborn child, men and women of childbearing age should use reliable birth control during treatment. Women must have a negative pregnancy test before they start using Aubagio®. On a reassuring note: In a recent analysis of 12 babies born to mothers who were using Aubagio® and became pregnant, no birth defects were reported.

Tecfidera™

In March 2013, the third oral drug, Tecfidera™ (BG-12, also called dimethyl fumarate), was approved for relapsing MS. The drug is given in capsule form, first at a dose of 120 mg twice a day. Then, after 7 days, the dose is typically increased to 240 mg twice a day. It is best taken with food.

Tecfidera™ is an oral immunomodulator, which means it reduces inflammation. It is believed to act in a unique way by activating the Nrf2 pathway, which helps the cells of the body protect themselves from the inflammation caused by MS. Tecfidera™ also may prevent nerve damage. The drug has been studied in over 2,600 patients in large studies called DEFINE and CONFIRM. Some people in the trials have been using the drug for more than 4 years. The DEFINE study involved 1,232 patients and compared the oral drug given twice or three times a day to a placebo over 96 weeks. Both dosing schedules were effective in reducing the probability of a relapse. Annually, the relapse rate was halved on the twice-daily regimen (the FDA-approved dosage schedule). Disability was also delayed, and there were large

reductions in the number of MS lesions seen on MRI scans. The 2-year CONFIRM trial of 1,400 patients showed that taking Tecfidera™ twice daily significantly reduced the average number of relapses and the number of brain lesions seen on MRI.

Side effects of the drug include non-serious events such as flushing (a sensation of heat or itching on the skin), abdominal pain, nausea, and diarrhea. These problems tend to lessen with continued use of the drug. There may also be an increased risk of infections, because Tecfidera™ can reduce the white blood cell count (also called the lymphocyte count). You will need to have blood tests before starting on Tecfidera™ to make sure your white blood cell count is normal; after that, you should have frequent blood tests based on your MS clinician's advice.

Support Programs for MS Disease-Modifying Therapies (DMTs)

Aubagio®, Genzyme Corporation:
www.aubagio.com, 855-MSONE2ONE (855-676-6326)

Avonex®, Biogen Idec:
www.avonex.com, 800-456-2255

Betaseron®, Bayer HealthCare:
www.betaseron.com, 800-788-1467

Copaxone®, Teva Neuroscience:
www.sharedsolutions.com or www.copaxone.com, 800-887-8100

Extavia®, Novartis:
www.extavia.com, 866-NOW-NOVA (888-669-6682)

Gilenya™, Novartis:
www.gilenya.com, 800-GILENYA (800-445-3692)

Rebif®, EMD Serono/Pfizer Inc:
www.mslifelines.com, 877-447-3243

Tecfidera™, Biogen Idec:
www.tecfidera.com, 800-456-2255

Tysabri®, Biogen Idec:
www.tysabri.com, 800-456-2255

MS News, Support, and Self-Help Groups

MS Views & News
www.msviewsandnews.org

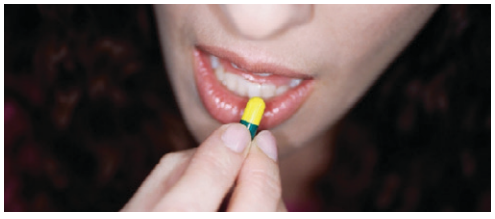
MS World
www.msworld.org

Multiple Sclerosis Association of America
www.msassociation.org, 800-532-7667

Multiple Sclerosis International Federation
www.msif.org

Multiple Sclerosis Foundation
www.msfocus.org, 888-MSFOCUS

National Multiple Sclerosis Society
www.nationalmssociety.org, 800-344-4867



What YOUR Neurology Team HAS Learned Recently

News from the American Academy of Neurology Meeting

Each year, members of your neurology team attend conferences to learn about the latest developments in multiple sclerosis (MS) diagnosis, treatment, and causes. Your MS clinicians may even present results of research studies they're working on at meetings. We asked several experts, including two *MS Perspectives'* advisors, for an update on the hottest news from the American Academy of Neurology (AAN) meeting, held in San Diego, California, in March 2013.

From Aliza Ben-Zacharia, DrNP, MS Perspectives' *Advisor*

The Study: A poster presented of the PREMiSe trial showed that percutaneous transluminal venous angioplasty (also called "liberation therapy") doesn't correct vein blockage (known as chronic cerebrospinal venous insufficiency or CCSVI)—and may actually make MS worse.*

Dr. Ben-Zacharia's Take on the Study: Many clinicians and researchers have investigated CCSVI as the reason for loss of myelin (the fatty coating around nerves) and axons (nerve fibers) in MS. Preliminary research has not supported using liberation therapy—a surgical procedure to open narrowed veins in the brain to restore normal blood flow. PREMiSe was the first rigorous trial of liberation therapy for MS performed in the United States. The study's key findings were that the treatment did not provide sustained improvement in MS patients and even may have led to more relapses and activity on magnetic resonance imaging (MRI) scans in the 6 months after the treatment. The Food and Drug Administration has warned that this treatment can cause deaths and injuries. Based on this new trial information, we do not recommend liberation therapy.

*See the Spring 2010 issue of *MS Perspectives* (available at www.MSperspectives.com) for background on CCSVI and MS.

From Stephen Krieger, MD, Assistant Professor of Neurology, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, The Mount Sinai Medical Center, New York

The Studies: Two presentations at the AAN meeting offered insight into an important clinical study known as the CombiRx trial, which was spearheaded by Fred Lublin, MD, of The Corrine Goldsmith Dickinson Center for MS in New York City. This study looked at whether a combination of two injectable disease-modifying therapies (Avonex®, an interferon beta-1a injection, and Copaxone®, a glatiramer acetate injection) was more effective than either drug alone. The preliminary results of the 3-year study, which were published in the *Annals of Neurology* in March of this year, did not show a significant benefit to the combination over either drug alone except in terms of some MRI findings. The AAN presentations looked at the 1,008 CombiRx subjects for another 4 years, and found that (A) the relapse rates for all three groups dropped to "exceedingly low values" and were lower for the combination group and the people taking Copaxone® alone than for Avonex® alone; and (B) the reduction in MRI activity seen during the initial 3 years of the study continued through to year 7 for all three groups and

was particularly "robust" for people who had initially received the combination treatment.

Dr. Krieger's Take on the Studies: On first look, the results of the CombiRx trial might seem disappointing since it was found that the combination of two injectable drugs we use often to treat MS wasn't better than either one individually. However, in today's world, that's not a terrible setback since there are now new oral therapies that offer options for treatment.

One reason the combination wasn't more effective is that the individual drugs worked so well. Both Copaxone® and Avonex® alone worked extremely well in preventing relapses, so a take-home message from this study is that these safe agents are more efficacious than we knew. We can expect a lot from our existing injectable drugs—so if they're working for you, then you might want to stick with them.

The analysis of data from the trial is still ongoing, as the presentations at the AAN meeting show. One further analysis is looking for biomarkers that can tell us who will be most likely to respond to Copaxone® or Avonex®, so we can make more personalized decisions about therapy. In the future, we also may see combination trials of injectable and oral medications, or two oral medications.

From Anthony Reder, MD, Professor of Neurology, University of Chicago, Chicago, Illinois

The Study: An oral presentation from Kaiser Permanente in California found that childhood obesity increased the risk of developing MS and clinically isolated syndrome (CIS), particularly among adolescent girls.

Dr. Reder's Take on the Study: This study shows that lifestyle may affect the chance of developing MS. If MS runs in your family, you can intervene early and without medication in children who are overweight and help them to reduce their risk of developing the disease. The study adds to the data we already have about preventing MS by getting adequate vitamin D and exercise during childhood—and now losing weight if a child is overweight.

The Study: A poster presentation demonstrated that smokers who have been diagnosed with CIS are (A) at higher risk of going on to develop MS, and (B) experience a shorter time to their first relapse than nonsmokers with CIS and healthy control subjects.

Dr. Reder's Take on the Study: This study highlights another modifiable risk factor for MS: smoking. The cigarette habit has previously been shown in several studies to worsen the disease course of MS, and this study shows it increases the risk of developing MS among people with CIS, and it increases the severity of the disease. It also brings home the message that if you're on an expensive medication for MS, you can undo all the good the medication is doing you by smoking.

From Barbara Green, MD, MS Perspectives' *Advisor*

The Study: An oral presentation compared the administration of a new type of interferon beta-1a injectable, called pegylated interferon, every 2 weeks versus every 4 weeks. The multicenter ADVANCE study had 1,512 patients and showed that both administration schedules reduced the rate of relapses, disability progression, and MRI changes over the 2 years of the trial.

Dr. Green's Take on the Study: This is an exciting study because it shows the potential of a more convenient alternative to a drug that we already know works very well for many patients.

The Study: Another oral presentation showcased MRI results from the DreaMS trial of a new agent in the same class as Gilenya™ (fingolimod): the selective sphingosine 1-phosphate receptor agonist currently called ONO-4641. The drug was effective in reducing new lesions and the accumulation of lesions seen on MRI at three tested doses versus a placebo.

Dr. Green's Take on the Study: This is a very early trial of a second-generation drug that is similar to Gilenya™ but more selective, so we hope it will have fewer side effects. The drug was effective at all three doses tested, at least from the perspective of MRI findings. Another company is also looking at a second-generation drug in this same class.

There will be more oral drugs available to patients with MS within the next decade, and we'll gain more and more information on their safety and effectiveness.

Ask the Clinician

Tracy Walker, FNP-C

Q. I keep hearing about all these new oral drugs that are being approved. Should I consider a change in my treatment?

A. It's very exciting to have new drugs available to manage multiple sclerosis (MS), but there are a lot of factors to consider before changing your therapy.

Effectiveness: Everyone wants the most effective drug for their MS, but the problem is there is no *one* drug that is the most effective for everyone, nor is there a blood test that can predict if a particular drug is going to work well for an individual person. It takes time to tell if a drug is effective and a person may have new disease activity during that time.

Safety: Potential risks and benefits can be a big factor when deciding on whether to switch treatments. A drug can be very effective but have serious potential side effects or health risks. Many people feel that the risk of their MS progressing is greater than the risk of a potential safety issue, while others feel just the opposite. Be sure you ask your provider about side effects and safety of your current treatment versus any new one you're considering. Also inquire about how well he or she thinks you are doing on your current treatment. Have new lesions appeared on your magnetic resonance imaging (MRI) scan? Have you had recent relapses without a full recovery? Are you experiencing on-going side effects? The bottom line is everyone has a different opinion regarding risks and benefits, which makes understanding both very important so your decision can be an informed one.

Lifestyle and Convenience: Another factor is choosing a drug that best fits your lifestyle and is easy to take. For some people that means a pill, even if it has to be taken more than once a day. For others, taking an injection or infusible treatment less frequently is more convenient or easier to remember. Others may decide that the potential side effects of a drug may interfere more

with their lifestyle than how the medication is taken. One thing is clear—no matter what therapy you are on, it won't work if you don't take it!

Experience: Experience means two different things—a person's individual experience with a medication, and the general population's experience with a medication. Many people may prefer an older drug over a newer drug, because we have a better idea of what people can expect when they take it. Others want the newest therapy available because they perceive that newer is better.

Cost: MS medications can become expensive very fast, and cost can limit the ability to take advantage of some therapies. Fortunately, most of our MS treatments have co-pay and other assistance programs for those who have little or no insurance. Before assuming one medication is going to be more expensive than another, do some investigating. Most of the programs (see the box on page 9) or your pharmacist can tell you what your cost will be, or whether there are coverage limitations for a certain treatment.

It is an exciting time in MS, with a lot of research in progress and new treatments being approved. Hopefully, as we continue to better understand the disease, we will learn more about when different therapies can be the most effective and in whom. In the meantime, having as many treatment options as possible is a good thing!

—Tracy Walker, FNP-C
Nurse Practitioner
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