



National
Multiple Sclerosis
Society

MS Learn Online Feature Presentation

Tecfidera®- What You Need To Know

Bruce Cohen: Tecfidera, which was previously known as BG-12, is the third oral disease-modifying therapy approved by the FDA for treatment of patients with relapsing forms of multiple sclerosis.

Gabriel Pardo: The other name that we know it as is DMF. That stands for dimethyl fumarate, which is actually the chemical compound that makes the medication.

Gabriel Pardo: If a patient fails to respond properly to a given medication, his or her physician will be inclined to use a medication that has a different mechanism of action that creates the effect on the disease through a different mechanism, hopefully, controlling the disease in a better way.

Bruce Cohen: Tecfidera is thought to work in MS by affecting a pathway called the Nrf2 pathway, which is important both in the proliferation of inflammatory cells, but also in protecting nerve cells from oxidative stress, and therefore it may have neuroprotective properties as well.

Gabriel Pardo: Tecfidera is considered a first line therapy. It can be used as the very first medication that a patient is placed on when they are discussing starting treatment for multiple sclerosis. It can also be used, of course, as a second line therapy, meaning patients that have been on other medications before and need to switch either because there is lack of efficacy or because they're having side effects or tolerability problems to their current medications.

Gabriel Pardo: Tecfidera is taken as an oral capsule twice daily. The regimen called for 240 mg twice a day. There is a titration pack at the beginning. For the first week, patients will take half the dose, 120 mg twice daily. Thereafter, the maintenance dose will continue to be 240 mg, or one capsule twice a day, morning and evening.

Bruce Cohen: The reason for that, I think, is to build up the tolerance to the medication. There are some early side effects that occur with the medication that tend to dissipate when it's continued, as a person develops tolerance.

Bruce Cohen: Tecfidera appears to have a very good safety profile in clinical trials, although one is always cautious with a brand-new medication since potential side effects may emerge that were not seen in the clinical trial as it gets into widespread use. Nonetheless, it appears to be a convenient regimen and it appears to be a well tolerated medication by most of the patients that were in the clinical trials.

Bruce Cohen: There were two large clinical trials that were published recently regarding the use of BG-12, or Tecfidera. The first was a study in relapsing-remitting MS patients, which used an endpoint of the risk of patients having a relapse during two years of follow-up. In that study there was a roughly 50% reduction in that risk compared to a placebo group over the two-year period.

Other endpoints that were looked at in that study included the annualized relapse rate, which was also reduced by a little over 50%, and the risk of progression of disability -- in other words, a change in a standard measurement of a person's neurologic examination, known as the EDSS, which was sustained for at least three months. That risk was reduced by about 38% for the currently recommended dose.

The second study looked at annualized relapse rate as the primary endpoint. That showed a 44% reduction compared to placebo for the twice daily dose that was approved by the FDA. There was also a reduction in the risk of relapse over two years, which was comparable to that seen in the other study. But in this particular study there was no benefit on the disability progression mark, so that the group that received Tecfidera did not do significantly better than those that received placebo over that two-year study.

Both studies showed benefits on the evolution of new MRI lesions, with reductions of 70% to 80% in the number of new white spots on MRIs, and one of the studies showed a reduction of about 50% in the number of new black holes, or T1 spots that we look at on MRIs.

Gabriel Pardo: There are three things that we always have to think about when we're going to use a medication. One, of course, is it efficacious? Is it doing what we want it to do in controlling the disease? Two, is it safe? Are we creating any other serious problems? But also the tolerability, the side effects of the drug.

The effects of the medication on MRI parameters were very good. We talk about the reduction of new or enlarging lesions, it went anywhere from 71% to 85% in the two studies. If we talk about the gadolinium-enhancing lesions, or the ones that are enhanced with contrast, it was between 74% and 90%. And there were also other parameters, such as the induction of what is called T1 hypointense lesions, or areas where we can document some degree of damage to the brain tissue itself. And the reduction of those lesions was anywhere between 57% to 72%.

There were no significant safety concerns, and that is the first statement, but there were some things that were identified, again, that we need to be vigilant over time. One of them is the induction of lymphopenia. Lymphopenia refers to the decreased number of white cells in your blood. The white cells are part of the immune system and they are responsible primarily for fighting infections.

It was less than 6% of the patients had that degree of lymphopenia. Despite that, there was no evidence of increased frequency or number of infections in the patients that were being treated with Tecfidera compared to those that were receiving a placebo. So, despite the identification of lymphopenia, there was not a correlation with increased either infections or serious infections secondary to the medication.

Another potential safety concern is the elevation of liver enzymes. Here, same as with the lymphopenia, there was no evidence of a clinical consequence of mild elevation of liver enzymes, meaning there was no evidence of liver damage at all.

Gabriel Pardo: There are certain tests that are needed before you start Tecfidera and while you're on the medication. The only one that is required in the package insert is obtaining a CBC, a complete blood count within six months of initiating therapy. And then it is required to repeat it a year later. Even though that is the requirement, it is very possible that most practitioners are going to have different ways to monitor this.

Gabriel Pardo: So, recently there has been some disclosure about cases of progressive multifocal leukoencephalopathy, or PML, in patients that have been taking Fumaderm. Fumaderm is a medication that is chemically similar to Tecfidera. Fumaderm has different fumarate salts, while Tecfidera has a single fumarate salt, dimethyl fumarate

At this point in time we have no cases reported in patients with multiple sclerosis that have developed PML while taking Tecfidera. The cases that have been reported are all from the psoriasis population, taking a slightly different compound-

A fourth case -- there have been a total of four cases reported -- was on a patient that was taking a fumaric acid compound that was not produced in a pharmacy but in a compounding pharmacy. Not produced by the industry pharmaceutical company, but by a compounding pharmacy, which decreases the ability for us to determine to what degree it was a pure product and the exact concentration that the patient was taking

Bruce Cohen: Tecfidera is notable for the fact that there were very few significant side effects in either of the two clinical trials. Most common side effects were flushing, which tends to occur shortly after the drug is taken and which can be mitigated by taking it with food. The second side effect was gastrointestinal disturbances, which could include nausea, vomiting and sometimes diarrhea. Both of these side effects were more common when the drug was first taken and tended to become less frequent as the drug was continued beyond the first month.

Gabriel Pardo: We cannot really compare this result with other medications. We cannot look at this result and say this medication is better, the same, or worse than any other given medication. We can only do that if we do a head-to-head

comparison. That means that we need to study the two medications at the same time in the same population, the same group of patients whereas to be able to determine if one medication is superior or inferior to another medication. In absence of any of those studies, and we do not have any of those for Tecfidera, we cannot say that the medication is better or worse than any other given medication for MS.

Gabriel Pardo: The pregnancy rating for Tecfidera is Pregnancy Category C.

Bruce Cohen: What that means is that there is some evidence of potential toxicity in animals, although none in humans, and the drug is generally not recommended for patients with MS who might be pursuing a pregnancy or who become pregnant.

Gabriel Pardo: If someone is considering a change to Tecfidera, there might be the need to have a washout period, and it depends on which medication they were taking before. For the conventional immunomodulators, and by that I mean those that we have been using for quite some time, basically interferons and glatiramer acetate, there is no need to do a washout period. You can go from using that medication one day to Tecfidera the next day. Other medications, like Tysabri, like Aubagio, or like Gilenya, it might be wise to have a washout period because they do have an effect on things like, for example, the white cell counts that may be reduced with the use of Tecfidera, or that there is a level of concern by using them in an overlapping fashion, and even though you might stop one medication, the biological effect of that medication can linger for some time. So, we do not want to use them jointly during that phase.

Gabriel Pardo: Tecfidera is available and accessible for commercial use in the United States.

Biogen does have a patient assistance program, and I do have to say here that every single pharmaceutical company that produces a medication for treatment of multiple sclerosis has a patient assistance program.

Bruce Cohen: I think the most important thing for a person with MS to do is to be informed. I think they need to use resources available, like those that are available from the National Multiple Sclerosis Society, and those that are available

from a variety of major medical centers and from the National Institutes of Health to educate themselves about the disease, about the ways it's treated, and about what to expect of treatments.

As with any treatment, be sure to consult with your physician to determine whether Tecfidera is right for you. For more information, visit nationalmssociety.org, or call 1-800-344-4867. To learn more about the patient assistance program visit tecfidera.com.