

Ingredient in new MS drug linked to serious brain disease

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Reports found four psoriasis patients who took similar drug developed rare but sometimes deadly condition.

(HealthDay)—The active ingredient in a drug that's expected to become a popular treatment for multiple sclerosis has been linked to four European cases of a rare but sometimes fatal brain disease called progressive multifocal leukoencephalopathy (PML).

The ingredient, dimethyl fumarate, is used in a drug called Fumaderm that was approved in Germany in 1994 to treat the skin condition psoriasis. It is also in a different but closely related medication called Tecfidera, which was just approved by the U.S. [Food and Drug Administration](#) in March for the treatment of [multiple sclerosis](#) (MS). It is known as a fumaric acid ester, which is commonly used as a [food additive](#) and has been used to treat psoriasis in Germany for 30 years.

According to reports published in the April 25 issue of the *New England*

Journal of Medicine, however, four [patients](#) who were taking Fumaderm to treat their psoriasis developed PML.

In a letter responding to the reports, Biogen, the company that makes both drugs, said Tecfidera may be safer because it contains only dimethyl fumarate, while Fumaderm also contains three other fumaric acid esters.

The company also noted that none of the patients taking Tecfidera during clinical trials (then known as BG-12) developed PML. Since Tecfidera is a pill rather than an injection, and was effective and well-tolerated by patients in clinical trials, analysts have predicted it would soon become the top-selling multiple sclerosis treatment.

But the German doctor who treated one of the psoriasis patients who got PML thinks there is still cause for concern.

Dr. Jorg Schulz, a neurologist at Rheinisch-Westfaelische Technische Hochschule Aachen, a research university in Aachen, said the two drugs are virtually identical once they are broken down in the body.

"The problem is that the studies with BG-12 covered a two-year period, but no longer periods," Schulz said, and he believes it may take prolonged treatment with the drug for PML to surface.

"With the publication of our case, we wish to create awareness that treatment with any form of fumaric acid may bear the risk of developing PML," Schulz said.

PML is caused by the JC virus, which normally lies dormant in the body and causes no harm. About half of multiple sclerosis patients have antibodies to the JC virus in their blood, suggesting a current or former infection. When the immune system is depleted by illnesses like cancer

or AIDS or suppressed by certain medications, the virus can flare and destroy nerve cells in the brain.

Ironically, PML is a lot like multiple sclerosis, but it progresses more rapidly as it causes weakness, paralysis, confusion, memory loss and loss of vision or speech. Quick treatment can stop the damage, although patients may be permanently disabled.

PML is rare, but it is so serious that Genentech pulled its psoriasis treatment Raptiva off the market in 2009 after reports of four cases in patients who were taking the biologic medication. Biologic drugs are medications derived from living organisms that are used to prevent certain diseases, including ones where the immune system malfunctions.

Another biologic, Tysabri, a treatment for multiple sclerosis and Crohn's disease, was shelved in 2005 for about a year after three patients involved in clinical trials of the drug developed PML. Tysabri returned to the market in 2006 with strict new safeguards in place. Before starting the drug, for example, patients must get an MRI of their brains. They also may get blood tests to check for antibodies to the JC virus. They also are monitored by doctors every three to six months while taking the medication, which is also made by Biogen.

No such precautions are currently recommended for Tecfidera, which has been hailed as a less toxic alternative to other treatments. Other multiple sclerosis drugs are known to cause flu-like symptoms, chest pain, and heart, liver and eye problems.

In [clinical trials](#), the main side effects reported with Tecfidera were comparatively mild, and included facial flushing, stomach upset and low white blood cell counts.

"The main reason why our [psoriasis] patient developed PML after three

years of treatment with Fumaderm is prolonged lymphocytopenia [low white blood cell counts]," Schulz said. "In both BG-12 trials published in the *New England Journal of Medicine* in 2012, 4 percent to 5 percent of patients developed this kind of severe lymphocytopenia and are in my view at risk to also develop PML."

Another expert noted another caveat.

About 3 percent of patients in the Tecfidera trials were taken off the medication when their white blood cell counts dropped too low, said Dr. Robert Fox, a staff neurologist at the Mellen Center for Multiple Sclerosis at the Cleveland Clinic in Ohio.

"The intensive monitoring of the clinical trial may have been what helped to prevent PML," said Fox, who was on the steering committee for one of the studies that tested the medication and who has been a paid consultant for Biogen.

Fox added that the PML case reports are "very important additions to our understanding of this class of therapy."

"Although we haven't seen any PML cases in patients treated with Tecfidera, I think there's good reason to apply the lessons learned here to Tecfidera," he said.

More information: For more on the risks and benefits of multiple sclerosis treatments, visit the [National Multiple Sclerosis Society](#).

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