Methylprednisolone was administered at a dose of 500 mg per day for 5 days.

In January 2011, MRI studies revealed regression of $T_2$-weighted hyperintensities, with almost complete absence of gadolinium enhancement. The patient's condition had improved despite the persistence of a marked sensory aphasia syndrome. PCR assays for the JC virus in the CSF and plasma were now negative.

Fumarate, unlike other immune-based therapies that may cause PML (e.g., rituximab, natalizumab, efalizumab, and infliximab), does not belong to the monoclonal antibody family. Although this patient may have been at higher risk for PML for other reasons, long-term treatment with fumarate was probably an important factor in its development, given the unrevealing evaluation for other causes of immune deficiency, the induction of an IRIS with 5 weeks after the withdrawal of fumarate, and the patient's clinical improvement and survival after a follow-up of more than 2 years. Similar to treatment with natalizumab, long-term treatment with fumaric acid and prior treatment with other immunosuppressants may have increased this patient's risk of PML.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


DOI: 10.1056/NEJMc1211805

TO THE EDITOR: Preparations containing various mixtures of fumaric acid esters are prescribed for psoriasis in several countries, in many cases for off-label use, and are regarded as safe. One such preparation is enteric-coated, slow-release Psorinovo (compounding pharmacy, Mierlo-Hout), in which the active agent is dimethyl fumarate and in which copper gluconate was used as an additive until 2010 (for a profile of the drug, see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

On November 5, 2012, a 42-year-old woman who reported having progressive right-sided hemiparesis since May consulted us for a second opinion. She had been given a diagnosis of possible multiple sclerosis in September and at that time received 3000 mg of intravenous methylprednisolone over 3 days, without effect. Her medical history was notable for psoriasis, for which she had been taking 420 mg of Psorinovo per day since 2007, supplemented by 1000 mg of calcium ascorbate per day and EPA-1000 fish oil capsules (EPA denotes the omega-3 fatty acid eicosapentaenoic acid).

Sequential magnetic resonance imaging (MRI) scans of the brain (Fig. 1) showed small, deep white-matter lesions and one large progressive lesion, which was suggestive of progressive multifocal encephalopathy (PML), as described in a study of imaging findings in relation to PML resulting from treatment with monoclonal antibodies. Hematologic studies revealed lymphopenia, with a count of 200 lymphocytes per cubic millimeter (normal range, 600 to 2900). We realized in retrospect that the lymphopenia had developed after the initiation of treatment with Psorinovo (see Table 1 in the Supplementary Appendix). The patient was seronegative for HIV, but a semiquantitative, real-time polymerase-chain-reaction (PCR) assay of a specimen of the cerebrospinal fluid was positive for the JC virus.

We made a diagnosis of PML, stopped treatment with Psorinovo on November 7, and then started treatment for PML with mefloquine and mirtazapine.

Initially, the hemiparesis remained progressive, even though the lymphopenia began to abate (Table 2 in the Supplementary Appendix).
On December 7, we noticed signs of an immune reconstitution inflammatory syndrome (IRIS) on MRI, with indications becoming more evident on December 13 (Fig. 1). We initiated treatment with intravenous methylprednisolone. Her clinical condition stabilized in early January 2013, and we observed the first signs of recovery on January 31.

We believe that treatment with Psorinovo contributed to the development of PML in our patient. First, lymphopenia developed during treatment with Psorinovo and is a well known side effect. Second, our patient had used no immunosuppressive medication before the onset of PML, and she was seronegative for HIV. Finally, the occurrence of IRIS after the discontinuation of Psorinovo argues in favor of a causal link.

We think this case report is of special relevance since preparations of fumaric acid esters, including dimethyl fumarate, are emerging drugs that may have a broader range of therapeutic indications in the near future.3-5

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This letter was updated on April 25, 2013, at NEJM.org.


DOI: 10.1056/NEJMc1215357

Manufacturer’s Response to Case Reports of PML

TO THE EDITOR: In the letters from Ermis et al.1 and van Oosten et al.2 published in this issue of the Journal, progressive multifocal leukoencephalopathy (PML) is reported in two patients with psoriasis who were being treated with Fumaderm (Biogen Idec) or a compounded version of