tensive brain lesions and vasogenic edema after starting fingolimod.⁶ The origin of tumefactive lesions in patients with MS during fingolimod treatment remains speculative. As fingolimod only prevents the lymph node egress of subsets of lymphocytes, one can imagine that in a minority of patients this will preferentially affect inhibitory immune cells. Fingolimod also has largely unknown effects on astrocytes, neurons, oligodendrocytes, and microglial cells in the CNS, which might have unpredictable side effects in certain individuals.⁷

A relationship between tumefactive MS lesions and fingolimod treatment remains uncertain. Although fingolimod is a promising and generally safe treatment of RRMS, doctors should be alert for unknown side effects. Precise registration and publication of these complications during fingolimod treatment is important.

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VARICELLA-ZOSTER VIRUS ENCEPHALITIS AND VASCULOPATHY IN A PATIENT TREATED WITH FINGOLIMOD

A 50-year-old man with multiple sclerosis (MS) was admitted with a seizure and coma in the setting of herpes zoster. The patient developed MS in 2003 and was switched to fingolimod in 2011, 4 months after discontinuing natalizumab (54 doses). He was clinically stable, but mostly wheelchair-bound with relatively preserved upper extremity function. Brain MRI obtained before starting fingolimod was stable. He had a history of chicken pox, and he had not received the herpes zoster (shingles) vaccine. Three months after starting fingolimod he developed herpes zoster. Oral valacyclovir was started 4 days after onset of the rash. Four days after initiating valacyclovir, the patient had a generalized seizure and was hospitalized. He was deeply comatose and required intubation. CSF analysis showed 27 leukocytes (84% lymphocytes, 9% neutrophils, 7% monocytes), 217 erythrocytes, glucose 61 mg/dL (normal 50–75), and protein 201 mg/dL (normal 15–45). CSF varicella-zoster virus (VZV) PCR was positive, and CSF showed a low-level positive JC virus PCR in the hospital laboratory. PCR tests for herpes simplex virus (HSV), cytomegalovirus, Epstein-Barr virus, and enteroviruses were

negative. Absolute lymphocyte count was 190 cells/ μ L (normal 1,100–4,800). MRI of the brain revealed 2 new punctate areas of restricted diffusion in the posterolateral medulla, most consistent with focal infarcts (figure). His MS lesions were unchanged. Gadolinium was not administered due to acute renal failure. Magnetic resonance angiography of the head was normal. He was diagnosed with VZV encephalitis, seizures, and a brainstem infarct believed to be a result of VZV vasculitis. There was no clinical evidence of PML. He was treated with levetiracetam, IV acyclovir for 21 days, and prednisone 1 mg/kg daily for 7 days for VZV vasculitis. During a complex hospitalization he slowly improved, and 1 month later he was awake and oriented with significant psychomotor slowing and persistent quadriparesis in this patient who was wheelchair-bound at baseline. He was transferred to a rehabilitation hospital for continued ventilator weaning. The case was reported to the Food and Drug Administration (via MedWatch) and to Novartis.

Discussion. This patient developed herpes zoster in the setting of fingolimod-related lymphopenia, which progressed to VZV encephalitis and multifo-

Editorial, page 1942

See pages 2000,
2004, and 2006

Brain MRI shows (A) a T2-weighted image of the medulla prior to the current episode, (B) a T2-weighted image with new signal abnormality predominantly in the posterolateral medulla on the left, (C) a diffusion-weighted image showing 2 punctate areas of restricted diffusion in the left medulla with corresponding abnormality on the apparent diffusion coefficient sequence (D).

cal vasculopathy. Though the average time between rash and onset of neurologic symptoms in VZV vasculopathy is months, they can occur simultaneously, as in this case.¹ Fingolimod decreases egress of lymphocytes from lymph nodes, thereby reducing the number of lymphocytes in circulation by 70%.² It is likely that the immunosuppression caused by fingolimod increased the risk of this severe VZV infection, though a causal link cannot be proven. In the 3 phase III fingolimod clinical trials, 1 study showed an increased incidence of herpes zoster infections in fingolimod-treated patients,³ there was a trend toward a higher incidence in a second trial,⁴ and no difference was seen in a third trial.⁵ Two fatal herpesvirus family infections (1 case of HSV encephalitis and 1 case of primary disseminated VZV infection) occurred in patients treated with a higher dose of fingolimod in clinical trials.⁴ The integrated safety analysis of all trial patients has not shown a definite increase in herpesvirus family infections in fingolimod-treated patients.⁶ Nonetheless, it remains likely that fingolimod-related immunosuppression increases the risk of rare severe herpesvirus family infections.

A low-level positive CSF JC virus PCR test was present in this patient in the absence of clinical or

radiologic evidence of PML. The acute onset of disease and presence of erythrocytes in the CSF also argue against PML. The JC virus PCR result could not be verified in an outside laboratory since subsequent CSF samples were contaminated with peripheral blood, so it is not clear whether this was a false-positive result or whether a low level of virus was indeed present in the CSF.

Neurology providers should be aware of the possibility of serious herpesvirus family infections in patients treated with fingolimod or other immunosuppressants. They should educate patients to urgently report any new rashes or neurologic symptoms. Antiviral treatment should be initiated at the first sign of herpes zoster in a patient on fingolimod, and parenteral antivirals may be needed. Though all patients should have immunity to VZV before initiating fingolimod, it is unknown if administering the herpes zoster vaccine would decrease the risk of VZV reactivation in fingolimod-treated patients. Since the use of live attenuated vaccines, like the shingles vaccine, are contraindicated in patients taking fingolimod, if given, this vaccine would need to be administered at least 1 month prior to initiation of fingolimod.

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SEVERE RELAPSES UNDER FINGOLIMOD TREATMENT PRESCRIBED AFTER NATALIZUMAB

The risk of progressive multifocal leukoencephalopathy (PML) associated with prolonged natalizumab use in JCV-seropositive patients might motivate clinicians to switch patients with multiple sclerosis (MS) to fingolimod.^{1,2} Many patients with MS taking natalizumab have failed first-line therapies such as interferon- β or glatiramer acetate, and are unlikely to respond to the same therapies after natalizumab.

Recommendation of fingolimod might appear logical after natalizumab withdrawal, which may cause disease rebound.³

Methods and Results. After the approval of the anti-JCV antibody test to recognize natalizumab-treated patients at risk of PML, we have planned passage to fingolimod of 3 JCV-positive patients (JCV antibody determination performed at least after 20 infusions in the 3 cases) treated with natalizumab for at least 24 months and willing to minimize the risk of PML (patient 1, female, age 25 years, disease duration 4 years, number of relapses the year before natalizumab: 1, treatment before natalizumab: subcutaneous interferon- β 1a, Expanded Disability Status Scale (EDSS): 2.0, natalizumab infusions: 24; patient 2, female, age 32 years, disease duration 6 years, number of relapses the year before natalizumab: 2, treatment before natalizumab: subcutaneous interferon- β 1a, EDSS: 1.5, natalizumab infusions: 26; patient 3, female, age 25 years, disease duration 13 years, number of relapses the year before natalizumab: 2, treatment

before natalizumab: IM interferon- β 1a, EDSS: 2.0, natalizumab infusions: 32). They had no relapses under natalizumab and no new lesions at the brain MRI performed every 6 months.

Fingolimod was initiated 3 (patient 1 and patient 2) to 4 (patient 3) months after natalizumab suspension to facilitate immune surveillance reconstitution,⁴ and to minimize the risk of postnatalizumab MS reactivation or rebound occurring 3–6 months after the last infusion.^{3,5}

Patients experienced, however, severe MS reactivation 16 days (patient 1), 19 days (patient 2), and 6 days (patient 3) after fingolimod initiation. Blood cell counts 1–2 weeks after fingolimod initiation displayed the expected lymphopenia (patient 1: 480 lymphocytes/mL; patient 2: 520 lymphocytes/mL; patient 3: 550 lymphocytes/mL). Patient 1 experienced nystagmus, gait ataxia, and right limb sensory disturbances. Patients 2 and 3 presented severe hemiparesis, associated in patient 3 with hemi-hypesthesia and dysarthria. EDSS increased in 1 week from 2.0 to 4.0 in patient 1, from 1.5 to 5.5 in patient 2, and from 2.0 to 5.0 in patient 3. Brain MRI scans, performed 2–7 days after clinical relapse onset, showed 28 new T2 lesions and 8 Gd+ T1 lesions in patient 1, 11 new T2 lesions and at least 6 Gd+ T1 lesions in patient 2 (figure), and reactivation and dimensional increase of a lesion in the internal capsule in patient 3.

They were treated with 1 g IV methylprednisolone for 5 consecutive days. During this treatment, patients 1 and 3 had a clinical worsening and were hospitalized to receive further 5 and 3 days of

Editorial, page 1942

See pages 2000, 2002, and 2006