

Rebound of Disease Activity After Withdrawal of Fingolimod (FTY720) Treatment

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Background: The oral sphingosine-1-phosphate receptor modulator fingolimod (FTY720) was recently approved for the treatment of relapsing-remitting multiple sclerosis. To date, data about a possible recurrence of disease activity after discontinuation of fingolimod treatment are scarce.

Objective: To describe a patient who discontinued fingolimod treatment after a local malignant melanoma was diagnosed. Three months after cessation, he had a striking rebound of multiple sclerosis activity.

Design: Case report and review of literature.

Setting: Institute of Clinical Neuroimmunology, Ludwig-Maximilians-University, Munich, Germany.

Patient: A 45-year-old man diagnosed as having relapsing-remitting multiple sclerosis.

Main Outcome Measures: Multiple sclerosis disease activity including annual relapse rate, Expanded Disability Status Scale score, and number of gadolinium-enhancing lesions on magnetic resonance imaging before, during, and after treatment with fingolimod.

Results: Three months after discontinuation of treatment with fingolimod, the patient experienced a severe relapse, with Expanded Disability Status Scale score progression from 2.5 to 4.5. On brain and spinal magnetic resonance imaging, he showed a rebound of disease activity, with a drastic increase of gadolinium-enhancing lesions (>20).

Conclusions: Two aspects relevant to any newly approved multiple sclerosis treatment with immunomodulatory properties are highlighted with this case: first, possible rebound of disease activity after discontinuation; second, the occurrence of a tumor as a possible treatment-related complication.

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APPROVAL STUDIES HAVE demonstrated the considerable efficacy of the sphingosine-1-phosphate receptor modulator fingolimod (FTY720), a new oral immunomodulatory agent that causes selective retention of certain immune cells in lymph nodes in relapsing-remitting multiple sclerosis (RRMS). Data about a possible recurrence of disease activity after discontinuation are scarce. We describe a patient with severe recurrence of disease activity shortly after discontinuation of fingolimod treatment, indicating a rebound of disease activity in this patient.

REPORT OF A CASE

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A 45-year-old man was diagnosed as having RRMS in August 2004. Therapy with interferon-beta 1a, 44 µg between Octo-

ber 2004 and October 2005 was terminated owing to severe local adverse effects. In October 2006, he entered the FREEDOMS (Efficacy and Safety of Fingolimod in Patients With Relapsing-Remitting Multiple Sclerosis) study, a phase 3 trial comparing the efficacy and safety of oral fingolimod with placebo. At entry, his Expanded Disability Status Scale (EDSS) score was 2.0, and brain magnetic resonance imaging (MRI) showed 2 gadolinium-enhancing lesions. The annual relapse rate before study entry was 2.0. He was treated with fingolimod, 0.5 mg, during the first 2 years of the core study and for 2 years during the extension period. Altogether, he had 3 mainly mild sensory relapses during the 4 years of fingolimod treatment, amounting to an annual relapse rate of 0.75. Relapses were treated with high-dose intravenous methylprednisolone pulse therapy, 1 to 2 g for 3 to 5 days, and were followed by nearly

complete clinical remission. Repeated brain and spinal MRI scans between 2007 and 2010 never showed any evidence for subclinical disease activity (no gadolinium-enhancing lesions), and the EDSS score remained stable during the study (1.5-2.5). As expected, blood lymphocyte counts decreased by 50% to 60% during fingolimod treatment. In October 2010, the study medication had to be discontinued (EDSS score, 2.5) when a superficially spreading malignant melanoma was detected in the right knee area (Clark level I, pT1a). After excision, there was no evidence of local spreading beyond the excision border or distant metastases. As part of the study protocol, fingolimod therapy had to be stopped. Two weeks later, the patient reported hypesthesias in both legs. Symptoms improved after treatment with intravenous methylprednisolone, 1 g for 3 days. At this point, peripheral lymphocyte counts returned to normal and were comparable to pretreatment levels. In January 2011, 3 months after study discontinuation, he experienced another striking relapse with severe exacerbation of neuropathic pain, worsening of hypesthesia, and new paresis of the left leg. His EDSS score increased significantly to 4.5. Brain MRI and subsequent spinal MRI showed multiple (>20) new gadolinium-enhancing lesions (**Figure**). Treatment with intravenous methylprednisolone, 1 g for 3 days, was initiated, leading to partial remission of symptoms. Cerebrospinal fluid analysis showed mild lymphocytic pleocytosis (6 μ l; to convert to $\times 10^9$ multiply by 0.001), no malignant cells, positive oligoclonal bands, and a normal CD4/CD8 ratio (2.3).

Because of the marked disease activity with an unusually high number of gadolinium-enhancing lesions on brain and spinal MRI as well as EDSS score deterioration (EDSS score after intravenous methylprednisolone therapy, 3.5), resumption of immunomodulatory treatment was indicated. At this point, fingolimod was not yet approved in Europe for the treatment of RRMS; therefore, escalation therapy with natalizumab was started after written informed consent had been given.

COMMENT

This case highlights 2 aspects that are potentially relevant to any newly approved MS treatment with immunomodulatory properties: (1) a possible rebound of disease activity after discontinuation, and (2) the occurrence of a tumor as a possible treatment-related complication.

Our patient presented with severe recurrence of disease activity shortly after discontinuation of treatment with fingolimod, a new oral MS drug that causes selective retention of certain immune cells in lymph nodes.^{1,2} Disease activity recurred with a clinical relapse 2 weeks after fingolimod treatment was stopped. At this point, peripheral lymphocyte counts had increased again and were comparable to pretreatment levels. Three months later, there was a drastic increase in gadolinium-enhancing lesions and another severe clinical relapse with significant EDSS score progression to 4.5. Blood lymphocyte counts and CD4/CD8 ratio in the cerebrospinal fluid were normal, pointing to immunological recovery. This is in line with pharmacodynamic data showing rapid recov-

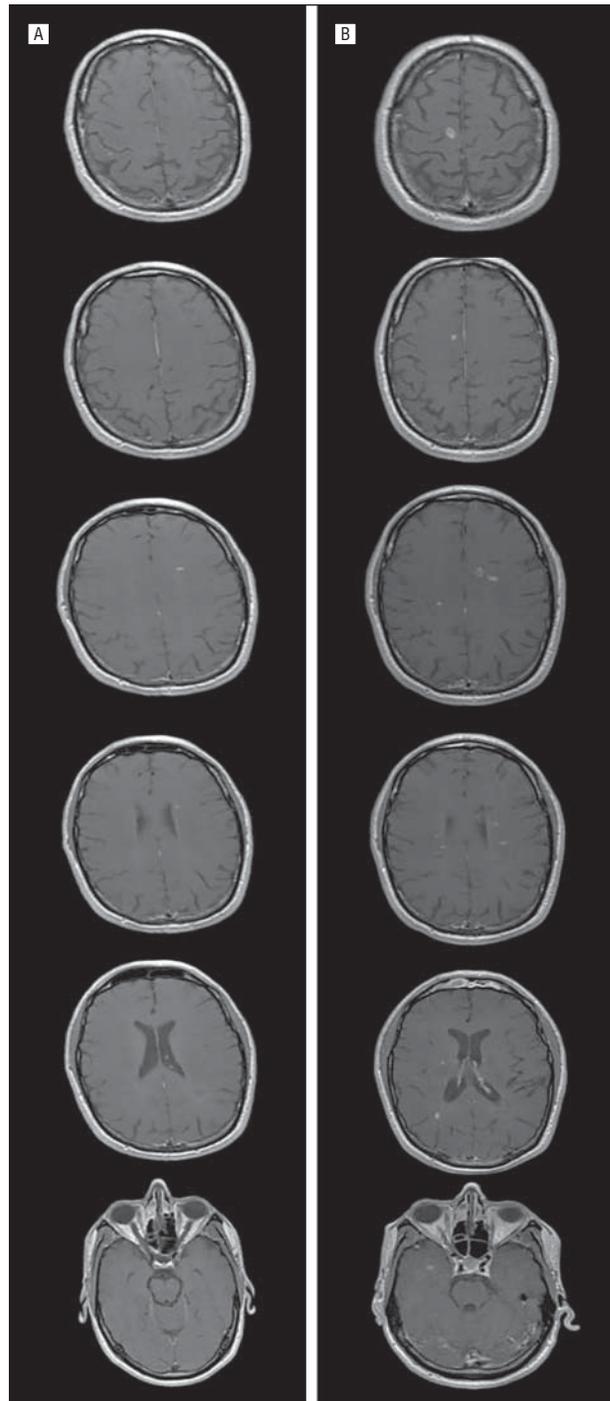


Figure. Gadolinium-enhancing lesions on T1-weighted magnetic resonance images before and after fingolimod treatment. A, Baseline T1-weighted magnetic resonance image taken in August 2006, with 2 gadolinium-enhancing lesions. B, Follow-up T1-weighted magnetic resonance image 3 months after withdrawal of fingolimod treatment in January 2011, with more than 20 gadolinium-enhancing lesions. Magnetic resonance images during fingolimod treatment never showed gadolinium-enhancing lesions (data not shown).

ery of lymphocyte counts starting several days after treatment cessation.^{3,4} Reappearance of disease activity has been previously described after natalizumab treatment interruption.⁵⁻⁷ As in our patient, disease activity usually recurred 3 to 7 months after cessation of natalizumab treatment. An analysis of more than 1800 patients who stopped

therapy with natalizumab showed that return of disease activity was particularly evident in patients who had highly active disease prior to natalizumab therapy.⁷ Our patient had an annual relapse rate of 2.0 and 2 gadolinium-enhancing lesions on MRI, indicating highly active disease before the start of treatment with fingolimod. However, after fingolimod discontinuation, he showed a much higher number of gadolinium-enhancing lesions on MRI compared with before fingolimod therapy. This is reminiscent of recent reports of patients who had an immune reconstitution inflammatory syndrome-like rebound with unusually severe relapses and high inflammatory disease activity on MRI after cessation of natalizumab therapy.⁶ It was assumed that such patients might have a rapid influx of immune cells into the cerebrospinal fluid and brain during reconstitution of the immune system. Further data are needed to identify reliable predictors of an elevated risk of recurrence or rebound of disease activity after discontinuation of treatment with natalizumab or fingolimod.

Our patient had to discontinue study medication following the diagnosis of malignant melanoma (Clark level I, pT1a). He had been treated with fingolimod, 0.5 mg once daily, for 4 years in the FREEDOMS studies (FTY720 2301 and 2301E1). In the FREEDOMS trial, 1 patient in the high-dose group (1.25 mg) and 1 patient in the placebo group presented with malignant melanoma (0.2%, each group).⁸ In the TRANSFORMS (Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis) trial, 3 cases (0.7%) of malignant melanoma occurred in the low-dose fingolimod group (0.5 mg once daily) vs none in the interferon group.⁹ Regular dermatological assessment was required as part of the study protocols. However, dermatological monitoring is not recommended in either the US Food and Drug Administration or the European Medicines Agency approval process because there is currently no evidence that fingolimod therapy increases the risk of melanoma. Obviously, with any new medication, single observations of potential adverse events such as this and others^{10,11} cannot be judged as treatment related before extensive data on large numbers of treated patients become available.

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