A 35-YEAR-OLD WOMAN WITH PROGRESSING MULTIPLE SCLEROSIS DESPITE THERAPY

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BACKGROUND

The patient is a 35-year-old woman who was diagnosed with multiple sclerosis (MS) 4 years ago. Her initial symptom was optic neuritis affecting her left eye. A magnetic resonance image (MRI) revealed 2 periventricular non–contrast-enhancing lesions at that time, in addition to a contrast-enhancing lesion in the left optic nerve. She was given a 3-day course of intravenous (IV) methylprednisolone followed by a 3-week taper of oral prednisone. Her vision improved over the next 6 weeks to normal acuity with some residual decrease in color sensitivity. No other treatment was initiated.

One year later she developed paresthesias in her feet associated with impaired balance on ambulation and urinary urgency. Repeat MRI scans revealed a contrast-enhancing partial segmental lesion in the mid thoracic spinal cord at the level of T7. A brain MRI revealed 4 periventricular lesions, 2 of which were the ones previously seen, and a right parietal juxtacortical lesion. None of the brain lesions enhanced following contrast infusion. Her history was otherwise unremarkable. She worked as a television weather reporter and a part-time model. She began treatment with interferon (IFN) β-1a 30 µg intramuscularly once weekly. After taking the medication, she experienced flu-like symptoms and headaches that were effectively managed with ibuprofen before the injections and fatigue that improved over time but did not completely resolve, recurring with each injection for 24 to 48 hours.

Over the next 18 months she had 2 additional relapses. The first was associated with paresthesias in her right face, which resolved spontaneously over 2 weeks and occurred following an upper respiratory infection. The second presented with paresthesias and clumsiness of her left arm. Imaging revealed a contrast-enhancing spinal cord lesion at the C6 level, and 4 new non-enhancing lesions in the cerebral white matter. Her symptoms improved over several weeks following another course of IV methylprednisolone. On discussion, the patient indicated that she was not taking her IFNβ every week because of the fatigue and its impact on her energy level and professional activities. After discussion regarding the importance of adherence and other treatment options, she chose to begin glatiramer acetate (GA). She had some reservations regarding injection site reactions, but also some anxiety regarding the potential side effects of natalizumab. She took GA for 6 months before experiencing another relapse, which presented with double vision and clumsiness of her left side. Her examination revealed a new left internuclear ophthalmoplegia and left-sided incoordination. Brain MRI revealed 3 new lesions compared to 7 months before, one of which was in the pons and enhanced following contrast infusion. On discussion, she reported missing 2 doses of GA weekly because of concerns over injection site erythema and the demands of her social and professional lifestyle. She was then placed on natalizumab injections administered IV every 4 weeks.

OUTCOME AND FOLLOW-UP

Since the patient began natalizumab treatment approximately 1 year ago, she has had no further relapses. Her balance is slightly impaired on tandem walking, and she occasionally experiences diplopia and paresthesias when she tires but she continues to maintain an active schedule. An MRI of the brain revealed 2 new lesions 1 year after starting natalizumab.

DISCUSSION

Interferon β and GA are effective first-line disease-modifying therapies that significantly reduce MRI evidence of disease burden, the incidence of relapse, and disease progression when used in clinical trials in patients with MS. However, no currently available
medication cures MS and most patients continue to experience at least occasional relapses despite disease-modifying therapy.1 The clinical course of MS is quite variable between individuals, and some patients exhibit a more aggressive course of frequent relapses and earlier progression to severe disability. At present, there are no validated guidelines for the identification of patients who are not responding adequately to treatment, and the optimal management of these patients is not well defined.2 The treatment goals for a patient with worsening MS despite disease-modifying therapy are to determine factors that may impact the response to the medication and to switch to alternative options in a timely manner when it becomes apparent that the current agent does not appear to be effective. An important consideration in this regard is the issue of adherence. This patient’s initial choice was motivated by the lack of visible injection site erythema. However, she did not tolerate the flu-like symptoms that caused her to miss doses of the medication frequently. She then switched to an alternate agent that did not cause the flu-like symptoms, but the disruptive effects of the dosing schedule and concerns regarding visible injection site reactions on her professional activities led to decreased adherence with this agent as well. Her intolerance of the previous agents and the evidence of breakthrough relapses and accumulating lesion burden on MRI led to her beginning treatment with natalizumab. Although she had no further lesions during the subsequent year on this agent, her follow-up MRI did demonstrate new lesions indicating that natalizumab, too, did not completely suppress her disease activity.

Natalizumab is one of 2 agents generally considered as second-line options for treatment of relapsing forms of MS. Natalizumab is a monoclonal antibody against the α/β1 subunit of the α4β1 adhesion molecule very late antigen-4 on lymphocytes. By preventing the binding of α4β1 to its ligand on endothelial cells-vascular cell adhesion molecule, natalizumab prevents the migration of lymphocytes from blood vessels into the central nervous system.3 In the Natalizumab Safety and Efficacy in Relapsing-Remitting MS (RRMS) clinical trial, natalizumab reduced the number of new or enlarging T2 lesions by 83%, and reduced the number of new relapses by 68%.4 The most common adverse events for patients in the natalizumab group included headache, fatigue, and urinary tract infections. Adverse events that were significantly more common with natalizumab than with placebo were fatigue (27% vs 21% of patients in the natalizumab and placebo groups, respectively) and allergic reactions (9% and 4%). In the Safety and Efficacy of Natalizumab in Combination with Avonex trial, natalizumab was investigated in combination with IFNβ-1a or placebo for patients with a breakthrough relapse despite therapy with IFNβ-1a 30 µg once weekly intramuscularly.5 Compared with IFNβ-1a 30 µg once weekly intramuscularly alone, the addition of natalizumab produced a significant 24% reduction in the relative risk of sustained disability (P = .02) and reduced the annualized rate of relapse by 55% over a 2-year period (P < .001). Combination therapy also significantly reduced the number of new T2 lesions compared with IFNβ-1a alone. Adverse events that were more common with combination therapy included anxiety, pharyngitis, sinus congestion, and peripheral edema. Two cases of progressive multifocal leukoencephalopathy (PML), one of which was fatal and the other debilitating, occurred among 589 patients randomized to the natalizumab group, and an additional case was identified in a clinical trial of natalizumab for Crohn’s disease. The 2 patients with MS developed PML after 2 years and approximately 2.5 years of combined use of natalizumab and IFNβ-1a 30 µg weekly intramuscularly. After a temporary suspension of natalizumab marketing, a risk minimization plan—the Tysabri Outreach: Unified Commitment to Health (TOUCH) program—was instituted to monitor for new cases of PML and other rare adverse events. Only physicians who are enrolled in the TOUCH program may prescribe natalizumab, and distribution is restricted to enrolled pharmacies and infusion sites. Natalizumab is approved for the treatment of relapsing forms of MS. However, because there are concerns about the risk of PML, it is generally recommended for patients who have not responded adequately to other therapies.6 To date, approximately 1.5 years after the resumption of monotherapy with natalizumab, no new cases of PML have been reported. Further surveillance is required to see if new cases will emerge with longer and expanded use.

Mitoxantrone is the only agent that is approved for the treatment of patients with non-relapsing secondary progressive MS (SPMS). It is indicated for reducing neurologic disability and/or the number of relapses in patients with SPMS, progressive-relapsing MS (PRMS), or for patients with worsening RRMS who have significant residual symptoms accumulating with
ongoing episodes. It is not approved for the treatment of primary progressive MS. The efficacy and safety of mitoxantrone were evaluated in a phase III clinical trial of 194 patients with SPMS (46% of patients) or worsening RRMS (54% of patients). Compared with placebo, treatment with the US Food and Drug Administration-approved mitoxantrone dose of 12 mg/m² significantly improved the study primary efficacy outcome (a composite end point that included Expanded Disability Status Scale [EDSS] score, ambulation index, the number of relapses treated with steroids, time to first relapse, and an assessment of

### Table. Approved Treatments for MS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Frequency</th>
<th>Common Adverse Effects*</th>
<th>Approved Indications</th>
<th>Recommended Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a</td>
<td>30 µg IM</td>
<td>Weekly</td>
<td>Flu-like and other symptoms occurring within hours to days following injection (eg, myalgia, fever, fatigue, headaches, chills, nausea, and vomiting)</td>
<td>Treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations</td>
<td>Blood cell counts, blood chemistries (including liver function tests), and thyroid function</td>
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<tr>
<td>IFNβ-1a</td>
<td>22 or 44 µg SC</td>
<td>3 times/wk</td>
<td>Injection site disorders, flu-like symptoms, abdominal pain, depression, elevation of liver enzymes, and hematologic abnormalities</td>
<td>Treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability</td>
<td>Blood cell counts, liver function tests, and thyroid function (with history of thyroid dysfunction or as clinically indicated)</td>
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<tr>
<td>IFNβ-1b</td>
<td>250 µg SC</td>
<td>Every other day</td>
<td>Lymphopenia, injection site reaction, asthenia, flu-like symptoms, headache, and pain</td>
<td>Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbation</td>
<td>Blood cell counts, blood chemistries (including liver function tests), and thyroid function</td>
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<tr>
<td>Glatiramer acetate</td>
<td>20 mg SC</td>
<td>Daily</td>
<td>Injection site reactions, vasodilatation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia</td>
<td>For the reduction of the frequency of relapses in patients with relapsing-remitting MS</td>
<td>Routine testing not required</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>300 mg IV infusion</td>
<td>Every 4 wks</td>
<td>Headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash</td>
<td>Treatment of patients with relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations; generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies</td>
<td>Gadolinium-enhanced MRI and cerebrospinal fluid analysis of JC virus DNA recommended before initiating treatment</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/m² IV infusion</td>
<td>Every 3 mos</td>
<td>Nausea, alopecia, urinary tract infection, and menstrual disorders (including amenorrhea)</td>
<td>For reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic progressive, progressive relapsing, or worsening relapsing-remitting MS (ie, patients whose neurologic status is abnormal between relapses)</td>
<td>Complete blood counts (including platelets), liver function tests, and pregnancy test (for women of childbearing potential) before each dose</td>
</tr>
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</table>

*According to the prescribing information provided by the respective manufacturers of each product. Because of the varying conditions under which clinical trials are conducted, the rates of adverse reactions with the different medications cannot be directly compared.

IFN = interferon; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; SC = subcutaneous.

Data from Natalizumab [prescribing information]; Mitoxantrone [prescribing information]; Interferon β-1a [prescribing information]; Interferon β-1b [prescribing information]; Glatiramer acetate injection [prescribing information]; and Interferon β-1a [prescribing information].
neurologic status), and also significantly improved each of the individual components. A lower dose of 5 mg/m² significantly improved only the mean EDSS score. The most common adverse events included nausea, urinary tract infection, menstrual disorders, amenorrhea, and mild alopecia. Persistent amenorrhea for 6 months or longer occurred in 25% of female patients at the 12 mg/m² mitoxantrone dose. Mitoxantrone has also been associated with a risk of cardiotoxicity, and quantitative testing of cardiac function (eg, echocardiography or multiple gated acquisition scan) is recommended before each dose. The drug must be discontinued for signs of emerging loss of cardiac contractility or congestive cardiomyopathy and heart failure may occur. Mitoxantrone has also been implicated as an uncommon cause of leukemia. The Table summarizes the dose, route of administration, indications, and most common adverse events associated with the 6 approved MS therapies.4,5,7-10

REFERENCES