MS disease activity in RESTORE
A randomized 24-week natalizumab treatment interruption study

ABSTRACT

Objective: RESTORE was a randomized, partially placebo-controlled exploratory study evaluating multiple sclerosis (MS) disease activity during a 24-week interruption of natalizumab.

Methods: Eligible patients were relapse-free through the prior year on natalizumab and had no gadolinium-enhancing lesions on screening brain MRI. Patients were randomized 1:1:2 to continue natalizumab, to switch to placebo, or to receive alternative immunomodulatory therapy (other therapies: IM interferon β-1a [IM IFN-β-1a], glatiramer acetate [GA], or methylprednisolone [MP]). During the 24-week randomized treatment period, patients underwent clinical and MRI assessments every 4 weeks.

Results: Patients (n = 175) were randomized to natalizumab (n = 45), placebo (n = 42), or other therapies (n = 88: IM IFN-β-1a, n = 17; GA, n = 17; MP, n = 54). Of 167 patients evaluable for efficacy, 49 (29%) had MRI disease activity recurrence: 0/45 (0%) natalizumab, 19/41 (46%) placebo, 1/14 (7%) IM IFN-β-1a, 8/15 (53%) GA, and 21/52 (40%) MP. Relapse occurred in 4% of natalizumab patients and in 15%–29% of patients in the other treatment arms. MRI disease activity recurred starting at 12 weeks (n = 3 at week 12) while relapses were reported as early as 4–8 weeks (n = 2 in weeks 4–8) after the last natalizumab dose. Overall, 50/167 patients (30%), all in placebo or other-therapies groups, restarted natalizumab early because of disease activity.

Conclusions: MRI and clinical disease activity recurred in some patients during natalizumab interruption, despite use of other therapies.

Classification of evidence: This study provides Class II evidence that for patients with MS taking natalizumab who are relapse-free for 1 year, stopping natalizumab increases the risk of MS relapse or MRI disease activity as compared with continuing natalizumab. Neurology® 2014:82:1-8

GLOSSARY

EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; IFN-β-1a = interferon β-1a; MP = methylprednisolone; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; QoL = quality of life; SDMT = Symbol Digit Modalities Test; VAS = Visual Analogue Scale.

Natalizumab (Tysabri, Biogen Idec Inc., Cambridge, MA) has demonstrated efficacy in the treatment of multiple sclerosis (MS).1,2 In patients who are anti–JC virus antibody–positive, natalizumab treatment duration increases the risk of progressive multifocal leukoencephalopathy (PML).3–5 although PML in patients with MS may have a better prognosis than PML in HIV-infected patients.6

Planned dosage interruption has been proposed, hypothetically, as a way to mitigate PML risk.7–15 To date, there have been no prospective controlled studies of the effects of natalizumab treatment interruption. Some studies suggest that withdrawal of natalizumab treatment for ≥3 months may be associated with return of MS disease activity.7–17 Following natalizumab

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discontinuation, MS disease activity exceeded prenatalizumab disease activity in some studies\textsuperscript{9,15,16,18,19} but not in others.\textsuperscript{13,14,20,21} The timing of the return of disease activity and optimal monitoring and treatment strategies for patients discontinuing natalizumab are not known.

The objectives of RESTORE, a randomized, partially placebo-controlled study, were to explore the course of MS disease activity and the effects on pharmacokinetic, pharmacodynamic, and immune parameters in patients undergoing an interruption of natalizumab therapy for up to 24 weeks as compared with those in patients remaining on natalizumab. It also assessed the effects of alternate therapies during natalizumab interruption. RESTORE was an exploratory study and was neither designed nor powered for any specific endpoint or to detect an effect of natalizumab treatment interruption on PML occurrence.

We present the clinical and MRI outcomes during natalizumab treatment interruption and after restarting natalizumab in RESTORE.

**METHODS**

**Study design.** In this phase 4, randomized, multicenter, partially placebo-controlled, parallel-group exploratory study, patients with MS receiving natalizumab were randomized into 3 treatment arms in a 1:1:2 ratio: natalizumab:placebo:alternate immunomodulatory therapy (other therapies: IM interferon-β-1a [IFN-β-1a] [Avonex, Biogen Idec Inc., Cambridge, MA], glatiramer acetate [GA] [Copaxone, Teva Neuroscience, Kansas City, MO], or methylprednisolone [MP]). In the other-therapies group, patients and their neurologist selected the immunomodulatory therapy on an individual basis; as such, the distribution of patients receiving IM IFN-β-1a, GA, and MP was not randomized, and the groups were unbalanced (figure 1). Planned enrollment was approximately 160 patients randomized 1:1:2 natalizumab:placebo:other therapies. As an exploratory study, the sample and randomization allocation were chosen to evaluate trends in radiologic and clinical disease recurrence in each group. Patients from 31 sites in North America and Europe were randomized using a centralized interactive voice response system at the baseline visit, and randomization was stratified by country and pretreatment disease activity (high vs low). High disease activity was defined as ≥2 relapses within 12 months prior to initiating natalizumab therapy. The study was performed between March 2010 and November 2011.

**Standard protocol approvals, registrations, and patient consents.** Each site’s institutional review board reviewed and approved the study protocol and amendments, and all participants provided written informed consent. The study was...
Primary research question. This analysis of patients with MS who were relapse-free for 1 year on natalizumab therapy was conducted to compare clinical and MRI outcomes during natalizumab treatment interruption with those in patients remaining on natalizumab. While the effects of alternative therapies during natalizumab interruption were also assessed, RESTORE was not designed to compare the efficacy of the different alternative therapies.

Classification of evidence. This study provides Class II evidence that for patients with MS taking natalizumab who are relapse-free for 1 year, stopping natalizumab increases the risk of MS relapse or MRI disease activity as compared with continuing natalizumab. Because of differences in baseline characteristics and the open-label design, the comparisons with the alternative immunotherapies group provide Class IV evidence.

 Patients. RESTORE enrolled patients between 18 and 60 years of age with relapsing forms of MS who had been treated with natalizumab for at least 12 months prior to randomization and who had no relapses during those 12 months.

Exclusion criteria included the presence of gadolinium-enhancing (Gd+) lesions on screening MRI; presence of antinatalizumab antibodies at screening; history of significant infectious illness or significant disease other than MS; and inability to undergo monthly MRI scans for 6 months. Patients were also excluded if they received immunosuppressive treatment within 24 months prior to randomization; treatment with IV immunoglobulin, plasmapheresis, or cytapheresis within 12 months prior to randomization; or treatment with systemic corticosteroids within 3 months prior to randomization.

Interventions. At the baseline visit (day 0), all patients received a standard 300-mg natalizumab infusion. Starting at week 4, patients randomized to natalizumab or placebo received infusions every 4 weeks through week 24 in a double-blind fashion. Patients randomized to other therapies who chose IM IFN-β-1a or GA received their first injections on day 0. Patients randomized to other therapies who chose MP received infusions every 4 weeks starting at week 12. All 3 other therapies were administered open-label. Clinical, MRI, and laboratory evaluations were performed every 4 weeks during the randomized treatment period starting at week 0, at the time of suspected relapse, and at the final visit. EDSS was assessed at day 0, at week 28, at the time of suspected relapse, and at the final visit. EDSS and SDMT evaluations were performed by clinical staff blinded to treatment assignment. The Central MRI Reading Center that performed MRI assessments was blinded to treatment allocation. Investigators assessed patient safety by physical examination (including vital signs), concomitant therapy and procedure recording, laboratory tests, and adverse event and serious adverse event recording.

Statistical analysis. All efficacy analyses were performed on an evaluable population that completed the study through at least week 4 and did not incur any of the following major protocol deviations: testing positive for anti-IFN-β-1a antibodies and choosing IFN-β-1a as an alternative immunomodulatory therapy, not receiving the day 0 (baseline) natalizumab dose, and being previously randomized into the study.

Baseline comparisons were performed using a 1-way analysis of variance for continuous variables and Fisher exact test for proportions. Other proportions are presented with exact binomial confidence intervals and were compared using Fisher exact test. Kaplan-Meier analyses were performed and p values from log-rank tests are provided.

RESULTS Patient demographics and disease characteristics. A total of 175 patients were enrolled. Forty-five patients (26%) were randomized to natalizumab, 42 patients (24%) were randomized to placebo, and 88 patients (50%) were randomized to other therapies. In the other-therapies group, 17 of 88 patients (19%) received IM IFN-β-1a, 17 of 88 patients (19%) received GA, and 54 of 88 patients (61%) received MP. Forty-three of 45 natalizumab patients (96%), 35 of 42 placebo patients (83%), and 73 of 88 other-therapies patients (83%) completed the study. Reasons for withdrawing from the study included withdrawal of consent, refusal to
return for the protocol-defined monthly visits, and inclusion/exclusion criteria violations.

Except for baseline EDSS score, baseline demographics and disease characteristics were similar across the groups (table 1). Seventy-three percent of RESTORE patients had prior IFN-β-1a use, 37% had prior GA use, and 33% had prior IFN-β-1b use.

MRI disease activity. During the randomized treatment period, 49 of 122 patients (40%) randomized to placebo or other therapies had MRI activity meeting disease recurrence criteria, while none of the patients randomized to natalizumab had MRI activity meeting the criteria ($p < 0.001$). Thirty-four percent (23/68) of patients with high disease activity prior to natalizumab treatment had MRI activity meeting criteria during the randomized treatment period; the proportion was 26% (26/99) for those with low disease activity prior to natalizumab treatment ($p = 0.305$; table 2). No MRI activity meeting defined disease recurrence criteria was detected prior to week 12. A total of 49 patients developed MRI findings that met defined criteria for disease recurrence; 3 patients (6%) at week 12, 37 patients (76%) at week 16 or 20, and 9 patients (18%) after week 20 (figure 2A).

Relapse. Twenty-three of 122 patients (19%) off natalizumab and 2 of 45 patients (4%) on natalizumab experienced relapses during the randomized treatment period ($p = 0.026$). Relapses occurred in 21% (14/68) of patients with high disease activity and in 11% (11/99) of patients with low disease activity prior to starting natalizumab ($p = 0.122$; table 2). Of 25 relapses occurring during the randomized treatment period, 2 (8%) occurred between weeks 4 and 8, 9 (44%) occurred between weeks 8 and 16, and 14 (56%) occurred between weeks 16 and 28 (figure 2B). Two patients with high disease activity (in GA and MP groups) experienced a relapse in both the randomized treatment period and in the follow-up period.

Natalizumab restart. During the randomized treatment period, 50 patients restarted open-label natalizumab, including 12 patients who experienced a clinical relapse without MRI activity and 7 patients who had both a clinical relapse and MRI activity. Thirty-one of 40 patients (78%) who met MRI criteria without experiencing a clinical relapse restarted natalizumab; an additional 2 patients were treated with steroids. Time to restarting natalizumab is shown in figure 2C.

QOL, fatigue, and cognition. Measures of QOL, fatigue, and cognition were exploratory measures and analyzed separately for patients who continued on their randomized treatment through week 28 and for those who restarted natalizumab earlier due to disease recurrence. Patients experiencing disease activity showed a mean decrease from baseline in VAS score at the time of relapse (results are provided in table e-1 and figure e-1 on the Neurology® Web site at Neurology.org).

Follow-up. At the week 52 follow-up visit, after 24 weeks of open-label natalizumab, one patient in the placebo group had 1 Gd+ lesion on MRI; no other patients in any group had MRI activity. Five percent of patients (8/155) had relapses during the

### Table 1 Baseline demographics, disease characteristics, and prior therapies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Natalizumab (n = 45)</th>
<th>Placebo (n = 42)</th>
<th>IM IFN-β-1a (n = 17)</th>
<th>GA (n = 17)</th>
<th>MP (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>41.2 ± 9.7</td>
<td>40.0 ± 10.4</td>
<td>45.1 ± 9.9</td>
<td>44.1 ± 7.9</td>
<td>40.1 ± 10.0</td>
</tr>
<tr>
<td>Female patients, %</td>
<td>82</td>
<td>74</td>
<td>82</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td>Race, white, %</td>
<td>82</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>EDSS score at baseline, mean ± SD*</td>
<td>3.0 ± 1.8</td>
<td>3.3 ± 1.8</td>
<td>2.8 ± 1.6</td>
<td>4.5 ± 2.1</td>
<td>3.0 ± 1.4</td>
</tr>
<tr>
<td>High disease activity prior to natalizumab, %b</td>
<td>42</td>
<td>45</td>
<td>24</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>Disease duration, y, mean ± SD</td>
<td>10.1 ± 5.9</td>
<td>10.1 ± 7.2</td>
<td>10.4 ± 4.5</td>
<td>7.8 ± 4.9</td>
<td>8.9 ± 6.7</td>
</tr>
<tr>
<td>No. of prior natalizumab infusions, median (range)</td>
<td>29 (12–49)</td>
<td>31 (13–51)</td>
<td>25 (12–46)</td>
<td>25 (13–45)</td>
<td>28 (13–50)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td>IFN-β-1a</td>
<td>35 (78)</td>
<td>30 (71)</td>
<td>12 (71)</td>
<td>11 (65)</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>18 (40)</td>
<td>18 (43)</td>
<td>6 (35)</td>
<td>8 (47)</td>
</tr>
<tr>
<td></td>
<td>IFN-β-1b</td>
<td>13 (29)</td>
<td>11 (26)</td>
<td>6 (35)</td>
<td>5 (29)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td>6 (13)</td>
<td>7 (17)</td>
<td>2 (12)</td>
<td>2 (12)</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone</td>
<td>6 (13)</td>
<td>4 (10)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>1 (2)</td>
<td>4 (10)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN-β-1a = interferon β-1a; MP = methylprednisolone.

*a* All baseline characteristics were well-balanced among the study groups (nominal $p > 0.05$) with the exception of EDSS score at baseline ($p = 0.016$).

*b* High disease activity was defined as ≥2 relapses occurring within the 12 months prior to initiating natalizumab therapy.
MRI criteria were defined as ≥1 new Gd-enhancing lesions of any size as determined by the central reader. High disease activity was defined as ≥2 relapses occurring within the 12 months prior to initiating natalizumab therapy. Other therapies included upper respiratory tract infection, nasopharyngitis, and influenza-type illness (table e-2). There were no deaths during the study. Four patients withdrew from the study during the randomized treatment period due to severe fatigue (placebo), moderate muscular weakness (placebo), mild hypoesthesia (IM IFN-β-1a), and a serious adverse event of brain abscess (MP). There were no deaths during the study.

**Safety.** During the randomized treatment and follow-up periods, the majority of patients in all groups had at least one adverse event: randomized treatment period: natalizumab, 84% (n = 38); placebo, 83% (n = 35); IM IFN-β-1a, 88% (n = 15); GA, 88% (n = 15); MP, 78% (n = 42); follow-up period: natalizumab, 58% (n = 25); placebo, 51% (n = 19); IM IFN-β-1a, 69% (n = 9); GA, 73% (n = 11); MP, 50% (n = 24). Adverse events were primarily mild or moderate in severity, and the most frequently reported adverse events were generally consistent with MS and disease-modifying therapy product labels, but also included upper respiratory tract infection, nasopharyngitis, and influenza-type illness (table e-2). Four patients withdrew from the study during the randomized treatment period due to severe fatigue (placebo), moderate muscular weakness (placebo), mild hypoesthesia (IM IFN-β-1a), and a serious adverse event of brain abscess (MP). There were no deaths during the study.

**DISCUSSION** Natalizumab is often used to treat patients whose disease has been inadequately controlled with other therapies, and natalizumab-treated patients are at significant risk of disease recurrence following treatment cessation. RESTORE is the largest randomized prospective study to date analyzing MS disease recurrence during natalizumab treatment interruption in a subpopulation of patients who had been stable on natalizumab for over a year with no Gd+ lesions at baseline. Disease recurred in a large proportion of RESTORE patients who discontinued natalizumab treatment, and radiologic disease recurrence was more frequent in patients with high disease activity (based on relapses) prior to natalizumab therapy than in patients with low disease activity prior to starting natalizumab.²² The safety evaluations were generally consistent with the labeled risk profile for each of the respective marketed products, notably for natalizumab.

Similar to smaller observational studies and retrospective analyses,⁸,¹⁰⁻¹²,¹⁵,¹⁸ RESTORE demonstrated that natalizumab treatment interruption resulted in occurrence of MRI disease activity as early as 12 weeks, and of clinical disease activity as early as 4–8 weeks, after the last natalizumab dose. The earlier recurrence of clinical disease vs radiologic disease may also reflect the more subjective nature of clinical relapse reporting, although our study design required objective EDSS changing for defining a clinical

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**Table 2** Patients with disease recurrence during the randomized treatment period

<table>
<thead>
<tr>
<th></th>
<th>All patients, n (%) (95% CI)</th>
<th>High disease activity, n (%) (95% CI)</th>
<th>Low disease activity, n (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with MRI disease recurrence</strong>¹²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49/167 (29) (22.6–36.9)</td>
<td>23/68 (34) (22.8–46.3)</td>
<td>26/99 (26) (17.9–36.1)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>0/45 (0) (0–7.9)</td>
<td>0/19 (0) (0–17.6)</td>
<td>0/26 (0) (0–13.2)</td>
</tr>
<tr>
<td>Placebo</td>
<td>19/41 (48) (30.7–62.8)</td>
<td>11/19 (58) (33.5–79.7)</td>
<td>8/22 (36) (17.2–59.3)</td>
</tr>
<tr>
<td>Other therapies</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IM IFN-β-1a</td>
<td>1/14 (7) (0.2–33.9)</td>
<td>0/4 (0) (0–60.2)</td>
<td>1/10 (10) (0.3–45.5)</td>
</tr>
<tr>
<td>GA</td>
<td>8/15 (53) (26.6–78.7)</td>
<td>5/7 (71) (29.0–96.3)</td>
<td>3/8 (38) (8.5–75.5)</td>
</tr>
<tr>
<td>MP</td>
<td>21/52 (40) (27.0–54.9)</td>
<td>7/19 (37) (16.3–61.6)</td>
<td>14/33 (42) (25.5–60.8)</td>
</tr>
<tr>
<td><strong>Patients with relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25/167 (15) (9.9–21.3)</td>
<td>14/68 (21) (11.7–32.1)</td>
<td>11/99 (11) (5.7–19.0)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>2/45 (4) (0.5–15.1)</td>
<td>2/19 (11) (1.2–33.1)</td>
<td>0/26 (0) (0–13.2)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7/41 (17) (7.2–32.1)</td>
<td>2/19 (11) (1.2–33.1)</td>
<td>5/22 (23) (7.8–45.4)</td>
</tr>
<tr>
<td>Other therapies</td>
<td></td>
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</tr>
<tr>
<td>IM IFN-β-1a</td>
<td>4/14 (29) (8.4–58.1)</td>
<td>2/4 (50) (6.8–93.2)</td>
<td>2/10 (20) (2.5–55.6)</td>
</tr>
<tr>
<td>GA</td>
<td>4/15 (27) (7.8–55.1)</td>
<td>3/7 (43) (9.9–81.6)</td>
<td>1/8 (13) (0.3–52.7)</td>
</tr>
<tr>
<td>MP</td>
<td>8/52 (15) (6.9–28.1)</td>
<td>5/19 (26) (9.1–51.2)</td>
<td>3/33 (9) (1.9–24.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; GA = glatiramer acetate; Gd = gadolinium-enhancing; IFN-β-1a = interferon-β-1a; MP = methylprednisolone.

¹²High disease activity was defined as ≥2 relapses occurring within the 12 months prior to initiating natalizumab therapy.

¹¹MRI criteria were defined as ≥1 new Gd-enhancing lesion of >0.8 cm³ or ≥2 or more Gd-enhancing lesions of any size as determined by the central reader.
relapse. While most studies report that disease recurs an average of ≥3 months after the last natalizumab dose, relapses occurring during the first 1–3 months have also been observed. The emergence of MRI disease activity is consistent with RESTORE pharmacodynamic data, which showed that pharmacodynamic markers were consistent with levels in non–natalizumab-treated patients at 16 weeks after the last dose.

In RESTORE, GA starting after the last dose of natalizumab and monthly MP starting 12 weeks after the last natalizumab dose did not appear to be effective in disease suppression, as compared with continued natalizumab treatment. Starting MP at 12 weeks may have been too late to prevent disease activity, although most patients randomized to MP did not have disease recurrence until after 12 weeks. There appeared to be less recurrence of MRI disease activity with IM IFN-β-1a than with other open-label treatments, although the IM IFN-β-1a group had a lower proportion of patients with high disease activity prenatalizumab than the other groups. However, patients were not randomly assigned to specific treatments within the other-therapy group, and RESTORE was neither designed nor adequately powered to compare the efficacy of the different alternative immunomodulatory therapies. Therefore, larger controlled trials would be needed to confirm this observation.

Findings on alternative immunomodulatory drug use during natalizumab treatment interruption have been mixed. A large retrospective study of more than 1,800 patients showed that during natalizumab treatment interruption, MS disease activity returned to baseline levels within 4–7 months, regardless of whether patients received immunomodulatory therapies. Data from 2 small studies suggested that immunomodulating therapies (IM IFN-β-1a or GA) reduced MS disease activity recurrence during natalizumab treatment interruption. In other studies, use of GA or MP, or fingolimod during natalizumab treatment interruption was associated with recurrence of disease activity to higher levels than that seen during natalizumab use. It is unknown whether other disease-modifying therapies might maintain the low rate of clinical and radiologic disease activity in natalizumab-treated patients who discontinue natalizumab.

Some studies have suggested that MS disease activity returns to a higher than baseline level during natalizumab treatment interruption, although larger studies have not shown evidence of overshoot. The nature of MRI disease recurrence in RESTORE will be characterized in more detail in a separate report.

This study used serial monthly MRI scans following natalizumab discontinuation and specific disease activity criteria for resuming natalizumab treatment. The majority of patients who experienced defined MRI disease activity restarted natalizumab during...
the randomized treatment period despite the absence of clinical symptoms, suggesting that physicians made clinical decisions based on MRI findings. It is plausible that use of MRI criteria for restarting natalizumab treatment following discontinuation reduced the occurrence of severe clinical relapses that have been reported in other studies. Results from RESTORE and other studies suggest that, in patients who discontinue natalizumab, brain MRI surveillance beginning 12–16 weeks after the last natalizumab infusion may be useful for identifying patients with a return of disease activity.24

The results suggest planned dosage interruption is likely not useful for the management of most patients switching to no treatment or to the disease-modifying therapies employed in this study. The extent and time course of disease recurrence described in this randomized prospective study are highly relevant for all patients discontinuing natalizumab treatment for any reason and—together with the recognition of risk factors for PML3—may also inform decisions about the timing and choice of alternative therapies.

AUTHOR CONTRIBUTIONS

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Biogen Idec provided funding for editorial support in the development of this article; Britt Anderson, PhD, from Infusion Communications, wrote the first draft of the manuscript based on input from authors, and Jackie Cannon from Infusion Communications copied edited and styled the manuscript per journal requirements. Biogen Idec reviewed and provided feedback on the paper to the authors. The authors had full editorial control and provided their final approval of all content.

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DISCLOSURE
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REFERENCES


