Natalizumab reduces relapse clinical severity and improves relapse recovery in MS

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Abstract

Objectives: Compare relapse clinical severity, post-relapse residual disability, and the probability of confirmed complete recovery from relapse between patients who relapsed during natalizumab (n=183/627 [29%]) and placebo (n=176/315 [56%]) treatments in the AFFIRM trial.

Methods: In this post-hoc analysis, relapse clinical severity and residual disability were defined by change in Expanded Disability Status Scale (EDSS) score occurring between pre-relapse and at-relapse assessment and between pre-relapse and post-relapse assessment, respectively. Patients were considered completely recovered from relapse when their post-relapse EDSS score was less than or equal to their pre-relapse EDSS score, and this was maintained for 12 or 24 weeks.

Results: At relapse, an increase in EDSS score of ≥0.5 points occurred in 71% of natalizumab and 84% of placebo patients (P=0.0088); an increase of ≥1.0 point occurred in 49% of natalizumab and 61% of placebo patients (P=0.0349) (mean increase in EDSS at relapse: natalizumab=0.77; placebo=1.09; P=0.0044). After relapse, residual disability of ≥0.5 EDSS points remained in 31% of natalizumab and 45% of placebo patients (P=0.0136) (mean post-relapse residual EDSS increase: natalizumab=0.06; placebo=0.28; P=0.0170). In patients with an increase in EDSS of ≥0.5 or ≥1.0 during relapse, natalizumab increased the probability of 12-week confirmed complete recovery from relapse by 55% (hazard ratio [HR]=1.554; P=0.0161) and 67% (HR=1.673; P=0.0319) compared to placebo, respectively.

KEYWORDS
Natalizumab; Relapse; Severity; Recovery; Placebo; Disability

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1. Introduction

In relapsing-remitting multiple sclerosis (RRMS), patients experience recurrent acute episodes of neurological deficits (relapses) followed by full, partial or no recovery. Importantly, the residual deficit after a relapse may persist (Leone et al., 2008; Lublin et al., 2003; Nickerson and Marrie, 2013; Vercellino et al., 2009), leading to increased disability over time (Sospedra and Martin, 2005; Weinschenker et al., 1989). An analysis of placebo arms from several clinical studies showed that relapses produce sustained residual deficits following the relapse as measured by the Expanded Disability Status Scale (EDSS) (Lublin et al., 2003); 42% of patients had a residual deficit of ≥ 0.5 points on EDSS, and 28% had a residual deficit of ≥ 1.0 point, at an average of 64 days post-relapse. A meta-analysis demonstrated that disease-modifying treatment effects on relapse rate significantly correlate with treatment effects on EDSS progression (Sormani et al., 2010). A reduction in relapse severity and/or improvement in recovery from relapses should, therefore, improve long-term disability prognosis in MS.

The Natalizumab (TYSABRI®, Cambridge, MA) Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis study (AFFIRM) showed that natalizumab reduced the annualized relapse rate by 68% relative to placebo (Polman et al., 2006). Beneficial effects of natalizumab on relapse rate have subsequently been confirmed in other studies (Fernandez et al., 2011; Lanzillo et al., 2012; Pucci et al., 2011; Putzki et al., 2010). However, it has not been shown whether natalizumab also affects relapse clinical severity, and recovery from relapse.

The aim of the present analysis was to compare the effects of natalizumab and placebo on relapse clinical severity, post-relapse residual disability, and the probability of complete recovery from relapse, for the first relapse experienced by patients in AFFIRM.

2. Methods

2.1. Participants

A detailed description of the methods and results of the AFFIRM study (Clinical trials.gov number NCT00027300) has been published previously (Polman et al., 2006). AFFIRM included adult patients (18-50 years) with a diagnosis of RRMS who had a score of 0.0 to 5.0 on the EDSS (Kurtzke, 1983), cranial magnetic resonance imaging (MRI) showing lesions consistent with MS, and at least one medically documented relapse within the 12 months before the baseline visit.

The current analysis included patients who experienced a relapse during the AFFIRM clinical trial and had on-study EDSS assessments before the relapse, at relapse (≤ 15 days following relapse), and after relapse (≥ 30 days after the relapse). To maintain the independence of the observations in the analysis, only the first relapse per patient fulfilling these criteria was considered. Patients were excluded if the post-relapse assessment was made during or after the occurrence of a subsequent relapse.

All patients provided written consent to participate in AFFIRM. The study protocol was approved by central and local ethics committees and was overseen by an independent safety-monitoring committee.

2.2. Design and assessments

AFFIRM was a randomized, double-blind, placebo-controlled, phase 3 study to examine the efficacy of 300 mg natalizumab monotherapy (n=627) versus placebo (n=315) in RRMS. Patients were treated by intravenous infusion with natalizumab or matching placebo every 4 weeks for up to 120 weeks. In the current analysis, we assessed the effect of natalizumab on the following parameters: 1) Relapse clinical severity, defined as the change in EDSS score between pre-relapse and at-relapse assessments; 2) Relapse-induced residual disability, defined as the change in EDSS score between pre-relapse and post-relapse assessments; 3) Probability of 12-week and 24-week confirmed complete EDSS recovery from disabling relapses. Patients were considered to have completely recovered from the relapse when their EDSS score was equal to or lower than their pre-relapse EDSS score, and this was maintained for at least 12 weeks or 24 weeks.

In AFFIRM, a relapse was defined in the study protocol as the appearance of new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 h, and accompanied by new objective neurological findings confirmed by an examining neurologist. As some definitions of relapse require an increase in the EDSS, for comparison in a sensitivity analysis we used an alternative definition of relapse, in which a relapse had to be accompanied (at time of relapse assessment) by an increase of ≥ 0.5 points on the EDSS, ≥ 1 point on two different Kurtzke functional system scores (KFSS) of the EDSS, or ≥ 2 points on one KFSS (Kappos et al., 2010).

2.3. Statistical analysis

Changes in EDSS scores were compared between treatment groups in the post-hoc analysis population. For relapse clinical severity and relapse-induced residual disability, a chi-square test was used to compare the proportions of patients with ≥ 0.5 and ≥ 1.0-point increases in EDSS score, and a t-test was used to compare the mean EDSS score changes between the treatment groups. The cumulative probability of complete recovery from relapse was estimated using a Kaplan-Meier

Conclusions: In AFFIRM, natalizumab treatment decreased the clinical severity of relapses and improved recovery from disability induced by relapses. These beneficial effects would limit the step-wise accumulation of disability.

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In 120 weeks of AFFIRM, 359 patients (natalizumab, 3.1. Study population

3. Results

3.1. Study population

In 120 weeks of AFFIRM, 359 patients (natalizumab, n=183 [29%]; placebo, n=176 [56%]) had protocol confirmed relapses. Out of those patients, 53 (29 [16%] natalizumab, 24 [14%] placebo) had no EDSS assessment at relapse, 5 (3 [2%] natalizumab, 2 [1%] placebo) had no post-relapse EDSS assessment, and 18 (8 [4%] natalizumab, 10 [6%] placebo) had a second relapse concurrent with or before post-relapse EDSS assessment. Thus, 283 [79%] patients (natalizumab, n=143 [78%]; placebo, n=140 [80%]) met the criteria for these analyses and were assessed for first relapse clinical severity and recovery.

There were no differences in baseline demographics (age, sex, disease duration) between the natalizumab and placebo groups (Table 1). Both groups experienced a mean of 1.6 relapses in the year prior to study entry (P=0.6713), and there were no significant differences between the two groups on baseline MRI measures (T1 Gd-enhancing lesions and T2 lesion volume). Mean EDSS score at baseline appeared slightly higher in the natalizumab-treated patients than in placebo-treated patients (natalizumab, 2.6; placebo, 2.3; P=0.0596). The mean time between pre-relapse and post-relapse EDSS assessments was similar for the two groups (16.1 weeks [standard deviation [SD]=6.9] for natalizumab and 16.9 weeks for placebo [SD=6.0]; P=0.2984). There was also no significant difference in the mean length of time separating EDSS assessments at relapse and post-relapse, which was 10.0 weeks (SD=4.0) for natalizumab and 9.6 weeks (SD=3.7) for placebo (P=0.3618). Fewer natalizumab patients (83%) than placebo patients (96%) experienced a first relapse that met the alternative definition of relapse used in the sensitivity analyses (P=0.0004). There was no significant difference between the groups in the proportion of patients administered steroids for relapse management (natalizumab, 66%; placebo, 71%; P=0.3023).

Table 1  Baseline demographics and disease characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=140)</th>
<th>Natalizumab (n=143)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, Mean (SD)</td>
<td>35.6 (7.9)</td>
<td>35.5 (8.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>68</td>
<td>69</td>
<td>0.80</td>
</tr>
<tr>
<td>Disease duration, years, median (range)</td>
<td>6 (0-31)</td>
<td>6 (0-27)</td>
<td>0.73</td>
</tr>
<tr>
<td>No. of relapses in prior year,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.6 (0.8)</td>
<td>1.6 (1.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1 (0-5)</td>
<td>1 (0-8)</td>
<td>0.85</td>
</tr>
<tr>
<td>EDSS score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>93 (66)</td>
<td>80 (56)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥3.0</td>
<td>47 (34)</td>
<td>63 (44)</td>
<td></td>
</tr>
<tr>
<td>EDSS score,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.3 (1.2)</td>
<td>2.6 (1.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.0 (0-5.0)</td>
<td>2.5 (0-5.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>T1 Gd-enhancing lesions, mean (SD)</td>
<td>2.6 (5.5)</td>
<td>2.9 (5.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>T2 Lesion volume, cm³,median (range)</td>
<td>9.9 (0.3-83.3)</td>
<td>9.7 (0.140.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Time between pre-relapse and post-relapse assessment, weeks, mean (SD)</td>
<td>16.9 (6.0)</td>
<td>16.1 (6.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Time between relapse and post-relapse assessment, weeks, mean (SD)</td>
<td>9.6 (3.7)</td>
<td>10.0 (4.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>Time of relapse,weeks, mean (SD)</td>
<td>39.7 (30.1)</td>
<td>38.6 (31.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>No. meeting alternative definition of relapse, n (%)</td>
<td>134 (96)</td>
<td>118 (83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. receiving steroids, n (%)</td>
<td>100 (71)</td>
<td>94 (66)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS=Expanded Disability Status Scale; Gd=gadolinium enhancing; SD=standard deviation
effects on the clinical severity of relapses were most apparent in patients with baseline EDSS score < 3.0. In this subgroup, 74% of natalizumab versus 51% of placebo patients experienced an increase in EDSS score of ≥ 0.5 points at first relapse assessment (P = 0.0019), while 50% of natalizumab versus 71% of placebo patients showed an increase of ≥ 1.0 point (P = 0.0048). Among those with baseline EDSS score ≥ 3.0, there was no significant difference between the percentage of natalizumab and placebo patients who experienced an increase in EDSS of either 0.5 (natalizumab, 68%; placebo, 70%; P = 0.8259) or 1.0 point (natalizumab, 48%; placebo, 43%; P = 0.5976) at relapse.

Fig. 2 shows the change in mean EDSS score from pre-relapse to relapse. Overall, natalizumab-treated patients had a smaller increase in EDSS compared with the placebo group (natalizumab, 0.77; placebo, 1.09; P = 0.0044). A significant difference between groups was observed in patients with a baseline EDSS score < 3.0 (natalizumab, 0.82; placebo, 1.24; P = 0.0043), but not in those with a baseline EDSS score ≥ 3.0 (natalizumab, 0.71; placebo, 0.81; P = 0.5554).

Multivariable analysis identified treatment group, steroid use, and baseline EDSS score as important covariates associated with EDSS increase during relapse. At relapse, EDSS increase of ≥ 0.5 points was independently associated with steroid treatment (P = 0.0001), baseline EDSS < 3.0 (P = 0.0007), and assignment to the placebo treatment group (P = 0.0326). EDSS increase of ≥ 1.0 point was independently associated with steroid treatment (P = 0.0004), and a treatment group interaction with baseline EDSS was observed; placebo patients with baseline EDSS < 3 were more likely to have a relapse with an increase in EDSS of ≥ 1.0 point (P = 0.0486).

3.3. Relapse-induced residual disability measured by EDSS

Residual disability (≥ 0.5-point increase in EDSS from pre- to post-relapse) remained in 31% and 45% of patients in the natalizumab and placebo groups, respectively (P = 0.0135) (Figure e-1). A similar trend was observed in the sensitivity analysis using the alternative relapse definition (natalizumab, 35%; placebo, 46%; P = 0.0634). A significant difference was observed among those with a baseline EDSS score < 3.0; 33% of those who received natalizumab showed a pre- to post-relapse residual EDSS increase of ≥ 0.5 points versus 47% of those given placebo (P = 0.0478). The difference was not significant in

Fig. 1 Proportion of patients an increase in EDSS score from pre-relapse to relapse (relapse severity). Legend: Proportion of patients with ≥ 0.5-point (A) and ≥ 1.0-point (B) increase in EDSS score from pre-relapse to relapse (relapse severity).

Fig. 2 Mean EDSS score change from pre-relapse to relapse (relapse severity).

relapse-induced residual EDSS impairment between natalizumab and placebo patients with a baseline EDSS score ≥ 3.0 (natalizumab, 29%; placebo, 40%; P = 0.1930).

The natalizumab group showed a smaller mean residual increase in EDSS after relapse relative to the placebo group (from pre- to post-relapse) (natalizumab, 0.06; placebo, 0.28; P = 0.0170) (Fig. 3). A similar trend was observed in the sensitivity analysis using the alternative relapse definition (natalizumab, 0.14; placebo, 0.28 P = 0.0953). In the subgroup with baseline EDSS score < 3.0, natalizumab-treated patients showed a trend toward smaller mean residual increase in EDSS per relapse relative to the placebo group (natalizumab, 0.13; placebo, 0.34; P = 0.0615). For patients with baseline EDSS score ≥ 3.0, no significant differences were observed between natalizumab and placebo (natalizumab, −0.02; placebo, 0.15; P = 0.2652).

In some cases, the post-relapse EDSS score was lower than the pre-relapse score, indicating a reduction (improvement) in disability. This was more frequent with natalizumab than placebo: a reduction in EDSS score of ≥ 0.5 points was seen in 24% of natalizumab and 11% of placebo patients (P = 0.0078) (Figure e-2).

3.4. Probability of confirmed complete EDSS recovery from relapse

In order to measure meaningful recovery, analyses for EDSS recovery from relapse only included patients with EDSS increases of ≥ 0.5 points (natalizumab, n = 102; placebo
n=118) or ≥1.0 point (natalizumab, n=70; placebo n=86) during relapse.

In patients with an increase in EDSS of ≥0.5 points during relapse, natalizumab increased the cumulative probability of 12-week and 24-week confirmed complete recovery from relapse by 55% (hazard ratio [HR], 1.55; 95% confidence interval [CI], 1.08-2.26; P=0.0161) (Fig. 4A) and 61% (HR, 1.60; 95% CI, 1.06-2.43; P=0.0236) relative to placebo, respectively.

In patients with an increase in EDSS of ≥1.0 point during relapse, natalizumab increased the cumulative probability of 12-week and 24-week confirmed complete recovery from relapse by 55% (HR, 1.55; 95% CI, 1.08-2.26; P=0.0161) (Fig. 4A) and 61% (HR, 1.60; 95% CI, 1.06-2.43; P=0.0236) relative to placebo, respectively.

Multivariable analysis identified natalizumab treatment group (P=0.0230) and lower change in EDSS during relapse (P=0.0024) as independent predictors of complete recovery from relapses with EDSS increase of ≥0.5 points. Natalizumab treatment was the only significant predictor of complete recovery from relapses with EDSS increase of ≥1.0 point (P=0.0379).

The primary analyses assessed the probability of complete EDSS recovery from relapse irrespective of ongoing disease activity. To exclude the possibility that the results were influenced by the known effects of natalizumab on reducing relapse frequency, additional analyses were performed with data censored at the next relapse. Results from these analyses were consistent with the primary findings. In patients with an increase in EDSS of ≥0.5 points during relapse, natalizumab increased the probability of 12-week and 24-week confirmed complete recovery by 54% (HR, 1.53; 95% CI, 1.04-2.25; P=0.0279) (Figure e-3A) and 72% (HR, 1.71; 95% CI, 1.09-2.69; P=0.0180) relative to placebo, respectively. In patients with an increase in EDSS of ≥1.0 point during relapse, there were trends toward natalizumab increasing the probability of 12-week and 24-week confirmed complete recovery by 51% (HR, 1.51; 95% CI, 0.92-2.4; P=0.0976) (Figure e-3B) and 67% (HR, 1.66; 95% CI, 0.93-2.97; P=0.0849) relative to placebo, respectively.

4. Discussion

In AFFIRM, natalizumab significantly reduced annualized relapse rate, sustained disability progression, and MRI measures of disease activity, compared with placebo in patients with RRMS (Polman et al., 2006). This analysis of data from AFFIRM extends the previous observations and demonstrates that natalizumab both reduced the clinical severity of relapses and improved recovery from relapse-induced disability compared with placebo. Natalizumab led to a significantly smaller mean EDSS increase during relapse and reduced residual EDSS post-relapse. Natalizumab also improved the overall rate of confirmed complete relapse recovery (assessed by the cumulative probability of 12-week and 24-week confirmed complete EDSS recovery from relapse).

The sudden onset or worsening of MS symptoms that occurs during a relapse is thought to be the clinical manifestation of acute inflammatory demyelinating events in the CNS (Frohman et al., 2008; Stadelmann et al., 2011); residual disability may result from incomplete remyelination, reduced CNS plasticity, axonal damage, or neuronal loss that follows (Fisniku et al., 2008; Giorgio et al., 2010; Horakova et al., 2012; Tallantyre et al., 2010). Natalizumab is known to attenuate the infiltration of effector immune cells into the CNS during inflammatory events that compromise the blood brain barrier. Thus, it can be seen as consistent with its well-
established mechanism of action that natalizumab reduced the clinical severity of relapse and decreased residual disability after a relapse. These findings may represent the clinical correlate of the effect of natalizumab on the reduced rate of conversion of Gd-enhancing lesions to chronic T1 hypointense lesions (black holes) (Dalton et al., 2004), which indicated that natalizumab might protect against permanent CNS damage when the blood brain barrier was compromised.

These findings are in contrast to those observed in a similar analysis with fingolimod in the phase 3 FREEDOMS study in patients with RRMS. In this study, while fingolimod significantly reduced the rate of confirmed relapses, residual disability following relapse appeared similar between the fingolimod and placebo groups (Cutter et al., 2013). These findings also contrast those from an analysis of teriflunomide in the phase 3 TEMSO study. While teriflunomide significantly reduced the annualized rate of relapses with residual EDSS increase, the risk of EDSS increase per relapse was the same between placebo and teriflunomide groups (O’Connor et al., 2013).

In this analysis, natalizumab also increased the probability of complete recovery from relapse compared to placebo for patients who experienced similar levels of EDSS worsening during the relapse. The observed treatment group differences in relapse recovery were shown to be independent of treatment effects on relapse frequency in sensitivity analyses and suggest that the mechanism of action of natalizumab may limit CNS tissue damage by altering the influx of inflammatory mediators. This interpretation is consistent with prior MRI observations (Dalton et al., 2004; Miller et al., 2007; Zivadinov et al., 2012). As natalizumab does not have an effect on relapse recovery when administered only after the onset of a relapse (O’Connor et al., 2004), our results suggest that the effect on relapse recovery requires that natalizumab be dosed prior to the relapse.

Incomplete clinical recovery from relapse and ongoing relapse activity can lead to accumulation of disability over time for patients with RRMS (Leone et al., 2008; Lublin et al., 2003; Nickerson and Marrie, 2013; Sospedra and Martin, 2005; Vercellino et al., 2009; Weinshenker et al., 1989). In this analysis natalizumab decreased relapsed-induced residual disability compared to placebo, but it did not completely prevent disability increase after relapse for all patients (mean relapse-induced residual disability increase was 0.06 EDSS points for natalizumab-treated patients compared to 0.28 EDSS points for placebo). Nonetheless, the current findings suggest that earlier intervention with natalizumab may improve long-term disability outcomes for RRMS patients, even for those who continue to experience on-treatment relapses, by lessening the extent of step-wise accumulation of impairment.

Studies (Prosperini et al., 2012; Sargento-Freitas et al., 2013; Wickstrom et al., 2013), including this analysis, have shown that natalizumab has a larger effect in patients with a lower baseline EDSS score. The EDSS subgroup results of this analysis, however, are difficult to interpret. EDSS is inherently less sensitive at higher levels of the scale (Cohen and Rudick, 2011), which may have contributed to the results. Consistent with this, relapse severity appeared lower in placebo patients with baseline EDSS ≥ 3.0 compared to those with baseline EDSS <3.0 (see Figs. 1 and 2), and multivariable analyses demonstrated that placebo patients with higher baseline EDSS were less likely to have a relapse with ≥1.0-point change on EDSS compared to those with lower baseline EDSS.

One limitation of the present study is that only the first relapse experienced by patients was considered. It is, therefore, unknown whether the beneficial effects of natalizumab would have been maintained, or increased, over subsequent relapses, but the number of patients having more than 1 relapse on natalizumab was very small (n=66/627 [11%]). Further studies would be required to determine whether the beneficial effects of natalizumab are maintained over subsequent relapses.

In summary, our analysis of data from the AFFIRM study demonstrated that natalizumab reduces relapse clinical severity and increases the probability of complete recovery from a disabling relapse. By reducing tissue damage after a relapse, natalizumab could help to stabilize RRMS and limit the development of further disability.

Author contributions

Study concept and design: Dr. Lublin, Dr. Pace, Dr. Belachew. Analysis and interpretation of data: Dr. Lublin, Dr. Cutter, Dr. Giovannoni, Dr. Pace, Dr. Belachew. Statistical analysis: Dr. Pace. Drafting the manuscript: Dr. Campbell. Critical revision of the manuscript for intellectual content: Dr. Lublin, Dr. Cutter, Dr. Giovannoni, Dr. Pace, Dr. Belachew.

Disclosures

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Dr. Cutter has received fees for serving on data and safety monitoring committees for Apotex, Biogen Idec, Cleveland Clinic, GlaxoSmithKline, Gilead Pharmaceuticals, Modigenetech/Prolor, Merck/Ono Pharmaceuticals, Merck, Neuren, PCT Bio, Revalesio, Sanofi, Teva, VivaSure, the NHLBI, the NINDS, the NMSS, and the NICHD, has received consulting, speaking, or advisory board fees from Alexion, Allozyne, Bayer, Celgene, Coronado Biosciences, the Consortium of MS Centers, Dogenix, Klein-Buendel, Genzyme, MedImmune, Novartis, Nuron Biotech, Receptos, Spinifex, Teva, and UBC, is employed by the University of Alabama at Birmingham and is president of Pythagoras, Inc.

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Dr. Campbell is an employee of Biogen Idec Inc. with company stock.
Dr. Belachew is an employee of Biogen Idec Inc. with company stock.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2014.08.005.

References


