

BRIEF REPORT

Natalizumab for Achieving Relapse-Free, T1 Gadolinium-Enhancing-Lesion-Free, and T2 Lesion-Free Status in Japanese Multiple Sclerosis Patients: A Phase 2 Trial Subanalysis

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ABSTRACT

Introduction: In a phase 2 trial of natalizumab in Japanese patients with relapsing-remitting multiple sclerosis (RRMS), treatment-related changes in relapses, brain lesions, and disability worsening were found to be comparable with those observed in the phase 3 studies of natalizumab in primarily non-Asian RRMS patients.

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Methods: This subanalysis of the placebo-controlled phase 2 trial of natalizumab in Japanese RRMS patients ($n = 94$) evaluated the effects of natalizumab versus placebo on the proportion of patients who achieved relapse-free, T1 gadolinium-enhancing (Gd+) lesion-free, and new/newly enlarged T2 lesion-free status, defined as “no evidence of inflammatory disease activity” (NEDA)-like status, after 24 weeks of treatment.

Results: In this subanalysis, significantly more natalizumab-treated than placebo-treated patients achieved NEDA-like status (76.6% vs. 31.9%; $P < 0.0001$). In addition, the odds ratio (95% confidence interval) for patients on natalizumab to reach NEDA-like status was 6.98 (2.80–17.38) compared with placebo patients.

Conclusion: These results confirm previous findings indicating that natalizumab is efficacious in Japanese patients with RRMS.

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Keywords: Gadolinium-enhancing lesions; Japanese patients; Natalizumab; Relapsing-remitting multiple sclerosis; T2 lesions

INTRODUCTION

The efficacy of natalizumab has been demonstrated in two pivotal phase 3 studies of primarily non-Asian patients with relapsing-remitting multiple sclerosis (RRMS) [1, 2]. In both studies, natalizumab reduced the frequency of relapses, mitigated the development of new brain lesions on magnetic resonance imaging (MRI) scans, and delayed the time to confirmed disability worsening relative to placebo. Recently, the results of a phase 2 study of natalizumab in Japanese patients with RRMS were reported, and treatment-related changes in relapses, brain lesions, and disability worsening were comparable to those from the phase 3 studies [3].

It has been demonstrated that the endpoint of “no evidence of disease activity” (NEDA) over 2 years, a composite measure of disease activity, including relapses, sustained Expanded Disability Status Scale (EDSS) score progression, and MRI activity, may predict long-term disability progression [4]. In a phase 3 study of natalizumab in non-Asian patients with RRMS, 37% of natalizumab-treated patients showed freedom from disease activity (i.e., no radiological or clinical disease activity) compared with 7% of placebo-treated patients ($P < 0.0001$) [5]. However, since it was unknown whether similar effects would be seen in Japanese patients, we conducted this subanalysis of the phase 2 trial in Japanese patients with RRMS to evaluate the effects of natalizumab versus placebo on the proportion of patients achieving relapse-free, T1 gadolinium-enhancing (Gd+) lesion-free, and new/newly enlarged T2 lesion-free status, defined as NEDA-like status.

METHODS

Japanese patients (aged 18–65 years) were eligible for the two-part phase 2 trial, if they had a diagnosis of RRMS (revised McDonald criteria) [6], ≥ 1 exacerbation within the previous year, and, for inclusion in part B of the trial, an EDSS [7] score of 0.0–5.5. In part A of the study, 12 patients received open-label

intravenous natalizumab 300 mg every 4 weeks for 24 weeks. Part B was a double-blind study in which 94 patients were randomized to natalizumab 300 mg or placebo every 4 weeks for 24 weeks (Fig. 1) [3]. This subanalysis pertains only to patients randomized in part B of the study. The methodology of the full study, along with its efficacy and safety data, has been previously published [3].

Clinical relapses were defined as new or recurrent neurological symptoms that were not associated with fever or infection and lasted for ≥ 24 h. Brain MRI scans were performed with T1 (with and without gadolinium) and T2 sequences.

The proportions of patients who were free of the following events during part B of the study were evaluated: relapses during weeks 0–24; T1 Gd+ lesions at week 24; new or newly enlarged T2 lesions at week 24; and relapses, T1 Gd+ lesions, and new/newly enlarged T2 lesions at week 24. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate differences in the likelihood of achieving event-free status between treatment groups. For comparisons between treatment groups, P values were based on Fisher exact tests.

Compliance with Ethics Guidelines

The study was conducted in accordance with Good Clinical Practice (GCP) guidelines, with applicable local regulations (including Japanese Ministry of Health, Labour and Welfare regulations), and with the Declaration of Helsinki of 1964, as revised in 2013. The protocol was approved by ethics committees at

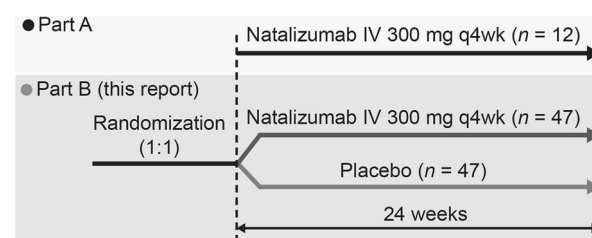


Fig. 1 Study flow diagram. *IV* intravenous, *q4wk* every 4 weeks

all sites, and all patients provided written informed consent.

RESULTS

This subanalysis included data from all patients randomized to natalizumab ($n = 47$) or placebo ($n = 47$) in part B of the study. A significantly larger proportion of natalizumab patients (76.6%) than placebo patients (31.9%) achieved relapse-free, T1 Gd+ lesion-free, and

new/newly enlarged T2 lesion-free status, or NEDA-like status, at week 24 ($P < 0.0001$). Figure 2 presents the percentages of patients with each type of event.

The likelihood of achieving relapse-free, T1 Gd+ lesion-free, and new/newly enlarged T2 lesion-free status was significantly greater with natalizumab treatment than with placebo (OR [95% CI], 6.98 [2.80–17.38]) (Table 1). Overall, natalizumab patients were seven times as likely as placebo patients to be free of any event. When the events were analyzed separately,

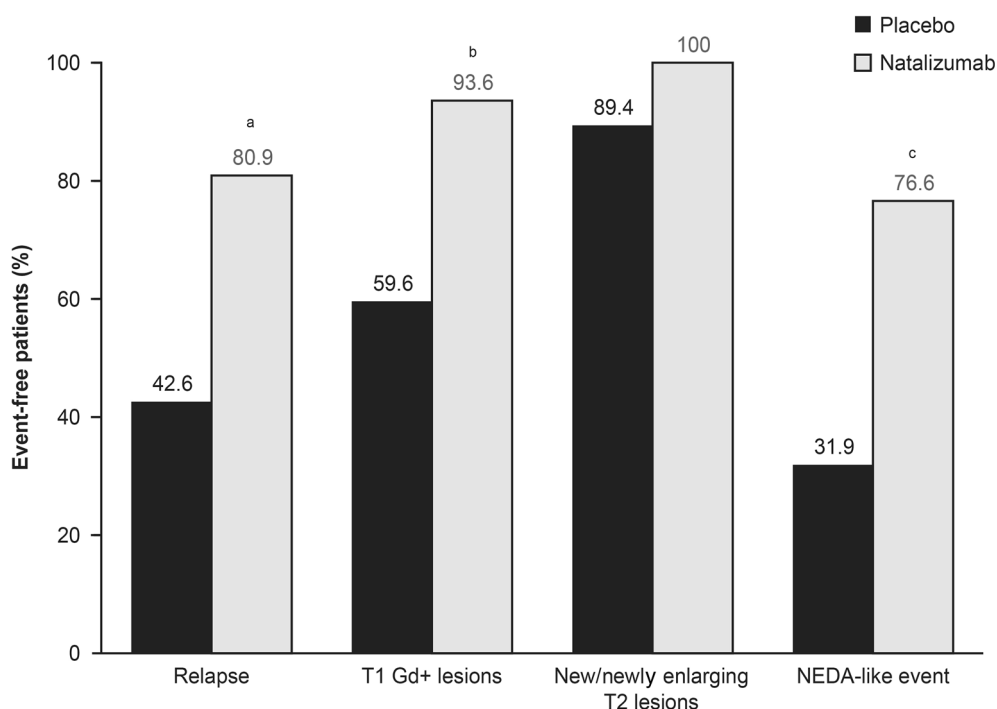


Fig. 2 Proportions of event-free patients at week 24. ^a $P = 0.0003$; ^b $P = 0.0002$; ^c $P < 0.0001$. Gd+ gadolinium-enhancing

Table 1 Likelihood of freedom from events for natalizumab versus placebo patients (at week 24)

Freedom from:	OR (95% CI)	P value
Relapse	5.70 (2.25, 14.43)	0.0003
T1 Gd+ lesions	9.95 (2.69, 36.76)	0.0002
New/newly enlarged T2 lesions	N/A ^a	0.0559
NEDA-like status	6.98 (2.80, 17.38)	<0.0001

CI confidence interval, Gd+ gadolinium-enhancing, N/A not applicable, OR odds ratio

^a The OR for being free of new/newly enlarged T2 lesions was not calculated because all natalizumab patients achieved new/newly enlarged T2 lesion-free status

natalizumab patients were nearly six times as likely to be free of relapses and nearly ten times as likely to be free of T1 Gd+ lesions as placebo patients at week 24.

DISCUSSION

In this subanalysis of data from the phase 2 study of natalizumab in Japanese patients with RRMS, a significantly larger proportion of natalizumab patients than placebo patients reached NEDA-like status after 24 weeks of treatment.

Therapeutic efficacy can be difficult to demonstrate in multiple sclerosis (MS) clinical trials, as the currently accepted clinically relevant measures of disease activity are infrequent (e.g., relapses) and/or slow to develop (e.g., disability worsening) [8]. A post hoc analysis of data from AFFIRM (a 2-year, randomized, placebo-controlled phase 3 trial of RRMS patients [$N = 942$]) was the first to include an assessment of individual outcomes as a composite measure: “freedom from disease activity”, defined as no relapses, no 12-week-confirmed disability worsening, no Gd+ lesions, and no new/newly enlarged T2-hyperintense lesions. In this trial, a larger proportion of natalizumab patients (37%) than placebo patients (7%) showed freedom from disease activity [5]. Similar composite endpoints have been evaluated in more recent MS clinical trials, though the terminology NEDA is becoming more frequently used [8].

Although the components and definitions of NEDA vary across studies [4], the proportion of natalizumab-treated patients who were free of relapses, T1 Gd+ lesions, and new/newly enlarged T2 lesions in the current analysis (77%) was comparable to that in previous reports of natalizumab treatment in Italian RRMS patients and in European, North American, Australian, and New Zealand patients with relapsing MS from the AFFIRM trial (37–87%) [5, 9]. The current study differs from the AFFIRM trial in that the proportion of patients free from new/newly enlarged T2 lesions in this study was not significantly larger with natalizumab than placebo. In

addition, a similar result was observed in changes of mean EDSS score, referentially collected, in both groups (baseline score: placebo 2.05 vs. natalizumab 2.45; and score at 24 weeks: placebo 2.16 vs. natalizumab 2.25) [3]. These may be due, at least in part, to the shorter duration of this study (24 weeks) compared with AFFIRM (2 years) [5].

Aside from studies of natalizumab, other disease-modifying therapies (DMTs) studies from around the world have assessed the proportions of patients achieving freedom from disease activity [10–13]. Other trials have examined the efficacy of certain DMTs (e.g., interferon beta-1a, interferon beta-1b, and fingolimod) exclusively in Japanese patients [14–16], though head-to-head comparator trials of the efficacy of DMTs in Japanese patients have not yet been conducted nor have NEDA data of other DMTs in Japanese patients been published. However, NEDA results are available in studies conducted mainly in Caucasian patients with MS (e.g., after 2 years of follow-up, NEDA-3 was reported in 70% of natalizumab treated patients vs. 44% of fingolimod treated patients) [17].

Our findings should be interpreted in light of some limitations. The number of patients evaluated was relatively small, and the 24-week study period was relatively short. Evidence suggests that EDSS worsening confirmed at ≥ 24 weeks is a meaningful intermediate clinical outcome measure that predicts clinically significant disability [18]; however, confirmed EDSS worsening, which is often a component of NEDA, was not incorporated into the composite endpoint in this analysis due to the short study period.

CONCLUSION

In conclusion, this subanalysis of data from the Japanese phase 2 study of natalizumab in RRMS patients demonstrates that a significantly larger percentage of natalizumab patients than placebo patients were free of relapses, T1 Gd+ lesions, and new/newly enlarged T2 lesions. These results are consistent with findings from non-Asian patient populations [1, 2] and

support the efficacy of natalizumab in Japanese patients with RRMS.

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Disclosures. Takahiko Saida (a coordinating investigator) has received funding from, held board membership for, spoken at scientific meetings for, prepared manuscripts for, and had consulting agreements with Astellas, Biogen, Bayer-Schering, Daiichi-Sankyo, Eisai, Kaketsuken, Merck Serono, Mitsubishi-Tanabe, Nihon, Novartis, Ono, Sanofi, TDS Japan, and Teijin. Jun-ichi Kira (a coordinating investigator) has been a consultant for Biogen and Novartis

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Compliance with Ethics Guidelines. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines, with applicable local regulations (including Japanese Ministry of Health, Labour and Welfare regulations), and with the Declaration of Helsinki of 1964, as revised in 2013. The protocol was approved by ethics committees at all sites, and all patients provided written informed consent.

Data Availability. The datasets generated and/or analyzed during the current study are not publicly available and are fully owned by Biogen, but are available from Nisha Lucas at nisha.lucas@biogen.com on reasonable request.

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