

Modeling the Efficacy of Natalizumab in Multiple Sclerosis Patients Who Switch From Every-4-Week Dosing to Extended-Interval Dosing

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Abstract

Natalizumab is approved for multiple sclerosis treatment at a dose of 300 mg every 4 weeks. Extended-interval dosing of natalizumab has been proposed as a strategy to mitigate the risk of progressive multifocal leukoencephalopathy, but the efficacy of extended-interval dosing is not established. Previous models suggesting lower efficacy when initiating natalizumab treatment with extended-interval dosing rather than every-4-week dosing are inconsistent with reports from clinical observations and real-world studies conducted in patient populations switching to extended-interval dosing after a period of receiving natalizumab every 4 weeks. Here, the efficacy of natalizumab extended-interval dosing was modeled specifically in patients switching from every-4-week dosing to extended-interval dosing. Published population pharmacokinetic/pharmacodynamic models were used to simulate the distribution of alpha-4 integrin saturations for different body weight categories and dosing intervals (every 5, 6, 7, 8, 10, or 12 weeks). Generalized estimating equations relating alpha-4 integrin saturation to probability of multiple sclerosis lesion or relapse were derived from RESTORE trial data, which included patients ($n = 175$) who discontinued natalizumab after being treated every 4 weeks for ≥ 1 year and had no relapses in the year before discontinuation. The model-based simulations described indicate that every-5-week or every-6-week dosing is likely to maintain the efficacy of natalizumab, particularly at body weights < 80 kg, in patients who switch after a period of stability on every-4-week dosing. The efficacy of natalizumab decreases as dosing intervals and body weight increase. Partial model validation was achieved in that observed outcomes in an independent clinical study were similar to those predicted by the models.

Keywords

alpha-4 integrin saturation, extended interval dosing, multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy

Relapsing-remitting multiple sclerosis (RRMS) is a progressive inflammatory disease leading to demyelination and axonal loss.^{1–3} Natalizumab administered intravenously at 300 mg every 4 weeks is highly efficacious in reducing multiple sclerosis (MS) disease activity as assessed by relapses, disability accumulation, and magnetic resonance imaging (MRI) lesions.^{1,4} Natalizumab is a humanized anti-alpha-4 integrin antibody that binds the alpha-4 subunit of alpha-4-beta-1, preventing leukocyte migration into parenchymal tissue.^{1,2,5}

Natalizumab treatment is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare brain infection caused by a pathogenic form of JC virus.^{6–8} The duration of natalizumab treatment, prior use of immunosuppressants, and anti-JC virus antibody status have been established as risk factors predicting the risk of PML.⁶ Administration of natalizumab at intervals longer than every 4 weeks (extended-interval dosing) has been proposed as a means to reduce PML risk. Retrospective analyses of data from the TOUCH (Tysabri Outreach: United Commitment to Health) program, through which all US patients taking natalizumab receive treatment, using prospective definitions of extended-

interval dosing and preplanned statistical analysis plans in groups of approximately 15 000–24 000 patients revealed that extended-interval dosing was associated with a significantly lower risk of PML than every-4-week dosing.⁹ Modest differences in dosing intervals between every-4-week dosing and the various extended-interval dosing regimens were associated with this benefit, suggesting that increasing the natalizumab dosing interval to approximately every 6 weeks may produce a meaningful reduction in PML risk while maintaining efficacy.

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Identifying extended-interval dosing schedules that maintain alpha-4 integrin saturation levels sufficient to achieve therapeutic efficacy in preventing MS disease activity but carry a reduced risk of PML would be of high clinical value. After a single intravenous administration of natalizumab, maximal alpha-4-beta-1 integrin saturation is maintained for 3 to 4 weeks, and saturation declines to 50% to 80% over the following 4 weeks.^{4,5,10} Previous modeling results examined the expected efficacy of natalizumab with varying doses, but those analyses were developed for patients newly initiating natalizumab.^{11–13} In real-world clinical practice, extended-interval dosing is typically introduced only after patients are stable on every-4-week dosing for a period of time.

Real-world retrospective analyses have supported the efficacy of natalizumab extended-interval dosing in patients switching from every-4-week dosing. In one study, patients who switched to extended-interval dosing (every-6-week or every-8-week dosing) after remaining stable on every-4-week dosing for 12 to 24 months showed comparable rates of relapse and a comparable number of new MRI lesions to patients who maintained every-4-week dosing.¹⁴ Another study compared extended-interval dosing regimens ranging from every 31 days to every 61 days initiated after ≥ 6 months of every-4-week dosing to continued every-4-week dosing, and no difference was observed in efficacy in any range of extended-interval dosing, suggesting that extended-interval dosing at up to approximately 2-month intervals can maintain the efficacy of natalizumab in preventing MS disease activity after a period of every-4-week dosing.¹⁰ Data collected through the ongoing TOP (Tysabri Observation Program), an open-label, prospective observational study of patients treated with natalizumab in clinical practice settings, also suggest that patients who switch to every-6-week dosing after remaining stable on every-4-week dosing for ≥ 1 year do not have an increased risk of relapse.¹⁴ However, such real-world analyses are limited by the potential for selection bias. Patients with less disease activity may be more likely to elect to switch to longer dosing intervals under the guidance of their physician.^{10,15}

RESTORE (Treatment Interruption of Natalizumab) and REFINE (Exploratory Study of the Safety, Tolerability, and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis) were exploratory randomized clinical trials that examined MS disease activity in patients who had remained relapse free on natalizumab every 4 weeks for ≥ 1 year and were randomly assigned to undergo a 24-week natalizumab interruption (RESTORE) or switch to every-12-week dosing (REFINE).^{16,17} Both studies included the collection of pharmacodynamic (PD) and pharmacokinetic (PK)

data as well as MRI and relapse outcomes for all patients. Based on an analysis of the timing of PK and PD changes following the cessation of natalizumab treatment in RESTORE, the mean trough natalizumab concentration in patients whose natalizumab treatment was interrupted declined rapidly from 38.4 $\mu\text{g/mL}$ 4 weeks after cessation to 3.8 $\mu\text{g/mL}$ at 12 weeks.¹² The mean alpha-4 integrin saturation level, however, declined at a slower rate, from 89.4% at 4 weeks to 31.3% at 12 weeks, and it plateaued at approximately 10% to 15% from 16 weeks onward. In patients whose natalizumab treatment was interrupted, gadolinium-enhancing (Gd+) lesions meeting the MRI rescue criteria (1 lesion $>0.8 \text{ cm}^3$ in volume or ≥ 2 lesions of any size) were observed in no patients at 4 or 8 weeks, in 2.5% of patients at 12 weeks, and in 41.8% of patients at 16 weeks. Clinical relapse in patients with natalizumab treatment interruption also occurred at an increased frequency after 12 weeks.¹⁷ The results from RESTORE suggest that in patients who are stable on natalizumab treatment for ≥ 1 year, the decline in alpha-4 integrin saturation level after the last dose of natalizumab corresponds with the return of disease activity and appears to be delayed compared with the fall in drug concentration level.

While previous models focused on patients initiated on natalizumab extended-interval dosing, which departs from common clinical practice, here we used data from RESTORE to model the efficacy of natalizumab extended-interval dosing in patients who were stable on every-4-week dosing and switched from every-4-week dosing to extended-interval dosing. Data from REFINE were used to validate model predictions.

Methods

Clinical Data

RESTORE (NCT01071083) was a prospective, randomized, partially placebo-controlled study designed to explore MS disease activity and PK/PD parameters of natalizumab during a 24-week interruption of every-4-week treatment.¹⁷ Enrolled patients ($n = 175$) diagnosed with RRMS had been stable on every-4-week natalizumab without a relapse for ≥ 1 year before the start of the study. Patients were randomly assigned at a 1:1:2 ratio to either continue natalizumab every 4 weeks ($n = 45$), switch to placebo ($n = 42$), or switch to an alternate therapy (intramuscular interferon beta-1a, glatiramer acetate, or methylprednisolone; $n = 88$). At 28 weeks, patients discontinued placebo or their alternate therapy and resumed natalizumab treatment. Clinical, MRI, and laboratory tests were conducted every 4 weeks over the 28-week randomized treatment period. If a patient developed protocol-defined MS disease recurrence, treatment with high-dose

corticosteroids or restarting natalizumab was permitted at the investigators' discretion. The protocol-defined disease recurrence criteria were as follows: (1) 1 Gd+ lesion $>0.8 \text{ cm}^3$, (2) ≥ 2 Gd+ lesions of any size, or (3) a relapse defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting ≥ 24 hours, and associated with specified increases in Expanded Disability Status Scale score.¹⁷

Model Building

A generalized estimating equations (GEE) model that includes the occurrence of ≥ 1 Gd+ lesion of any size (Y/N) at 4, 8, 12, and 16 weeks as a repeated-measure correlated response variable and alpha-4 integrin saturation level at corresponding time points as the explanatory variable was used to fit the data from RESTORE. Data after 16 weeks were excluded, as a large proportion of patients with natalizumab interruption restarted treatment after 16 weeks following the return of disease activity.¹⁷ The mean response was modeled using a logit link function with an exchangeable working correlation matrix between time points. Specifically, with γ_{ij} representing the Gd+ lesion status of patient i at the j th visit ($j = 1, \dots, 4$), the model for the probability of lesion occurrence μ_{ij} was $g(\mu_{ij}) = \beta_0 + x_{ij}\beta_1$, where x_{ij} was the alpha-4 integrin saturation level of patient i at the j th visit and the logit link function was $g(\mu_{ij}) = \log(\mu_{ij}/[1-\mu_{ij}])$ with a binomial underlying distribution. The predicted values of the probability of lesion occurrence for given saturation levels were derived from the model with robust estimate of variance. If patients met the disease recurrence criteria and were treated with rescue treatment, their response values at subsequent visits were imputed as "Y" regardless of the actual scan results.

A similar GEE model was also built to assess the relationship of the Gd+ lesion counts at 4, 8, 12, and 16 weeks with the alpha-4 integrin saturation level at corresponding time points. A log link function with a negative binomial underlying distribution was used in the model for the mean number of lesions. The probability of the occurrence of clinical relapse was also assessed using a GEE model with the occurrence (Y/N) of relapse over the periods from baseline to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, and 13 to 16 weeks as the repeated-measure response variable and alpha-4 integrin saturation level at 4, 8, 12, and 16 weeks as the explanatory variable. A logit link function with a binomial underlying distribution was used.

Simulations

Simulations of alpha-4 integrin saturation for different dosing regimens (every 5, 6, 7, 8, 10, or 12 weeks) and body weight categories were developed based on published PK/PD models.¹⁸ For each simulated patient,

the binary response (Y/N) of lesion (or relapse) occurrence or the number of lesions was simulated from the models described above. For each dosing regimen and body weight category, the proportion of patients with Gd+ lesions, the mean number of Gd+ lesions, and the cumulative probability of relapse were computed based on 500 simulated patients. The simulation of each of the patient population was repeated 10 000 times.

Model Validation

Models were retrospectively validated using data from REFINE (NCT01405820), an exploratory, dose- and frequency-blinded, prospective, randomized, dose-ranging study to evaluate the efficacy and safety of multiple regimens of natalizumab dosing.¹⁶ Enrolled patients were diagnosed with RRMS and had been taking natalizumab every 4 weeks for ≥ 1 year without a relapse before the start of the study. Patients were randomized equally to 1 of the 6 following blinded dosing regimens for 60 weeks: 300 mg intravenously every 4 weeks, 300 mg subcutaneously every 4 weeks, 300 mg intravenously every 12 weeks, 300 mg subcutaneously every 12 weeks, 150 mg intravenously every 12 weeks, or 150 mg subcutaneously every 12 weeks. After 60 weeks, all patients resumed 300 mg intravenous dosing and were followed for an additional 12 weeks. The primary end point was combined unique active MRI lesions (new Gd+ lesions and new or newly worsening T2 lesions) over 60 weeks of treatment. The primary end point was assessed through clinical, MRI, and laboratory tests performed at 12, 24, 36, 48, and 60 weeks.

REFINE population data, including sample size and body weight distribution, from the 300 mg every-4-week ($n = 51$) and every-12-week ($n = 45$) groups were used as the basis for the simulated populations in the model validation. Simulation results (10 000 each) for REFINE patients on natalizumab 300 mg intravenously every-4-week and every-12-week dosing were compared with observed study results through 24 weeks. Results were limited to 24 weeks, as $>20\%$ of the patients in the every-12-week group experienced a relapse and received rescue treatment at this time.

Results

Modeling Results

When modeling the probability of Gd+ lesion occurrence by trough alpha-4 integrin saturation, the estimates (\pm standard error [SE]) for the model parameter were $\beta_0 = -0.59 \pm 0.28$ and $\beta_1 = -0.09 \pm 0.01$ ($P < .0001$) for the logit response. The probability of Gd+ lesion occurrence increased at alpha-4 integrin saturation levels $<40\%$ (Figure 1). To illustrate the distribution of the alpha-4 integrin saturation level

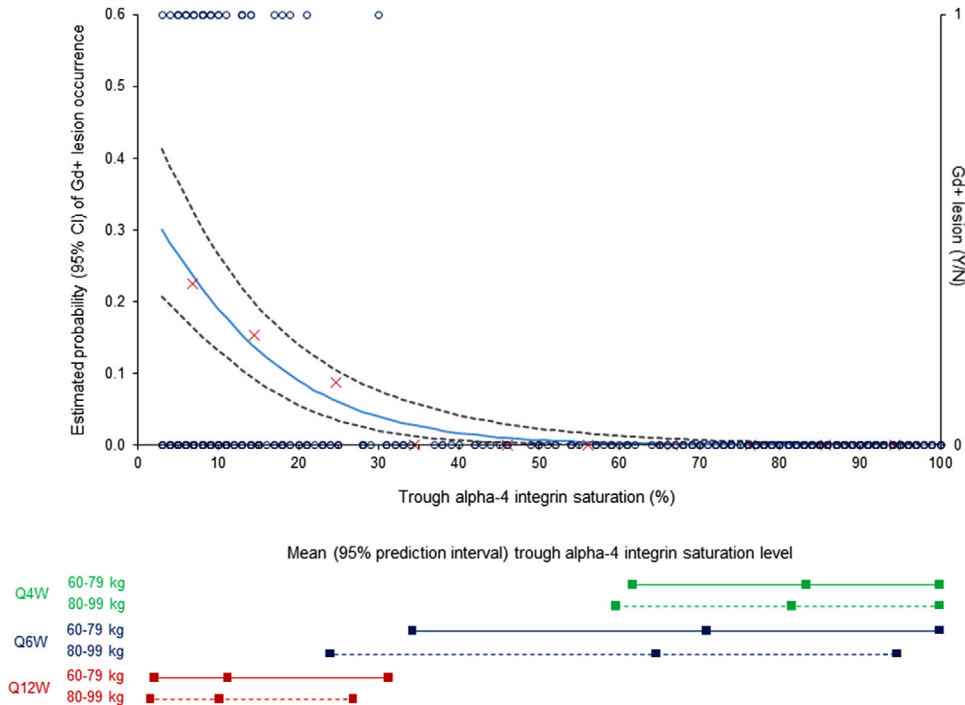


Figure 1. Estimated probability of gadolinium-enhancing (Gd+) lesion occurrence at 48 weeks by trough alpha-4 integrin saturation level. The resulting fitted curve of the probability of Gd+ lesion occurrence with 95% confidence intervals (CIs) is shown. Open circles represent the observed occurrence (Y/N) of Gd+ lesions, and red X marks represent the proportion of occurrence of lesions within each 10% bin or interval of alpha-4 integrin saturation level (eg, 0%-10%, 11%-20%) plotted versus the mean saturation level with each bin. Q4W, every 4 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

predicted at 1 year for various dosing intervals and body weight categories, the mean and 95% prediction interval (confidence interval [CI]) derived from the previous PK/PD model¹⁸ (Table S1) are plotted in Figures 1 through 3 for the every-4-week, every-6-week, and every-12-week dosing regimens and the 60- to 79-kg and 80- to 99-kg body weight groups. The 95% CIs were fully above 40% saturation for both body weight groups receiving every-4-week dosing. A small portion of the lower 95% CI for every-6-week dosing fell below 40% saturation, with a larger portion below 40% in the higher body weight group (80-99 kg). With every-12-week dosing, the 95% CIs were fully below 40% saturation.

Similarly, the estimated mean number of Gd+ lesions at 48 weeks was low, with trough alpha-4 integrin saturation level above 40%; lesion numbers rose as alpha-4 integrin saturation level fell below 40% (Figure 2). The estimates (\pm SE) for the model parameter were $\beta_0 = 1.22 \pm 0.36$ and $\beta_1 = -0.13 \pm 0.02$ ($P < .0001$) for the log response.

For the model of relapse probability, the estimates (\pm SE) for the model parameter were $\beta_0 = -2.18 \pm 0.31$ and $\beta_1 = -0.02 \pm 0.01$ ($P < .0001$) for the logit response. Whereas the number and probability of Gd+ lesions increased sharply in the models, the simulated probability of relapse occurrence rose gradually with

decreasing alpha-4 integrin saturation level without a notable difference in the rate of change above and below 40% saturation (Figure 3).

Simulated Efficacy Outcomes by Body Weight and Dosing Interval Category

The models were then used to simulate the proportion of patients with Gd+ lesions, the mean number of Gd+ lesions, and the cumulative probability of relapse at 48 weeks for various dosing regimens and weight categories. The simulated proportion of patients with Gd+ lesions at 48 weeks was $<1.0\%$ for all examined body weight categories with every-4-week or every-5-week dosing and for patients <80 kg with every-6-week dosing (Figure 4). The simulated proportion of patients with Gd+ lesions rose sharply at less frequent dosing intervals, reaching 17.4% to 20.7% with every-12-week dosing. Similar trends were observed for the simulated mean number of Gd+ lesions at 48 weeks, with the most pronounced increases in number of lesions occurring with every-8-week to every-12-week dosing (Figure 5).

The simulated probability of relapse remained $<10\%$ for all examined body weight categories with every-4-week or every-5-week dosing and for patients <80 kg with every-6-week dosing. The probability of relapse

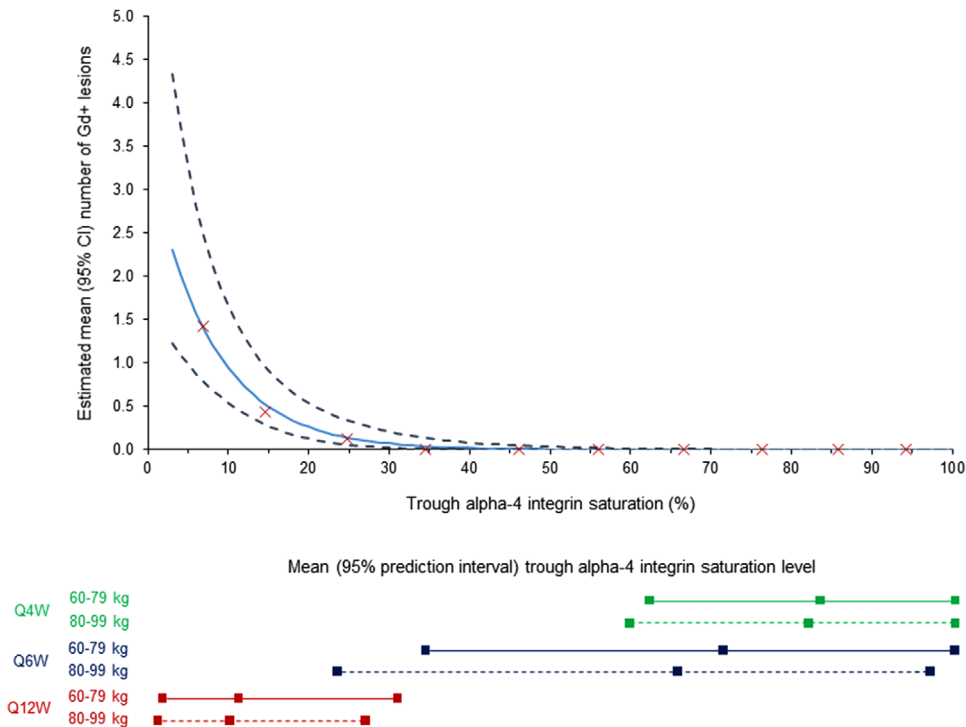


Figure 2. Estimated mean number of gadolinium-enhancing (Gd+) lesions at 48 weeks by trough alpha-4 integrin saturation level. The resulting fitted curve of the mean number of Gd+ lesions with 95% confidence intervals (CIs) is shown. Red X marks represent the mean lesion number within each 10% bin or interval of alpha-4 integrin saturation level (eg, 0%-10%, 11%-20%, etc) plotted versus the mean saturation level with each bin. Q4W, every 4 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

increased at less frequent dosing intervals, reaching 24.8% to 26.5% with every-12-week dosing (Figure 6).

Model Validation

Model-based simulations based on REFINE patient demographics were similar to actual observed values in REFINE, supporting the validity of the models. Specifically, the simulated proportion of patients with Gd+ lesions, the mean number of Gd+ lesions, and the cumulative probability of relapse at 24 weeks with every-4-week or every-12-week dosing predicted by the models were within the range of variability (95%CI) of the observed values in REFINE (Table 1). The predicted mean proportion of every-4-week-dosed patients with Gd+ lesions at 24 weeks was 0.1%, while 2.0% (95%CI, 0%-10.5%) of patients had Gd+ lesions at 24 weeks in REFINE's every-4-week dosing arm. The predicted mean proportion of every-12-week-dosed patients with Gd+ lesions at 24 weeks was 18.9%, while 24.4% (95%CI, 12.9%-39.5%) of patients had Gd+ lesions at 24 weeks in REFINE's every-12-week dosing arm. Although the simulated results for the every-4-week dosing regimen were lower than the observed results, all simulated results were within the 95%CIs of the observed results for both every-4-week and every-12-week dosing on all 3 measures of predicted disease activity return.

Discussion

The model-based simulations described here suggest that for patients who are stable on natalizumab every 4 weeks and switch to dosing intervals from every 5 weeks to every 12 weeks, the probability of disease activity return depends on dosing interval and body weight. The efficacy of natalizumab decreases as dosing interval and body weight increase, and the predicted probability of disease activity return is greater with dosing intervals longer than every 6 weeks and for patients with body weight >80 kg. Modeling results indicate that every-5-week and every-6-week dosing at body weights <80 kg are likely to maintain the efficacy of natalizumab in patients who switch after a period of stability on every-4-week dosing.

Prior models that simulated disease outcomes for patients initiating natalizumab at different dosing intervals concluded that extended-interval dosing might not provide adequate disease control¹⁸; the current modeling results indicate that for some dosing intervals and body weights, extended-interval dosing of up to every 6 weeks is likely to maintain efficacy in patients who switch to extended-interval dosing after a stable period on every-4-week dosing. Importantly, these models predict efficacy in patients who have taken natalizumab every 4 weeks for ≥ 1 year before switching

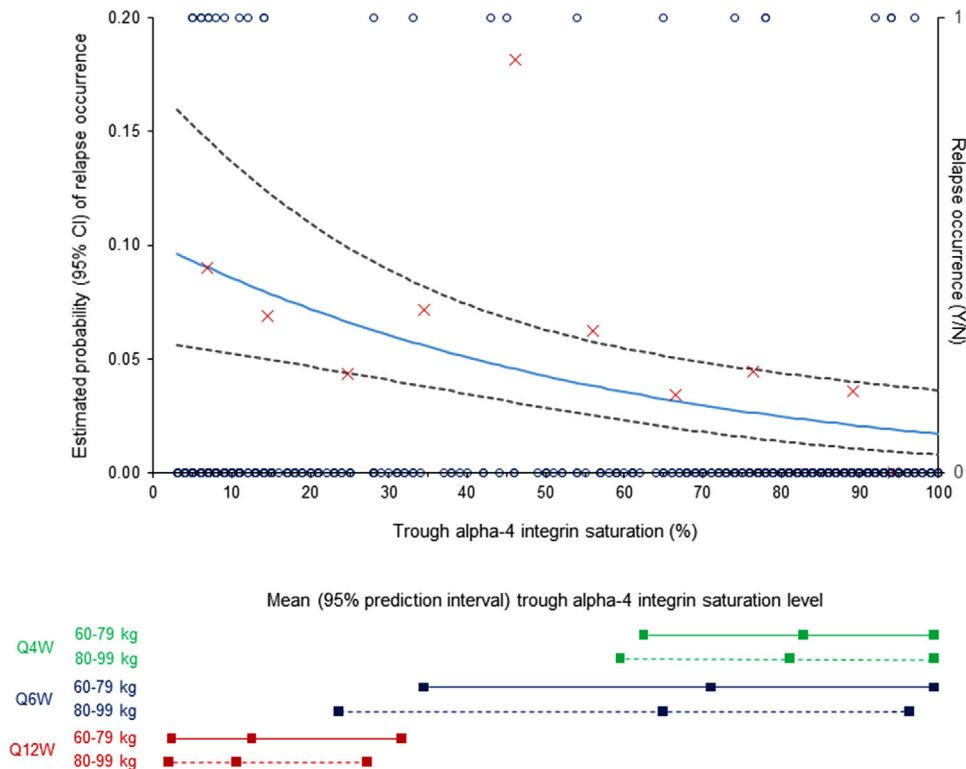


Figure 3. Estimated probability of relapse at 48 weeks by trough alpha-4 integrin saturation level. The resulting fitted curve of the probability of relapse occurrence with 95% confidence intervals (CIs) is shown. Open circles represent the observed occurrence of relapse (Y/N), and red X marks represent the proportion of occurrence within each 10% bin or interval of alpha-4 integrin saturation level (eg, 0%-10%, 11%-20%, etc) plotted versus the mean saturation level with each bin. Q4W, every 4 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

to extended-interval dosing. Clinical outcome data from the RESTORE and REFINE studies provide evidence of apparent delays in pharmacodynamic changes in patients who are stable on natalizumab every 4 weeks for ≥ 1 year: the decline in alpha-4 integrin saturation level after the last every-4-week dose of natalizumab appears to be slower than the decline in drug concentration level. This delay reflects slow dissociation of natalizumab from alpha-4 integrin, resulting in slower desaturation of alpha-4 integrin relative to drug elimination. Such apparent delays, which are unaccounted for in previous PK efficacy models of patients initiating extended-interval dosing, may help to account for the observation that despite the rapid decline in PK concentration by 4 weeks after dosing, MS disease activity does not recur for some time after that.

Differences in MS disease state for patients initiating with extended-interval dosing versus switching to extended-interval dosing may further explain these observations. Levels of ongoing central nervous system (CNS) inflammation are typically high when natalizumab treatment is initiated. In contrast, it is rare to detect signs of CNS inflammation after prolonged treatment with natalizumab. The observation that patients who switch from every-

4-week dosing to extended-interval dosing exhibit less disease activity than those initiating treatment with extended-interval dosing is consistent with the hypothesis that lower levels of alpha-4 integrin saturation may be sufficient to control MS disease under a lower inflammatory state. Alternatively, it has been observed that prolonged natalizumab exposure decreases the surface expression of alpha-4 integrin on lymphocytes,¹⁹ which could lower the likelihood of lymphocyte migration at the same receptor saturation levels. The extent to which a lower inflammatory CNS state and/or lower alpha-4 integrin surface expression might underlie the greater efficacy associated with switching from every-4-week dosing to extended-interval dosing compared with initiating treatment with extended-interval dosing is an area for further study. Regardless of the underlying mechanism, these new models are more consistent with published observations from real-world clinical practice that showed the effectiveness of natalizumab to be maintained in patients who switched from every-4-week dosing to extended-interval dosing.^{10,14,15} Our modeling work supports the current clinical practice of switching patients from every-4-week dosing to extended-interval dosing, suggesting that it may achieve better efficacy

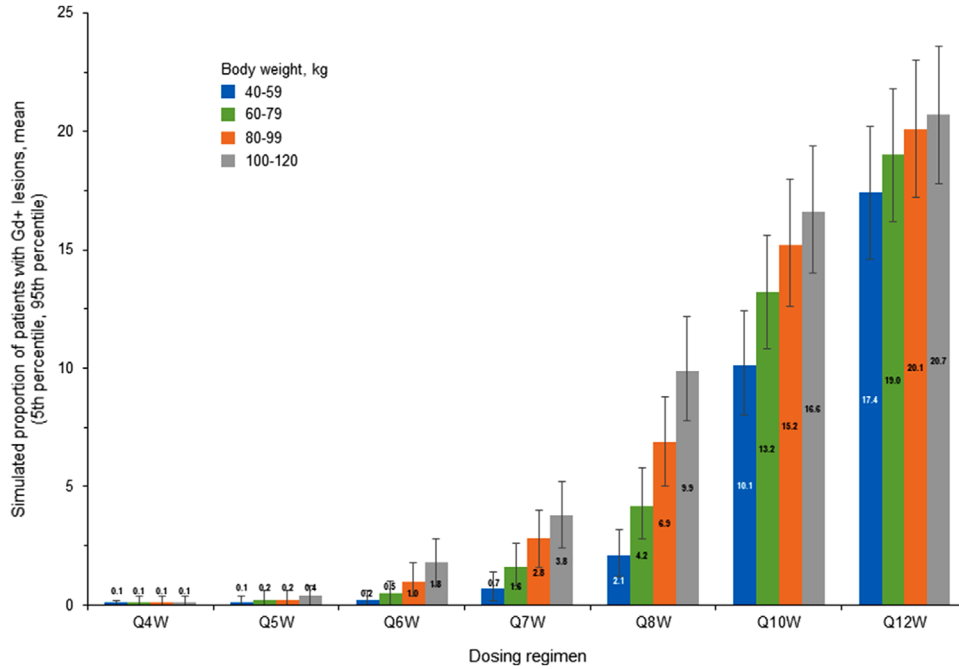


Figure 4. Simulated proportion (%) of patients with gadolinium-enhancing (Gd+) lesions at 48 weeks by body weight. Simulated patient population: N = 500 for each dosing interval and body weight combination. Q4W, every 4 weeks; Q5W, every 5 weeks; Q6W, every 6 weeks; Q7W, every 7 weeks; Q8W, every 8 weeks; Q10W, every 10 weeks; Q12W, every 12 weeks.

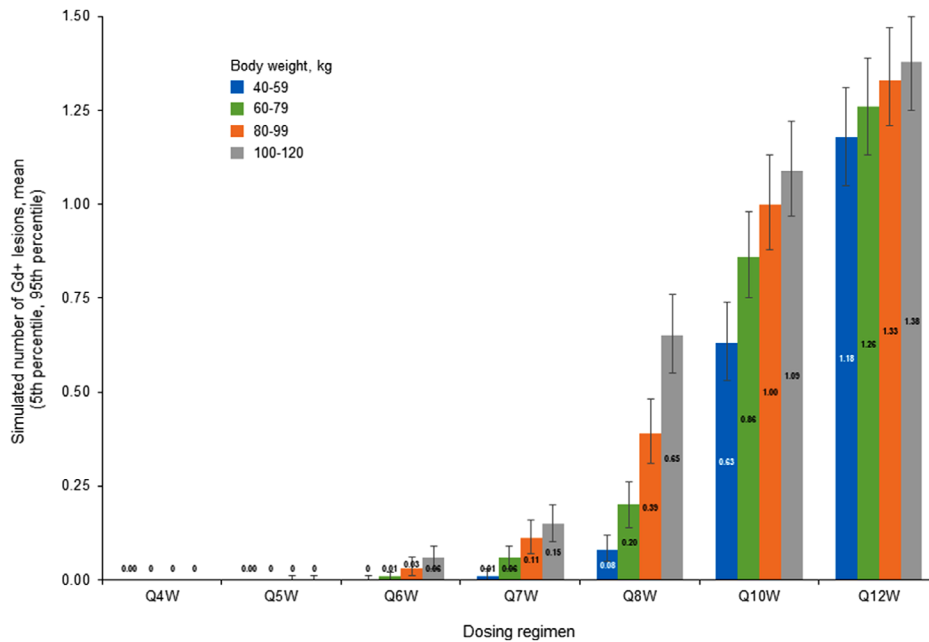


Figure 5. Simulated number of gadolinium-enhancing (Gd+) lesions at 48 weeks by body weight. Simulated patient population: N = 500 for each dosing interval and body weight combination. Q4W, every 4 weeks; Q5W, every 5 weeks; Q6W, every 6 weeks; Q7W, every 7 weeks; Q8W, every 8 weeks; Q10W, every 10 weeks; Q12W, every 12 weeks.

outcomes than initiating natalizumab treatment with longer dosing intervals.

Overall, the models support the importance of body weight as a covariate, but the clinical importance of this covariate may differ depending on the dosing interval. The efficacy of natalizumab every 4 weeks in reducing

MS disease activity regardless of body weight is well established.^{1,4} Initial trials for natalizumab used weight-based dosing (1, 3, or 6 mg/kg), which was deemed unnecessary for phase 3 trials, as efficacy plateaued at total doses above 300 mg and models suggested that body weight variation between 40 kg and 100 kg had

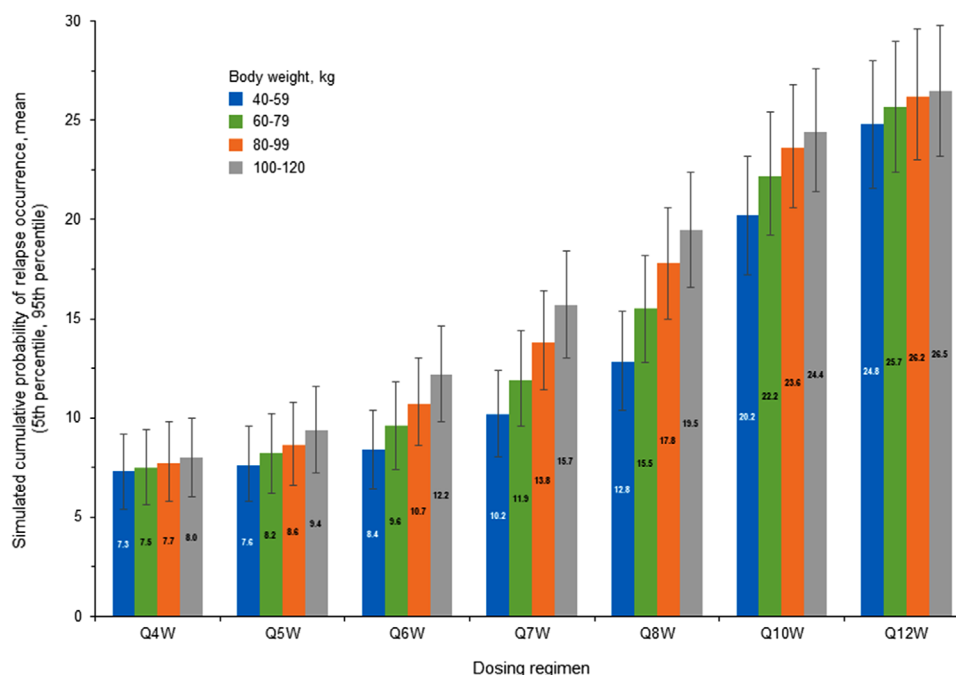


Figure 6. Simulated cumulative probability of relapse at 48 weeks by body weight. Simulated patient population: N = 500 for each dosing interval and body weight combination. Q4W, every 4 weeks; Q5W, every 5 weeks; Q6W, every 6 weeks; Q7W, every 7 weeks; Q8W, every 8 weeks; Q10W, every 10 weeks; Q12W, every 12 weeks.

a limited effect on natalizumab clearance with every-4-week dosing.⁵ Similarly, our results consistently showed that body weight does not contribute substantially to efficacy with every-4-week dosing. However, our models also suggest that body weight may be a consideration at longer dosing intervals; for example, in patients switching to every-8-week dosing, the models predict that approximately 7% more of the 100- to 120-kg population than the 40- to 59-kg population will experience relapse and MS lesions.

Alpha-4 integrin saturation's relationship with Gd+ lesion occurrence was different from its relationship with relapse occurrence. Gd+ lesion occurrence and the number of Gd+ lesions predicted at 48 weeks with every-4-week, every-6-week, and every-12-week dosing were low with alpha-4 integrin saturation levels above 40% and increased only as alpha-4 integrin saturation levels fell below 40%. In contrast, the simulated probability of relapse occurrence rose gradually with decreasing alpha-4 integrin saturation level, suggesting that clinical relapse may be a more complex manifestation of disease activity than MRI lesion occurrence. One limitation of the current models is that they do not include other efficacy measures that may be important in clinical practice, such as disability worsening, as the models were restricted to the efficacy data collected in RESTORE.

The models described here have received external validation through the demonstration that simulated

outcomes based on every-12-week dosing were consistent with observed outcomes in the REFINE clinical trial. While the CIs for the predicted disease activity return parameters are wide and estimates are close to 0, the CIs are not wider than those observed in REFINE, and low estimates of disease activity return are expected with every-4-week dosing. These results should be considered preliminary until prospective validation is available. The lack of external validation for other dosing intervals is a limitation. It should be noted that natalizumab has both linear and nonlinear elimination patterns, which can cause disproportionate changes in integrin binding that may lead to high/uneven variability in alpha-4 integrin saturation.^{11,12} An ongoing prospective study of the efficacy of natalizumab in patients who switch to every-6-week dosing after remaining stable on every-4-week dosing for ≥ 1 year compared with those who remain on every-4-week dosing (NOVA [A Study to Evaluate Efficacy, Safety, and Tolerability of extended-interval dosing of Natalizumab (BG00002) in Participants With RRMS Switching From Treatment With Natalizumab SID in Relation to Continued SID Treatment—Followed by Extension Study Comprising SC and IV Natalizumab Administration], ClinicalTrials.gov identifier NCT03689972) will provide rigorous clinical data regarding the effectiveness of switching to every-6-week dosing. NOVA will also collect detailed PK/PD data, offering further information about the

Table 1. Simulation Results Based on RESTORE Study Population Models Versus Observed REFINE Study Results

REFINE Population	Natalizumab 300 mg Intravenously	
	Every 4 Weeks	Every 12 Weeks
Number of patients ^a	51	45
Weight range, n (%), kg		
40-59	15 (29.4)	11 (24.4)
60-79	25 (49.0)	24 (53.3)
80-99	10 (19.6)	9 (20.0)
100-120	1 (2.0)	1 (2.2)
Proportion of patients with Gd+ lesions at 24 weeks, %		
Mean of 10000 simulations (5th percentile, 95th percentile)	0.1 (0, 2.0)	18.9 (8.9, 28.9)
Observed proportion in REFINE (95%CI)	2.0 (0-10.5)	24.4 (12.9-39.5)
Mean number of Gd+ lesions at 24 weeks		
Mean of 10 000 simulations (5th percentile, 95th percentile)	0 (0, 0)	1.3 (0.8, 1.7)
Observed mean number in REFINE (95%CI)	0.2 (0-0.5)	1.2 (0-2.8)
Cumulative probability of relapse occurrence over 24 weeks, %		
Mean of 10 000 simulations (5th percentile, 95th percentile)	3.7 (0, 7.8)	12.7 (4.4, 22.2)
Observed cumulative probability in REFINE (95%CI)	5.8 (0-12.2)	10.9 (1.9-19.9)

CI, confidence interval; Gd+, gadolinium enhancing; REFINE, Exploratory Study of the Safety, Tolerability, and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis; RESTORE, Treatment Interruption of Natalizumab.

Modified intent-to-treat population is defined as all randomized subjects in REFINE who received ≥ 1 dose of study treatment and had ≥ 1 efficacy assessment.

^aNumber of patients in modified intent-to-treat population with available baseline body weight.

relationship among natalizumab dose, body weight, and alpha-4 integrin saturation and potentially providing further validation for the models described here.

The implications of the data generated by the model simulations here could be particularly beneficial for patients at higher risk of PML, as a recent retrospective study showed that extended-interval dosing is associated with a lower risk of PML than every-4-week dosing.⁹ In that analysis, the average dosing interval for extended-interval dosing patients was approximately every 6 weeks, and the majority of patients had received every-4-week dosing for ≥ 1 year before the beginning of extended-interval dosing. Thus, the population outcomes simulated in our models may be relevant to this extended-interval dosing population, where lower PML risk has been observed.

Conclusions

Model simulations predict that for patients who switch to extended-interval dosing after ≥ 1 year of stability

on every-4-week dosing, the probability of disease activity depends on dosing interval and body weight. As compared with previous models that assessed outcomes associated with extended-interval dosing use at treatment initiation, the efficacy outcomes predicted by these models are more consistent with extended-interval dosing outcomes reported in clinical practice. Although extended-interval dosing is associated with lower risk of PML compared with every-4-week dosing, caution is warranted with extended-interval dosing intervals longer than every 6 weeks and in patients with higher body weight who are considering switching to extended-interval dosing as a PML risk mitigation strategy. Additional data are needed to define the benefit-risk profile of extended-interval dosing and to further validate these models.

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Conflicts of Interest

K.K.M. and N.C. are employees of and hold stock and/or stock options in Biogen. I.C. and P.-R.H. were employees of Biogen at the time of the analyses and may hold stock and/or stock options in Biogen.

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Data Accessibility

The data sets generated and/or analyzed during the current study are not publicly available. The authors and company are fully supportive of allowing independent assessment and verification of these results. Requests for deidentified data should be made via the established company data-sharing policies and processes as detailed on the website <http://clinicalresearch.biogen.com/>.

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Supplemental Information

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