Similar Clinical Outcomes for Natalizumab Patients Switching to Every-6-Week Dosing Versus Remaining on Every-4-Week Dosing in Real-World Practice

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Objective

- To compare relapse and disability outcomes in propensity score–matched TYSABRI Observational Program (TOP) patients who switched to every-6-weeks (Q6W) dosing with outcomes in patients who remained on every-4-weeks (Q4W) dosing.

Conclusions

- These analyses of real-world data from TOP demonstrate no significant difference in risk of relapse or 24-week confirmed disability worsening (CDW) between propensity score–matched patients who switched to natalizumab Q6W dosing after ≥1 year on Q4W dosing and patients who remained on Q4W dosing.
  - These results also confirm and extend a previous analysis of TOP data that suggested maintenance of effectiveness in patients who switched from standard interval dosing to extended interval dosing.[1]
- While Q6W patients appeared to experience fewer serious adverse events (SAEs) than Q4W patients, conclusions regarding safety of Q6W and Q4W dosing are limited by small patient sample sizes.
- While propensity score matching and adjustment were used to account for several potentially important covariates, findings are limited by possible selection biases from unmeasured covariates.
- These results, combined with other real-world and clinical studies, including the ongoing, randomized, prospective NOVA trial (NCT03689972), will provide a more complete understanding of the effectiveness of natalizumab in patients who switch to Q6W dosing after ≥1 year of Q4W dosing.

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Introduction

- Natalizumab 300 mg Q4W is an effective therapy for relapsing-remitting multiple sclerosis (RRMS)[1] but is also associated with increased risk of progressive multifocal leukoencephalopathy (PML) in anti–JC virus (JCV) seropositive patients.[2,3]
- Analyses of the TYSABRI Outreach: United Commitment to Health (TOUCH) Prescribing Program safety database have demonstrated that natalizumab extended interval dosing (average dosing interval of approximately 6 weeks) is associated with lower risk of PML than Q4W dosing.[4]
  - The TOUCH database does not capture efficacy data; therefore, these studies cannot assess whether natalizumab effectiveness is maintained with extended interval dosing.
- TOP (ClinicalTrials.gov Identifier: NCT00493298) is an ongoing, multinational prospective study of natalizumab safety and effectiveness in patients with RRMS in real-world clinical practice.[5,6]
  - Data collected in TOP include exact infusion dates (since 2014), physician-intended dosing frequency, and dates of planned changes in dosing frequency, facilitating assessment of the relative effectiveness of different dosing regimens.
  - A previous analysis of relapse outcomes in TOP showed no difference between patients who switched to Q6W and those who remained on Q4W dosing.[7]
- Comparative disability outcome data for Q4W and Q6W natalizumab dosing in well-matched real-world populations are lacking.
  - Such data would contribute to the benefit-risk profile of natalizumab Q6W dosing.

1. Polman CH, *et al. N Engl J Med.* 2006;354:899-910; 2. Bloomgren G, *et al. N Engl J Med.* 2012;366:1870-1880; 3. Ho P-R, *et al. Lancet Neurol.* 2017;16:925-933; 4. Zhovtis Ryerson L, *et al. Neurology.* 2019;93: e1452-e1462; 5. Butzkueven H, *et al. J Neurol Neurosurg Psychiatry.* 2014;85:1190-1197; 6. Butzkueven H, *et al. J Neurol Neurosurg Psychiatry.* 2020;91:660-668; 7. Butzkueven H, *et al.* ECTRIMS; September 11–13, 2019; Stockholm, Sweden. P1033.

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Methods

- Data in TOP as of November 2019 were used to identify patients with Q4W and Q6W dosing patterns based on physicians' intended dosing on study case report forms.
  - The Q6W group included patients who had a single physician-intended change in frequency of dosing from Q4W to Q6W; patients in the Q4W group had all intended dosing indicated as Q4W.
- Patients were required to have received natalizumab Q4W for ≥1 year prior to the physician-intended switch to Q6W dosing.
  - Patients were also required to have sufficient demographic and disease characteristic information for propensity score matching.
  - Patients with any dosing intervals ≥12 weeks or <3 weeks during the Q4W dosing period were excluded.
- All Q4W patients with on-natalizumab follow-up greater than or equal to the switch time from Q4W to Q6W for a given Q6W patient were considered as potential matches for that patient.
  - Q4W patients were allowed to match to >1 Q6W patient.
- Patients were matched 1:1 at the time of Q4W to Q6W switch (for Q6W patients) or the corresponding exposure-matched time point (for Q4W patients) using propensity score–based caliper matching,[1] with age, sex, Expanded Disability Status Scale (EDSS) score, time from multiple sclerosis (MS) onset, natalizumab exposure duration, and relapse activity (both prior to TOP enrollment and while on Q4W dosing) as covariates.
- Adjusted annualized relapse rates (ARRs) of the matched populations were calculated using negative binomial regression with robust standard error estimation.
- Hazard ratios of time to first relapse and time to 24-week CDW (defined as an increase in EDSS score of ≥1.0 point in patients with a baseline score 1.0 to 5.5 or an increase of 0.5 points in patients with a baseline score of ≥6.0, confirmed after 24 weeks) were estimated using Kaplan-Meier and Cox methods.

1. Austin PC. *Pharm Stat.* 2011;10:150-161.

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Results (1 of 4)

Included patients (unique patients)

- There were 236 unique Q6W patients that met inclusion requirements and 1295 unique Q4W patients that met inclusion requirements, including the additional requirement for Q4W patients to have sufficient follow-up to be considered a potential match for any Q6W patient at the time of the switch from Q4W to Q6W dosing (Table 1, before propensity score matching).

Table 1. Demographic and disease characteristics at TOP baseline for unique patients before and after propensity score matching

	Before propensity score matching		After propensity score matching	
Covariate	Q6W (n=236)	Q4W (n=1295)	Q6W (n=236)	Q4W (n=210)
Age, mean (SD), years[a]	35.3 (9.7)	37.0 (9.6)	34.7 (10.0)	35.3 (9.7)
Female, n (%)	159 (67.4)	930 (71.8)	159 (67.4)	138 (65.7)
Duration of MS symptoms, mean (SD), years[b]	9.09 (7.06)	8.71 (6.45)	9.05 (6.92)	9.09 (7.06)
EDSS score, mean (SD)[c]	3.33 (1.30)	3.60 (1.54)	3.50 (1.41)	3.33 (1.30)
ARR in the prior year, mean (SD)[d]	2.01 (0.92)	2.04 (0.92)	1.98 (0.93)	2.01 (0.92)
Anti-JCV antibody positive				
Yes	76 (32.2)	427 (33.0)	76 (32.2)	61 (29.0)
No	148 (62.7)	771 (59.5)	148 (62.7)	133 (63.3)
Missing	12 (5.1)	97 (7.5)	12 (5.1)	16 (7.6)

SD=standard deviation.
[a]Age at first dose of natalizumab.
[b]Disease duration at first dose of natalizumab.
[c]Baseline EDSS is last EDSS prior to initiation of natalizumab when available and last EDSS prior to TOP enrollment otherwise.
[d]ARR in the year prior to the first dose of natalizumab.

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Results (2 of 4)

Included patients (best-possible-match patients)

- All potential matches for each of the 236 Q6W patients were identified.
- Duplication of the 1295 Q4W patients was allowed in order to achieve the best match, resulting in 35,695 potential Q4W matches (Table 2, before propensity score matching).
  - Propensity score–based 1:1 caliper matching yielded 236 pairs of Q6W and Q4W patients, which was the population utilized for all effectiveness comparisons (Table 2, after propensity score matching).
  - Twenty-six Q4W patients were matched to >1 Q6W patient to achieve the best match (210 of the 236 matched Q4W patients were unique; Table 1, after propensity score matching).

Covariate balance between Q6W and Q4W patients

- After propensity score matching, demographic and disease characteristics were well balanced between the Q6W and Q4W dosing groups, with all standardized differences <0.061 (6.1%; Table 2).
- Mean (SD) follow-up times for matched Q6W and matched Q4W patients after the Q4W/Q6W switch time point were 2.00 (1.30) and 1.89 (1.15) years, respectively.

Table 2. Demographic and disease characteristics at time of switch to Q6W dosing (Q6W patients) or matching exposure time point (Q4W patients) before and after propensity score matching

	Before propensity score matching			After propensity score matching		
Covariate	Q6W (n=236)	Q4W[a] (n=35,695)	Standardized difference	Q6W (n=236)	Q4W (n=236)	Standardized difference
Age, mean (SD), years	40.1 (9.6)	43.1 (9.7)	−0.308	40.1 (9.6)	39.6 (10.6)	0.052
Female, n (%)	159 (67.4)	25,625 (71.8)	−0.096	159 (67.4)	157 (66.5)	0.018
Patients with relapses on Q4W prior to Q6W switch, n (%)[b]	101 (42.8)	14,000 (39.2)	0.073	101 (42.8)	103 (43.6)	−0.017
EDSS score, mean (SD)	3.29 (1.33)	3.51 (1.54)	−0.148	3.29 (1.33)	3.38 (1.43)	−0.061
Number of relapses in the year prior to initiation of natalizumab, mean (SD)	2.01 (0.92)	2.05 (0.99)	−0.038	2.01 (0.92)	1.98 (0.94)	0.036
Duration of MS symptoms, mean (SD), years	13.91 (7.19)	14.47 (6.84)	−0.080	13.91 (7.19)	13.95 (7.42)	−0.006
Natalizumab exposure, mean (SD), years	4.31 (2.24)	5.32 (2.3)	−0.447	4.31 (2.24)	4.35 (2.33)	−0.017

[a]All potential matches with duplication of patients to achieve best match.
[b]For Q6W patients, number of patients experiencing relapse prior to the Q4W to Q6W switch time point; for Q4W patients, number of patients experiencing relapse during the matched exposure period prior to the Q4W to Q6W switch time point.

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Results (3 of 4)

Clinical outcomes: ARR

- ARR did not differ significantly between Q6W and Q4W patients (Figure 1).
  - Most patients in both groups were free from relapse (Q6W group, 186 of 236 [78.9%]; Q4W group, 189 of 236 [80.1%]).

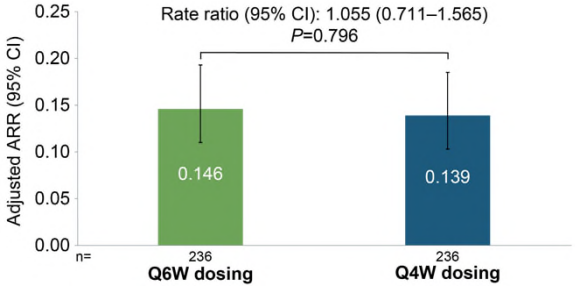
Clinical outcomes: time to first relapse

- The cumulative probability of remaining relapse free did not differ significantly between Q6W and Q4W patients (*P*=0.711; Figure 2).

Clinical outcomes: confirmed disability worsening

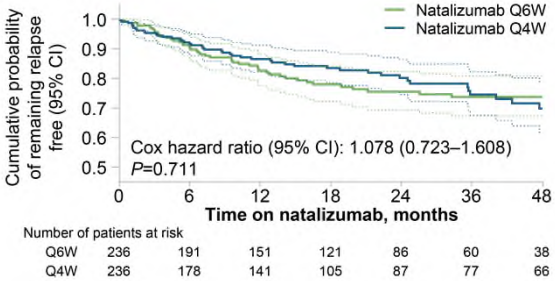
- The cumulative probability of 24-week CDW did not differ significantly between Q6W and Q4W patients (*P*=0.578; Figure 3).

Figure 1. Adjusted ARR in Q6W and Q4W patients (all-possible matches)



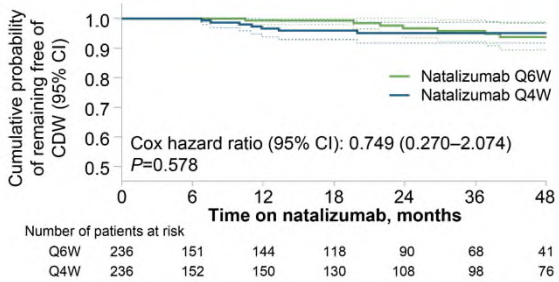
CI=confidence interval.

Figure 2. Cumulative probability of remaining relapse free in Q6W and Q4W patients (all-possible matches)



P value equivalent to log-rank test.

Figure 3. Cumulative probability of remaining free of 24-week CDW in Q6W and Q4W patients (all-possible matches)



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Safety outcomes in unique propensity score–matched Q6W and Q4W patients

- Safety outcomes were assessed in the unique patient cohorts to avoid possible duplication of potentially rare safety events.
- SAEs were experienced by 8.5% of patients on Q6W dosing and 15.7% on Q4W dosing (Table 3).
  - Treatment-related SAEs were experienced by 1.7% and 4.8% of Q6W and Q4W patients, respectively.
- There were 4 confirmed cases of PML in the unique patient cohort, 2 in each treatment arm (Table 4).
  - The duration of natalizumab exposure was >5.5 years for the Q6W and >3.4 years for the Q4W PML patients.
  - All cases had prior use of immunosuppressants; 2 patients (1 in each arm) had a JCV index value >1.5.

Table 3. Safety outcomes in propensity score–matched unique patients

Outcome, n (%)	Q6W (n=236)	Q4W (n=210)
Patients with ≥1 SAE	20 (8.5)	33 (15.7)
Patients with ≥1 treatment-related SAE[a]	4 (1.7)	10 (4.8)
Patients diagnosed with PML	2 (0.8)	2 (1.0)
Opportunistic infections[b]	0	0
Other infections[b]	2 (0.8)	5 (2.4)
Malignancy	2 (0.8)	3 (1.4)
Death	1 (0.4)	1 (0.5)

[a]Includes relation to study medication recorded as related, possibly related, or unknown.
[b]Infections requiring hospitalization.

Table 4. Risk factor information for PML cases

	Q6W		Q4W	
Risk factor	Patient 1	Patient 2	Patient 1	Patient 2
Natalizumab exposure, doses	105	48	62	42
Proportion of doses received on Q6W basis[a]	2.9%	22.9%	0	0
Natalizumab exposure, years	8.54	5.54	5.23	3.46
Prior immunosuppressant use (Y/N)	Y	Y	Y	Y
JCV index[a]	4.09	1.17	1.19	2.27

[a]Q4W patients received all doses on Q4W basis; doses received before dosing information was recorded in TOP were assumed to be administered Q4W.
[b]Highest JCV index >6 months prior to PML diagnosis reported.