Disability Progression After Switching from Natalizumab to Fingolimod or Interferon Beta/Glatiramer Acetate Therapies

A NARCOMS Analysis

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Background: ***Physicians must weigh the benefits against the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab, especially beyond 2 years. However, disability progression associated with switching therapies versus continuing natalizumab therapy after 2 years has not been fully evaluated.***

Methods: ***In this retrospective analysis using the NARCOMS Registry, disability progression (Patient-Determined Disease Steps [PDDS] scale) and physical health-related quality of life (HRQOL) worsening (12-item Short Form Health Status Survey Physical Component Score [SF-12 PCS]) were compared between participants switching to fingolimod (n = 50) or interferon beta (IFNβ)/glatiramer acetate (GA) (n = 71) therapy and those continuing natalizumab (n = 406) after 2 years or more of treatment (median follow-up: natalizumab, 4 years; fingolimod, 4.5 years; IFNβ/GA, 5 years).***

Results: ***Participants continuing to take natalizumab had less disability progression (mean PDDS change: natalizumab, 0.3; fingolimod, 0.6; IFNβ/GA, 0.7; P = .0036), were less likely to report disability progression (proportion with PDDS increase: natalizumab, 31%; fingolimod, 46%; IFNβ/GA, 42%; P = .0296), and had less worsening in physical HRQOL (mean SF-12 PCS change: natalizumab, −1.4; fingolimod, −2.8; IFNβ/GA, −4.6; P = .0476) than those switching treatment.***

Conclusions: ***Although all medication groups exhibited some level of worsening, switching from natalizumab treatment after 2 years was associated with increased disability progression and worsening physical HRQOL. The risk of disability progression from disease activity and the risk of PML should be considered when making natalizumab treatment decisions.*** ***Int J MS Care*****. 2016;18:230–238.**

Natalizumab was shown to be highly effective at suppressing disease activity and preventing disability progression over 2 years in patients with relapsing-remitting multiple sclerosis (MS) in the pivotal, randomized, placebo-controlled, phase 3 AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) trial.[1] Reports from several registry and observational studies have confirmed the effectiveness of natalizumab in clinical practice during follow-up as long as 6 years[2-5]; in each study, mean Expanded Disability Status Scale scores were stable for patients treated with natalizumab throughout follow-up.

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Factors besides efficacy, however, must be taken into account when making natalizumab treatment decisions. The most important of these factors is the patient's risk of progressive multifocal leukoencephalopathy (PML), a rare but serious and sometimes lethal adverse event associated with natalizumab treatment.[6] Risk of PML can be stratified by anti–JC virus (JCV) antibody status.[7] Patients who are anti–JCV antibody negative have a very low risk (approximately 1 in 10,000) of PML.[8] In anti–JCV antibody–positive patients, the risk of PML is higher, and it increases with natalizumab treatment duration, especially beyond 2 years.[7] Because of this increased risk, natalizumab treatment decisions are often reevaluated after 2 years of treatment regardless of disease status and risk factors, and it is not uncommon for patients to switch to alternative MS therapies. To make informed, individualized treatment decisions, physicians and patients must consider both the risk of PML and the risk of disability progression from uncontrolled MS disease activity.[9] However, the risk of disability progression associated with switching treatment after 2 years of natalizumab use has not been fully evaluated.

In this study, we retrospectively compared participant-reported disability progression and changes in physical health-related quality of life (HRQOL) from the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry. Disability was measured by the Patient-Determined Disease Steps (PDDS) scale[10] and the 12-item Short Form Health Status Survey Physical Component Score (SF-12 PCS)[11] between participants who continued taking natalizumab and those who switched to fingolimod or interferon beta (IFNβ)/glatiramer acetate (GA) therapy after 2 years of natalizumab treatment.

Methods

Participants and Treatment Groups

In the NARCOMS Registry,[12] participants with MS confidentially provide information about their treatment and disease characteristics through an enrollment form and semiannual surveys. The self-report PDDS scale and SF-12 are routine components of these surveys. The NARCOMS Coordinating Center is located at the University of Alabama at Birmingham, and NARCOMS is approved by the local institutional review board committee. All the participants enrolled in the NARCOMS Registry have provided written or electronic informed consent for the use of their de-identified data for research purposes.

Participants included in these analyses must have indicated at least 2 continuous years of natalizumab treatment with 1 or more follow-up assessments between the Spring 2006 and Spring 2013 surveys. Participants who completed all the follow-up surveys and those with a missing survey who indicated continuous disease-modifying therapy (DMT) use on subsequent surveys were included.

Participants were excluded from these analyses if they did not report PDDS scale scores in the first survey indicating natalizumab treatment (baseline) or did not have at least one report of PDDS scale scores 6 months or more after the qualifying 2 years of natalizumab treatment. Participants who switched from natalizumab therapy to DMTs other than fingolimod, IFNβ, or GA were also excluded.

Treatment groups were defined by DMT use after the qualifying 2 years of natalizumab treatment. Participants in the natalizumab group indicated natalizumab use only for the duration of their follow-up. Participants in the fingolimod group indicated the number of months of fingolimod use in one or more follow-up surveys and could also have one or more surveys indicating IFNβ/GA or other treatments (prednisone, adrenocorticotrophic hormone, mycophenolate mofetil, or methotrexate). Participants in the IFNβ/GA group indicated the number of months of IFNβ/GA use on at least one follow-up survey and could also have one or more surveys indicating symptomatic treatments.

Outcome Measures and Assessments

The PDDS scale and SF-12 PCS outcome measures have previously been described and validated in MS populations.[13-17] Briefly, the PDDS scale consists of 9 steps ranging from 0 (no disability) to 8 (bedridden). The SF-12 consists of 12 questions that can be subdivided into those involving physical or mental health. Scores are normalized to the general population, and higher scores indicate better HRQOL.

Changes in PDDS scale scores and SF-12 PCSs were assessed between the first survey indicating natalizumab treatment (baseline) through the final follow-up survey (no later than Spring 2013), inclusive. To determine whether there were differences in PDDS scale and SF-12 PCS changes between treatment groups before treatment switch, changes in PDDS scale scores were also assessed

in each group during the qualifying 2 years of continuous natalizumab treatment.

Statistical Analyses

Comparisons of baseline characteristics between treatment groups were made by the Wilcoxon test for continuous variables and by the χ^2 test for categorical variables. The proportion of participants in each treatment group with increased PDDS scale scores was compared using the likelihood ratio test or the Fisher exact test. Mean changes in PDDS scale scores and SF-12 PCSs were compared using analysis of variance. Median total follow-up time was compared by the Wilcoxon test. Because participation in the NARCOMS Registry is voluntary and participants are not randomized to treatments, logistic models and propensity score matching were performed separately to avoid potential covariate imbalances that might confound interpretation of any potential treatment group differences. Bonferroni correction was used to adjust for multiple comparisons.

Covariate Logistic Models and Propensity Score Matching

Logistic models were used to adjust for covariates predictive of PDDS scale score and SF-12 PCS change; covariates considered were age, sex, total follow-up time, and baseline PDDS scale scores and SF-12 PCSs. Where applicable, logistic regression models were assessed for goodness of fit using the lack-of-fit log-likelihood ratio χ^2 test, conducted at the .05 level. As an independent analysis, propensity scores (derived from age, sex, starting PDDS scale score, and relapse history) were used to match participants with similar demographic and disease characteristics across treatment groups. The matching of participants based on similarity of propensity score was performed independently for natalizumab-to-fingolimod and natalizumab-to-IFNβ/GA comparisons.

Results

Participant Characteristics and Disposition

In total, 604 participants in the NARCOMS Registry reported 2 or more continuous years of natalizumab treatment with one or more follow-up assessments. Of those participants, ten were excluded from this analysis for having no PDDS scale score reported at the first survey indicating natalizumab use, 57 for lacking one or more PDDS scale score reports after 2 years of natalizumab treatment, and ten for indicating subsequent use of a DMT other than natalizumab, fingolimod, or IFNβ/GA. Thus, 527 participants were included in this study: 406 who continued taking natalizumab and 50 and 71 who switched to fingolimod and IFNβ/GA, respectively, after 2 years of natalizumab treatment (Figure 1).

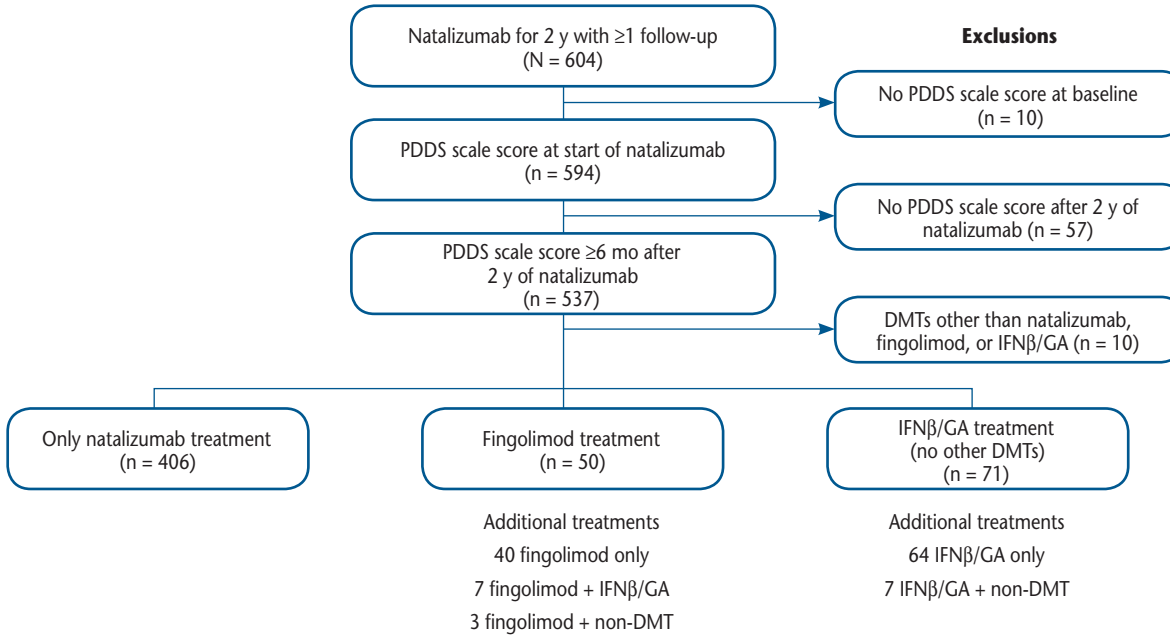

***Figure 1.* Study profile**

DMT, disease-modifying therapy; GA, glatiramer acetate; IFNβ, interferon beta; PDDS, Patient-Determined Disease Steps.

None of the baseline characteristics or demographic measures differed significantly between treatment groups (Table 1). In the unmatched participant population, median (range) total follow-up time was longer for participants who transitioned to fingolimod (54 [18–72] months) or IFNβ/GA (60 [24–72] months) therapy than for those who continued taking natalizumab (48 [12–72] months) ($P < .0001$). Participants who switched to IFNβ/GA therapy had longer median (range) follow-up time after switching (18 [0–54] months) than participants who switched to fingolimod therapy (12 [0–42] months) ($P = .0123$).

All 50 participants who switched to fingolimod therapy and 45 of 71 participants who switched to IFNβ/GA therapy were successfully matched based on similarity of propensity score to participants who continued taking natalizumab. Owing to differences in PDDS scale scores and age, a higher proportion of females than males matched in the IFNβ/GA group. Baseline demographics and disease characteristics were highly similar between the matched participants (Table 2). Median (range) total follow-up time did not differ significantly between matched participants who continued taking natalizumab (48 [18–72] months) and those who switched to fingolimod therapy (54 [18–72] months) ($P = .08$) but was significantly lower in matched participants who continued taking natalizumab (54 [24–72] months) than in those who switched to IFNβ/GA therapy (60 [24–72] months) ($P = .006$).

Table 1. Baseline characteristics and demographic measures

Characteristic	Natalizumab group (n = 406)	Fingolimod group (n = 50)	IFNβ/GA group (n = 71)	*P* value
Age, mean (SD), y	49.4 (9.3)	49.1 (8.4)	50.0 (8.8)	.8858
Female sex, %	79.5	70.0	81.7	.2489
White race, %	93.6	88.0	93.0	.2992
Employed, %	38.0	44.0	38.0	.7104
With health insurance, %	97.8	98.0	98.6	>.9999
Age at diagnosis, mean (SD), y	36.4 (9.4)	36.6 (9.0)	36.5 (9.0)	.9614
Experienced relapse in previous 6 mo, %	20.4	16.0	19.7	.9570
PDDS scale score				.1334
Mean (SD)	3.4 (2.1)	3.6 (2.0)	3.9 (2.3)	
Median (range)	3 (0–8)	4 (0–7)	4 (0–7)	
SF-12 PCS, mean (SD)	37.9 (11.3)	39.9 (11.8)	37.0 (11.3)	.3644

Abbreviations: GA, glatiramer acetate; IFNβ, interferon beta; PDDS, Patient-Determined Disease Steps; SD, standard deviation; SF-12 PCS, 12-item Short Form Health Status Survey Physical Component Score.

Table 2. Baseline characteristics of participants matched by propensity score

Characteristic	Natalizumab group (n = 50)	Fingolimod group (n = 50)	Natalizumab group (n = 45)	IFNβ/GA group (n = 45)
Female sex, %	66	66	82	7
Age, mean (SD), y	49.8 (6.9)	49.1 (8.4)	50.1 (7.9)	49.5 (8.1)
Relapse in previous 6 mo, No. (%)[a]				
No	34 (68)	34 (68)	33 (73)	33 (73)
Yes	8 (16)	8 (16)	7 (16)	8 (18)
PDDS scale score, No. (%)[b]				
0–2	15 (30)	15 (30)	11 (24)	11 (24)
3–5	24 (48)	24 (48)	21 (47)	21 (47)
6–7	9 (18)	9 (18)	12 (27)	12 (27)

Abbreviations: GA, glatiramer acetate; IFNβ, interferon beta; PDDS, Patient-Determined Disease Steps; SD, standard deviation.
[a]Relapse response collected as: Yes, No, Unsure.
[b]PDDS response by group (n): natalizumab = 48, fingolimod = 48; propensity score–matched groups, n = 44.

Proportion of Participants with PDDS Scale Score Increases

A smaller proportion of the participants who continued taking natalizumab had at least a 1-point PDDS scale score increase during total follow-up than those who switched to fingolimod or IFNβ/GA therapy (natalizumab, 31%; fingolimod, 46%; IFNβ/GA, 42%; $P = .0296$) (Figure 2A). In addition, when adjusted for relapse activity ($P = .2026$), sex ($P = .0138$), time of follow-up ($P = .7727$), and starting PDDS scale score ($P < .0001$), the group difference in the likelihood of an at least 1-point PDDS scale score increase persisted ($P = .0243$). There was no association between an at least 1-point increase in PDDS scale score and reported relapse during follow-up ($P = .1495$).

In the propensity score–matched natalizumab-to-fingolimod and natalizumab-to-IFNβ/GA comparisons, a nominally smaller proportion of the participants who continued taking natalizumab than those who switched to fingolimod or IFNβ/GA therapy exhibited an at least 1-point PDDS scale score increase, but these differences were not statistically significant after correcting for multiple comparisons (Figure 2B and C).

Mean PDDS Scale Score Increases

Participants who continued taking natalizumab also reported less disability increase as measured by mean

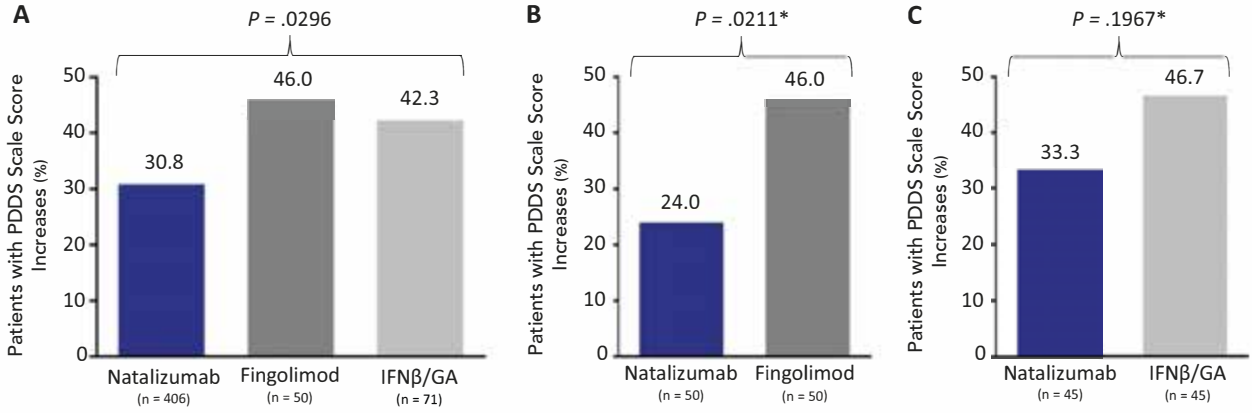

Figure 2. **Proportions of participants with Patient-Determined Disease Steps (PDDS) scale score increases as determined by unadjusted (A), natalizumab-fingolimod propensity score–matched (B), and natalizumab–interferon beta (IFNβ)/glatiramer acetate (GA) propensity score–matched (C) analyses**

**P* values not significant after correcting for multiple comparisons.

(SD) unadjusted PDDS scale scores during total follow-up (0.3 [1.0] points) than participants who switched to fingolimod therapy (0.5 [1.1] points) or IFNβ/GA therapy (0.6 [1.1] points) (P = .0141) (Figure 3A). The PDDS scale score change during the 2 years when all the participants were treated with natalizumab did not differ significantly between the treatment groups (P = .1). Older age (P = .0016), male sex (P = .0373), and lower baseline PDDS scale score (P < .0001) were associated with increased PDDS scale score worsening; neither follow-up time (P = .95) nor presence or absence of reported relapse during follow-up (P = .08) was related to PDDS scale score change. After adjusting for the relevant significant covariates of age, sex, and baseline PDDS scale score, the mean PDDS scale score increase during total follow-up was lower in participants who continued taking natalizumab (0.3 points) than in those who switched to fingolimod (0.6 points) or IFNβ/GA (0.7 points) therapy (P = .0036) (Figure 3B).

In the propensity score–matched natalizumab-to-fingolimod and natalizumab-to-IFNβ/GA comparisons, the mean PDDS scale score increase seemed to be lower for participants who continued taking natalizumab than for those who switched to fingolimod or IFNβ/GA therapy, but these differences were not statistically significant after correcting for multiple comparisons (Figure 3C and D).

SF-12 PCS Change

Participants who continued taking natalizumab reported less worsening in physical HRQOL than participants who switched to fingolimod or IFNβ/GA as measured by unadjusted change in SF-12 PCS. During total follow-up, there was no significant change from baseline in SF-12 PCS for participants who continued taking natalizumab (mean [SD], −1.3 [12.8]); in contrast, mean (SD) SF-12 PCS scores worsened significantly from baseline for participants who switched to fingolimod (−4.2 [12.8]) or IFNβ/GA (−4.3 [15.1]) therapy. Differences in mean unadjusted SF-12 PCS change across groups, however, were not significant (P = .1279) (Figure 4A). Older age (P < .0001) and higher baseline SF-12 PCS (P < .0001) predicted greater worsening of SF-12 PCS from baseline; follow-up time (P = .29), sex (P = .14), and relapse activity during follow-up (P = .17) were not related to changes in physical HRQOL. After adjusting for the relevant covariates, participants who continued taking natalizumab had less worsening in mean SF-12 PCS from baseline than those who switched to fingolimod or IFNβ/GA therapy (natalizumab, −1.4; fingolimod, −2.8; IFNβ/GA, −4.6), and differences between the groups were significant (P = .0476) (Figure 4B).

In both propensity score–matched data sets, participants who continued taking natalizumab seemed to have less worsening in SF-12 PCS than those who switched to

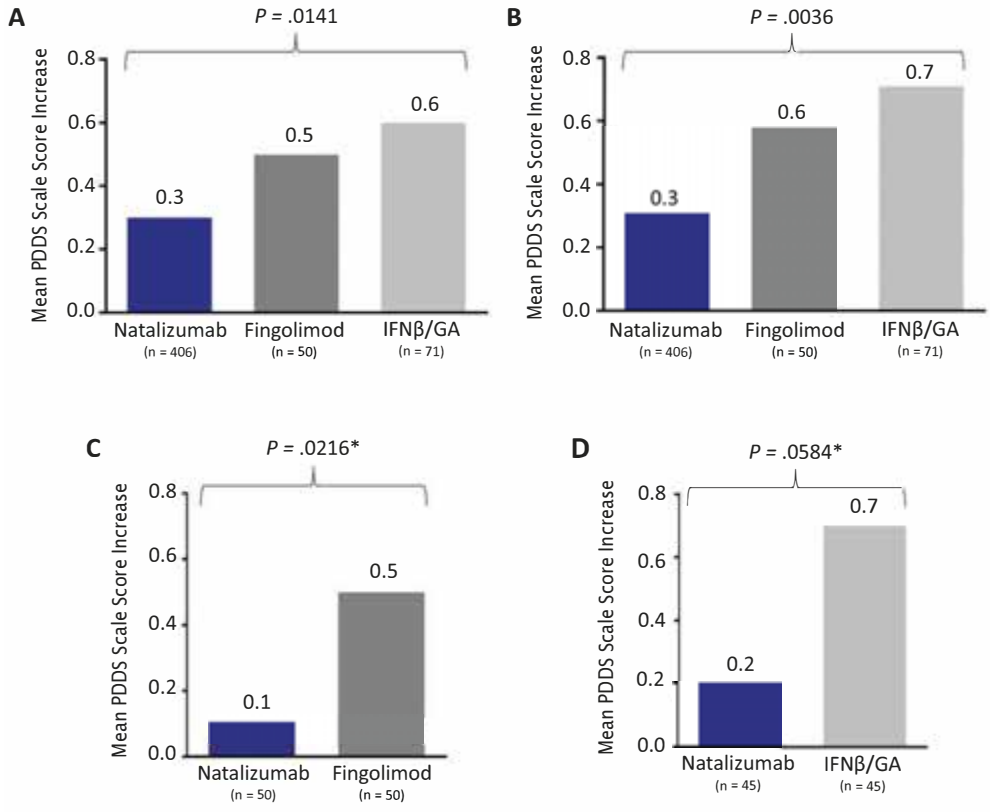

***Figure 3.* Mean Patient-Determined Disease Steps (PDDS) scale score increases determined by unadjusted (A), covariate-adjusted (B), natalizumab-fingolimod propensity score–matched (C), and natalizumab–interferon beta (IFNβ)/glatiramer acetate (GA) propensity score–matched (D) analyses**

**P* values not significant after correcting for multiple comparisons.

another treatment. However, these differences were not statistically significant (Figure 4C and D).

Discussion

In this study, although all the groups had participants who reported worsening, NARCOMS participants who continued taking natalizumab were less likely to report disability progression and had less mean disability increase and less worsening in physical HRQOL than participants who switched to fingolimod or IFNβ/GA therapy after 2 years of natalizumab treatment. These findings were consistent whether disability and physical HRQOL values were unadjusted or adjusted for relevant covariates and whether treatment group comparisons were restricted (by propensity score matching) to participants with similar baseline characteristics and demographics. Previous NARCOMS research has shown that the median time to PDDS scale score change of at least 1 point for those discontinuing DMTs is approximately 5 years.[18] The mean changes in PDDS scale scores, as well as the proportion of patients with an at least 1-point change in PDDS scale score observed in this study, are consistent with the average 4 years of follow-up.

This study focused on the consequences of natalizumab treatment persistence versus switching specifically after 2 years of natalizumab therapy to help better inform common natalizumab treatment decisions made in clinical practice. Physicians often reevaluate natalizumab treatment after 2 years because of PML concerns, but few studies have provided information on the risk of ongoing disease activity for patients who switch from natalizumab treatment at that time.

It was first observed that patients who discontinue natalizumab use are at risk for returning MS disease activity and disability progression when patients in the phase 3 pivotal trials had to discontinue treatment when natalizumab was temporarily withdrawn from the market.[2,19,20] After discontinuation of natalizumab therapy, disease activity returned, with 21% of patients experiencing a relapse within 8 months of stopping treatment,[19] and disability, which had been stable for 2 years with natalizumab use, increased.[2] However, these data provided no information on whether the return of disease activity and disability progression could be mitigated by switching to alternative therapies. In the phase 4, randomized RESTORE trial,[21] which enrolled patients who were stable while taking natalizumab treat-

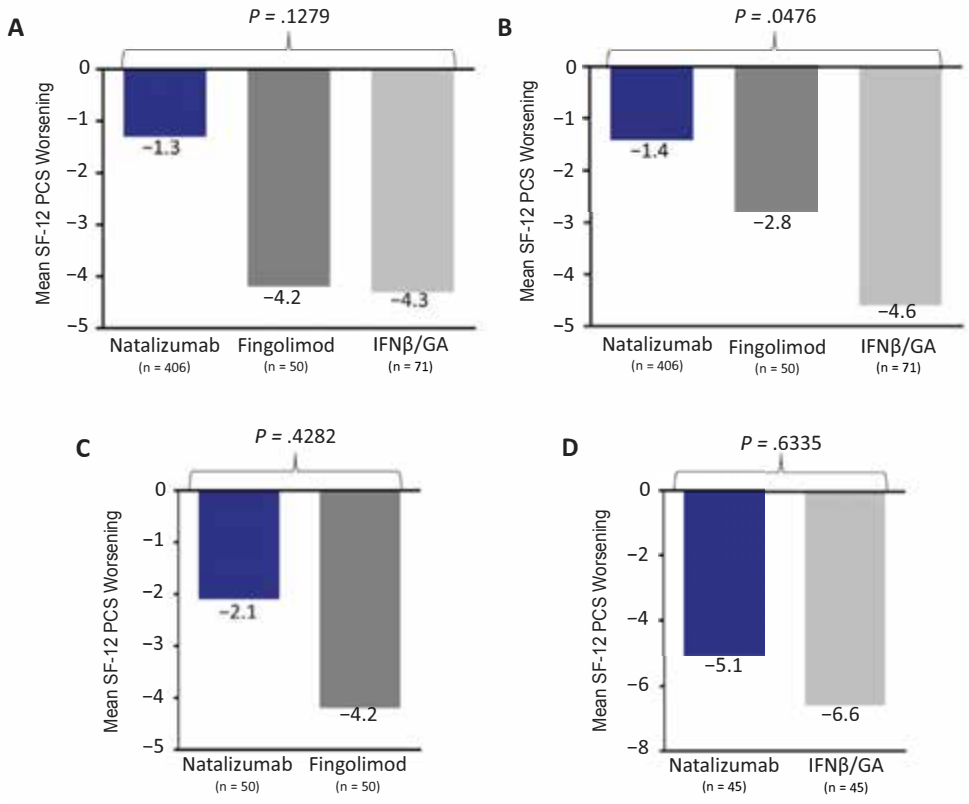

Figure 4. Mean 12-item Short Form Health Status Survey Physical Component Score (SF-12 PCS) worsening determined by unadjusted (A), covariate-adjusted (B), natalizumab-fingolimod propensity score–matched (C), and natalizumab–interferon beta (IFNβ)/glatiramer acetate (GA) propensity score–matched (D) analyses

ment for at least 1 year, 40% of patients randomized to discontinue natalizumab use and receive placebo or other therapies (IFNβ, GA, or methylprednisone) had magnetic resonance imaging (MRI) activity and 19% experienced relapses during the 24-week randomized period, whereas no patients had MRI activity and 4% experienced relapses in the natalizumab-treated group. This study suggested that switching to other therapies would not prevent the return of relapse and MRI disease activity associated with natalizumab treatment interruption, but this study did not address disability progression.[21] The more recent and relevant prospective TY-STOP study (n = 124) demonstrated that after 2 years of natalizumab treatment, patients who continued taking natalizumab had significantly lower mean annualized relapse rates and radiologic disease activity in the following year than those who ceased treatment or switched to IFNβ, GA, or fingolimod therapy. However, differences in mean disability measured by the Expanded Disability Status Scale were not statistically significant.[22] Several other studies have indicated various levels of return of MS disease activity in patients who switched treatments after natalizumab, but they had either small sample sizes or lower requirements for the duration of natalizumab treatment before treatment switch than the present study.[23-27] The results of this study are consistent with those of previous studies and expand on them by quantifying the differences in self-reported disability progression and physical HRQOL changes associated with treatment decisions.

One advantage of the present study's design is that the NARCOMS Registry allowed for tracking of participant outcomes over much longer follow-up durations (median, 4–5 years compared with 1 year in the TY-STOP study). Longer follow-up periods may be particularly important for comparing disability and HRQOL measures between treatment groups because differences in the rate of progression may take several years to manifest as observable, statistically significant differences in means.

Because baseline characteristics were similar between treatment groups in this study and there was no difference in disability progression between groups during the qualifying 2 years of natalizumab treatment, the principal remaining concern in this study was total follow-up time, which differed significantly across treatment groups in the unadjusted analysis. Logistic models, however, demonstrate that both disability progression and change in SF-12 PCS were not related to total follow-up time. Furthermore, similar treatment group differences

were observed in the matched natalizumab-to-fingolimod analysis (when there was no significant difference in total follow-up time) as in the unmatched analyses. This finding suggests that differences between groups in follow-up times do not account for the increase in disability progression and worsening in physical HRQOL associated with switching from natalizumab to other treatments.

Potential confounding from covariates not considered in the models, however, remains a possibility. Indeed, all the logistic models attempting to account for the proportion of patients with disability progression had a statistically significant lack-of-fit test result, suggesting, at least for this measure, that there might be important covariates between the groups that were not considered. For example, patients in this NARCOMS cohort were not questioned at the start about anti–JCV antibody status, which may have been a relevant covariate. It is also possible that factors such as the duration of time between the last dose of natalizumab and the start of the other treatment may have affected the outcome.

The results of the unadjusted, adjusted, and propensity score–matched analyses all favored continuing natalizumab use, but differences between analyses were observed. Of particular note, the magnitude of the differences for mean PDDS scale score increase and the proportion of participants with PDDS scale score change were observed to be larger when participants were matched by propensity score. However, none of the differences were statistically significant in the matched analysis after correcting for multiple comparisons. One potential source of variability arises from the use of only the PDDS scale score and the SF-12 PCS, which, as patient-reported outcome measures, rely on subjective reports of disability. Additional studies with larger sample sizes using subjective and objective outcome measures, such as anti–JCV antibody status, natalizumab dosing information, and MRI changes, are needed to define the differences (if any) between matched participants who continue taking natalizumab and those who switch to other treatments after 2 years.

A limitation of this study design is that, as a retrospective analysis, it does not allow randomization between the treatment groups. Thus, interpretation of the observed treatment effects is subject to potential confounding due to uncontrolled covariates between the groups, including clinical measures that are not available in a self-report registry such as NARCOMS. Logistic models and propensity score matching to adjust for relevant covariates have both been shown to be effective strategies for reducing these potential confounders.[28] However, unlike true randomization, these techniques can address only the measured covariates considered in the models.

The findings of this study highlight the importance of considering the risk of PML and the risk of continued MS disease activity when making treatment decisions after 2 years of natalizumab treatment. Careful individualized assessment of the benefits and risks associated with continuing natalizumab treatment is necessary to maximize the quality of patient care. □

PracticePoints

- In this retrospective analysis of patients with MS who completed 2 years of treatment with natalizumab, those who continued taking natalizumab reported less disability progression and less worsening in health-related quality of life than those who switched to fingolimod or interferon beta/glatiramer acetate therapy.
- When making treatment decisions after 2 years of natalizumab therapy, it is important to consider the benefits of natalizumab therapy and the risk of uncontrolled MS disease activity in addition to the patient's risk of progressive multifocal leukoencephalopathy.

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