

An update on the use of natalizumab in the treatment of multiple sclerosis: appropriate patient selection and special considerations

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Abstract: In the context of an increasing repertoire of multiple sclerosis (MS) therapeutics, choosing the appropriate treatment for an individual patient is becoming increasingly challenging. Natalizumab, a humanized monoclonal antibody directed against alpha4beta1 integrin, has proven short-term and long-term efficacies in terms of relapse rate reduction, prevention of disability progression, and reduction of magnetic resonance imaging-detectable activity. It is well tolerated and has further been shown to improve patients' quality of life. Its use is limited by the risk of progressive multifocal leukoencephalopathy (PML), which occurs at an overall incidence of 3.78 cases per 1,000 patients. Three major risk factors for the occurrence of natalizumab-associated PML have been identified: John Cunningham virus (JCV) seropositivity, prior use of immunosuppressants, and treatment duration ≥ 2 years. Therefore, in patients considered for natalizumab therapy, as well as in patients receiving natalizumab, effective control of MS activity has to be balanced against the risk of an opportunistic central nervous system infection associated with a high risk of significant morbidity or death. Discontinuation of natalizumab is an issue in daily clinical practice, since it is an option to reduce the PML risk. However, after cessation of natalizumab therapy, currently, there is no approved strategy for avoiding postnatalizumab disease reactivation available. In this paper, short-term and long-term safety and efficacy data are reviewed. Issues in daily clinical practice, such as selection of patients, monitoring of patients, and natalizumab discontinuation, are discussed.

Keywords: safety, long-term outcome, pediatric multiple sclerosis, adherence, PML, treatment discontinuation

Introduction

Multiple sclerosis (MS) is a chronic disabling disease of the central nervous system (CNS), affecting >2 million people worldwide.^{1,2} The disease usually starts in early adulthood, but the age range for disease onset is wide, with both pediatric cases and new onset of disease above the age of 50 years;^{3,4} 85%–90% of people with MS experience relapses and remissions of neurologic symptoms (relapsing–remitting MS [RRMS]), particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation.^{5,6} Over time, the majority of untreated patients develops a pattern of progressive worsening with or without superimposed relapses; after 20–25 years, approximately 90% of untreated RRMS patients will have secondary progressive MS.⁷ Compared to the normal population, life expectancy is reduced by 8–12 years in the MS population untreated with a disease-modifying therapy.⁸

The unpredictable disease course, as well as the progressive nature of the disease with ongoing physical and mental impairment, significantly impacts patients' quality of life,⁹ social¹⁰ and family lives,¹¹ and employment status.¹² Although quality-of-life

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reduction occurs in parallel with increasing physical disability,¹³ “invisible” symptoms of MS such as fatigue, as well as cognitive and affective disorders, may contribute significantly to a decrease in quality of life early in the disease course.^{14,15}

Interferons and glatiramer acetate were approved for RRMS in the mid-1990s in the US and Europe on the basis of prospective, randomized, placebo-controlled trials.^{16–19} Treatment response, as measured by relapse rate, disability progression, and magnetic resonance imaging (MRI) parameters, varies considerably among patients. However, approximately 30% of patients have an excellent response to interferon or glatiramer acetate.²⁰ In contrast, occurrences of relapses and MR activity within the first 12–18 months after treatment initiation are good predictors for future increase in Expanded Disability Status Scale (EDSS) scores in patients treated with interferon beta.²¹

Natalizumab, a humanized monoclonal antibody, was approved by the US Food and Drug Administration (FDA) in 2004 on the basis of interim analysis of two phase III studies, Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) and Safety and Efficacy of Natalizumab in Combination with Avonex (R) (IFN β -1a) in Patients with Relapsing-Remitting MS (SENTINEL).^{22,23} The introduction of natalizumab into the market in 2004 was a milestone in MS therapy. Its profound suppression of clinical and MR activities led to the introduction of a new goal in MS therapy, namely, “freedom from disease activity”²⁴ and therefore induced a paradigm shift in MS therapy with lower tolerance to MS activity in patients treated with disease-modifying agents.²⁵ However, only 3 months after its first approval, natalizumab was temporarily withdrawn from the market after the occurrence of three progressive multifocal leukoencephalopathy (PML) cases, two in phase III MS trials^{26,27} and one in a patient with inflammatory bowel disease.²⁸ In 2006, natalizumab was reintroduced into the US market and released in the European Union, together with a Global Risk Management Plan, to be carried out mandatorily in the US (TOUCH®: TYSABRI Outreach: Unified Commitment to Health) and voluntary in the remaining parts of the world (TYGRIS®: TYSABRI Global Observation Program in Safety).

Currently, 13 disease-modifying therapies have been approved by the European Medicines Agency (EMA) and the FDA, including three oral preparations (fingolimod,^{29,30} dimethyl fumarate,^{31,32} and teriflunomide)^{33,34} as well as alemtuzumab given as an intravenous 5 day course in year 1 and a 3 day course in year 2. The increasing armamentarium of

approved MS therapeutics makes treatment decisions more complex, both to clinicians and to patients.

For the herein-presented review, a PubMed search was performed using the terms “natalizumab AND multiple sclerosis”, “natalizumab AND PML”, “natalizumab AND adherence”, “natalizumab AND safety”, and “natalizumab AND fingolimod” without time restriction. Congress abstracts from 2014 and abstracts published before 2014 referred to in the selected articles were included.

Natalizumab: short- and long-term clinical efficacy

Natalizumab is a humanized monoclonal antibody that specifically binds to the α 4 subunit of α 4 β 1 integrin.³⁷ In experimental autoimmune encephalomyelitis, it has been shown to prevent the migration of encephalitogenic T cells into the CNS and to reduce brain inflammation.³⁸ After promising phase II trials,^{39,40} natalizumab was approved on the basis of two large phase III trials, AFFIRM and SENTINEL.^{22,23}

AFFIRM was a prospective, placebo-controlled randomized trial involving 942 patients who had experienced at least one attack during the previous 12 months with a baseline EDSS between 0 and 5.0.²² Patients were randomized in a 2:1 ratio to receive monthly natalizumab 300 mg intravenous infusion or placebo over up to 28 months. After 1 year, the annualized relapse rate (ARR) was reduced by 68% in natalizumab-treated patients compared to placebo group ($P < 0.001$). The risk of 12-week sustained disability progression after 2 years was reduced by 42% compared to placebo ($P < 0.001$).²² In the SENTINEL study, intramuscular interferon-beta1a monotherapy was compared to natalizumab plus interferon-beta1a in 1,171 MS patients with relapse activity during the preceding year.²³ Natalizumab plus interferon beta was superior to interferon beta1a with respect to relapse rate reduction (0.34 vs 0.75; $P < 0.001$) and the risk of 12-week sustained disability progression (24%; $P = 0.02$).²³ Both trials showed a profound suppression of new T2 lesions and contrast-enhancing lesions (83% reduction of new T2 lesions vs placebo in AFFIRM,²² 83% reduction of new T2 lesions vs interferon-beta1a in SENTINEL).²³ When clinical and MR end points were combined, as done in a retrospective analysis of the AFFIRM trial, the proportion of patients free from disease activity over 2 years in the natalizumab group was five-fold greater than in the placebo group (37% vs 7%; $P < 0.0001$).²⁴

Hence, natalizumab may also have beneficial effects on fatigue, cognition, and quality of life. Fatigue is a major

complaint in MS, affecting 54%–95% of patients.⁴¹ It negatively affects patients' quality of life and has a weak correlation with disease duration, relapse rate, or disability.^{42,43} In an one-arm open-label trial on 195 natalizumab-treated patients over 12 months, fatigue was significantly reduced.⁴⁴ Secondary outcome parameters such as cognition, health-related quality of life, sleepiness, and depression were also improved. Another prospective open-label trial on 153 RRMS patients reported an improvement of cognitive function after 1 year and 2 years under natalizumab therapy compared to baseline.⁴⁵ Wickström et al⁴⁶ retrospectively analyzed the working ability in patients with sickness benefit before treatment with natalizumab. They found an increase in patients' working ability-to-employment rate ratio in patients who started natalizumab treatment. Health-related quality of life was incorporated as a tertiary outcome measure in the phase III trials.⁴⁷ As shown in the pooled retrospective analysis, health-related quality of life, as measured by the Short Form (36) Health Survey (SF-36) score, significantly improved during treatment with natalizumab compared to treatment with placebo or interferon beta. The impact of the treatment was more pronounced on the physical aspects compared to the mental aspects of health-related quality of life.⁴⁷

Therefore, although not confirmed by class I evidence, several recent data indicate that natalizumab may have beneficial effects on patients' quality of life, fatigue, cognition, and social performance.^{44–47}

Recently, two phase IV studies evaluated the long-term safety and efficacy of natalizumab therapy (Safety of TYSA-BRI Redosing and Treatment [STRATA] MS;⁴⁸ Tysabri Observational Program [TOP]).⁴⁹ The STRATA MS study enrolled patients from the pivotal phase III trials (AFFIRM,²² SENTINEL,²³ Glatiramer acetate and Natalizumab Combination Evaluation [GLANCE],⁴⁰ and Study of Tysabri Against Rebif in relapsing multiple Sclerosis [STARS] EudraCT number: 2004-004130-14) after natalizumab dosing was suspended due to the occurrence of three PML cases.^{26–28} Upon natalizumab reapproval, eligible patients from the pivotal trials were invited to participate in the open-label, prospective, multinational, single-arm STRATA study.⁴⁸ A total of 1,094 patients were enrolled. According to their original natalizumab feeder studies, patients had been treated previously with interferon beta-1a, glatiramer acetate, natalizumab, or placebo. Median time between last dosing in the pivotal trials and first natalizumab infusion in STRATA was 85 weeks. Totally, 632 patients remained in STRATA at week 240. Overall, the unadjusted relapse rate remained low at 0.17. Patients originally randomized

to natalizumab had a lower ARR versus patients originally randomized to placebo (0.15 vs 0.22). A significant difference between groups was noted during the first year ($P<0.01$) and during the overall study period ($P<0.01$) but not during other individual years.⁴⁸

The EDSS remained stable during the 240-week observation period in both groups. However, it has to be noted that patients who were originally randomized to placebo during the feeder study entered STRATA with a higher baseline EDSS score (3.13 vs 2.90; $P=0.027$) when entering STRATA.⁴⁸

The TOP study is an ongoing, multicenter, prospective, open-label study investigating natalizumab in clinical practice settings.⁴⁹ The primary end point of TOP is long-term safety (incidence and type of serious adverse events). Secondary end points include relapse and EDSS outcomes. At 5 years, 4,821 patients were enrolled. The ARR (95% confidence interval [CI]) decreased from 1.99 (1.95–2.03) in the year before study entry to 0.31 (0.29–0.32) after natalizumab therapy ($P<0.0001$) and remained low during the 5-year period. Although relapse rate reduction was observed across the whole study population, patients with a low EDSS at baseline, fewer relapses in the preceding year, and fewer or no prior immunomodulatory or immunosuppressive therapy had the lowest on-treatment relapse rates. The cumulative risk of confirmed 6-month disease progression, as measured by the EDSS, was 16% over 5 years, while the cumulative probability of confirmed EDSS improvement was 29%. The probability of confirmed EDSS improvement was significantly higher than the probability of confirmed EDSS worsening ($P<0.0001$).⁴⁹

In summary, although differences in patient groups enrolled in STRATA, as well as the study design, cannot exclude unbiased findings, both studies suggest that early treatment initiation may provide a persistent advantage with respect to subsequent suppression of clinical activity.

Natalizumab: safety

The most serious adverse events reported under therapy with natalizumab are PML, infections, and hypersensitivity.^{22,23}

The risk of PML is the major limiting factor in natalizumab therapy. PML is an opportunistic CNS infection, caused by the John Cunningham virus (JCV).⁵⁰ Three major risk factors for natalizumab-associated PML have been identified: 1) positive serostatus for anti-JCV antibodies; 2) prior use of immunosuppressants; and 3) duration of natalizumab therapy.⁵¹ As of December 3, 2014, the overall PML incidence in natalizumab-treated patients was 3.78 cases per

1,000 patients (95% CI: 3.46–4.12 per 1,000 patients),⁵² with the highest risk in JCV-positive patients who have received prior immunosuppression and who have exceeded treatment duration of 24 months (11.2/1,000; 95% CI: 8.6–14.3).⁵² The overall PML incidence in a recently published prospective open-label study was 3.73 cases per 1,000 patients (TOP),⁴⁹ which is consistent with the most recently reported PML risk in the postmarketing setting.

MRI is the most sensitive paraclinical tool in the detection of PML lesions, which can be present up to months before clinical symptoms occur.⁵³ Although PML is usually diagnosed during natalizumab therapy, it has also been reported to occur up to 109 days after natalizumab suspension for reasons other than suspected or laboratory-proven PML.⁵⁴

Natalizumab-associated PML is usually treated with plasma exchange^{55,56} and is often complicated by the occurrence of immune reconstitution inflammatory syndrome (IRIS).^{55,56} While natalizumab-associated PML is fatal in approximately 20% of cases, most patients survive with significant morbidity and irreversible disability.^{55–58} Early detection of PML,⁵⁸ or even detection of PML in clinically asymptomatic patients,⁵⁹ leads to better functional outcomes and reduced mortality.

Infections, reported in 3.2% of patients receiving natalizumab monotherapy, comprised the most frequently reported serious adverse event in the phase III trial, compared to 2.6% of patients on the placebo arm.²² The risk of infection was also assessed in the phase IV open-label studies.^{48,49} Infections, including urinary tract infections and pneumonia, were reported to occur in 1.9%–4% of patients.^{48,49} Opportunistic infections other than PML were found with an incidence of 0.2% in TOP,⁴⁸ which is in line with the reported risk of <1% in phase III trials.^{22,23} The most common reported opportunistic infections other than PML were associated with herpes virus (herpes zoster and herpes meningitis). Serious hypersensitivity reactions (0.5%) and anaphylaxis or anaphylactic shock (0.2%) occurred with a lower incidence in the long-term open-label studies^{48,49} as compared to the phase III trials (1.3% and 0.8%, respectively).^{22,23}

Natalizumab: patient selection

Against the background of an increasing spectrum of MS therapeutics, selection of the appropriate drug for an individual patient at a given time point during the disease course is complex. While neurologists may tend to consider primarily safety and efficacy measures, derived from randomized controlled trials, patients' view on the disease and its treatment may differ from the doctor's perspective.^{60,61} Social,

cognitive and emotional factors, employment status, education, risk tolerance, and his/her ability to adhere to a selected treatment have to be considered. Furthermore, it is difficult to predict treatment response in an individual patient. Apart from disease activity,⁶² different immunologic patterns may influence the response to immune therapies.⁶³

Early and effective disease control has been shown to delay long-term consequences of MS.⁶⁴ On the basis of the available evidence on interferon beta, estimates indicate a 20%–40% reduction of disability progression with the early use of interferon beta.⁶⁴ The observed reduction of MS-associated mortality rates in the interferon beta-1b (IFNB-1b) extension study supports the long-term benefits of interferon beta.⁸

Although the disease course is highly unpredictable, some indicators of early accrual of disability have been identified. A high relapse frequency within the first years after disease onset, a short first interattack interval, and a short interval to reach EDSS score of 3.0 increase the probability of early conversion to secondary progressive MS.⁶⁵ As current immune therapies are only modestly effective in the progressive phase of the disease, it is important to avoid conversion to secondary progressive MS. High T2 lesion load and rapid increase of MR burden correlate with disability 20 years later, although with a high variance.⁶⁶ Conversely, patients with a low T2 lesion load and fewer new T2 lesions show significantly less disability progression over 10 years.⁶⁷ Timely implementation of an effective treatment in patients at risk for early disability may therefore improve patients' long-term outcome.^{64,68}

Natalizumab is highly effective in preventing relapses, disease progression, and MR activity^{22,23} and further has a positive impact on patients' quality of life.⁴⁷ Its wide use is limited by the risk of PML. As per the EMA⁶⁹ and FDA⁷⁰ approval, natalizumab is indicated in patients with one or more relapses during the previous year and nine or more T2 lesions or one contrast-enhancing lesion on MRI despite treatment with interferon beta or glatiramer acetate. In patients with two or more relapses and increase of T2 lesion load or at least one contrast-enhancing lesion on brain MRI, natalizumab may be prescribed independent of the pretreatment.^{69,70}

Assessment of prior immunosuppressive therapy and treatment duration, as well as JCV antibody testing, is performed in order to stratify for the natalizumab-associated PML risk.⁵¹ However, this risk stratification does not allow a precise prediction of the individual PML risk. More recently, it has been suggested that patients with low JCV antibody titers carry a lower natalizumab-associated PML risk than patients with

high titers.⁷¹ Further immunologic markers for the prediction of the individual PML risk, such as leukocyte cell membrane markers or JCV-specific activated T effector memory cells, are currently discussed.⁷² Despite the implementation of risk stratification, the PML incidence has not decreased since 2010.⁷⁴ The reasons for this are currently unknown.⁷³

In JCV-negative patients, the PML risk is considered to be negligible (0.1/1,000; 95% CI: 0.01–0.35),⁵² irrespective of treatment duration, and the benefit of effective disease control outweighs the risk. The reported prevalence of JCV seropositivity in the general MS population is 57.6% and is increasing with age.⁷⁴ The conversion rate per year during natalizumab therapy is approximately 3%,⁷⁵ but this was higher (14.5%) in a recent report.⁷⁶ It is unknown to what extent treatment duration in patients who convert from seronegativity to seropositivity during natalizumab therapy increases the PML risk. In contrast, it is generally advised to stop natalizumab treatment in patients who display all three PML risk factors, ie, JCV seropositivity, prior immunosuppressant use, and treatment duration of >2 years, in whom the PML risk is 1:90.⁷⁷

JCV-positive patients with high disease activity may receive natalizumab at least for 24 months, since during this period, the PML risk appears to be low (0.7/1,000; 95% CI: 0.5–1.0 in patients without prior immunosuppression).⁵² However, after 24 months of treatment, the PML risk increases significantly (5.2/1,000; 95% CI: 4.4–6.2)⁵² and treatment continuation or cessation on the basis of a risk–benefit analysis has to be discussed again. In case of treatment continuation, MR monitoring every 3–6 months has been advised.⁷⁷ The MRI appearance of natalizumab-associated PML is heterogeneous and fluctuating and may also involve cortical gray matter.⁵³ Fluid-attenuated inversion recovery is the most sensitive sequence for detection of PML lesions. Diffusion-weighted imaging may allow detection of active demyelination in PML lesions.⁵³

Keeping in mind the limited treatment period due to the increasing PML risk after 24 months, and thus, the need for sequential therapies, the unknown consequences of sequential immune therapies, and the uncertainty with respect to the individuals' response to another compound, alternative effective options in patients with highly active MS may be considered.

According to the approval,^{78,79} fingolimod is indicated in patients with ≥ 1 relapse during 1-year interferon beta therapy, ≥ 9 T2 lesions, and ≥ 1 contrast-enhancing lesion on MRI. A nonresponder can also be defined as a patient with an unchanged or increased relapse rate or ongoing severe

relapses, as compared to the previous year, or patients with rapidly evolving severe RRMS, defined by ≥ 2 disabling relapses in 1 year, and fulfilling the above-mentioned MR criteria.^{78,79} Although not comparable due to different study protocols and different study populations, fingolimod showed a 54% reduction of ARR,²⁹ while natalizumab showed a 68% reduction in ARR²² in phase III trials. Using MSBase, an international, prospectively acquired cohort study, 578 patients who switched from injectables to either natalizumab or fingolimod were analyzed with respect to disease control.⁸⁰ Quasi-randomization with propensity score-based matching was used in order to select patient groups with comparable baseline characteristics. Although the ARR decreased in both groups (1.5–0.2 in natalizumab vs 1.3–0.4 in fingolimod), there was a 50% relative difference in relapse hazard ($P=0.002$). The rate of sustained disability progression after a mean follow-up of 12 months did not differ between the groups; however, patients who received natalizumab had a 2.8 times higher rate of disability improvement ($P<0.001$).⁸⁰ Another approach used JCV serology in highly active patients to determine treatment with either natalizumab or fingolimod.⁸¹ There was a trend in favor of natalizumab in time to first relapse and a significant difference in the secondary outcome (time to relapse or gadolinium-enhancing lesions; $P=0.041$).⁸¹

Adverse events of special interest in fingolimod-treated patients are reactivation of viral infections, thromboembolic events, macular edema, hypertension, respiratory conditions, and skin cancer and other malignancies.^{29,30} Until now, no clear association between fingolimod and PML has been reported. The interim analysis of the LONGTERM trial (mean follow-up: 3.7 years) revealed no additional safety concerns.⁸² Therefore, fingolimod seems to have a lower risk of severe adverse events, but at least as suggested by recent data, natalizumab may exert a better disease control.

Alemtuzumab has been approved by the EMA in 2013⁸³ and by the FDA in November 2014.⁸⁴ In two phase III studies,^{35,36} the efficacy of alemtuzumab was compared to the effect of an active comparator, ie, subcutaneous interferon beta-1a, which is considered the most effective interferon beta preparation.⁸⁵ In Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE MS I and CARE MS II), alemtuzumab reduced the ARR by 55% ($P<0.0001$) and 49% ($P<0.0001$), respectively, compared with subcutaneous IFNb-1a.^{35,36} The risk of 6-month sustained disability progression was reduced by 30% in CARE MS I (not significant) and by 42% in CARE MS II ($P=0.0084$), respectively.^{35,36} Important adverse events

were infusion-associated reactions (3%), infections (71% vs 56%), and autoimmune adverse events, such as thyroid disorders (34.2%, including thyroid cancers), immune thrombocytopenia (ITP; 1%), nephropathy (0.3%), and cytopenias (<1%).^{35,36} The first case of ITP in the phase II CAMMS223 trial remained unrecognized and died.⁸⁶ Following this index case, a monitoring program was implemented to detect and manage ITP and other serious adverse events.

According to a recent review, alemtuzumab should be reserved for use in patients who fail on first-line disease-modifying therapies.²⁰ However, its wide label, defining active RRMS by clinical or imaging criteria, independent from pretreatment,⁸³ opens the opportunity to select patients on a more individual basis. Again, while both phase III and their extension studies have demonstrated convincing efficacy, the risk of serious adverse events other than PML, as well as a monthly monitoring requirement for 48 months after the last infusion may limit its widespread use.^{35,36}

While randomized prospective studies comparing highly effective compounds such as natalizumab, fingolimod, or alemtuzumab are not available (and probably will never be available), treatment decisions will be taken on an individual risk–benefit analysis. Apart from safety and efficacy parameters, patients' personal factors, risk tolerance, and the ability to adhere to stringent monitoring requirements have to be considered before treatment initiation.

Natalizumab in pediatric MS

In 2%–5% of cases, MS manifests before the age of 18 years.³ The high relapse rate irrespective of the use of first-line immunomodulatory treatment,⁸⁷ the unfavorable long-term prognosis,³ and the high rate of treatment discontinuation (44%) due to intolerability, nonadherence, or lack of efficacy⁸⁸ may suggest an early implementation of highly effective therapies. Natalizumab is contraindicated in patients below the age of 18 years. However, in pediatric MS patients with highly active disease, both clinical and MR activities were significantly reduced compared to the same in the pretreatment period, with good tolerability.^{89,90} Serious adverse event rates, such as infections or anaphylaxis associated with neutralizing antibodies, were similar to or even lower than the reported rates in adults.^{89,90} JCV seropositivity was found in only 38% of patients in one series.⁸⁹ This is in line with previously published data⁹¹ showing a lower seroprevalence in patients below the age of 20 years. However, specific infection rates are so far unknown in the pediatric MS population.

Given the unfavorable long-term prognosis and the high incidence of breakthrough disease in the pediatric MS

population, natalizumab may be considered due to its high efficacy and the lower JCV seroprevalence.

Natalizumab: treatment discontinuation

According to a recent review, adherence to injectable disease-modifying therapies in MS ranges from 41% to 88%,⁹² depending on the definition used. A recent report on 1,381 patients who failed on first-line therapies showed better adherence rates to natalizumab compared with interferon beta or glatiramer acetate.⁹³ The authors concluded that this increased adherence might be due to the requirement for active physician participation and monitoring during natalizumab infusion.⁹³ When compared to fingolimod, however, the risk of being nonadherent to natalizumab was 1.9-fold higher.⁹⁴ Treatment satisfaction and the association between treatment satisfaction ratings and adherence were assessed in 226 MS patients treated with interferon-beta, glatiramer acetate, or natalizumab.⁹⁵ Although there were no significant differences in the overall treatment satisfaction, patients treated with natalizumab reported significantly greater satisfaction with the medication to treat or prevent MS and had higher convenience scores than patients treated with intramuscular interferon beta-1a. The rate of adherence ranged between 53% and 93% in patients receiving interferon or glatiramer acetate, compared to 97% in patients receiving natalizumab.⁹⁵ Therefore, on the basis of the available data, adherence in patients treated with natalizumab may be less critical compared to adherence in patients receiving injectable therapies.

Due to its safety concerns, natalizumab discontinuation is a common issue in daily clinical practice, and cessation of natalizumab therapy is an option to diminish the PML risk.

However, recent data have shown consistently that disease activity returns 3–6 months after natalizumab discontinuation.^{62,96,97} Disease control was incomplete when patients switched to interferon beta, glatiramer acetate, or monthly methylprednisolone in retrospective series.^{96,98,99} The Randomized Treatment Interruption of Natalizumab (RESTORE) trial was a randomized, partially placebo-controlled exploratory study to investigate MS disease activity return during a 24-week interruption of natalizumab.¹⁰⁰ After a 1-year clinically stable period under natalizumab, patients were randomized to placebo, natalizumab, or other therapies (glatiramer acetate, intramuscular interferon-beta1a, or methylprednisolone) for a 24-week period, followed by a follow-up period of 28 weeks, in which patients resumed open-label natalizumab therapy. During the randomized treatment

period, 40% of patients receiving placebo or another therapy showed MR activity, compared to 0% of patients receiving natalizumab. With respect to clinical activity, 19% of the natalizumab group versus 4% on natalizumab experienced relapses. MR activity reoccurred as early as 12 weeks after natalizumab interruption, and clinical activity was first seen as soon as 4–8 weeks after natalizumab interruption.¹⁰⁰ In an observational class III study, clinical and MR activities were significantly lower in patients continuing natalizumab compared with the same in natalizumab quitters or switchers to interferon beta, glatiramer acetate, or fingolimod.¹⁰¹

There are no established guidelines for the timing and choice of treatment in patients who discontinue natalizumab. Pre-natalizumab disease activity⁶² seems to influence postnatalizumab MS activity levels. It is unknown whether neurological deficits acquired during natalizumab interruption may be regained. Switching to interferon or glatiramer acetate does not seem to result in adequate disease control, even if started immediately after natalizumab cessation (class IV evidence, refer results of RESTORE).¹⁰⁰

Fingolimod has shown superior efficacy to intramuscular interferon beta-1a.³⁰ Until now, no association between fingolimod and PML has been confirmed. Considering this and its reported efficacy,^{29,30} fingolimod may be an alternative candidate in patients who want or need to stop natalizumab.

In two observational studies, patients who switched to fingolimod within 6 months after natalizumab discontinuation had reduced ARR compared with those who remained untreated or switched to interferon beta or glatiramer acetate.^{102,103} However, other studies reported increased relapse rates and severe relapses in patients switching to fingolimod within 3–4 months after natalizumab.^{104,105} Investigators from the MSBase Registry¹⁰⁶ studied 89 patients who switched from natalizumab to fingolimod. Patients with a 2- to 4-month washout period had a relative relapse risk of 2.12 compared to the no-washout group.

In a double-blind, placebo-controlled design, clinical and MR activities were investigated in 142 RRMS patients switching from natalizumab to fingolimod after a 8-week, 12-week, or 16-week washout period. Patients with a shorter washout period demonstrated lower clinical and MR activities compared to patients with a longer washout period.¹⁰⁷

Currently, the evidence-based risk of a postnatalizumab relapse outweighs the theoretical increase in PML risk due to overlapping therapies.¹⁰⁸ As indicated by several studies, fingolimod may be an option in patients who want to or need

to discontinue natalizumab, in particular if the washout period is kept short.^{106,107}

There is no information available for the switch from natalizumab to recently licensed oral disease-modifying therapies such as dimethyl fumarate or teriflunomide. However, the recently reported occurrence of PML during dimethyl fumarate monotherapy,¹⁰⁹ as well as with dimethyl fumarate from a compound pharmacy¹¹⁰ and in a patient receiving fumaric acid for psoriasis,¹¹¹ may require caution in JCV-positive patients. From the aspect of disease control, alemtuzumab may be an alternative in highly active patients.^{35,36} However, there is no experience with switching from natalizumab to emerging treatment options using monoclonal antibodies with profound consequences on the immune system.

Conclusion

Natalizumab is a highly effective and well-tolerated therapy for patients with active MS. Recent data have demonstrated sustained efficacy on long-term use with no new safety concerns. Treatment is limited by the risk of PML. Although risk stratification allows estimation of a low, intermediate, or high PML risk, current strategies do not allow risk prediction in the individual patient. Other effective treatment options, such as fingolimod or alemtuzumab, may be considered on an individual basis, since there are no class I comparative trials available. Discontinuation of natalizumab may lead to recurrence of disease activity. Pre-natalizumab activity levels as well as duration of the washout period may influence the postnatalizumab relapse risk. Fingolimod may help to diminish recurrence of disease activity, in particular, if the washout period is kept short. There are no data available on switching from natalizumab to new orals or to other monoclonal antibodies, such as alemtuzumab.

Disclosure

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References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med*. 2000;343(13):938–952.
2. Tullman MJ. Overview of epidemiology, diagnosis, and disease progression associated with multiple sclerosis. *Am J Manag Care*. 2013;19 (2 suppl):S15–S20.

3. Renoux C, Vukusic S, Mikaeloff Y, et al; Adult Neurology Departments KIDMUS Study Group. Natural history of multiple sclerosis with childhood onset. *N Engl J Med*. 2007;356(25):2603–2613.
4. Solaro C, Ponzio M, Moran E, et al. The changing face of multiple sclerosis: prevalence and incidence in an aging population. *Mult Scler*. Epub 2015 Jan 12.
5. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*. 1996;46(4):907–911.
6. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain*. 2009;132(5):1175–1189.
7. Trojano M, Paolicelli D, Bellacosa A, Cataldo S. The transition from relapsing-remitting MS to irreversible disability: clinical evaluation. *Neurol Sci*. 2003;24(suppl 5):S268–S270.
8. Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNB-1b trial. *Neurology*. 2012;78(17):1315–1322.
9. Rudick RA, Miller DM. Health-related quality of life in multiple sclerosis: current evidence, measurement and effects of disease severity and treatment. *CNS Drugs*. 2008;22(10):827–839.
10. Mikula P, Nagyova I, Krokavcova M, et al. Social participation and health-related quality of life in people with multiple sclerosis. *Disabil Health J*. 2015;8(1):29–34.
11. Uccelli MM. The impact of multiple sclerosis on family members: a review of the literature. *Neurodegener Dis Manag*. 2014;4(2):177–185.
12. Sundström P, Nystrom L, Svenningsson A, Fordgren L. Sick leave and professional assistance for multiple sclerosis individuals in Västerbotten County, Northern Sweden. *Mult Scler*. 2003;9(5):515–520.
13. Baumstarck K, Pelletier J, Boucekine M, Auquier P. MusiQoL study group. Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: A 2-year longitudinal study. *Rev Neurol (Paris)*. 2015;171(2):173–180.
14. Putzki N, Fischer J, Gottwald K, et al; “Mensch im Mittelpunkt” Study Group. Quality of life in 1000 patients with early relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2009;16(6):713–720.
15. Fernandez-Jimenez E, Arnett PA. Impact of neurological impairment, depression, cognitive function and coping on quality of life in people with multiple sclerosis: a relative importance analysis. *Mult Scler*. Epub 2014 Dec 22.
16. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43(4):655–661.
17. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol*. 1996;39(3):898–904.
18. PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352(9139):1498–1504.
19. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology*. 1995;45(7):1268–1276.
20. Sorensen PS. New management algorithms in multiple sclerosis. *Curr Opin Neurol*. 2014;27(3):246–259.
21. Sormani MP, Rio J, Tintorè M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler*. 2012;19(5):605–612.
22. Polman CH, O'Connor CW, Havrdova E, et al; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899–910.
23. Rudick RA, Stuart WH, Calabresi PA, et al; SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):911–923.
24. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the natalizumab safety and efficacy in relapsing-remitting multiple sclerosis (AFFIRM) trial. *Lancet Neurol*. 2009;8(3):254–260.
25. Havrdova E, Galetta S, Stefoski D, Comi G. Freedom from disease activity in multiple sclerosis. *Neurology*. 2010;74(suppl 3):S3–S7.
26. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med*. 2005;353(4):375–381.
27. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med*. 2005;353(4):369–374.
28. Van Assche G, Van Ranst M, Sciort R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med*. 2005;353(4):362–368.
29. Kappos L, Radue EW, O'Connor P, et al; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387–402.
30. Cohen JA, Barkhof F, Comi G, et al; TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402–415.
31. Fox RJ, Miller DH, Phillips JT, et al; CONFIRM Study Investigators. CONFIRM Study Investigators. Placebo-controlled phase III study of oral BG-12 or glatiramer acetate in multiple sclerosis. *N Engl J Med*. 2012;367(12):1087–1097.
32. Gold R, Kappos L, Arnold DL, et al; DEFINE Study Investigators. DEFINE Study Investigators. Placebo-controlled phase III study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367(12):1098–1107.
33. O'Connor P, Wolinsky JS, Confavreux C, et al; TEMSO Trial Group. Randomized trial of oral teriflunomide in relapsing multiple sclerosis. *N Engl J Med*. 2011;365(14):1293–1303.
34. Confavreux C, O'Connor P, Comi G, et al; TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2014;383(9923):247–256.
35. Cohen JA, Coles AJ, Arnold DL, et al; CARE-MS I Investigators. Alemtuzumab versus interferon beta-1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012;380(9856):1819–1828.
36. Coles AJ, Twyman CL, Arnold DL, et al; CARE-MS II Investigators. CARE-MS II investigators. *Lancet*. 2012;380(9856):1829–1839.
37. Bielekova B, Becker BL. Monoclonal antibodies in MS: mechanisms of action. *Neurology*. 2010;74(suppl 1):S31–S40.
38. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha1beta integrin. *Nature*. 1992;356(6364):63–66.
39. Tubridy N, Behan PO, Capildeo R, et al. The effect of anti-alpha4 integrin antibody on brain lesion activity in MS. *Neurology*. 1999;53(3):466–472.
40. Goodman AD, Rossman H, Bar-Or A, et al; GLANCE Investigators. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. *Neurology*. 2009;72(9):806–812.
41. Wood B, van der Mei I, Ponsonby AL, et al. Prevalence and occurrence of anxiety, depression and fatigue over time in multiple sclerosis. *Mult Scler*. 2012;19(2):217–224.
42. Bakshi R, Shaikh ZA, Miletich RS, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler*. 2000;6(3):181–185.
43. Bergamaschi R, Romani A, Versino M, Poli R, Cosi V. Clinical aspects of fatigue in multiple sclerosis. *Funct Neurol*. 1997;12(5):247–251.
44. Svenningsson A, Falk E, Celius EG, et al; Tynergy Trial Investigators. Natalizumab reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *PLoS One*. 2013;8(3):e58643.

45. Iaffaldano P, Viterbo RG, Paolicelli D, et al. Impact of natalizumab on cognitive performance and fatigue in relapsing multiple sclerosis: a prospective, open-label, two-year observational study. *PLoS One*. 2012;7(4):35843.
46. Wickström A, Nyström J, Svenningsson A. Improved ability to work after one year of natalizumab treatment in multiple sclerosis. Analysis of disease-specific and work-related factors that influence the effect of treatment. *Mult Scler*. 2013;19(5):622–630.
47. Rudick RA, Miller D, Hass S, et al; AFFIRM and SENTINEL Investigators. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol*. 2007;62(4):335–346.
48. O'Connor P, Goodman A, Kappos L, et al. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS study. *Neurology*. 2014;83(1):78–86.
49. Butzkueven H, Kappos L, Pellegrini F, et al; TYSABRI Observational Program (TOP) Investigators. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. *J Neurol Neurosurg Psychiatry*. 2014;85(11):1190–1197.
50. Ferenczy MW, Marshall LJ, Nelson CD, et al. Molecular biology, epidemiology, and pathogenesis of progressive multifocal leukoencephalopathy, the JC-virus induced demyelinating disease of the human brain. *Clin Microbiol Rev*. 2012;25(3):471–506.
51. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med*. 2012;366(20):1870–1880.
52. Biogen Idec. *Biogen Idec Medinfo*; 2015. Available from: <http://www.Tysabri.com>. Accessed January, 2015.
53. Wattjes MP, Barkhof F. Diagnosis of natalizumab-associated progressive multifocal leukoencephalopathy using MRI. *Curr Opin Neurol*. 2014;27(3):260–270.
54. Fine AJ, Sorbello A, Cortepeter C, Scarazzini L. Progressive multifocal leukoencephalopathy after natalizumab discontinuation. *Ann Neurol*. 2014;75(1):108–115.
55. Dahlhaus S, Hoepner R, Chan A, et al. Disease course and outcome of 15 monocentrically treated natalizumab-associated progressive multifocal leukoencephalopathy patients. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1068–1074.
56. Wenning W, Haghighi A, Laubenberger J, et al. Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. *N Engl J Med*. 2009;361(11):1075–1080.
57. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9(4):438–446.
58. Vermersch P, Kappos L, Gold R, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. *Neurology*. 2011;76(20):1607–1704.
59. Dong-Si T, Richman S, Wattjes MP, et al. Outcome and survival of asymptomatic PML in natalizumab-treated MS patients. *Ann Clin Transl Neurol*. 2014;1(10):755–764.
60. Rothwell PM, McDowell Z, Wong CK, Dorman PJ. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ*. 1997;314(7094):1580–1583.
61. Heesen C, Kleiter I, Nguyen F, et al. Risk perception in natalizumab-treated patients and their neurologists. *Mult Scler*. 2010;16(12):1507–1512.
62. O'Connor PW, Goodman A, Kappos L, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. *Neurology*. 2011;76(22):1858–1865.
63. Lassmann H, Brück W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview [review]. *Brain Pathol*. 2007;17(2):210–218.
64. Sormani MP, Bruzzi P. Can we measure long-term treatment effects in multiple sclerosis? [review]. *Nat Rev Neurol*. 2015;11(3):176–182.
65. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis, a geographically based study. 10. Relapses and long-term disability. *Brain*. 2010;133(7):1914–1929.
66. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse-onset of multiple sclerosis. *Brain*. 2008;131(3):808–817.
67. Simon JH, Kinkel RP, Kollman C, et al; CHAMPIONS Investigators Group. Ten-year follow-up of the "minimal MRI lesion" subgroup from the original CHAMPS multiple sclerosis prevention trial. *Mult Scler*. 2015;21(4):415–422.
68. Trapp BD, Ransohoff R, Rudick RA. Axonal pathology in multiple sclerosis: relationship to neurologic disability [review]. *Curr Opin Neurol*. 1999;12(3):295–302.
69. European Medicine Agency (EMA). *Product Information Tysabri*; 2014. Available from: <http://www.ema.europa.eu>. Accessed December, 2014.
70. US Food and Drug Administration (FDA). *Product Information Tysabri*; 2014. Available from: <http://www.FDA.gov>. Accessed December, 2014.
71. Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC-virus antibody levels in derm or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. 2014;76(6):802–812.
72. Antoniol C, Stankoff B. Immunological markers for PML prediction in MS patients treated with natalizumab. *Front Immunol*. 2015;5:668.
73. Cutter GR, Stüve O. Does risk stratification decrease the risk of natalizumab-associated PML? Where is the evidence? *Mult Scler*. 2014;20(10):1304–1305.
74. Olsson T, Achiron A, Alfredsson L, et al. Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort. *Mult Scler*. 2013;19(11):1533–1538.
75. Lee P, Plavina T, Castro A, et al. A second generation ELISA (STRATIFY JCVM Dx Select TM) for detection of JC virus antibodies in human serum and plasma to support progressive multifocal leukoencephalopathy risk stratification. *J Clin Virol*. 2013;57(2):141–146.
76. Outteryck O, Zéphir H, Salleron J, et al. JC-virus seroconversion in multiple sclerosis patients receiving natalizumab. *Mult Scler*. 2014;20(7):822–829.
77. Tur C, Montalban X. Natalizumab: risk stratification of individual patients with multiple sclerosis. *CNS Drugs*. 2014;28(7):641–648.
78. European Medicine Agency (EMA). *Product Information Gilenya*; 2015. Available from: <http://www.ema.europa.eu>. Accessed January 27, 2015.
79. US Food and Drug Administration (FDA). *Product Information Gilenya*; 2015. Available from: <http://www.fda.gov>. Accessed January 27, 2015.
80. Kalincik T, Horakova D, Spelman T, et al; MSBase Study Group. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol*. 2015;77(3):425–435.
81. Carruthers RL, Rotstein DL, Healy BC, Chitnis T, Weiner HL, Buckle GJ. An observational comparison of natalizumab versus fingolimod using JCV serology to determine therapy. *Mult Scler*. 2014;20(10):1381–1390.
82. Rosenstiel PV, Gottschalk R, Cappiello L, Zhang Y, Said M, Kappos L. Long-term safety of fingolimod: interim evaluation of data from the longterms trial. *Mult Scler Relat Disord*. 2014;3(6):752.
83. European Medicine Agency (EMA). *Product Information Lemtrada*; 2015. Available from: <http://www.ema.europa.eu>. Accessed January 27, 2015.
84. US Food and Drug Administration (FDA). *Lemtrada (Alemtuzumab)*; 2015. Available from: <http://www.fda.org>. Accessed March 31, 2015.
85. Filippini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2013;6:CD008933.
86. Cuker A, Coles AJ, Sullivan H, et al. A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. *Blood*. 2011;118(24):6299–6305.
87. Gorman M, Healy B, Polgar-Turcsanyi M, Chitnis T. Increased relapse-rate in pediatric-onset compared to adult-onset multiple sclerosis. *Arch Neurol*. 2009;66(1):54–59.

88. Yeh EA, Waubant E, Krupp LB, et al; Network of Pediatric MS Centers of Excellence. Multiple sclerosis therapies in pediatric patients with refractory disease. *Arch Neurol*. 2011;68(4):437–444.
89. Kornek B, Aboul-Enein F, Rostasy K, et al. Natalizumab therapy for highly active multiple sclerosis. *JAMA Neurol*. 2013;70(4):469–475.
90. Ghezzi A, Pozzilli C, Grimaldi LM, et al; Italian MS Study Group. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. *Mult Scler*. 2013;19(8):1106–1112.
91. Trampe AK, Hemmelmann C, Stroet A, et al. Anti-JC virus antibodies in a large German natalizumab-treated multiple sclerosis cohort. *Neurology*. 2012;78(22):1736–1742.
92. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review on the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm*. 2013;10(1 suppl A):S24–S40.
93. Halpern R, Agarwal S, Borton L, Oneacre K, Lopez-Bresnahan MV. Adherence and persistence among multiple sclerosis patients after one immunomodulatory failure: retrospective claims analysis. *Adv Ther*. 2011;28(9):761–775.
94. Bergvall N, Petrilla AA, Karkare SU, et al. Persistence with and adherence to fingolimod compared with other disease-modifying therapies for the treatment of multiple sclerosis: a retrospective US database claims analysis. *J Med Econ*. 2014;17(10):696–707.
95. Glanz BI, Musallam A, Rintell DJ, et al. Treatment satisfaction in multiple sclerosis. *Int J MS Care*. 2014;16(2):68–75.
96. Borriello G, Prosperini L, Mancinelli C, Gianni C, Fubelli F, Pozzilli C. Pulse monthly steroids during an elective interruption of natalizumab: a post-marketing study. *Eur J Neurol*. 2012;19(5):783–788.
97. West TW, Cree BA. Natalizumab dosage suspension: are we helping or hurting? *Ann Neurol*. 2010;68(3):395–399.
98. Rossi S, Motta C, Studer V, et al. Effect of glatiramer acetate on disease reactivation in MS patients discontinuing natalizumab. *Eur J Neurol*. 2013;20(1):87–94.
99. Stüve O, Cravens PD, Frohman EM, et al. Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. *Neurology*. 2009;72(5):396–401.
100. Fox RJ, Cree BAC, De Sèze J, et al. MS disease activity in RESTORE: a randomized 24-week natalizumab interruption study. *Neurology*. 2014;82(17):1491–1498.
101. Clerico M, Schiavetti I, De Mercanti SF, et al. Treatment of relapsing remitting multiple sclerosis after 24 doses of natalizumab. Evidence from an Italian spontaneous, prospective, and observational study (TY-STOP Study). *JAMA Neurol*. 2014;71(8):954–960.
102. Havla J, Tackenberg B, Hellwig K, et al. Fingolimod reduces recurrence of disease activity after natalizumab withdrawal in multiple sclerosis. *J Neurol*. 2013;260(5):1382–1387.
103. Laroni A, Brogi D, Milesi V, Abate L, Uccelli V, Mancardi G. Early switch to fingolimod may decrease the risk to disease recurrence after natalizumab interruption. *Mult Scler*. 2013;19(9):1236–1237.
104. Centonze D, Rossi S, Rinaldi F, Gallo P. Severe relapses under fingolimod treatment prescribed after natalizumab. *Neurology*. 2012;79(19):2004–2005.
105. Sempere AP, Martín-Medina P, Berenguer-Ruiz L, et al. Switching from natalizumab to fingolimod: an observational study. *Acta Neurol Scand*. 2013;128:e6–e10.
106. Jokubaitis VG, Li V, Kalincik T, et al; MSBase Study Group. Fingolimod after natalizumab and the risk of short-term relapse. *Neurology*. 2014;82:1204–1211.
107. Kappos L. Disease control and safety in relapsing-remitting multiple sclerosis (RRMS) patients switching from natalizumab to fingolimod: a 32 week, rater- and patient blind, randomized, parallel-group study (TOFINGO). *Mult Scler*. 2013;19(S1):50. Oral presentation 167.
108. Giovannoni G, Naismith RT. Natalizumab to fingolimod washout in patients at risk for PML: when good intentions yield bad outcomes. *Neurology*. 2014;82(14):1196–1197.
109. FDA. *FDA Drug Safety Communication: FDA Warns About Case of Rare Brain Infection PML with MS Drug Tecfidera*; 2014. Available from: www.fda.gov/Drugs/DrugSafety/ucm424625.htm. Accessed January 25, 2015.
110. Ermis U, Wiesmann M, Nolte K, et al. Fumaric acid-associated progressive multifocal leukoencephalopathy (PML), treatment and survival in a patient with psoriasis. *Kongress der Deutschen Gesellschaft für Neurologie*. 2011;14:30–40.
111. van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. *N Engl J Med*. 2013;368(17):1659–1661.

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