

The role of natalizumab in the treatment of multiple sclerosis: benefits and risks

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Abstract: Natalizumab, a monoclonal antibody that blocks lymphocyte infiltration in the central nervous system, is a valuable tool in the treatment of relapsing forms of multiple sclerosis (MS). In a phase III clinical trial comparing natalizumab with placebo over 2 years, natalizumab reduced annualized relapse rate by 68%, 12-week confirmed disability progression by 42%, and reduced contrast-enhancing lesions by 92%. In *post hoc* analyses, natalizumab treatment was associated with 37% of patients achieving no evidence of disease activity (*versus* 7% on placebo) and 30% achieving sustained disability improvement (*versus* 19% on placebo). Natalizumab did not achieve a statistically significant primary composite disability outcome in a trial of 887 patients with secondary progressive MS, but it did demonstrate a benefit on a prespecified component of the 9-Hole Peg Test. The greatest risk of natalizumab treatment is progressive multifocal leukoencephalopathy (PML), with a 23% mortality rate. Risk stratification on the basis of immunosuppressant exposure, natalizumab treatment duration and anti-John Cunningham virus (JCV) antibody status and index has greatly improved clinical decision making. Other potential serious natalizumab-associated risks reported in clinical trials and postmarketing settings include infusion reactions, hepatotoxicity and rare, serious opportunistic infections. With more than a decade of continuous postmarketing experience, natalizumab remains a very effective option for patients with relapsing forms of MS. To optimize appropriate selection of natalizumab for patients with relapsing MS, however, a thorough understanding of individual patient risk factors for PML or other adverse events is also required.

Keywords: multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy

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Introduction

As a highly effective treatment for relapsing multiple sclerosis (MS), natalizumab has provided dramatic benefits to patients with MS for more than a decade. Natalizumab prevents lymphocytes from adhering to the endothelium of the blood–brain barrier, which reduces lymphocyte infiltration into the central nervous system (CNS). Specifically, natalizumab binds onto the α_4 subunit of the $\alpha_4\beta_1$ integrin on the surface of lymphocytes, blocking attachment to the vascular cell adhesion molecule 1 on the vascular endothelial cells in the brain and spinal cord blood vessels.¹ The robust effect on the blood–brain barrier has led to impressive therapeutic benefits on annualized relapse rates (ARRs) and gadolinium-enhanced lesions on

magnetic resonance imaging (MRI) in relapsing MS.² This mechanism, however, impacts immune surveillance in the CNS, as manifested in progressive multifocal leukoencephalopathy (PML). To optimize appropriate selection of natalizumab for patients with relapsing MS, a thorough understanding of individual MS patient risk factors for PML or other adverse events is required.

Phase III clinical trial results

AFFIRM: placebo-controlled trial in patients with relapsing–remitting MS

The 2-year, phase III Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis

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trial (AFFIRM) [ClinicalTrials.gov identifier: NCT00027300] investigated the efficacy of natalizumab in patients with relapsing–remitting MS. Using a 2:1 natalizumab to placebo randomization, 942 patients were enrolled in the study. The two prespecified primary outcomes, rate of clinical relapse at 1 year and cumulative probability of sustained progression of disability at 2 years, were met. Twelve-week confirmed disability progression occurred in 17% of patients on natalizumab and in 29% of patients on placebo, yielding a 42% relative benefit (hazard ratio 0.58; $p < 0.001$). The ARR at year 1 was 0.26 on natalizumab and 0.81 on placebo (68% benefit, $p < 0.001$). Over 2 years, the relative reduction in the ARR was maintained at 68% (0.23 on natalizumab, 0.73 on placebo; $p < 0.001$).³

The AFFIRM trial also highlighted the robust effects of natalizumab on MRI assessments of disease activity. New or enlarging T2-hyperintense lesions were reduced by 83% over 2 years with natalizumab treatment compared with placebo ($p < 0.001$). Overall, 57% of patients on natalizumab were free of new or enlarging T2-hyperintense lesions over 2 years compared with only 15% of patients on placebo. Natalizumab treatment was associated with a 92% reduction in contrast-enhanced lesions ($p < 0.001$). Based on an MRI scan at 2 years, a remarkable 97% of patients were free of contrast-enhanced lesions compared with 72% of patients on placebo.³

The mean change in T1-hypointense lesion volume increased by 548 mm³ on placebo and decreased by 1508 mm³ on natalizumab ($p < 0.001$). Similarly, the reduction median percentage of change in T1-hypointense lesion volume compared with placebo over 2 years was significant (–23.5% versus –1.5%, respectively; $p < 0.001$). Over the 2-year study, brain parenchymal fraction (BPF) reductions were not significant between natalizumab and placebo (–0.80% and –0.82%, respectively; $p = 0.822$). During the first year, natalizumab-treated patients had greater brain volume loss than patients on placebo (–0.56% versus –0.40%, respectively; $p = 0.002$). BPF was substantially reduced with natalizumab treatment in the second year to –0.24% compared with –0.43% on placebo ($p = 0.004$).⁴ This rate of brain volume loss on natalizumab over the second year (–0.24%) is similar to the 0.1–0.3% per year rate in healthy individuals due to age-related decline.⁵

No evidence of disease activity (NEDA) is an ideal treatment goal for patients with MS.⁶ In the AFFIRM trial, 37% of natalizumab-treated patients compared with 7% of placebo patients ($p < 0.0001$) achieved this goal. NEDA was defined as no relapses, no 12-week confirmed Expanded Disability Status Scale (EDSS) progression and no contrast-enhancing or new or enlarging T2 lesions over 2 years.⁷ The highest NEDA rates were in natalizumab-treated subgroups with age younger than 35 years, disease duration less than 2 years, one or fewer relapses in the past year, EDSS less than 3.0 and no contrast-enhancing lesions on baseline scan. For those natalizumab-treated patients with one or more contrast-enhancing lesion on baseline scan, 30.8% achieved NEDA at 2 years compared with only 2.2% of placebo-treated patients.⁸ Natalizumab treatment also increased the likelihood of sustained disability improvement confirmed at 12 weeks. In a *post hoc* analysis, 29.6% of natalizumab-treated patients and 18.7% of placebo-treated patients in the AFFIRM trial had sustained disability improvement (69% relative benefit, $p = 0.006$).⁹

The safety of natalizumab was examined in the AFFIRM study. Serious adverse events occurred in 19% of natalizumab-treated patients compared with 24% treated with placebo ($p = 0.06$). Relapse of MS was the most frequent serious adverse event and was more common in the placebo arm (13% versus 6% on natalizumab, $p < 0.001$). Adverse events reported more commonly in patients on natalizumab than placebo included headache (38% versus 33%, respectively), fatigue (27% versus 21%, respectively), arthralgia (19% versus 14%, respectively), allergic reaction (9% versus 4%, respectively) and dermatitis (7% versus 4%, respectively). Serious adverse events that occurred in less than 1% of patients receiving natalizumab but in no placebo-treated patients included anaphylactic reaction, hypersensitivity reaction, urinary tract infection and cervical dysplasia. One patient treated with natalizumab died of recurrence of malignant melanoma; in retrospect, the patient had a new skin lesion at the time of natalizumab initiation. Another patient died from alcohol intoxication after 25 doses of natalizumab. Six percent of natalizumab-treated patients developed persistent neutralizing antibodies, confirmed at least once more than 42 days apart, and had an increase in infusion-related adverse events and a loss of efficacy of natalizumab.³

SENTINEL: natalizumab in combination with interferon in patients with relapsing–remitting MS

In the SENTINEL (The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis) trial [ClinicalTrials.gov identifier: NCT00030966], 1171 patients with relapsing–remitting MS who had relapsing disease in the past year on interferon β 1a were randomly assigned to interferon β 1a intramuscularly plus either 300 mg natalizumab infusion or placebo infusion every 4 weeks for up to 116 weeks. Twenty-nine percent of patients on interferon β 1a and placebo had sustained disability progression compared with 23% of patients in the combination group (24% relative reduction, $p = 0.02$). ARR was 0.34 on the combination of interferon and natalizumab *versus* 0.75 on interferon and placebo (55% relative reduction, $p < 0.001$).¹⁰

Natalizumab-associated adverse events, including PML, were reported in the SENTINEL trial. Infusion reactions occurred in 24% of combination-treated patients as opposed to 20% of interferon-alone treated patients. Serious infections occurred in 2.7% of patients on combination treatment and 2.9% of patients on interferon alone.¹⁰ A patient on combination treatment developed PML after 28 doses of natalizumab that resulted in disabling ataxia, cognitive impairment, mild neglect and mild left hemiparesis.¹¹ Another patient died of PML after 37 natalizumab infusions in combination with interferon injections in the open-label extension of the SENTINEL trial.¹²

ASCEND: natalizumab in patients with secondary progressive MS

To evaluate efficacy and safety in secondary progressive MS (SPMS), natalizumab was compared with placebo in the randomized, double-blind, multicenter ASCEND trial [ClinicalTrials.gov identifier: NCT01416181] of 887 patients over 96 weeks. To be eligible, patients had to have disability progression unrelated to relapses in the year prior to enrollment and an EDSS of 3.0–6.5 (mean 5.2, 63% of patients had EDSS 6.0–6.5). Baseline characteristics of the population studied included mean age of 47 years, 62% female, mean 16.5 years since first MS symptoms, mean 4.8 years since SPMS diagnosis, 24% with enhancing lesions and 29% with relapses in the past 2 years. Natalizumab did not achieve the primary composite disability outcome in this population; the

proportion of progressors was numerically but not statistically higher in the placebo group than the natalizumab group (48% *versus* 44%, respectively; $p = 0.287$). Natalizumab demonstrated a significant benefit on the 9-Hole Peg Test, a pre-specified component of the primary endpoint ($p = 0.001$). Twenty-three percent of placebo-treated patients progressed in disability on this upper extremity function test compared with 15% of natalizumab-treated patients. In terms of common adverse events, nasopharyngitis and upper respiratory infections occurred more frequently on natalizumab, while MS relapses occurred more frequently on placebo.¹³

Progressive multifocal leukoencephalopathy

Prevalence and clinical outcomes

Approximately 167,300 patients have been treated with natalizumab in the postmarketing setting worldwide as of 28 February 2017. In addition, natalizumab exposure has now reached more than 559,749 patient-years. A total of 714 cases of PML (711 MS related and three Crohn's disease related) have been confirmed. Natalizumab exposure duration prior to PML has ranged from 8 to 134 doses. Fourteen percent of patients had fewer than 25 doses. As of 6 March 2017, 23% of patients diagnosed with natalizumab-associated PML have died. Based on postmarketing cases as of August 2013, mean time from PML diagnosis to death was 4.7 months.¹⁴ The diagnosis of PML is typically based on MRI and detection of John Cunningham virus (JCV) DNA *via* polymerase chain reaction in the cerebrospinal fluid.¹⁵ Factors associated with improved survival are younger age, lower JCV viral load and more localized brain involvement demonstrated by MRI at the time of diagnosis, as well as less functional disability prior to diagnosis.¹⁶ A single center in Germany reported survival of 31 out of 32 natalizumab-treated patients with PML. Worse functional outcome from PML was associated with higher age, higher initial JCV copy number in cerebrospinal fluid and more extensive PML disease on MRI.¹⁷

PML risk factors

The presence of serum antibodies to JCV is a known risk factor for the development of PML. Anti-JCV antibodies are detected using a two-step enzyme-linked immunosorbent assay and

Table 1. PML risk analysis of 32,801 natalizumab-treated patients with multiple sclerosis based on duration of treatment, immunosuppression exposure and anti-JCV antibody index.*

Natalizumab exposure, months	Anti-JCV antibody positive patients without prior IS use, per 1000 patients (95% CI)			Patients with prior IS use, per 1000 patients (95% CI)
	Index ≤ 0.9	Index $>0.9-\leq 1.5$	Index >1.5	
1–12	0.01 [0–0.03]	0.1 [0–0.2]	0.2 [0–0.5]	0.3 [0–1.9]
13–24	0.05 [0–0.1]	0.3 [0–0.6]	0.9 [0.3–1.6]	0.4 [0–2.3]
25–36	0.2 [0–0.4]	0.8 [0.1–1.5]	2.6 [1.4–3.9]	3.6 [1.4–7.4]
37–48	0.4 [0–1.0]	2.0 [0.2–3.8]	6.8 [4.4–9.1]	8.3 [4.3–14.5]
49–60	0.5 [0–1.2]	2.4 [0–2–4.5]	7.9 [4.9–10.9]	8.4 [3.7–16.6]
61–72	0.6 [0–1.5]	3.0 [0.2–5.8]	10 [5.6–14.4]	5.5 [1.1–16.0]

*Adapted from EMA (2017)¹⁹ and Koendgen et al. (2016).²⁰
CI, confidence interval; IS, immunosuppressant; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy.

antibody levels are reported as an index value (titer equivalent). For patients with MS without immunosuppressant medication exposure, the median anti-JCV antibody index is higher for patients with PML than those without PML (2.4 *versus* 1.4, respectively; $p < 0.0001$). The median index values in patients with MS with prior immunosuppressant medication exposure was the same regardless of PML status (1.6 for both groups, $p = 0.82$).¹⁸

The major risk factors for PML on natalizumab therapy are anti-JCV-positive status (including index), prior immunosuppressant medication use and natalizumab treatment duration. An analysis of these risk factors was performed on 32,801 natalizumab-treated patients from four large post-marketing studies. For patients who were anti-JCV antibody negative, the estimated risk was 0.1/1000 patients (95% confidence interval 0.01–0.35). Table 1 demonstrates increasing risk of PML with higher index (especially >1.5), longer treatment duration and prior immunosuppressant use (including mitoxantrone, methotrexate, azathioprine, cyclophosphamide or mycophenolate).^{19,20} Higher anti-JCV antibody index values suggests an enhanced replication of the JCV outside the kidney, such as in the brain.²¹ Despite a widespread understanding of these risk factors, the overall rate of natalizumab-related PML is still increasing.²² However, since 2013, the rate of this increased incidence of natalizumab-associated PML has slowed.²³

Only five natalizumab-treated patients with MS who developed PML were anti-JCV antibody negative prior to PML development (Biogen,

personal communication, 27 October 2016). One of the cases occurred in a 70-year-old woman without immunosuppressant medication exposure who was anti-JCV antibody negative 2 weeks prior to her first symptoms of PML.²⁴ The estimated false negative rate of the assay for anti-JCV antibody status is 2.2%.²⁵

Natalizumab-treated patients with MS who are anti-JCV antibody negative are at risk of seroconversion to become anti-JCV antibody positive.²⁶ This rate is higher than the annualized PML rate of 1–2% in the general population.²⁷ Biogen has reported that the rate of seroconversion from anti-JCV antibody negative to positive and remaining positive on subsequent testing is 3–8% annually.¹⁴ However, some cohorts have had higher seroconversion rates; annual rates from negative to positive serostatus were 10.3% in 339 German and 8.5% in 243 French patients with MS.²⁸ In the STRATIFY-2 study [ClinicalTrials.gov identifier: NCT01070836], rates of serostatus change to anti-JCV antibody positive were similar in patients who were or were not treated with natalizumab.²⁹

L-selectin (CD62L) has been proposed as another biomarker for PML risk. An unusually low percentage of CD4+ cells express CD62L on their surface in patients with MS on long-term natalizumab treatment compared with those not on natalizumab. An even lower percentage of CD62L-expressing CD4+ cells were found in patients with MS who developed natalizumab-related PML.^{30,31} In one study using thawed peripheral blood mononuclear cells (PBMCs), low CD62L values increased a patient's relative

risk of developing PML by 55-fold ($p < 0.0001$).³² The use of CD62L as a biomarker for PML risk was not validated by Biogen using cryopreserved PBMCs in a study of 21 patients who developed PML and 104 matched natalizumab-treated patients without PML. Lymphocyte viability when thawed strongly affects the percentage of cells expressing CD62L.³³

MRI monitoring

Earlier detection of PML through the use of periodic MRI scans, prior to the onset of symptoms, is associated with favorable survival and functional outcomes compared with PML diagnosis after the onset of symptoms.^{16,34} In an analysis of 372 postmarketing natalizumab PML cases as of 5 June 2013, 30 (8.1%) were classified as asymptomatic.¹⁴ Asymptomatic PML lesions on MRI imaging are often in the frontal lobe (77.8%), unilobar (66.7%), nonenhancing (86.7%), high-signal intensity on diffusion imaging (60%) and involve the mixed cortical gray matter and juxtacortical white matter (72.2%).¹⁵

To better detect PML early, the MAGNIMS (Magnetic Resonance Imaging in MS) study group recommended MRI screening every 3–4 months using FLAIR (fluid-attenuated inversion recovery), T2-weighted, and diffusion-weighted sequences in patients at high risk for PML (i.e. those who were anti-JCV seropositive and had treatment durations of >18 months). Anti-JCV seronegative patients should be imaged annually using the same protocol.³⁵

Alternative dosing and dose interruption

To further reduce PML risk, one strategy being explored is reducing the frequency of natalizumab dosing. Based on a retrospective chart review of 2004 natalizumab-treated patients from nine US MS centers, 905 patients receiving extended dosing (ranging from every 4 weeks and 3 days to every 8 weeks and 5 days) were less likely to have new T2 lesions and relapses than 1099 patients on standard dosing. However, 10% of extended-dosing patients had contrast-enhancing lesions compared with 6% on standard dosing. The four cases of PML in this cohort were in the standard dosing patients.³⁶ Importantly, off-label dosing regimens have not been proven. In addition, the retrospective data analysis was not randomized, so selection bias regarding dosing frequency was introduced.

Previous attempts to reduce PML risk using 6-month planned dosing interruption backfired; 27.9% of 68 patients in one series had relapsing disease within 6 months, often with severe disability progression.³⁷ In the RESTORE trial [ClinicalTrials.gov identifier: NCT01071083], 46% of patients randomized to placebo for 24 weeks of dose interruption had one new contrast-enhanced lesion of over 0.8 cm³ or two or more enhanced lesions of any size compared with no patients on continuous natalizumab treatment ($N = 41$ for placebo, $N = 45$ for natalizumab). Over 24 weeks, 4% of continuous natalizumab-treated patients relapsed *versus* 17% on placebo.³⁸ Based on analysis of phase III natalizumab clinical trials and extensions, the mean number of enhancing lesions gradually increased over 6 months up to placebo-treated levels after natalizumab discontinuation.³⁹ Rebound or overshooting of MRI activity beyond baseline pre-natalizumab MRI activity after natalizumab discontinuation has been reported.⁴⁰

Switching therapy from natalizumab

If a patient becomes anti-JCV antibody positive on natalizumab treatment or has a rising antibody index, both the clinician and the patient should jointly discuss the risks and benefits of continuing natalizumab or switching therapy. Switching to an alternative disease-modifying therapy (DMT) carries the risk of development of worsening long-term disability progression.⁴¹ However, patients must understand the full consequences of the risk of PML, including death, *versus* the risk of worsening, and potentially permanent, disability.

Switching from natalizumab to fingolimod has been investigated in multicenter trials consisting of more than 70% of patients with anti-JCV antibody positive MS. Relapses during the transition were lowest, with a 12-week or less washout, and active MRI lesions were lowest with an 8-week washout.^{42,43} In an Italian multicenter, prospective, observational cohort, the cumulative probability of a first relapse 1 year after switching from natalizumab to fingolimod was 15.01% compared with 26.84% after switching to interferon or glatiramer acetate.⁴⁴ LaGanke *et al.* reported no relapses in switching 200 patients from natalizumab to alemtuzumab at their center. Of the 162 patients with EDSS measurements, EDSS improved in 69 patients and worsened in 2 patients switched to alemtuzumab. Only 3 out of 160 patients had new FLAIR

lesions on MRI imaging.⁴⁵ MRI imaging to screen for pre-existing PML prior to switching to alemtuzumab is important since a death occurred in this clinical setting.⁴⁶

Based on Swedish register data of 256 patients switched from natalizumab due to anti-JCV antibody positive status, fewer relapses occurred in the cohort switched to rituximab than fingolimod (1.8% versus 17.6%) over 1.5 years after the cessation of natalizumab. Contrast-enhancing lesions were also less common on rituximab versus fingolimod (1.4% versus 24.2%).⁴⁷ Rituximab, however, lacks regulatory approval for MS. Analysis of a trial switching patients from natalizumab to dimethyl fumarate reported a 19.6% risk of protocol-defined relapse over 1 year in 506 patients. The ARR was 0.114 on natalizumab and 0.248 on dimethyl fumarate.⁴⁸ Daclizumab is also being studied in a natalizumab-switch study [ClinicalTrials.gov identifier: NCT02881567].⁴⁹

Postmarketing safety and effectiveness studies

TYGRIS

Large postmarketing observational studies have further examined both the effectiveness and safety of natalizumab.⁵⁰ The Tysabri Global Observational Program in Safety (TYGRIS) study [ClinicalTrials.gov identifier: NCT00477113] prospectively followed 4938 patients with MS to determine the rate of serious adverse events including infections and malignancies. PML occurred in 3 out of 2207 US patients and 41 out of 4227 European/Canadian patients. In 23 of the total PML cases, anti-JCV antibody status was positive for 6 or more months prior to PML diagnosis, consistent with previous observations^{51,52}; antibody status was unknown or not reported in the other 21 cases. Eleven of the total 6434 patients experienced other serious opportunistic infections, including tuberculosis, aspergilloma, atypical mycobacterial infection, *Candida* pneumonia, cryptococcal fungemia/meningitis and herpetic meningoencephalitis. No malignancy signal was revealed; overall incidence of malignancy rates on natalizumab treatment had 95% confidence intervals encompassing incidence rates in the European/Canadian and US populations. Of the 77 deaths, 94.8% of the fatalities were considered not related or unlikely to be related to natalizumab.⁵³

TOP and MSBase

The Tysabri (natalizumab) Observational Program (TOP) [ClinicalTrials.gov identifier: NCT00493298] is an open-label, nonrandomized, 10-year observational study initiated in July 2007.⁵⁴ The study follows patients with MS on natalizumab who switched from injectable interferon or glatiramer acetate ($N = 4688$), switched from fingolimod ($N = 162$) or were treatment naïve ($N = 552$). Switching to natalizumab resulted in substantially lower ARRs than baseline rates (1.99–0.2, respectively, from injectable DMTs to natalizumab, 2.05–0.35, respectively, from fingolimod to natalizumab, and 2.06–0.16, respectively, to natalizumab in the treatment-naïve group). After switching to natalizumab for 96 weeks, 24-week confirmed disability improvement occurred in 21.4% of patients switching from fingolimod, 22.1% of patients switching from injectable DMTs and 33.2% of treatment-naïve patients. PML occurred in 0.7% of injectable-DMT switch patients, 0.6% of fingolimod switch patients and 0.4% of treatment-naïve patients.⁵⁵ Of the 496 patients who completed 4 years of natalizumab treatment, 83.5% of patients remained free of 24-week confirmed disability over 4 years (10.9% had progressive disease over months 0–24 and 6.3% over months 25–48).⁵⁶

This ongoing 10-year observational study also provides insight into the safety profile of natalizumab. Out of the 4821 patients enrolled, 18 developed PML, with 89% survival. Twelve other serious opportunistic infections were reported, including two cases of herpes meningitides, two cases of herpes zoster and two cases of pneumonia. Twenty-four patients developed 12 types of malignancies, including 7 cases of breast cancer. The causes of the nine deaths were three suicides, two pulmonary emboli and single cases each of urosepsis (in a patient with PML), drowning, autonomic nervous system imbalance and thermal burn.⁵⁴

Effectiveness of natalizumab has also been evaluated using global cohorts such as MSBase. In an analysis of propensity-matched patients with relapsing–remitting MS, natalizumab treatment was associated with ARRs similar to alemtuzumab but lower than fingolimod and interferon β . However, of 15,783 patients treated between August 1994 and June 2016, only 189 patients were treated with alemtuzumab.⁵⁷ In a pooled analysis of TOP and MSBase registries, 732

propensity-matched treatment-naïve patients with relapsing MS were selected. Chosen patients had active disease defined as one or more baseline-enhancing MRI lesions or one or more relapses in the past 12 months. ARR was 0.63 on interferon β or glatiramer acetate and 0.20 on natalizumab (64% reduction, $p < 0.0001$).⁵⁸

Other safety considerations

Pregnancy

Pregnancy outcomes after natalizumab exposure treatment were evaluated in a global registry of 376 patients with MS and Crohn's disease. Discontinuation of natalizumab occurred during the first trimester in 76.6% of patients and during the 3-month period prior to conception in 18.9% of patients. Fifty-seven minor or major birth defects were detected in 30 infants. Using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification, the major birth defect rate in the natalizumab pregnancy registry was 5.05%. This rate was higher than the MACDP background rate of 2.67% in the general US population. No specific pattern of malformations was observed. The spontaneous abortion rate of 9.0% after natalizumab exposure was lower than that of the general population (13.1–15.9%).⁵⁹

Hepatotoxicity

Natalizumab may have direct hepatic toxic effects, as postmarketing hepatotoxicity has been reported, including cases of hepatic failure. An increased number of circulating autoreactive immune cells with natalizumab treatment may unmask autoimmune hepatitis.⁶⁰ Of 4938 patients with MS in the TYGRIS study, hepatotoxic events occurred in six patients, including four with confounders or an alternative cause.⁵³ One 28-year-old patient on natalizumab died from either reactivation of or acute infection with hepatitis B virus.⁶¹

Conclusion

The therapeutic options to treat relapsing forms of MS have greatly expanded over the past two decades. With the introduction of monoclonal antibody treatments, multiple highly effective options are available to help reduce the risk of disability for those living with MS.⁶² Understanding the mechanism of action of each monoclonal antibody therapy and its duration of immunological impact

is critical for treatment selection for each patient. In terms of long-term safety and efficacy of intravenous monoclonal antibody therapies in MS, the full profile for alemtuzumab is being established and data collection on ocrelizumab is just beginning.^{63–65} With more than a decade of post-marketing experience in more than 167,300 patients (as of February 2017), the benefit to risk ratio of natalizumab has been robustly characterized. Clinical studies have demonstrated the substantial efficacy of natalizumab,^{3,9} but risks associated with natalizumab treatment, such as PML, have also been identified. Stratification of PML risk, including assessment of anti-JCV antibody status with index testing, is a key component to help guide healthcare providers and patients with MS as to when to initiate or continue natalizumab treatment. While the array of therapies for MS keeps rapidly growing, natalizumab has continued and will continue to be a highly important option in preventing disability in people living with MS.

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