Natalizumab: Perspectives from the Bench to Bedside

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Probably no other disease-modifying drug for multiple sclerosis has a more fascinating story than natalizumab from both the bench to bedside perspective and the postmarketing experience standpoint. Natalizumab is a monoclonal antibody that inhibits the trafficking of lymphocytes from the blood into the central nervous system by blocking the adhesion molecule α 4-integrin. Natalizumab was approved as a disease-modifying drug for relapsing remitting multiple sclerosis only 12 years after the discovery of its target molecule—a time line that is rather fast for drug development. However, a few months after its U.S. Food and Drug Administration approval, natalizumab was withdrawn from the market because of an unanticipated complication—progressive multifocal leukoencephalopathy. It was later reinstated with required adherence to a strict monitoring program and incorporation of mitigation strategies.

The development of therapeutic monoclonal antibodies shows the importance of a target-centered approach to modify the course of multiple sclerosis (MS) (Buttmann and Rieckmann 2008). Natalizumab is the first monoclonal antibody approved for the treatment of relapsing MS after convincingly showing clinically and radiologically significant effects in phase III trials (Stüve and Bennett 2007). In this review, we highlight the evolution of natalizumab from bench to bedside, summarize findings from pivotal clinical trials of natalizumab, and discuss the relevant adverse effects, particularly multifocal leukoencephalopathy, lessons learned from risk mitigation strategies, as well as several other

aspects related to natalizumab use in clinical practice.

DISCOVERY AND MECHANISM OF ACTION

Natalizumab (Tysabri, Biogen Idec, Cambridge, MA) is a humanized recombinant immunoglobulin (Ig)G4 monoclonal antibody that blocks the α 4-integrin-mediated leukocyte–endothelial interaction, resulting in inhibition of trafficking of lymphocytes from the blood into the central nervous system (CNS) (Stüve and Bennett 2007). The discovery of the target molecule for natalizumab dates back to 1992 (Yednock et al. 1992); however, the interaction be-

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tween endothelium and lymphocytes has been studied since the mid-1960s when it was first shown in rats that lymphocytes enter lymph nodes through specialized blood vessels called high endothelial venules (Gowans and Knight 1964). Later, in the 1980s and early 1990s, several studies focused on the mapping of molecules involved in the process of lymphocyte migration, highlighting the role of integrins and selectins, particularly the cellular adhesion molecules, including intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) (Osborn et al. 1989; Springer 1994; Butcher and Picker 1996). The integrin very-late-activating antigen 4 ($\alpha 4\beta 1$ -integrin; VLA-4) was identified as a receptor for VCAM-1, and the VCAM-1/VLA-4 ligand–receptor pair was suggested to play a major role in the recruitment of mononuclear leukocytes to inflammatory sites in vivo (Elices et al. 1990). In an attempt to further identify the adhesion receptors involved in lymphocyte homing to inflamed brain endothelium, scientists at Stanford University and Athena Neurosciences collaborated on investigating this question in the animal model of MS, experimental autoimmune encephalomyelitis (EAE) (Yednock et al. 1992). Using an in vitro adhesion assay on frozen sections of EAE, they showed that lymphocytes and monocytes selectively bind to the lumen of the vessels, consistent with an endothelial interaction. They found that this binding was blocked by antibodies against the $\alpha 4$ -integrin molecule and not by antibodies against numerous alternative adhesion receptors (Yednock et al. 1992). This finding was followed by an in vivo experiment in which administration of antibodies to $\alpha 4$ -integrin to EAE rats ameliorated the paralysis and prevented the accumulation of leukocytes in the CNS as evidenced by immunohistochemical studies of brains from EAE rats. This was the first study providing direct evidence to suggest that therapies based on interfering with $\alpha 4\beta 1$ -integrin may be useful in treating inflammatory disease of the CNS such as MS (Yednock et al. 1992). The expression of adhesion molecules VLA-4 and VCAM-1 was later shown in an MS autopsy brain using immunohistochemical analysis (Verbeek et al. 1995). These studies led to the

first phase I safety and pharmacokinetic study of a humanized $\alpha 4$ -integrin antibody, natalizumab (Antegren, Athena Neurosciences, South San Francisco, CA) (Sheremata et al. 1999).

EARLY CLINICAL STUDIES

A phase I, randomized, placebo-controlled, five-level dose-escalation trial of a single IV dose of natalizumab (with doses ranging from 0.03 to 3.0 mg/kg), showed that all tested doses were safe and well tolerated, and justified further trials (Sheremata et al. 1999). An open-label safety and drug interaction study of natalizumab in combination with interferon (IFN)- β -1a in 38 patients with MS provided safety and tolerability data to support efficacy trials of combination therapy (Vollmer et al. 2004). A phase II, randomized, double-blind, placebo-controlled trial of natalizumab in 72 patients with active relapsing MS showed a significant reduction in the number of new active lesions on magnetic resonance imaging (MRI) over the first 12 weeks of the study, but no significant difference in the second 12 weeks of the study (Tubridy et al. 1999). Another phase II trial aimed at assessing the effect of a single dose of IV natalizumab (vs. placebo) soon after the onset of relapses in 180 patients with MS (O'Connor et al. 2004). This study showed that natalizumab did not hasten clinical recovery after relapse; however, a significant decrease in the volume of enhancing lesion volume was noted at 1 and 3 weeks after treatment (O'Connor et al. 2004). Another important phase II trial assessed the efficacy of two doses of monthly natalizumab (3 mg/kg and 6 mg/kg) versus placebo for 6 months, followed by a 6-month observation (Miller et al. 2003). The study showed that both of the tested doses of natalizumab led to fewer inflammatory brain lesions and fewer relapses over a 6-month period in patients with relapsing MS (Miller et al. 2003).

PIVOTAL CLINICAL TRIALS

The two pivotal phase III trials of natalizumab in patients with relapsing forms of MS include AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) and SEN-

TINEL (Safety and Efficacy of Natalizumab in Combination with IFN- β -1a in Patients with Relapsing Remitting Multiple Sclerosis) studies (Polman et al. 2006; Rudick et al. 2006). In the AFFIRM study, the efficacy and safety of natalizumab as a monotherapy in relapsing remitting MS patients was investigated, whereas the SENTINEL study was designed to evaluate the efficacy and safety of natalizumab in combination with intramuscular IFN- β -1a (Avonex).

In the AFFIRM study, a total of 942 patients were randomly assigned in a 2:1 ratio to receive intravenous natalizumab 300 mg (627 patients) or placebo (315 patients) every 4 weeks for up to 116 weeks (Polman et al. 2006). The inclusion criteria required patients ages 18 to 50 years, diagnosis of relapsing remitting MS, a baseline-Expanded Disability Status Scale (EDSS) score of ≤ 5 , at least one relapse within the 12 months before the study, and MRI lesions consistent with MS. The primary end points were the rate of clinical relapses at 1 year, and rate of sustained disability progression as measured by EDSS at 2 years. Secondary end points at 1 year included the number of new or enlarging T2-hyperintense lesions, the number of gadolinium-enhancing lesions, and the proportion of relapse-free patients. Secondary end points at 2 years included the rate of clinical relapse, the volume of T2 lesions, the number of new T1 hypointense lesions, and disability progression as measured by the Multiple Sclerosis Functional Composite. The median disease duration was 5 years. Natalizumab monotherapy significantly reduced the rate of clinical relapse at 1 year by 68% and the risk of sustained disability progression at 2 years by 42% compared with placebo, accumulation of new or enlarging hyperintense T2 lesions at 2 years by 83%, and the number of gadolinium-enhancing lesions by 92% at both 1 and 2 years. The proportion of relapse-free patients at 2 years in the natalizumab group was 67% (vs. 41% in the placebo group, $p < 0.001$) (Polman et al. 2006).

In the SENTINEL trial, a total of 1171 patients, who despite IFN- β -1a therapy had at least one relapse during the 12-month period before the study, were randomly assigned in a 1:1 ratio to receive continued intramuscular IFN- β -1a in

combination with natalizumab 300 mg (589 patients) or placebo (582 patients) intravenously every 4 weeks for up to 116 weeks (Rudick et al. 2006). Similar to the AFFIRM study, inclusion criteria included patients ages 18 to 50 years, diagnosis of relapsing remitting MS, a baseline EDSS score of ≤ 5 , at least one relapse within the 12 months before the study, and MRI lesions consistent with MS. Primary and secondary end points were also defined identical to the AFFIRM study. The similar inclusion criteria and end-point definition allowed clinically useful conclusions to be drawn from these two studies. Combination therapy with natalizumab was associated with 55% relative reduction in annualized relapse rate (0.34% compared with 0.75% with IFN- β -1a), 83% reduction in the number of new or enlarging T2 lesions at 2 years, 89% reduction in the number of the gadolinium-enhancing lesions, and 24% reduction in relative risk of sustained disability progression at 2 years (Rudick et al. 2006).

Later, in a phase II, randomized, double-blind, placebo-controlled trial called Glatiramer Acetate and Natalizumab Combination Evaluation (GLANCE), safety and tolerability of combination therapy with natalizumab added to glatiramer acetate (GA) was compared to GA only (Goodman et al. 2009). The incidence of infection and infusion reactions was similar in both groups, and no hypersensitivity reactions were reported. It was concluded that the combination of natalizumab and GA seemed safe and well tolerated during 6 months of therapy (Goodman et al. 2009).

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

In February 2005, only about 3 months after its first approval, natalizumab was voluntarily withdrawn from the market by its manufacturers, Biogen Idec and Elan Corporation (Dublin, Ireland). This decision followed the observation of three cases of progressive multifocal leukoencephalopathy (PML). Two patients developed PML in the SENTINEL trial in which they received natalizumab in combination with IFN- β -1a (Kleinschmidt-DeMasters and Tyler

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2005; Langer-Gould et al. 2005). The third patient received natalizumab in a clinical trial of Crohn's disease (Van Assche et al. 2005). Given that approximately 3000 individuals had been treated with natalizumab at that time, the risk of developing PML with natalizumab use was estimated at 1 in 1000 (Berger and Koralnik 2005).

PML is a rare but life-threatening demyelinating disease of the CNS caused by infection of oligodendrocytes by John Cunningham virus (JCV), a human polyomavirus that was named after the initials of the patient from whom it was first isolated in 1971 (Berger and Houff 2006). Approximately half of the world's population is already infected by JCV by age 20 and perhaps as many as 70% by late age. JCV infection almost never causes symptoms in immunocompetent individuals (Berger and Khalili 2011). PML is strongly associated with immunosuppressed status and predominantly occurs in patients with acquired immune deficiency syndrome (AIDS); however, it has been reported with monoclonal antibodies and various other immunosuppressants.

Postmarketing studies of natalizumab showed that median treatment duration to onset of PML symptoms was 25 months (range: 6–80 months) (Clifford et al. 2010). The most common presenting symptoms included changes in cognition, personality, and motor function, and less commonly seizures (Clifford et al. 2010). Clinical suspicion of PML should warrant discontinuation of natalizumab, acquisition of MRI, and assessment of JCV in the cerebrospinal fluid (CSF). Management of natalizumab associated PML requires plasma exchange or immunoabsorption to hasten removal of natalizumab and to reestablish immune surveillance of the CNS (Khatiri et al. 2009). Paradoxically, the effective clearance of natalizumab and restoration of immune surveillance may result in worsening of neurologic deficits and MRI lesions, consistent with the development of immune reconstitution inflammatory syndrome (IRIS), a potentially life-threatening complication (Tan et al. 2011). Corticosteroid therapy provides a modest benefit in natalizumab-associated PML-IRIS (Tan et al. 2011). Recently,

punctuate pattern of MRI lesions has been suggested as a useful imaging feature in a presymptomatic stage of PML (Hodel et al. 2016).

Natalizumab was later reintroduced to the market in June 2006, and approved by the Food and Drug Administration (FDA) for highly active MS, with a black box warning regarding risk of PML, and with required adherence to a special restricted distribution program developed by the FDA known as TOUCH (Tysabri Outreach Unified Commitment to Health) aimed at minimizing the risks of use of natalizumab.

RISK MITIGATION

Postmarketing analyses have identified three factors (alone or in combination) that contribute to the risk of natalizumab-associated PML: (1) positive serostatus for anti-JCV antibodies, (2) prior exposure to immunosuppressants, and (3) increased duration of natalizumab therapy (Gorelik et al. 2010; Bloomgren et al. 2012). Serum levels of anti-JCV antibody, measured as index, may help in further defining the risk of PML in anti-JCV, antibody-positive MS patients with no prior immunosuppressant use who are treated with natalizumab (Plavina et al. 2014). Table 1 shows the estimated risk of PML associated with natalizumab use depending on these three factors (Berger and Fox 2016a, 2016b). Based on these factors and associated risk estimates, mitigation strategies need to be incorporated. The JCV antibody serology status needs to be checked at least every 6 months. In case of seroconversion, the risk–benefit profile of natalizumab treatment should be revisited.

If any clinical suspicion for PML exists, the patient should be promptly evaluated even if their JCV antibody serostatus is negative (Ontaneda and Fox 2013). Patients who are JCV antibody negative with a previous history of exposure to immunosuppressants are usually tested for JCV antibody status every 3 months. JCV antibody seroconversion may be accelerated in patients treated with natalizumab. A recent study estimated a seroconversion rate of 8.5%–10.3% per year in natalizumab-treated patients (Schwab et al. 2016).

Table 1. Estimated risk of PML associated with natalizumab use^a

Anti-JCV antibody negative	Duration of exposure to natalizumab (months)	Anti-JCV antibody positive	
		No prior immunosuppressant use	Prior immunosuppressant use
<1/1000	1 to <24	<1/1000	2.5:1000
	≥ 24	8:1000	23:1000

PML, Progressive multifocal leukoencephalopathy; JCV, John Cunningham virus.

^aBased on Berger and Fox (2016b).

Although the risk stratification identified factors that can prevent PML in patients with MS under natalizumab, its introduction into clinical practice has not been a success with regard to its intended purpose. The rate of natalizumab-associated PML has not only not decreased (Cutter and Stüve 2014), but the latest data published by Berger and Fox indicate that the absolute number of cases and the relative risk of PML have actually doubled (Berger and Fox 2016a, 2016b). The reason for this failure of risk stratification is not completely understood. It certainly appears that many neurologists may have difficulties interpreting the risk-stratification algorithm. The primary focus may be on the JCV serostatus when assessing the overall risk of natalizumab-associated PML, and neglecting other risk factors. For instance, prior pharmacological immunosuppression increases PML susceptibility in patients who at the time of natalizumab initiation are JCV negative, but subsequently seroconvert without being identified as seroconverters. Also, the duration of natalizumab therapy is a major risk modifier that should not be ignored, but that may be difficult to monitor in daily clinical practice. Finally, disease reactivation observed after cessation of natalizumab (see below) may lead to reluctance in patients and care providers to discontinue natalizumab even if the risk of PML is considered high. Effective sequential pharmacotherapies following natalizumab need to be identified.

OTHER ADVERSE EFFECTS

Although the main safety concern with natalizumab is the development of PML, other aspects of natalizumab safety merit attention. In the AFFIRM trial, overall the most common side

effects associated with the treatment were headache, fatigue, and infections in both the natalizumab and placebo groups. The adverse events that were significantly more common in the natalizumab group were fatigue and allergic reaction. Infections occurred at a rate of 1.52 per patient/year in the natalizumab group and 1.42 per patient/year in the placebo group without any significant difference. Infections were generally mild-to-moderate in severity and did not result in drug discontinuation. Common infections included nasopharyngitis, influenza, respiratory tract infections, and urinary tract infections. Serious infections occurred in 3.2% of patients in the natalizumab group versus 2.6% of patients in the placebo group. The most common serious infections in the natalizumab group included pneumonia and urosepsis. The most common serious adverse event was relapse of MS in 6% of patients with natalizumab and 13% with placebo. Infusion-related reactions (defined as symptoms within 2 h after the start of drug administration) were significantly more common in the natalizumab group (24%) versus the placebo group (18%). The most common infusion-related reaction was headache. Most reactions were managed with symptomatic treatment and did not lead to discontinuation of the medication. Hypersensitivity reactions requiring discontinuation of natalizumab occurred in 4% of patients and included urticaria, allergic dermatitis, and anaphylactic or anaphylactoid reactions (Polman et al. 2006).

In the SENTINEL trial, the most common side effects in both the natalizumab combination therapy group and IFN- β -1a-only group were headache and nasopharyngitis. Adverse events that were significantly associated with natalizumab combination therapy included anxi-

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ety, pharyngitis, sinus congestion, and peripheral edema. The most common serious adverse event was relapse of the disease in 5% of patients in the natalizumab combination therapy group and 9% of patients in the IFN- β -1a group. Infections occurred at a rate of 1.54 per patient/year with combination therapy and 1.53 per patient/year with IFN- β -1a. Common infections included nasopharyngitis, urinary tract infection, sinusitis, and upper respiratory tract infection. Infusion-related reactions occurred more frequently in the combination therapy group (24% vs. 20% in the placebo group), although the difference was not statistically significant. Similar to the AFFIRM trial, the most common infusion-related reaction was headache, and most reactions did not result in discontinuation of the medication. Hypersensitivity reactions occurred in 1.9% of patients in the combination therapy group (Rudick et al. 2006).

There were more cases of cancer in the natalizumab group in the AFFIRM trial (five cases) compared with one case in the placebo group. The five cases of cancer among natalizumab-treated patients included three cases of breast cancer, one case of cervical cancer (stage 0), and one case of newly diagnosed metastatic melanoma (Polman et al. 2006). There has also been other case reports of melanoma in MS patients treated with natalizumab (Bergamaschi and Montomoli 2009; Laroni et al. 2011); however, it is debatable whether this is a casual association versus merely a coincidence. Long-term prospective data and pharmacovigilance programs are warranted to investigate the risk of cancer with natalizumab use.

There are rare reports of clinically significant hepatic injury in association with natalizumab use. Monitoring liver function is therefore required (Dubey et al. 2016), and natalizumab should be discontinued in patients with evidence of liver injury (Bezabeh et al. 2010).

DISEASE REACTIVATION AFTER CESSATION OF NATALIZUMAB

Although natalizumab is a highly effective treatment for active MS, some patients need to discontinue the treatment to reduce the risk of

PML, or for other reasons such as pregnancy. Several lines of evidence from pivotal clinical trials and case series indicate the return of disease activity once natalizumab is stopped. Although some studies suggest no dramatic increase in disease activity 6 months or 14 months after treatment cessation (Miller et al. 2003; Stüve et al. 2009), others believe that a rebound may in fact occur (Vellinga et al. 2008; Larochelle et al. 2016). A post hoc analysis of patients who received natalizumab in AFFIRM, SENTINEL, and GLANCE trials before suspension in 2005, including monthly follow-up for 8 months after cessation of natalizumab, showed that despite an increase in disease activity after 3 months, the average disease activity did not exceed the pre-treatment level (O'Connor et al. 2011), a finding that indicates possible lack of rebound. It is still possible that a subgroup of patients may be more susceptible to show highly active disease after discontinuation of natalizumab therapy (Schaaf et al. 2011). It has recently been suggested that assessment of the T helper (Th)17-cell/interleukin (IL)-17 axis might help to predict rebound MS activity after natalizumab cessation (Haas et al. 2016).

ANTI-IDIOTYPIC ANTIBODIES

In the AFFIRM study, antibodies against natalizumab were detected in 9% of patients who received natalizumab monotherapy with 3% classified as transiently positive and 6% as persistently positive (defined as positive result on at least two visits that were 6 weeks apart) (Polman et al. 2006). In the SENTINEL study, 12% of patients treated with natalizumab combined with IFN- β -1a developed anti-natalizumab antibodies; with 6% classified as persistently positive (Rudick et al. 2006). Patients with persistently positive antibodies to natalizumab were found to have loss of clinical efficacy as measured by relapse rate, disability progression, and MRI activity compared with antibody-negative patients (Calabresi et al. 2007). These patients also had an increase in infusion-related adverse events (Polman et al. 2006; Rudick et al. 2006). However, in patients with transiently positive patients, efficacy was achieved after

about 6 months of treatment when patients' antibody status became negative (Calabresi et al. 2007). It is therefore recommended that patients with ongoing disease activity or persistent infusion-related adverse events while being treated with natalizumab be tested for antibodies against natalizumab (Calabresi et al. 2007; Fox et al. 2007).

PREGNANCY

There are no studies on the effects of natalizumab on human fertility (Amato and Portaccio 2015); however, α 4-integrins and their ligands are believed to be widely involved in mammalian development (Wehner et al. 2009). Natalizumab is classified as pregnancy level C by the FDA. Women treated with natalizumab are therefore recommended to use adequate contraception or stop natalizumab 3 months before conception. However, there exists a risk of accidental fetal exposure to disease-modifying therapies in women of childbearing age.

In a prospective controlled observational study of 102 pregnancies in women exposed to natalizumab during the first trimester of pregnancy as compared with 95 pregnancies in disease-matched women and 98 pregnancies in healthy control subjects, natalizumab did not appear to increase the baseline risk of malformations in comparison with disease-matched patients (Ebrahimi et al. 2015). The mean birth weight and length were significantly less compared to healthy control subjects (3159 g and 50.3 cm, respectively) but comparable to those observed in disease-matched patients. The rate of spontaneous abortion, however, was significantly higher in exposed pregnancies (17.3%) and in disease-matched patients (21.1%) compared to healthy control subjects (4.1%) (Ebrahimi et al. 2015). In another prospective observational study of 35 women with MS who became accidentally pregnant while being treated with natalizumab, 29 women delivered 28 healthy children, one child was born with hexadactyly, five pregnancies ended in an early miscarriage, and one woman decided to undergo an elective termination of pregnancy (Zohren et al. 2008). Although these data may

suggest that elective termination of pregnancy because of natalizumab exposure may not be necessary, women should still be advised to stop natalizumab in the course of planned pregnancy until more long-term data become available.

Mild-to-moderate hematological alterations (mainly thrombocytopenia and anemia) have been reported in 10 of 13 infants whose mothers received natalizumab during the third trimester of pregnancy (Haghikia et al. 2014).

Excretion of natalizumab into breast milk has been reported (Baker et al. 2015). Although natalizumab is not orally bioavailable, it is still recommended to avoid natalizumab during lactation.

OBSERVATIONAL STUDIES

Long-term observational studies are crucial in defining the best practice in the use of natalizumab for MS. So far, a number of observational studies have confirmed the effectiveness of natalizumab in clinical practice (Mancardi et al. 2011; Piehl et al. 2011; Fernandez et al. 2012), with some studies even reporting a greater reduction in disease activity to the active treatment arm of the AFFIRM trial (Fernandez 2013; Totaro et al. 2014). There are two large, ongoing observational studies of natalizumab, including STRATA (Safety of Tysabri Redosing and Treatment) and TOP (Tysabri Observational Program) (Planas et al. 2014). STRATA is a long-term (up to 10 years), open-label, multinational, follow-up study of natalizumab monotherapy in patients who completed the AFFIRM, SENTINEL, and GLANCE trials and their open-label extensions (O'Connor et al. 2014). TOP is a 10-year prospective, open-label, postmarketing observational study of the long-term safety and efficacy of natalizumab in clinical practice settings in Europe, Australia, Canada, and Argentina (Butzkueven et al. 2014). Interim analysis of both studies confirm natalizumab's overall safety profile and showed that treatment with natalizumab consistently lowers annualized relapse rates and stabilizes EDSS scores (Butzkueven et al. 2014; O'Connor et al. 2014).

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COST EFFECTIVENESS

With the emergence of novel oral and infusion treatments for MS, there is a need for real-world cost-effectiveness evaluation of disease-modifying drugs. The annual cost of natalizumab when it was first approved in the United States in November 2004 was \$25,850, more than 50% higher than IFN- β and GA (Hartung et al. 2015). As with several other disease-modifying drugs, natalizumab cost has increased over time, estimated at \$64,233 in 2013 (Hartung et al. 2015). Yet, several studies support favorable cost-effectiveness for natalizumab compared with other disease-modifying treatments such as IFN- β , GA, and fingolimod in terms of cost per relapse avoided (Gani et al. 2008; Chiao and Meyer 2009; O'Day et al. 2011).

CONCLUDING REMARKS

The development of natalizumab, its bench-to-bedside story, and the lessons learned from its postmarketing experience highlight both the value of a molecular-targeted approach and the risks of unexpected adverse events associated with novel biological therapeutics. Although natalizumab remains a highly effective therapy for relapsing forms of MS, there remains more to be learned with respect to its long-term safety profile.

COMPETING INTEREST STATEMENT

A.S. has no disclosures. O.S. serves on the editorial boards of *JAMA Neurology*, *Multiple Sclerosis Journal*, and *Therapeutic Advances in Neurological Disorders*. O.S. has served on data-monitoring committees for Pfizer and Sanofi-Aventis without monetary compensation. O.S. collaborated with Medscape on educational initiatives. O.S. represented Novartis in front of a Scientific Advisory Group at the European Medicines Agency (EMA). O.S. has advised Genentech and Sanofi-Aventis. O.S. has participated in a Teva-sponsored meeting. O.S. has consulted for Huron Life Sciences and Navigant Consulting. O.S. received travel support from Pfizer.

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