CHAPTER

16

Currently Approved Disease-Modifying Drugs: Monoclonal Antibody Natalizumab

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OUTLINE

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system (CNS),[1] in which the presence of leukocytes in cerebral perivascular spaces in areas of disease activity is one of the pathological hallmarks.[2–4] An absolute requirement for the influx of leukocytes from the peripheral blood into the CNS is their expression of adhesion

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molecules, which are composed of integrins. The alpha4-beta1 (α4-β1) integrin (very late activation antigen-4 (VLA-4)) is one of the four main integrins required for the firm arrest of leukocytes following their rolling adhesion.[5]

16.1 TARGETING THE α4 INTEGRIN

Natalizumab (Tysabri®) is a recombinant humanized monoclonal IgG4-antibody that binds, among others, to the α4-subunit of the α4-β1 integrin, and interferes with the α4-mediated binding to its natural ligands of the extracellular matrix and endothelial lining, vascular cell adhesion molecule-1 (VCAM1), and fibronectin.[6–7] Therefore, inhibition of leukocyte migration and extravasation is believed to be the leading mode of action although additional mechanisms might modulate the therapeutic and adverse effects of natalizumab (see Fig. 16.1). Apart from this obvious effect related to cell migration, various other effects on the immune system have been reported. For instance, natalizumab seems to exhibit effects on B-cell function as well.[8] On the other hand, natalizumab seems to spare the regulatory T-cell population,[9] decreases the overall frequency of plasmacytoid dendritic cells, key regulators in the development of both innate and adaptive immune responses, but increases their phenotype toward more activated and mature cells.[10]

In vivo, antibodies against VLA-4 interfere with the binding of leukocytes to cerebral blood vessels, and effectively prevent symptoms of experimental autoimmune encephalomyelitis (EAE), an animal model mimicking certain features of MS.[11] In this model system blocking the α4 integrin reduced the influx of T cells and monocytes into the CNS and substantially ameliorated the clinical course of EAE.[12] The efficacy seen in preclinical model systems based on a pan immunological concept relevant for lymphocyte migration into the CNS prompted

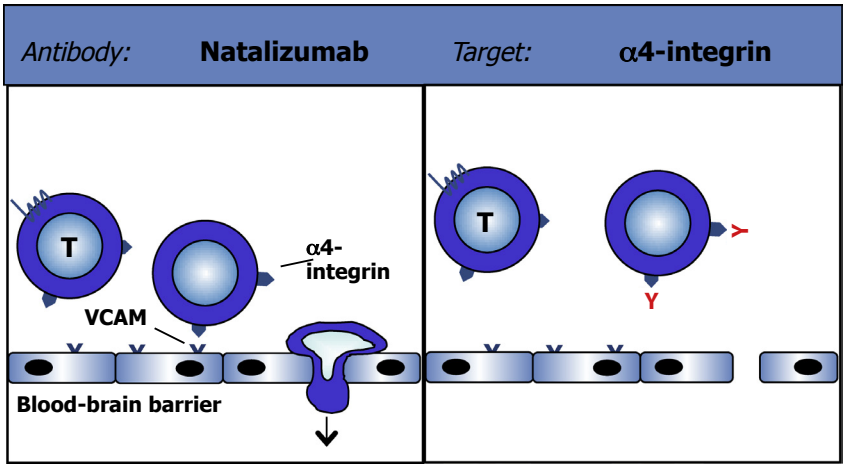

FIGURE 16.1 Natalizumab interferes with the α4 integrin, which is critically involved in the process of cell migration across the blood–brain barrier. By blocking the interaction between VLA-4 and VCAM, natalizumab inhibits the transmigration of immunocompetent cells, especially of T cells, out of the blood vessel into the central nervous system.

that translation of this therapeutic concept from bench to bedside by initiating a clinical trial program in patients with MS.

16.2 EFFICACY OF NATALIZUMAB

16.2.1 Clinical Trials

After the first successful phase-II and phase-IIb trials,[13,14] natalizumab was tested in two large multicenter randomized controlled phase-III studies.[15,16] In the AFFIRM trial, a total of 942 patients received either natalizumab 300 mg every 4 weeks intravenously or placebo.[15] Treatment with natalizumab resulted in a relapse rate reduction (the primary end point of the study) of 68%. Seventy-six percent of natalizumab-treated but only 53% of placebo-treated patients remained relapse free. Confirmed disability progression, as measured by the Expanded Disability Status Scale (EDSS), was reduced over the 2 years of treatment by 42% as compared to placebo (17% vs. 29%), when disability progression was confirmed after 12 weeks. These clinical data were mirrored by paraclinical measures assessed by magnetic resonance imaging (MRI): gadolinium (Gd)-enhancing lesions on T1-weighted images were reduced by over 90%, in line with the previous results from the phase-IIb study (see Fig. 16.2).[14] Positive effects of natalizumab treatment were also reported for quality of life assessments, requirement for concomitant glucocorticosteroid pulse treatments, or MS-related hospitalizations.[17] Furthermore, a post hoc analysis of the disability assessment revealed that one out of four patients with an EDSS ≥2.0 improved in their level of disability as measured by the EDSS.[18] Further analyses demonstrated that natalizumab treatment decreased clinical severity of relapses and improved recovery from disability induced by relapses, suggesting that these beneficial effects might limit the stepwise accumulation of disability.[19]

At the same time the AFFIRM trial was conducted, a second phase-III study, the SENTINEL trial, included 1171 patients pretreated with interferon beta1a (IFNβ1a) that had at least one relapse under this treatment. Natalizumab was administered in combination with IFNβ1a and compared to IFNβ1a treatment alone.[16] The results of SENTINEL corroborated the data from the AFFIRM study. Natalizumab treatment resulted in a relapse rate reduction of 53% in comparison to treatment with IFNβ1a alone. Similarly, MRI data revealed a reduction of 89% of Gd-enhancing lesions and 83% reduction of new or new enlarging T2 lesions over 2 years.

Since there were two cases of progressive multifocal leukoencephalopathy (PML) as severe side effects in the SENTINEL trial, natalizumab was licensed as monotherapy only for patients with highly active RRMS based mainly on the data from the AFFIRM trial. Highly active RRMS was defined by the licensing bodies as at least two severe relapses per year of patients that do not respond to first-line therapy (IFNβ or glatiramer acetate (GA)). This restricted approval was introduced as a consequence to the PML cases for risk–benefit considerations (see later).

16.2.2 No Evidence of Disease Activity

The results of the AFFIRM trial changed substantially the expectations toward pharmacotherapies today. By combining clinical as well as paraclinical measures we can assess the

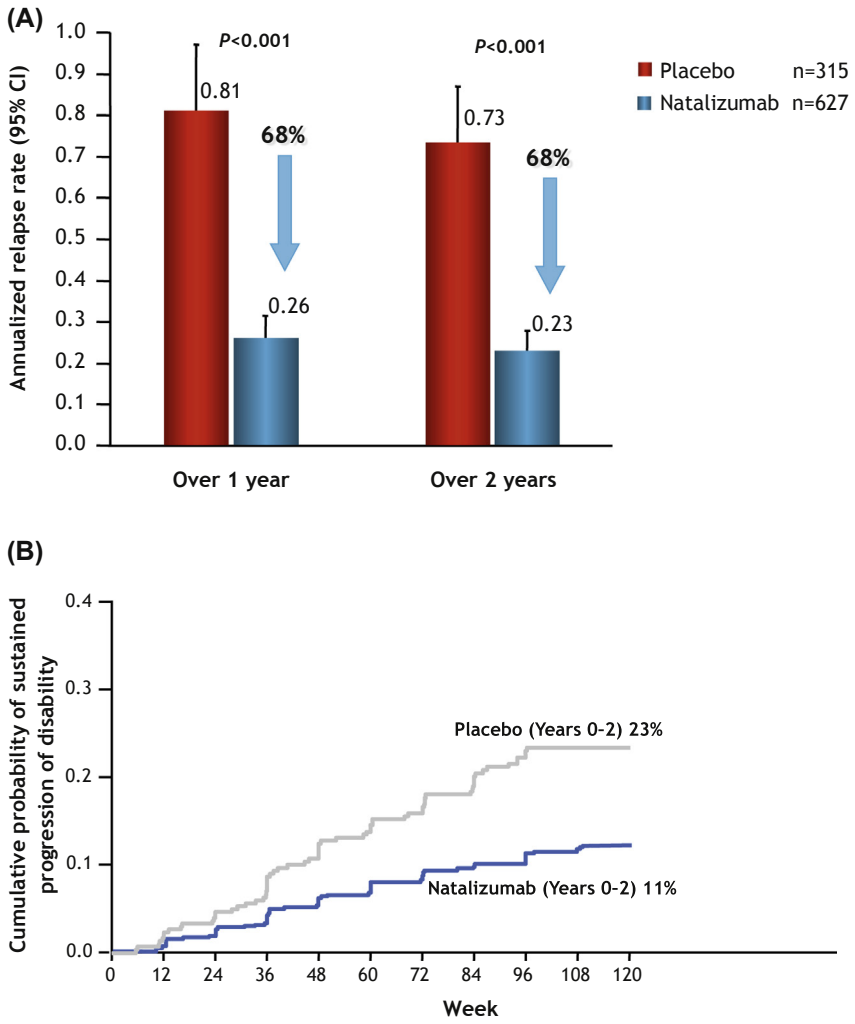

FIGURE 16.2 Natalizumab: Clinical efficacy on annualized relapse rate (A) and disability progression confirmed after 24 weeks (B) against placebo in the AFFIRM trial.[15]

percentage of patients that did not reveal activity on various outcome measures, such as relapses and disability progression measured by the EDSS as well as various MRI measures.[20] A post hoc analysis of this pivotal natalizumab trial revealed that more than 37% of patients in the natalizumab group remained free of disease activity as defined by the absence of relapses, no sustained disease progression, no Gd-enhancing lesions, and no new or enlarging lesions, while only 7% in the placebo group remained free of these combined disease activity measures.[21] Consequently, the terms "freedom of measurable disease activity" and "no evidence of disease activity (NEDA)" were introduced as possible outcome measures for MS clinical trials (Fig. 16.3). Some authors suggest that cognition should be added as an additional assessment to this composite measure in daily practice.[22]

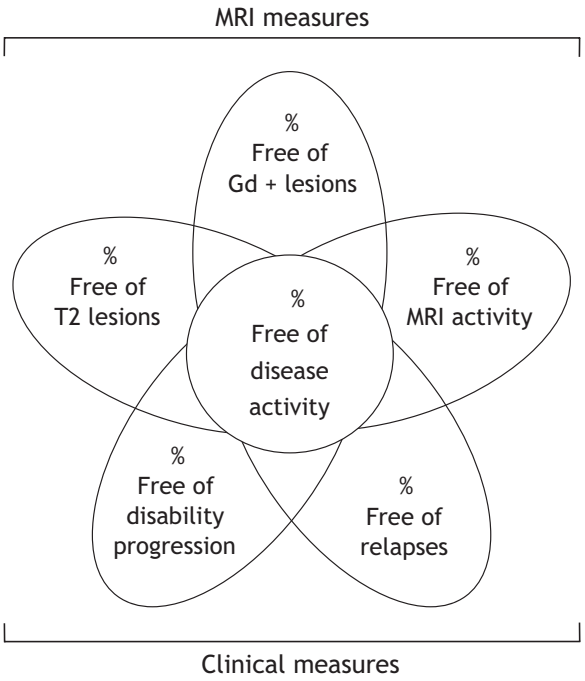

FIGURE 16.3 A novel approach to study the overall efficacy of a treatment is the assessment of the absence of clinical and radiological disease activity. Absence of activity is defined as no activity on clinical measures (no relapses and no sustained disability progression) and radiological measures (eg, no Gd-enhancing lesions, no new or enlarging T2-hyperintense lesions, no overall activity on cranial magnetic resonance imaging, MRI). The composite of the two is classified as the absence of combined activity, also coined "freedom of disease activity" or "no evidence of disease activity."

NEDA seems intuitively appealing and has been compared with disease remission in rheumatoid arthritis, which clearly highlights the remarkable progress in MS therapy over the past two decades. However, before NEDA becomes a new standard efficacy measure in MS trials, its prognostic utility in assessing MS disability will need to be established.[23]

16.2.3 Clinical Efficacy in the Real World

In numerous observational studies the profound clinical and paraclinical efficacy of natalizumab seen in the phase-III trial program could be replicated in a real-world setting. The level of efficacy appeared even more pronounced since the label for the drug given by the authorities preselects for a more clinically active patient population compared to the inclusion criteria in AFFIRM. One large observational study corroborating such findings is the so-called Tysabri Observational Program (TOP), recruiting patients outside the United States.[24] Interestingly, the clinical benefit seen in patients treated with natalizumab seems to be associated with an increase in the percentage of patients showing stable or even ameliorated electrophysiological parameters assessed by evoked potentials.[25]

Besides positive effects on relapse rate and disability progression an increase in walking speed in MS patients treated with natalizumab could be demonstrated in a prospective open-label study (TIMER).[26] Furthermore, it was shown that natalizumab, as used in a real-life setting, might improve MS-related fatigue based on the results from a one-armed uncontrolled study. In addition, other parameters related to patients' quality of life seemed to improve with natalizumab treatment.[27]

16.3 SAFETY

Overall, natalizumab was well tolerated in the large phase-III trials.[15,16] Side effects included headaches and fatigue on infusion days. Allergic reactions occurred in about 4% of natalizumab-treated patients, most of them after the second or third infusion with urticaria, headache, flush, and hypotonia.[28] However, besides this type-I hypersensitivity reaction delayed type-III reactions also have been reported.[29,30] The occurrence of allergic reactions is linked to the presence of anti-natalizumab antibodies. In the AFFIRM trial 68% of the patients with infusion-related reactions were positive for anti-natalizumab antibodies.[31] Approximately 10% of natalizumab-treated patients develop transiently anti-natalizumab antibodies that persist in 6%. Antibodies usually develop within the first 12 weeks of treatment. In patients tested positive for anti-natalizumab antibodies further infusions should be halted and retesting should be performed after 4–6 weeks. Patients persistently positive for anti-natalizumab antibodies should not be exposed again to the drug due to an increased risk for allergic reactions and the neutralizing effect on natalizumab efficacy.

Elevations of liver enzymes and bilirubin were observed in 0.1% of natalizumab-treated patients. However in nearly all cases this side effect was clinically not relevant.

As already mentioned, there were two cases of PML in the SENTINEL trial and another case in a study of natalizumab in Crohn's disease.[32–34] Since these patients had concomitant treatment with IFNβ or previous immunosuppressive treatment, it was originally suspected that PML occurs as a result of a combination therapy, which is why the approval was and still is restricted to monotherapy.

16.3.1 Progressive Multifocal Leukoencephalopathy

PML is an opportunistic demyelinating disease of the brain. It is caused by reactivation of the John Cunningham virus (JCV), a double-stranded DNA virus belonging, together with the SV-40 and BK viruses, to the family of polyomaviridae.[35] PML is not a natalizumab-specific side effect, albeit integrin blocking therapies seem to specifically heighten its risk; it has been diagnosed in the context of many other immunoactive drugs as well, specifically in immunocompromised patients, in particular in patients with reduced cellular immunity, including in patients with HIV, patients with hematological diseases, or patients receiving immunosuppressive medication (see Fig. 16.4).[36] Primary infection by JCV takes place in childhood and is asymptomatic. This virus persists in the tonsillar tissue, bone marrow, kidney, and spleen.[37,38] The presence of JCV-DNA has been detected in urine, different blood compartments, and in cerebrospinal fluid (CSF).[39,40] JCV viruria was found as frequently in HIV-positive individuals as in control subjects, suggesting that its detection has no clinical value.[41] JCV-DNA has

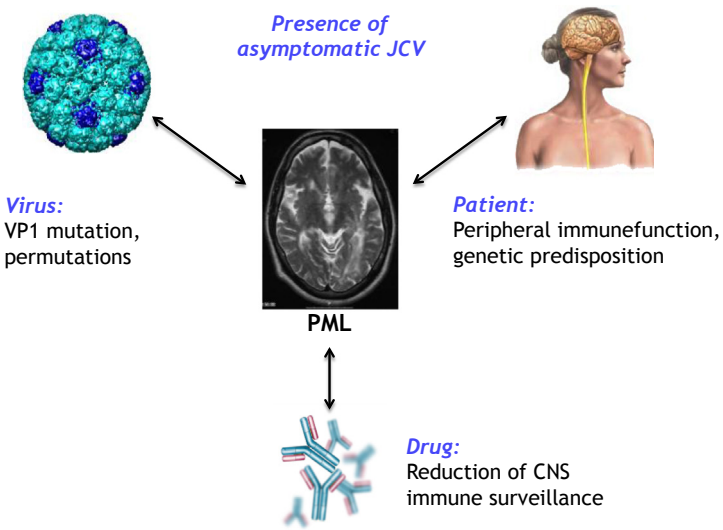

FIGURE 16.4 Progressive multifocal leukoencephalopathy (PML) is caused by the John Cunningham virus that needs to mutate before it can infect glial cells in the central nervous system. Predisposing factors for the development of PML are an immunodeficiency (either in the context of other diseases or iatrogenic by the application of immunosuppressive drugs) and potentially host genetics. More details in the text.

been detected in peripheral blood mononuclear cells (PBMCs) in HIV-positive patients with and without PML but not in HIV-negative control subjects. There was no specificity for any leukocyte subtype, but JCV-DNA detection correlated with low $CD4^+$ lymphocyte counts.[41] Thus, JCV-DNA load in PBMCs has no predictive value as a screening tool for PML.

Currently, our knowledge about transmission of JCV infection and its circle of life in the healthy human population is limited. The transmittable form of JCV is commonly referred to as the JCV archetype, as it is thought that all other genotypes originate from it. The JCV-archetype is detectable in the urine and sewage. In contrast, the JCV-PML type appears more neurotropic, and can be isolated from brains of PML patients. This pathological variant is characterized by deletions, duplications, and point mutations in a specific JCV regulatory region. Most likely, episodically and on low-level replicated JCV archetype within the kidney explains urine excretion and JCV-DNA in plasma of immunocompromised patients. There is growing evidence on persistency of JCV in the CNS. Usually JCV DNA can be found in oligodendrocytes and astrocytes, and the current pathogenic concept implies a lytic infection of glial cells causing PML.[42,43] A newly described phenotype of this disease comprises a direct infection of neurons. This distinct clinical and radiological syndrome is named JCV granule cell neuronopathy, characterized by exclusive or predominant cerebellar atrophy.[44] In the context of natalizumab only a single case of this variant has been reported so far.[45]

No pathognomonic initial symptoms of PML have been defined, which often makes an early clinical diagnosis of this disorder very challenging. Some of the classic clinical signs and symptoms of PML include rapidly progressive dementia, motor dysfunction, and vision loss, which can be difficult to differentiate from MS relapses.

The clinical outcome of natalizumab-treated PML patients seems much better than in patients with HIV-associated PML, but early diagnosis (see later) and consequent treatment appear relevant.[46] Critical for the diagnosis of PML are the presence of JCV-DNA in the CSF assessed by polymerase chain reaction and MRI. Present therapeutic strategies in the context of natalizumab-associated PML include discontinuation of natalizumab and plasmapheresis/immunoadsorption (PLEX/IA). This may accelerate the occurrence of immune reconstitution inflammatory syndrome (IRIS), which is relevant to eliminate the virus from the CNS. During IRIS corticosteroids are applied.[47] In addition, other treatment strategies have been reported, all of which require further studies before treatment recommendations can be given.[48]

16.3.2 The Anti-JCV-Antibody

So far, three different risk factors could be identified that are associated with a risk of developing PML while receiving treatment with natalizumab: (1) treatment duration beyond 24 months and (2) prior treatment with an immunosuppressive drug (independent of the immunosuppressant used, its exposition time, and the time frame between last application of the immunosuppressive therapy and treatment initiation with natalizumab).[49]

Of specific interest is the risk stratification based on the presence of the so-called anti-JCV antibody. Since JCV infection is a prerequisite for the development of PML, an enzyme-linked immunosorbent assay (ELISA) that detects JCV antibodies in human serum or plasma was developed, optimized, and validated. The seroprevalence reported for MS patients (and controls) is in a range of 50–60% for most of the countries.[50] Based on this assay PML risk stratification became possible (see Fig. 16.5).[51]

In case the anti-JCV antibody test turns out negative, the risk of developing PML remains very low (≤0.09/1000), given a false negative rate of 2–3% of the ELISA. The test should be repeated every 6 months to detect possible seroconversion (rate: 2–3% per year).

In case of a positive anti-JCV antibody test the PML risk during the first 2 years of treatment is calculated with 1/1000 independent of a prior immunosuppressive treatment course (0.56/1000 without prior immunosuppression; 1.6/1000 in case of prior immunosuppression). Beyond 24 months of treatment prior use of immunosuppressive therapy becomes relevant in risk determination: in case of such a therapy the calculated risk is 11.1/1000; if not the risk estimate is 4.6/1000. These numbers are based on PML incidences calculated in 2012. The PML risk may indeed cumulate over time with extended therapy, and the denominator may decrease due to risk stratification in clinical practice. Hence, these incidence numbers may not exactly mirror the individual risk, but could help clinicians in advising their patient.

Furthermore, an analysis was conducted to analyze whether anti-JCV antibody levels, measured as index, may further define PML risk in seropositive patients.[52] This analysis was based on the association between serum or plasma anti-JCV antibody levels and PML risk in anti-JCV antibody-positive MS patients from natalizumab clinical studies and postmarketing sources. For PML and non-PML patients, the probabilities of having an index below and above a range of anti-JCV antibody index thresholds were calculated using all available data and applied to the PML risk stratification algorithm (Table 16.1).

Given the longitudinal stability of the anti-JCV antibody index in the majority of patients, anti-JCV antibody levels in serum/plasma, measured as index, may differentiate PML risk in anti-JCV antibody-positive MS patients, however only in those with no prior

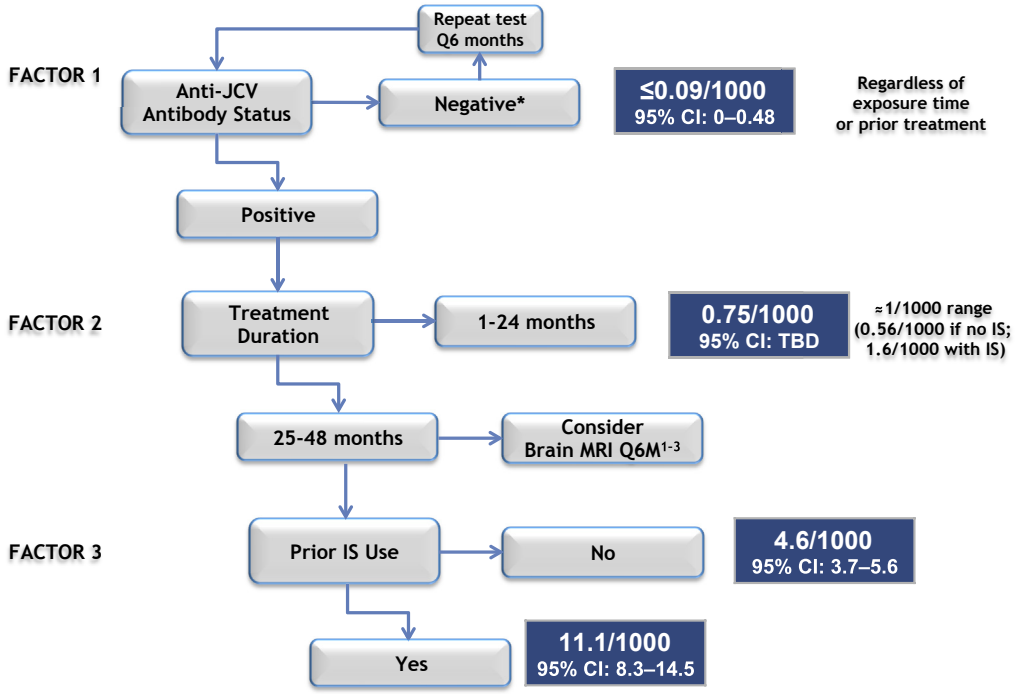

FIGURE 16.5 Risk estimates for developing progressive multifocal leukoencephalopathy (PML).[49] The estimate of PML incidence in anti-John Cunningham virus (JCV) antibody-negative patients assumes that all patients received at least one dose of natalizumab and that one hypothetical PML case tested negative for anti-JCV antibodies prior to the onset and diagnosis of PML. *The estimate of PML incidence in anti-JCV antibody-negative patients assumes that all patients received at least 1 dose of natalizumab and that 1 hypothetical PML case tested negative for anti-JCV antibodies prior to the onset and diagnosis of PML. IS, immunosuppressant.

TABLE 16.1 PML Risk Estimates by Index Threshold in Anti-JCV Antibody Positive Patients With No Prior Immunosuppressants Use. PML Risk Estimates for Anti-JCV Antibody Index Thresholds Were Calculated Based on the Current PML Risk Stratification Algorithm (see Fig. 16.5)[52]

	PML Risk Estimates (95% CI) Per 1000 Patients (No Prior IS Use)		
Index Threshold	**1–24 Months**	**25–48 Months**	**49–72 Months**
≤0.9	0.1 (0–0.41)	0.3(0.04–1.13)	0.4(0.01–2.15)
≤1.1	0.1 (0–0.34)	0.7(0.21–1.53)	0.7 (0.08–2.34)
≤1.3	0.1 (0.01–0.39)	1.0(0.48–1.98)	1.2 (0.31–2.94)
≤1.5	0.1(0.03–0.42)	1.2(0.64–2.15)	1.3 (0.46–2.96)
>1.5	1.0 (0.64–1.41)	8.1(6.64–9.8)	8.5 (6.22–11.28)

immunosuppressant use. This additional information might help to stratify the PML risk in patients at risk. However, further data should be collected to better understand the real value of this measurement.

16.3.3 Other Potential Biomarkers Predicting Progressive Multifocal Leukoencephalopathy

Additional biomarkers have been proposed that might be helpful in the process of predicting the PML risk in patients treated with natalizumab.[53] One proposed biomarker is the presence of lipid-specific immunoglobulin M oligoclonal bands in the CSF (IgM bands). In a study based on 24 MS patients who developed PML and another 343 who did not while treated with natalizumab the presence of IgM bands was associated with a reduced risk of developing PML.

A biomarker accessible from the peripheral venous blood is the percentage of L-selectin (CD62L) expressing $CD4^+$ T lymphocytes.[54] The surface expression of this adhesion molecule was analyzed and found to be significantly lower in patients treated long-term with natalizumab when compared with patients not receiving natalizumab treatment or healthy controls. An unusually low percentage (9-fold lower) was highly correlated with the risk of developing PML in the patient group with available pre-PML samples when compared with non-PML natalizumab-treated patients.

All these findings underline that there is an urgent need for reliable biomarkers helping in stratifying the risk for PML in the context of natalizumab treatment in daily practice. All attempts appear very interesting; however, there is a need for larger numbers and assay validation prior to an implementation in the clinical routine.

16.3.4 Pharmacovigilance

As there is currently no proven treatment for patients suffering from PML under natalizumab treatment other than accelerated clearance of therapy,[55] the early establishment of a diagnosis remains crucial. Upon the (re-) approval of natalizumab, each country initiated a risk management program to closely monitor patients at risk, which usually includes a three-step diagnostic algorithm for natalizumab-treated patients with new or worsening neurological signs and symptoms. Early suspension of natalizumab treatment and strategies for clinical, MRI, and laboratory assessments have been proposed.[56]

Based on our current understanding, younger age at diagnosis, less functional disability prior to PML diagnosis, lower JC viral load at diagnosis in the CSF, and more localized brain involvement by MRI at the time of diagnosis seems to predict improved survival in natalizumab-associated PML.[57] In addition, PML patients asymptomatic at diagnosis have a better survival and less functional disability than those who were symptomatic at diagnosis.[58] Thus, early detection of changes on MRI suspicious for PML is critical. Asymptomatic natalizumab-associated PML manifestations on MRI show a rather localized disease, frequently located in the frontal lobes, affecting the cortical gray matter and adjacent juxtacortical white matter.[59] Diffusion-weighted imaging and fluid-attenuated inversion recovery appear very sensitive and helpful in early detection and discrimination from MS lesions on MRI.[60]

16.4 NATALIZUMAB IN THE CURRENT TREATMENT ALGORITHM

In the phase-III study AFFIRM, natalizumab was investigated in a large population of treatment-naïve patients. In clinical practice, however, natalizumab is commonly used as a second-line therapy predominantly driven by the label defined by the authorities. Since head-to-head studies have not been performed mimicking treatment decision scenarios in clinical practice, collected evidence from the real world can be helpful in obtaining insights into the feasibility of treatment strategies. One powerful data source for addressing such specific questions is MSBase, an ongoing, international, observational registry acquiring real-world data from patients with MS. Using quasirandomization with propensity score-based matching specific patient subpopulations with comparable baseline characteristics can be selected and investigated.[61]

16.4.1 Switching to Natalizumab

In patients with ongoing disease activity despite treatment with a platform therapy, specifically IFNβ or GA, clinicians either switch among different platform therapies or to either fingolimod or natalizumab.

Using large, real-world, propensity-matched datasets from MSBase it could be demonstrated that compared to changing the treatment regimen between IFNβ and GA, switching to natalizumab reduced the annualized relapse rate in year 1 by 65–75%, treatment discontinuation events by 48–65%, and the risk of confirmed disability progression by 26%. The results were consistent regardless of the prior treatment identity.[62]

An alternative scenario is the switch from an injectable therapy either to fingolimod or natalizumab. Addressing this question MSBase demonstrated that in active MS during treatment with injectable disease-modifying therapies, switching to natalizumab is more effective than switching to fingolimod in reducing relapse rate and short-term disability burden.[63]

These results demonstrate that, although formally never tested in the clinical trial program, natalizumab is a powerful therapy not only in treatment-naïve patients, but specifically also in patients failing on a platform therapy.

16.4.2 Stopping Natalizumab

Given the mode of action of natalizumab and its half-life as an IgG4 monoclonal antibody it is plausible that after treatment cessation disease activity will return. Thus, a discussion of how to continue MS therapy after stopping treatment with natalizumab is ongoing.

The RESTORE study investigated to which extent other treatment modalities could compensate for the efficacy of natalizumab:[64] Eligible patients, relapse-free through the prior year on natalizumab, were randomized to continue natalizumab, to switch to placebo, or to receive alternative immunomodulatory therapy (IFNβ, GA, or methylprednisolone). MRI and clinical disease activity recurred despite the use of other therapies. A specific MRI analysis revealed that in most patients recurring radiological disease activity during natalizumab interruption did not exceed prenatalizumab levels or levels seen in historical control patients,[65] emphasizing that there is no collective evidence for an MS rebound after treatment discontinuation.[66]

In MSBase the risk of relapse after stopping natalizumab and switching to fingolimod was investigated and compared with experience switching from IFNβ to GA and those previously

treatment-naive. Furthermore, predictors of time to first relapse on fingolimod were determined. Relapse rates were generally low across all patient groups in the first 9 months on fingolimod; however, 30% of patients with disease activity on natalizumab relapsed within the first 6 months on fingolimod. Independent predictors of time to first relapse on fingolimod were the number of relapses in the prior 6 months.[67] Similar data were obtained in a French study, which described an increased risk of MS reactivation during the washout period or shortly after fingolimod initiation. Based on these observations a washout period shorter than 3 months is recommended when switching from natalizumab to fingolimod.[68]

16.4.3 Natalizumab and Pregnancy

Natalizumab is usually withdrawn 3 months before pregnancy; however, data on exposure to natalizumab during pregnancy are accumulating. In one study 101 women with RRMS exposed to natalizumab during the first trimester of pregnancy were identified. Exposure to natalizumab in early pregnancy did not seem to increase the risk of adverse pregnancy outcomes in comparison to a group of patients not exposed to natalizumab.[69] In another case series of 12 women with 13 pregnancies and highly active MS who were treated with natalizumab during their third trimester of pregnancy mild-to-moderate hematologic alterations in 10 of 13 infants including thrombocytopenia and anemia were observed.[70] These findings were transient and resolved during the 4 months after birth; none of the infants needed any specific treatment.

16.5 OUTLOOK

Given its mode of action natalizumab could also be used as a treatment in other immune-driven disorders or disease entities in which the immune system plays a critical role for tissue damage, such as stroke. Therefore, it is not surprising that natalizumab is currently explored in different indications.

A current unmet need in MS therapy is the lack of efficient treatment options for progressive forms of this disease. In an open-label, phase-IIA, proof-of-concept study the efficacy of natalizumab in progressive MS was investigated.[71] Seventeen patients completed this 60-week study; primary end point was changed in CSF osteopontin, a biomarker of intrathecal inflammation, which decreased significantly when compared to baseline under natalizumab therapy. Magnetization transfer ratio increased in both cortical gray and normal-appearing white matter and correlated with decreases in CSF neurofilament light chain, a marker for tissue damage. Additional experimental as well as clinical evidence prompted a large phase-III study investigating safety and clinical efficacy of natalizumab in secondary-progressive MS (ASCEND). This study, however, did not achieve statistical significance on the primary or secondary endpoints.[72]

Chronic inflammatory demyelinating polyradiculoneuropathy is an autoimmune disease, most likely T-cell-driven, affecting the peripheral nervous system. Conceptionally, natalizumab might be clinically effective in this indication as well. Whereas a first-case report could not reveal any benefit,[73] another series of three cases documented disease stabilization and even clinical improvement.[74] Further studies are warranted investigating the efficacy of natalizumab in this disabling disease.

Experimental evidence points to a potential role of VLA-4 in T-cell trafficking during brain ischemia. In various model systems the blockade of the α4 integrin prompted beneficial effects,[75–77] although also controversial data exist.[78] A phase-II study was just completed, in which natalizumab was tested in patients with acute ischemic stroke when given at ≤6 h or at >6 to ≤9 h from when they were last known normal (ACTION).[79] Primary end point of the study is the change in infarct volume from baseline to day 5 assessed by magnetic resonance imaging (MRI) in participants. The results of this study have not been published yet.

16.6 CONCLUSION

Natalizumab is a highly effective treatment for patients with relapsing forms of MS with a risk of developing PML, prompting a thorough risk–benefit assessment. Today, neurologists have to make complex treatment decisions together with their patients, sometimes on the basis of very limited clinical data and evidence. It becomes even more complex, since risk perceptions between patients and treating physician can differ dramatically, as shown for the PML risk perception in the context of natalizumab.[80]

Thus, optimal assessment of risks and benefits remain challenging.[81] However, withholding a potent therapy with proven efficacy on disease activity (see Fig. 16.6), prevention of disability, and improvement in quality of life can also cause harm to patients with a disabling disease, such as MS.

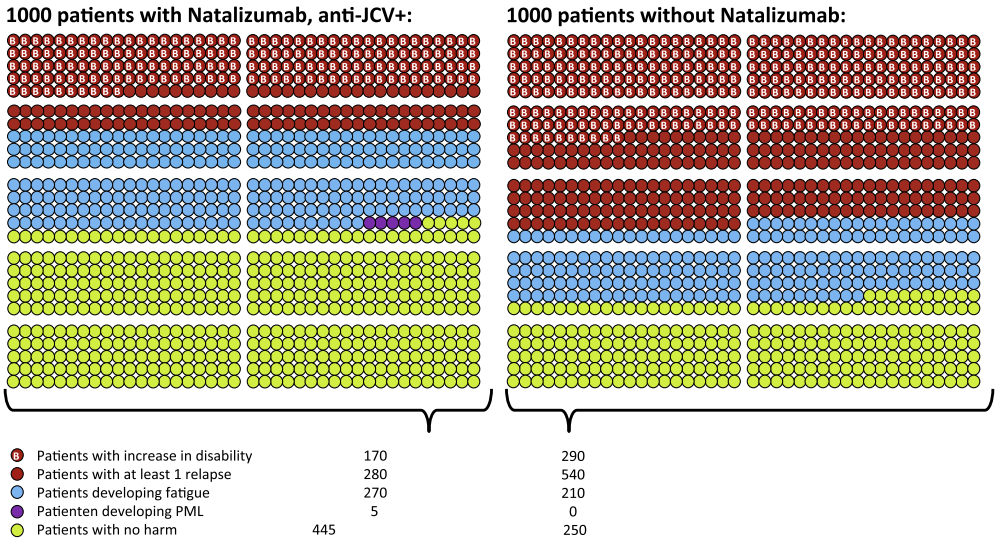

FIGURE 16.6 Balancing risk and benefit. This cereal-box plot was compiled based on the results of the AFFIRM study.[15] The left part demonstrates risk and benefit in an estimated 1000 patients positive for anti-John Cunningham virus antibody. In contrast, on the right, an estimated 1000 patients who did not receive natalizumab treatment. It becomes evident that no treatment increases the number of patients who do not experience no harm. *Adapted from Wolfgang Gaissmaier, with thanks.*

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