α4-Integrin (and Other Leukocyte Integrin)-Targeting Agents

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Abbreviations

CD	Crohn's disease
CDI	*Clostridioides difficile* infection
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
ELISA	Enzyme-linked immunosorbent assay
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HSV	Herpes-simplex virus
IBD	Inflammatory bowel disease
ICAM-1	Intercellular adhesion molecule 1
JCV	JC virus
LAD	Leukocyte adhesion deficiency
LFA-1	Lymphocyte function-associated antigen-1

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MAdCAM1	Mucosal address cell adhesion molecule
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PLEX	Plasma exchange
PML	Progressive multifocal leukoencephalopathy
TB	Tuberculosis
TNF-α	Tumor necrosis factor α
UC	Ulcerous colitis
VCAM-1	Vascular cell adhesion molecule 1
VLA-4	Very late antigen-4
VZV	Varicella-zoster virus

Introduction

Integrins are transmembrane receptors that play a key role in cell adhesion and intracellular signaling. Integrins located on the leukocyte surface are essential for the recruitment of leukocytes from the vasculature to the tissues and are successfully used as therapeutic targets to modulate inflammation [1, 2]. The first drugs targeting the integrin molecules were the α4-integrin subunit inhibitor natalizumab and the lymphocyte function-associated antigen-1 (LFA-1) β2-integrin inhibitor efalizumab [1]. Their main mechanism of action is based on blocking the migration of lymphocytes and therefore decreasing the inflammatory reaction in the brain and the intestinal mucosa. These drugs were initially developed for treating autoimmune disorders, such as multiple sclerosis (MS) and inflammatory bowel disease (IBD) for natalizumab, and psoriasis for efalizumab [1]. Early in the introduction process of the drug, several cases of PML were reported with the use of natalizumab and efalizumab, which led to the withdrawal of both drugs. After a review process taking into consideration the efficacy of the drug for progressive MS and the stratification of the individual risk for developing PML, natalizumab was reintroduced for therapy of severe forms of MS, in particular in patients with low risk for the development of PML [2]. However, natalizumab is only rarely used in patients with IBD due to the availability of equally effective and safer drugs [3]. Vedolizumab, a novel α4-integrin-targeted agent, specifically blocking α4β7 integrin only present in the intestinal mucosa, has not been associated with PML and is approved for IBD [4, 5]. In this chapter, we will review the mechanism of action and potential infection risk of natalizumab and vedolizumab, and we will describe the proposed preventive and therapeutic measures for decreasing the risk of infection in patients receiving these drugs.

Integrins Overview

Integrins: A Complex Structure with Unique Biology

Integrins represent an important family of transmembrane receptors that mediate cell–cell and cell–extracellular matrix interactions and play a key role in cell

adhesion. These complex receptors are type I αβ-heterodimers comprising two subunits, and each integrin is named for the one α-chain and one β-chain that compose it. To date, 24 different heterodimers have been identified in humans, derived from the combination of 18 α and 8 β subunits. The complex structure contributes to the distinct functions of each integrin as well as their distribution and tissue specificity. All integrins carry out two main functions: cell adhesion and intracellular signaling [1].

In contrast to most receptors, transmitting information from the cell's exterior to the interior, integrins propagate signals in a bidirectional way. The heterodimeric receptors undergo large conformational changes in the extracellular domains in response to signaling events inside the cell, initiated by various intracellular adaptor molecules. This process, known as "inside-out signaling," leads to integrin activation and an increased affinity for their ligands and is therefore essential for ligand binding and cell adhesion. In the absence of activating signals, integrins have an inactive, bent conformation, and the ligand-binding site is not exposed, thus not readily accessible to ligands. In the opposite direction, ligand binding induces integrin clustering (a process which brings the signaling domains of integrin-proximal proteins close together), which in turn leads to the initiation of intracellular signal transduction, implicating various intracellular enzymes and involved in multiple cellular functions in a process commonly known as "outside-in signaling" [1, 6] (Fig. 14.1).

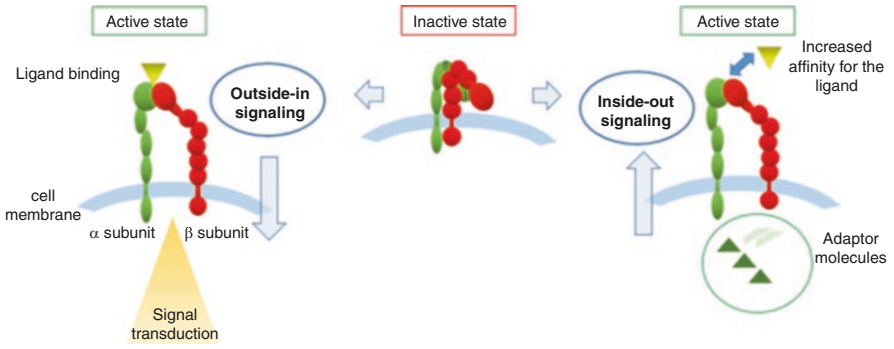

Fig. 14.1 Mechanism of action of integrins. Integrins propagate signals in a bidirectional way: large conformational changes in the extracellular domains occur as a response to signaling events inside the cell ("inside-out signaling"), leading to integrin activation which is required for ligand binding and cell adhesion. In the absence of activating signals, integrins have an inactive, bent conformation, and the ligand-binding site is not readily accessible. In the opposite direction, ligand binding induces integrin clustering, leading to integrin-mediated intracellular signal transduction ("outside-in signaling")

Leukocyte Integrins

Six integrins are exclusively expressed on the surface of leukocytes αLβ2, αMβ2, αxβ2, αDβ2, α4β7, and αEβ7, while the seventh one, α4β1, is also expressed in several other cells [1, 7]. These molecules serve distinct functions and purposes in the immune system and are involved in multiple steps of the leukocyte adhesion cascade [7]. αLβ2, also known as LFA-1, is required for the formation of the immunological synapse, facilitating the interaction between T cells and antigen-presenting cells, but is also involved in many other facets of the immune response, including adhesion, activation, and trafficking of leukocyte populations [8]. αMβ2 integrin is essential for neutrophil function as well as for complement-mediated phagocytosis and is involved in the defense against bacterial and fungal infections [9]. The role of αxβ2 is central in the regulation of the inflammatory function of recruited tissue macrophages [9]. αDβ2 is expressed on monocytes/macrophages and particularly those found in atherosclerotic lesions (foam cells) [10]. α4β7 and αEβ7 integrins direct lymphocyte trafficking from vessels to the intestinal mucosa [11]. Finally, α4β1integrin also known as very late antigen-4 (VLA-4) [12] binds to ligands present on endothelial cells and mediates adhesion of leukocytes to all inflamed tissues and organs, including the central nervous system. The central role of integrins in inflammation is further highlighted by the severe immune dysregulation observed in patients with leukocyte adhesion deficiency (LAD) syndromes. Patients with LAD-I due to mutations in the β2 subunit present impaired immunity and recurrent infections [13].

Integrins as Therapeutic Targets

In light of the prominent role of leukocyte integrins in leukocyte recruitment in tissues and their role in the pathogenesis of many inflammatory disorders, these molecules were early recognized as promising therapeutic targets to modulate inflammation. Four leukocyte integrins have been therapeutically targeted by monoclonal antibodies in clinical trials: α4β7, α4β1, αEβ7, and αLβ2. Natalizumab (anti-α4), vedolizumab (anti-α4β7), and efalizumab (anti-αLβ2) were the first developed therapeutic agents [1]. New molecules with different targets or new applications of molecules directed to the same targets are continuously emerging in parallel with a deeper understanding of the function of integrins [1, 6]. For instance, new monoclonal antibodies and small molecules targeting β7-containing integrins and their ligands are in development for the treatment of inflammatory bowel disease (IBD).

Leukocyte integrins are not the only ones therapeutically targeted. The platelet integrin αIIbβ3 was the first one to be targeted in the 1990s by abciximab, an antigen-binding fragment (Fab) of a chimeric mouse human monoclonal antibody, used for the prevention of thrombotic complications before or after percutaneous coronary intervention in selected patients [14]. Two additional antagonists, eptifibatide [15] and tirofiban [16], followed. Even though these drugs are not largely used

due to the availability of more effective and safe treatments, they laid the foundation for further integrin antagonist development. Finally, the use of integrins as therapeutic targets in oncological treatments and as probes in imaging to evaluate prognosis and treatment response is emerging (αvβ3, αvβ5, αvβ6, α5β1), renewing interest in this family of adhesive molecules [1]. Monoclonal antibodies inhibiting leukocyte integrins remain the most successful examples of therapeutic targeting of integrins in clinical practice and the most interesting ones from an infectious complications point of view and will be the focus of this chapter.

Leukocyte-Integrin-Targeting Agents

Monoclonal Antibodies: Mechanism of Action

Natalizumab (Tysabri; Biogen Idec and Elan Corporation), the first successful drug targeting leucocyte integrins, is a humanized IgG4 monoclonal antibody, which binds with the α4 subunit present in α4β7 and α4β1 integrins, thus inhibiting the binding of their physiological ligands. α4β1 (or VLA-4) is expressed on practically all leukocytes, except for mature granulocytes. Via its complex interactions with the vascular cell adhesion molecule 1 (VCAM-1) and fibronectin, α4β1 participates in leukocyte slow rolling, adhesion, and transmigration via the endothelium to all inflamed tissues and organs, as well as in pro-inflammatory signaling in the endothelial cells. The second target of natalizumab, α4β7 integrin, binds to mucosal address cell adhesion molecule (MAdCAM1) which is predominantly expressed on the endothelial cells of the intestinal vasculature thus mediating lymphocyte homing to the gut mucosa [1].

Vedolizumab (Entyvio; Millennium Pharmaceuticals), a humanized IgG1 monoclonal antibody, targets an epitope formed by both α4 and β7 subunits and is therefore a specific antagonist of α4β7 integrin, inhibiting the homing of T lymphocytes to the intestinal mucosa [17]. The clinical indication of natalizumab and vedolizumab will be discussed in the next section.

Abrilumab, a second human monoclonal IgG2 antibody directed against a combinatorial epitope only present in α4β7, has been shown in a phase 2b randomized controlled trial to induce remission in patients with ulcerative colitis (UC) [18].

Etrolizumab is a humanized IgG1 monoclonal antibody directed against the β7 unit, present in both α4β7 and αEβ7 integrins. α4β7 integrin interacts with MAdCAM1 and is the most significant determinant of lymphocyte recruitment in the intestine, while αEβ7 via its binding to E-cadherin mediates the adhesion of intraepithelial lymphocytes to the epithelial cells. αEβ7 is also present on dendritic cells producing anti-inflammatory cytokines involved in the development of regulatory T cells [19]. Blocking both pathways effectively inhibits the trafficking of lymphocytes into the gut and provides a promising therapeutic strategy for UC (phase II study) and Crohn's disease (CD) (ongoing phase III trials) [20, 21].

Efalizumab (Raptiva; Genentech), a recombinant humanized monoclonal antibody, binds to the αL unit of the αLβ2 (LFA-1), preventing the binding of T cells to

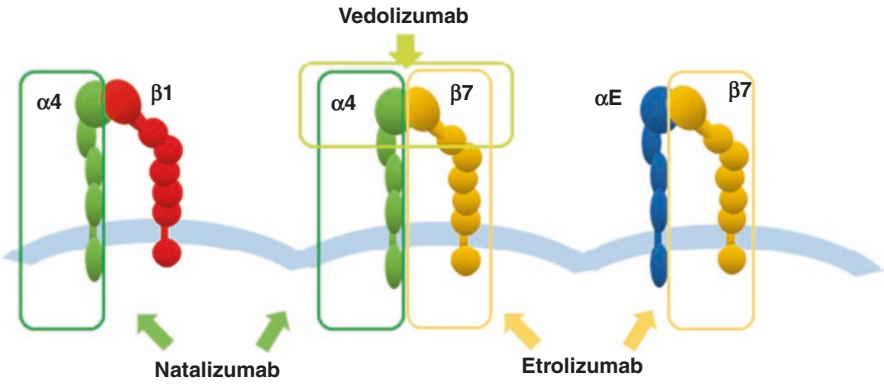

Fig. 14.2 The three integrins, α4β7, α4β1, and αEβ7 that are targeted by monoclonal antibodies. Natalizumab targets the α4 subunit (green) present in α4β1 and α4β7 integrins. Etrolizumab targets the β7 subunit (yellow) present in α4β7 and αEβ7. Vedolizumab targets an epitope formed by both the α4 and β7 subunits (light green) and inhibits specifically the α4β7 integrin (adapted from [1])

the intercellular adhesion molecule 1 (ICAM-1), which is found on antigen-presenting cells, endothelial cells, and keratinocytes [1]. Figure 14.2 illustrates the targets of monoclonal antibodies targeting leukocyte integrins currently used or in late-stage clinical trials.

Other Therapeutic Agents

Besides monoclonal antibodies, efforts have been devoted to the development of peptide or small-molecule antagonists, including allosteric inhibitors designed to inhibit the activation of integrins by blocking the large conformational changes of their extracellular domains. These allosteric inhibitors failed to enter clinical trials due to limited specificity and unexpected systemic toxicity [1]. Non-allosteric, small-molecule inhibitors are actively investigated. AJM300 is a small molecule inhibiting the α4 subunit and has been proven successful in inducing remission in UC [22]. Finally, another small molecule, lifitegrast, binds to αLβ2, blocking the binding of ICAM1 which is overexpressed in corneal and conjunctival tissues in patients with dry eye disease and is used locally as ophthalmic solution to reduce inflammation in those patients [23].

Approved Indications of Integrin-Targeting Agents

Two leukocyte integrin antagonists are currently available on the market, namely, natalizumab and vedolizumab. A third one, efalizumab, was initially approved for the treatment of chronic plaque psoriasis but was withdrawn from the market in 2009 due to major risk of adverse events [24].

Natalizumab

The prominent role of α4β1 for the entry of T lymphocytes in the CNS provides the theoretical background for its use as a target for CNS diseases [2]. In 1992, Yednock and al. first described the use of antibodies against the α4β1 integrin to inhibit the migration of leukocytes into the CNS in a murine experimental model of autoimmune encephalitis [25]. Natalizumab was developed subsequently for the treatment of multiple sclerosis (MS), an idiopathic inflammatory disease of the CNS characterized by demyelinating lesions affecting mostly the white matter of the brain and spinal cord. For decades, MS was treated with nonspecific anti-inflammatory and immunomodulatory drugs such as corticosteroids, interferon β1b, and glatiramer acetate. In more recent years, progress was made in the understanding of the pathophysiology of MS, notably the key role played by activated T lymphocytes recruited from the blood to the CNS and the ensuing inflammatory reaction due to the release of pro-inflammatory cytokines. In this context, natalizumab was studied in randomized controlled trials and proved to be effective in reducing CNS inflammatory lesions and relapses in patients with severe relapsing-remitting MS, either as monotherapy [26] or as part of a combination therapy [27]. Natalizumab was approved in 2004 in the USA and in Europe for the treatment of severe relapsing-remitting MS with no response on first-line therapies, and in severe primary relapsing MS [28].

Due to its dual action also targeting the α4β7 integrin, natalizumab was investigated as a therapeutic agent in CD, a type of IBD characterized by mucosal ulceration and inflammation that can involve any portion of the gastrointestinal tract. Natalizumab was shown to be more effective than placebo in inducing and maintaining remission in moderate to severe CD in multiple clinical studies [29–31] and was approved for this indication in patients who had an inadequate response to or were unable to tolerate conventional CD therapies and tumor necrosis factor α (TNF-α) inhibitors. Nevertheless, the use of natalizumab for CD is now limited because of safer therapeutic options [3].

Vedolizumab

The successful use of natalizumab in CD provided the incentive for the development of other molecules targeting more specifically the α4β7 integrin without the collateral targeting of α4β1, which mediates the most serious adverse events. Vedolizumab was therefore developed to be used specifically in IBD. The pathogenesis of IBD is complex and incompletely understood but involves genetic susceptibility, environmental triggers, and aberrant interactions between the immune system and gut microorganisms, leading to an augmented permeability of the mucosal barrier and homing of activated lymphocytes, creating a vicious circle of local inflammation [32]. Nonspecific anti-inflammatory therapies such as corticosteroids, aminosalicylates, and oral immunomodulators were the cornerstone of the treatment of IBD. In the recent years, more potent and specific agents showed encouraging results in moderate to severe disease, such as Janus kinase inhibitors, TNF-α inhibitors, and integrin antagonists.

Vedolizumab demonstrated promising results for the treatment of IBD in early studies [33] that were confirmed in two randomized controlled trials demonstrating its superiority compared to placebo in achieving maintenance in UC (GEMINI 1 study) and CD (GEMINI 2 study) [4, 5]. Based on these data, vedolizumab was approved in 2014 for both moderate to severe UC and moderate to severe CD. Since then, its efficacy has been confirmed in subsequent randomized (GEMINI 3 study) [34] and multiple cohort studies.

Infectious Complications of Integrin-Targeting Agents

Natalizumab

The clinical impact of integrin inhibition on infection risk is largely derived from the experience with natalizumab, the first-in-class drug available on the market. Initial data from pivotal clinical trials were surprisingly reassuring regarding the global infectious risk of natalizumab, as no major increase in infections was noted. In 2006, post-marketing data revealed two of cases of progressive multifocal encephalopathy (PML) in patients receiving natalizumab [35]. This rare but life-threatening complication led to its transient withdrawal from the market in 2005 to perform safety analyses, before it was reintroduced in 2006 together with a global risk management plan (TOUCH prescribing program). More than 800 cases of natalizumab-induced PML have been described since then, with an estimate incidence of approximately 0.4% of patients treated with natalizumab (https://medinfo.biogen.com/s/).

PML is a rare disease caused by the reactivation of the JC virus (JCV) in brain cells [36]. This small DNA virus from the polyomaviridae family seems to be acquired during youth and usually leads to asymptomatic infection or a nonspecific influenza-like illness. The reported seroprevalence varies between 39% in the United States [37] and 48–69% in European countries [38]. After the primary infection, it establishes a persistent asymptomatic infection in urothelial cells as well as in oligodendrocytes and astrocytes. JCV causes no disease in immunocompetent individuals as JCV replication is controlled by specific cytotoxic T cells. Intermittent asymptomatic JCV viruria can be detected in healthy persons [39].

PML was first described in 1958 as a very rare disease affecting highly immunocompromised patients with hematological malignancies [40], but its relationship with JCV was only described in 1971 [36]. PML became better recognized during the AIDS pandemic, as it affected up to 5% of persons with AIDS, and it was associated with high mortality [41].

PML is mostly a white matter inflammatory disease, but it can sometimes involve the gray matter as well, when JCV replication involves granule cell neurons. The

symptoms vary widely depending on the affected area of the brain but most frequently consist in altered mental status, motor deficits, ataxia, or visual symptoms, further complicating the diagnosis when these symptoms occur in a patient with MS. Brain MRI in patients with PML typically shows subcortical T2-enhancing lesions not corresponding to cerebrovascular territories, and without mass effect or contrast enhancement. Some degree of contrast enhancement has been seen in PML associated with natalizumab use that can be difficult to differentiate from active MS lesions [42]. The diagnosis of PML can be confirmed by a positive JCV PCR in the cerebrospinal fluid (CSF). Although the sensitivity and specificity of JCV PCR are excellent, a negative test cannot rule out PML [43]. In cases of high clinical and radiological suspicion, but negative JCV PCR in the CSF, a definitive diagnosis may require a brain biopsy, which characteristically shows a histopathological triad of demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei [44].

There is no specific therapy against PML, and the management primarily relies on restoring immunity. In the case of PML induced by natalizumab, early removing the drug with plasma exchange (PLEX) or immunoadsorption is the most important therapeutic strategy. Nevertheless, the quick restoration of immunity by drug removal can be complicated by an immune reconstitution inflammatory syndrome (IRIS) that can lead to cerebral edema and death if left untreated [45]. This entity has been mostly described in patients managed with PLEX and is usually treated aggressively with the administration of high-dose corticosteroids. The reported mortality of natalizumab-associated PML is lower than in AIDS-related PML, ranging from 18 to 23% [46]. However, most survivors have residual moderate to severe disabilities [47]. Of note, a small case series published in 2019 showed potential benefit of immunotherapy with the checkpoint inhibitor pembrolizumab in eight patients with confirmed PML, but none of these cases were related to the use of natalizumab [48].

Natalizumab has been also associated with an increased risk of herpes viruses reactivation, in particular herpes-simplex virus (HSV) and varicella-zoster virus (VZV). Most cases are mild mucocutaneous diseases, but some cases of life-threatening HSV or VZV encephalitis have also been reported [49–51]. A high index of suspicion for HSV and VZV reactivation is therefore needed in patients receiving natalizumab, and acyclovir should be initiated promptly if necessary. Given the relatively low incidence of HSV and VZV reactivation, routine antiviral prophylaxis with acyclovir/valaciclovir in patients receiving natalizumab is not recommended. Other infections such as tuberculosis (TB) have exceptionally been described in patients receiving natalizumab [52]. No increase in the incidence of gastrointestinal infections has been reported in patients treated with natalizumab.

Vedolizumab

The larger source of data regarding vedolizumab safety comes from the GEMINI long-term safety study, which consists in the continued follow-up of patients included in the three GEMINI studies, as well as the enrollment of vedolizumab-naive patients. The final analysis was published in 2020 and included more than 2000 patients with up to 9 years of follow-up, and a total of 7999 person-years (PYs) [53]. In this study, the rate of serious infections was 18/1000 PYs in patients with UC and 33/1000 PYs with CD, as compared to the higher rate of serious infections of 38/1000 PYs in patients with IBD receiving no treatment [54]. Infectious complications in patients receiving vedolizumab consisted mostly in anal abscesses, pneumonia, gastroenteritis, and appendicitis.

The only reported opportunistic infection associated with the use of vedolizumab was an increased number of *Clostridioides difficile* infections (CDI) ranging from 3.6/1000 PYs (CD) to 4.9/1000 PYs (UC), with most cases being mild to moderate. There was no case of intestinal TB and only a few cases of primary TB in patients living in high-endemic countries. Overall, the rate of infection following vedolizumab exposure was significantly lower than with TNF-α inhibitors [55]. Only one case of PML has been described in over 470,000 PYs of vedolizumab exposure and occurred in a patient with multiple other risk factors (HIV infection, CD4 count <300 cell/mm^3, prior immunosuppression) [56]. No increase in risk of herpesvirus was observed in patients with IBD treated with vedolizumab, including HSV, VZV, and cytomegalovirus (CMV). Thus, neither antiviral prophylaxis nor preemptive strategies against CMV are recommended in this population.

Efalizumab

As with natalizumab, early data on efalizumab safety profile were reassuring, with no major risk of infection reported [57]. Only a marginal increase in minor infections was reported in some studies, mostly viral upper respiratory tract infections, streptococcal pharyngitis, and mild mucocutaneous infections [58]. In 2008, the FDA issued a warning after three confirmed cases of PML were diagnosed in patients who had been receiving efalizumab for more than 3 years. Efalizumab was eventually withdrawn from the market in 2009 due to this concern and the availability of less toxic alternatives for the treatment of psoriasis.

Figure 14.3 summarizes the infectious complications reported for each molecule.

	Infectious risk	Infection
Natalizumab	High	PML (JCV)
	Intermediate	HSV infection VZV infection
	No increase	Bacterial infections Mycobacterial infections Fungal infections Parasitic infections Other viral infections
Vedolizumab	High	None
	Intermediate	*Clostridioides difficile* infection
	No increase	Other bacterial infections Mycobacterial infections Fungal infections Parasitic infections Other viral infections
Efalizumab	High	JCV (PML)
	Intermediate	*Streptococcus pyogenes* pharyngitis Viral upper respiratory tract infections Impetigo Cellulitis
	No increase	Other bacterial infections Mycobacterial infections Fungal infections Parasitic infections Other viral infections

Fig. 14.3 Infection risk and complications by therapeutic molecule. *JCV* JC virus; *PML* progressive multifocal encephalopathy; *HSV* herpes simplex virus; *VZV* varicella zoster virus

Prevention Strategies in MS Patients Receiving Natalizumab

PML Risk Stratification

The prevention of PML in patients receiving natalizumab relies on a stringent risk stratification system and serial MRI monitoring [59]. Risk stratification is based on three components identified by the intensive global risk management program and later validated in large cohorts [60], namely (1) JCV positive serostatus, (2) cumulate use of immunosuppressive drugs, and (3) natalizumab treatment duration, especially beyond 2 years [59–61]. Patients with all of the above factors present the highest risk for PML [60] and require the most intensive monitoring strategy. Monitoring is recommended during treatment and for 6 months after discontinuation of natalizumab, as some cases of PML have been reported up to 6 months after cessation of treatment [59, 62].

JCV Serostatus and MRI

JCV serostatus before the initiation of natalizumab represents the single most important risk factor for subsequent PML development. Determining JCV serostatus is the cornerstone of risk stratification algorithms to define the intensity of PML monitoring needed (Fig. 14.4). The presence of anti-JCV specific IgG is a prerequisite for PML development, and the risk of PML is negligible in their absence. In a study using data from post-marketing sources, clinical studies and an independent Swedish registry, the incidence of PML was 0.09 cases or less per 1000 patients (95% CI, 0 to 0.48) in the absence of anti-JCV antibodies. At the other extreme, patients with positive antibodies, a history of immunosuppression and more than 2 years of natalizumab treatment, presented the highest incidence of 11.1 cases per 1000 patients (96% CI, 8.3 to 14.5) [60].

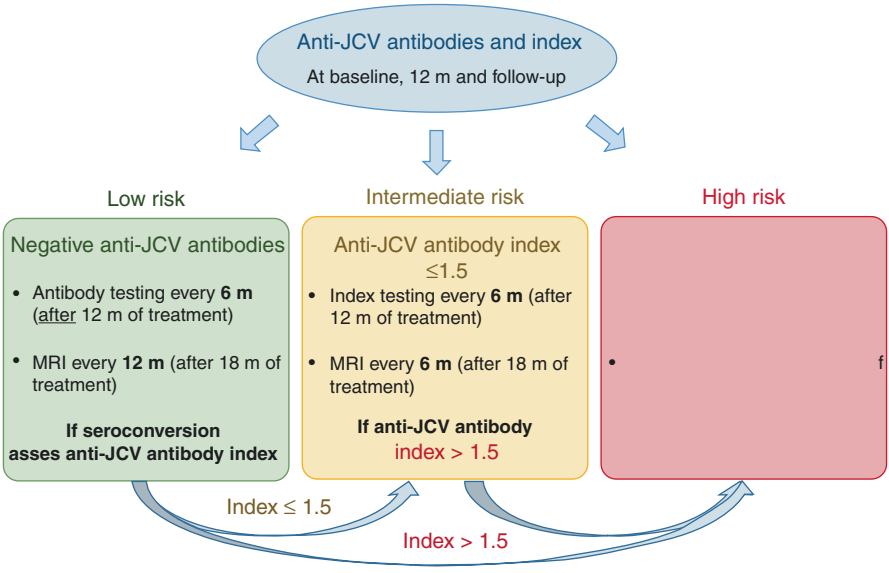

Fig. 14.4 Algorithm for PML prevention and monitoring according to anti-JCV antibody stratification in patients with no history of immunosuppressive treatment, adapted from [59]. All patients should undergo anti-JCV antibody or index testing and brain MRI at baseline and at 12 months. No additional testing is routinely recommended in the first year of treatment. Thereafter antibody or index testing should be performed every 6 months for seronegative and patients with index ≤1.5, respectively. After 18 months of treatment, the frequency of MRI testing is determined by risk category. A dynamic evaluation of PML risk based on index testing is recommended, with a modification of monitoring strategy when patients change "risk category" from a lower to a higher one (curved arrows). Anti-JCV antibody status is only one component of PML risk stratification. Previous immunosuppressive treatment and natalizumab therapy beyond 2 years are the other two, and the presence of these additional risk factors should prompt evaluation of more frequent MRI testing (every 3–4 months as "high-risk patients"). Monitoring is recommended for the whole duration of treatment plus another 6 months. More frequent monitoring and additional workup are indicated in case of new or worsening symptoms

The quantitative anti-JCV serum antibody index allows a more accurate differentiation between negative and positive samples and more reliable results than assays providing only absolute cutoff values [63]. This index refers to the normalized ratio between the signal derived from IgG antibodies in the serum of the patient and the signal from an anti-JCV positive cutoff calibrator sample. An index value of <0.20 is regarded as negative, a value >0.40 positive, and values between 0.20 and 0.40 are considered indeterminate. A longitudinal study including data from 2522 non-PML and 71 PML patients showed that the anti-JCV antibody index value was significantly higher in non-immunosuppressed patients who developed PML compared with non-PML patients ($p < 0.0001$) [63]. An index of ≤1.5 is associated with a lower incidence of PML, and this cutoff could be used to determine monitoring intensity [59, 61, 63]. An anti-JCV antibody index of >1.5 is not a contraindication for treatment continuation, as many patients with a high index will not develop PML. Therefore, the antibody index has a high sensitivity and a low specificity in predicting PML [64].

The risk of anti-JCV antibodies seroconversion was evaluated in a large Dutch cohort of MS patients on natalizumab treatment. Out of 179 patients with available longitudinal blood samples, 86 (48%) tested negative initially and 23 patients among them (26.7%) subsequently seroconverted, contributing to an estimated annual rate of seroconversion of 7.1% and cumulatively leading to more than 25% of seronegative patients becoming seropositive in 4 years [65]. Based on these data, testing for anti-JCV antibodies and anti-JCV index is recommended every 6 months beyond the first year of treatment in seronegative patients (low risk) and patients with a baseline index of ≤1.5, respectively (intermediate). In the risk of developing PML being very low during the first year of treatment (1 in 10,000 to 1 in 1000), no anti-JCV antibody monitoring is routinely recommended during this interval [63].

JCV antibodies are traditionally qualitatively assessed using a two-step enzyme-linked immunosorbent assay (ELISA) method [66]. A second-generation ELISA is commercially available (STRATIFY JCV Dx Select; Focus Diagnostics), though mostly in reference centers, presenting an improved performance, especially in low antibody concentrations where its enhanced resolution allows to significantly decrease "indeterminate" results [67].

The second essential element of monitoring is brain MRI, which is highly performant for the early detection of PML, even months before symptom development [59]. Current recommendation regarding MRI frequency is based on expert opinion. A baseline MRI is recommended for all patients and at least annually during treatment. After the first year, the frequency of MRI depends on the risk category but is generally recommended every 6 months in low- and intermediate-risk patients and every 3–4 months in high-risk patients [59, 61].

Previous Immunosuppression

Previous immunosuppression is associated with a considerably higher incidence of PML which is estimated at 0.88/1000 patients in the presence of previous

immunosuppression versus 0.31/1000 patients in the absence of immunosuppression [60]. The exact mechanism via which previous immunosuppression increases the risk of PML is not fully understood. A possible explanation is that a prolonged impairment of cell-mediated immunity permits viral reactivation and the accumulation of genetic rearrangements leading to the emergence of neuropathogenic JCV prototypes (as opposed to the non-pathogenic archetype ones), which are more frequently present in patients having received immunosuppression before natalizumab [68].

Duration of Natalizumab Treatment

The risk of PML increases with longer duration of treatment, reaching a peak in incidence of 2 cases per 1000 patients in patients receiving natalizumab for more than 48 months [60]. The greatest increase appears after 24 months (and until 48 months) with an incidence of 5.2/1000 patients versus 0.6/1000 patients in the first 24 months of treatment [63]. However, patients having received a single or only a few infusions of natalizumab are usually analyzed in the group of duration inferior to 24 months, contributing to an artificially lower estimation of risk of PML in this group. Long-term data beyond 4 years of treatment are scarce, so that the risk of PML is not clearly delineated in patients with longer exposures [64].

Additional Biomarkers for Risk Stratification

Despite the advances in prevention strategies, PML continues to be a limiting factor for the use of natalizumab, underlining the need for more accurate prediction models. In this setting, many immunological biomarkers have been proposed [64, 69]. CD62L/L-selectin, a cell-adhesion molecule expressed on T lymphocytes, has been identified as a potential tool for PML prediction, with low CD62L in blood mononuclear cells being associated with a 55-fold increase in the relative risk of PML [70]. The presence of lipid-specific immunoglobulin M bands in the CSF, a recognized marker in highly inflammatory MS, was independently associated with decreased PML risk (OR 45.9, 95% CI 5.9–339.3, $p < 0.0001$) [71]. This marker is independent of JCV serostatus as opposed to CD62L and could be a promising in risk stratification.

Additional Preventive Strategies

Given the low effect of natalizumab and vedolizumab in the net state of immunosuppression, additional preventive measures such as the use of antimicrobial and antiviral prophylaxis with co-trimoxazole or valaciclovir, respectively, are not routinely recommended [61].

The risk of hepatitis B virus (HBV) reactivation has not been accurately determined with the use of natalizumab and vedolizumab. No cases of HBV infection are reported in the major clinical trials with both molecules [72, 73], and only one case of fatal acute liver failure due to HBV is reported with natalizumab in the post-marketing setting (though serologic markers do not allow to distinguish between primary infection and reactivation in this case) [74]. Although preventive strategies for HBV are not well established, screening for the presence of HBV infection with HBsAg and anti-HBc before initiation of treatment is appropriate in order to assess the risk of HBV reactivation (based on the presence of HBsAg and the agent used) and decide whether a preventive strategy needs to be introduced [72].

Finally, natalizumab and vedolizumab do not seem to modify vaccine response [75, 76], though a reduction in immunogenicity of the oral cholera vaccine has been observed with vedolizumab in one study [76]. Of note, live vaccines are not contraindicated. As additional immunosuppressive agents can be required in the setting of MS and IBD, an update of the vaccine schedule including HBV/HAV and measles-mumps-rubella-varicella (MMR-V) vaccines in seronegative patients, as well as pneumococcal conjugate vaccine and diphtheria-tetanus-pertussis vaccine (dTP), is recommended.

Conclusions

Leukocyte integrins are privileged therapeutic targets for inflammatory modulation in MS and IBD and are currently targeted by two monoclonal antibodies, natalizumab and vedolizumab. The advent of these molecules has substantially improved the prognosis of patients living with MS and IBD but also highlights the challenge of the use of biologicals in modern medicine. On the one hand, integrins-targeting agents specifically inhibit leukocyte integrins resulting in an excellent efficacy for decreasing MS activity without increasing the net state of immunosuppression. On the other hand, the very same aimed therapeutic effect mediated by the blockade of leukocyte recruitment to the brain is also the principal determinant of the risk for developing PML, a life-threatening disease. Assessment of risk/benefit ratio and the absence of other therapeutic options for severe forms of MS have resulted in the reintroduction of the drug in the clinical practice. While the use of an accurate risk stratification and universal prevention strategies has led to improved management of patients receiving natalizumab, the use of novel specific biomarkers may help to further characterize the risk for PML in these patients. The evaluation of novel therapeutic approaches for natalizumab-associated PML, including immunomodulatory drugs such as checkpoint inhibitors, adoptive T-cell transfer, and anti-JCV specific antivirals, is highly needed to decrease the burden of disease.

References

1. Ley K, Rivera-Nieves J, Sandborn WJ, Shattil S. Integrin-based therapeutics: biological basis, clinical use and new drugs. Nat Rev Drug Discov. 2016;15(3):173–83. https://doi.org/10.1038/nrd.2015.10.
2. Ransohoff RM. Natalizumab for multiple sclerosis. N Engl J Med. 2007;356(25):2622–9. https://doi.org/10.1056/NEJMct071462.
3. Nelson SM, Nguyen TM, McDonald JW, MacDonald JK. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2018;8:CD006097. https://doi.org/10.1002/14651858.CD006097.pub3.
4. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710. https://doi.org/10.1056/NEJMoa1215734.
5. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711–21. https://doi.org/10.1056/NEJMoa1215739.
6. Baiula M, Spampinato S, Gentilucci L, Tolomelli A. Novel ligands targeting alpha4beta1 integrin: therapeutic applications and perspectives. Front Chem. 2019;7:489. https://doi.org/10.3389/fchem.2019.00489.
7. Mitroulis I, Alexaki VI, Kourtzelis I, Ziogas A, Hajishengallis G, Chavakis T. Leukocyte integrins: role in leukocyte recruitment and as therapeutic targets in inflammatory disease. Pharmacol Ther. 2015;147:123–35. https://doi.org/10.1016/j.pharmthera.2014.11.008.
8. Nicolls MR, Gill RG. LFA-1 (CD11a) as a therapeutic target. Am J Transplant. 2006;6(1):27–36. https://doi.org/10.1111/j.1600-6143.2005.01158.x.
9. Jawhara S, Pluskota E, Cao W, Plow EF, Soloviev DA. Distinct effects of integrins alphaX-beta2 and alphaMbeta2 on leukocyte subpopulations during inflammation and antimicrobial responses. Infect Immun. 2017;85(1) https://doi.org/10.1128/IAI.00644-16.
10. Van der Vieren M, Le Trong H, Wood CL, Moore PF, St John T, Staunton DE, et al. A novel leukointegrin, alpha d beta 2, binds preferentially to ICAM-3. Immunity. 1995;3(6):683–90. https://doi.org/10.1016/1074-7613(95)90058-6.
11. Berlin C, Berg EL, Briskin MJ, Andrew DP, Kilshaw PJ, Holzmann B, et al. Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. Cell. 1993;74(1):185–95. https://doi.org/10.1016/0092-8674(93)90305-a.
12. Hemler ME, Huang C, Schwarz L. The VLA protein family. Characterization of five distinct cell surface heterodimers each with a common 130,000 molecular weight beta subunit. J Biol Chem. 1987;262(7):3300–9.
13. Abram CL, Lowell CA. Leukocyte adhesion deficiency syndrome: a controversy solved. Immunol Cell Biol. 2009;87(6):440–2. https://doi.org/10.1038/icb.2009.32.
14. Coller BS. Platelet GPIIb/IIIa antagonists: the first anti-integrin receptor therapeutics. J Clin Invest. 1997;100(11 Suppl):S57–60.
15. Phillips DR, Scarborough RM. Clinical pharmacology of eptifibatide. Am J Cardiol. 1997;80(4A):11B–20B. https://doi.org/10.1016/s0002-9149(97)00572-9.
16. Cook JJ, Gardell SJ, Holahan MA, Sitko GR, Stump GL, Wallace AA, et al. Antithrombotic efficacy of thrombin inhibitor L-374,087: intravenous activity in a primate model of venous thrombus extension and oral activity in a canine model of primary venous and coronary artery thrombosis. J Pharmacol Exp Ther. 1999;289(1):503–10.
17. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis. 2016;10(12):1437–44. https://doi.org/10.1093/ecco-jcc/jjw092.
18. Sandborn WJ, Cyrille M, Hansen MB, Feagan BG, Loftus EV Jr, Rogler G, et al. Efficacy and safety of Abrilumab in a randomized, placebo-controlled trial for moderate-to-severe ulcerative colitis. Gastroenterology. 2019;156(4):946–57 e18. https://doi.org/10.1053/j.gastro.2018.11.035.

19. Hadley GA, Higgins JM. Integrin alphaEbeta7: molecular features and functional significance in the immune system. Adv Exp Med Biol. 2014;819:97–110. https://doi.org/10.1007/978-94-017-9153-3_7.
20. Sandborn WJ, Vermeire S, Tyrrell H, Hassanali A, Lacey S, Tole S, et al. Etrolizumab for the treatment of ulcerative colitis and Crohn's disease: an overview of the phase 3 clinical program. Adv Ther. 2020;37(7):3417–31. https://doi.org/10.1007/s12325-020-01366-2.
21. Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet. 2014;384(9940):309–18. https://doi.org/10.1016/S0140-6736(14)60661-9.
22. Yoshimura N, Watanabe M, Motoya S, Tominaga K, Matsuoka K, Iwakiri R, et al. Safety and efficacy of AJM300, an Oral antagonist of alpha4 integrin, in induction therapy for patients with active ulcerative colitis. Gastroenterology. 2015;149(7):1775–83 e2. https://doi.org/10.1053/j.gastro.2015.08.044.
23. Donnenfeld ED, Karpecki PM, Majmudar PA, Nichols KK, Raychaudhuri A, Roy M, et al. Safety of Lifitegrast ophthalmic solution 5.0% in patients with dry eye disease: a 1-year, multicenter, randomized, placebo-controlled study. Cornea. 2016;35(6):741–8. https://doi.org/10.1097/ICO.0000000000000803.
24. Carson KR, Focosi D, Major EO, Petrini M, Richey EA, West DP, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a review from the research on adverse drug events and reports (RADAR) project. Lancet Oncol. 2009;10(8):816–24. https://doi.org/10.1016/S1470-2045(09)70161-5.
25. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. Nature. 1992;356(6364):63–6. https://doi.org/10.1038/356063a0.
26. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899–910. https://doi.org/10.1056/NEJMoa044397.
27. Rudick RA, Panzara MA. Natalizumab for the treatment of relapsing multiple sclerosis. Biologics. 2008;2(2):189–99. https://doi.org/10.2147/btt.s1956.
28. Clerico M, Artusi CA, Liberto AD, Rolla S, Bardina V, Barbero P, et al. Natalizumab in multiple sclerosis: long-term management. Int J Mol Sci. 2017;18(5) https://doi.org/10.3390/ijms18050940.
29. Targan SR, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE trial. Gastroenterology. 2007;132(5):1672–83. https://doi.org/10.1053/j.gastro.2007.03.024.
30. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353(18):1912–25. https://doi.org/10.1056/NEJMoa043335.
31. Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, et al. Natalizumab for active Crohn's disease. N Engl J Med. 2003;348(1):24–32. https://doi.org/10.1056/NEJMoa020732.
32. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. World J Gastroenterol. 2014;20(1):91–9. https://doi.org/10.3748/wjg.v20.i1.91.
33. Parikh A, Fox I, Leach T, Xu J, Scholz C, Patella M, et al. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(8):1691–9. https://doi.org/10.1097/MIB.0b013e318281f538.
34. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147(3):618–27 e3. https://doi.org/10.1053/j.gastro.2014.05.008.
35. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006;354(9):924–33. https://doi.org/10.1056/NEJMoa054693.

36. Padgett BL, Walker DL, ZuRhein GM, Eckroade RJ, Dessel BH. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet. 1971;1(7712):1257–60. https://doi.org/10.1016/s0140-6736(71)91777-6.
37. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. PLoS Pathog. 2009;5(3):e1000363. https://doi.org/10.1371/journal.ppat.1000363.
38. Bozic C, Subramanyam M, Richman S, Plavina T, Zhang A, Ticho B. Anti-JC virus (JCV) antibody prevalence in the JCV epidemiology in MS (JEMS) trial. Eur J Neurol. 2014;21(2):299–304. https://doi.org/10.1111/ene.12304.
39. Egli A, Infanti L, Dumoulin A, Buser A, Samaridis J, Stebler C, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. J Infect Dis. 2009;199(6):837–46. https://doi.org/10.1086/597126.
40. Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. Brain. 1958;81(1):93–111. https://doi.org/10.1093/brain/81.1.93.
41. Power C, Gladden JG, Halliday W, Del Bigio MR, Nath A, Ni W, et al. AIDS- and non-AIDS-related PML association with distinct p53 polymorphism. Neurology. 2000;54(3):743–6. https://doi.org/10.1212/wnl.54.3.743.
42. Sahraian MA, Radue EW, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: a review of the neuroimaging features and differential diagnosis. Eur J Neurol. 2012;19(8):1060–9. https://doi.org/10.1111/j.1468-1331.2011.03597.x.
43. Swinnen B, Saegeman V, Beuselinck K, Wouters A, Cypers G, Meyfroidt G, et al. Predictive value of JC virus PCR in cerebrospinal fluid in the diagnosis of PML. Diagn Microbiol Infect Dis. 2019;95(3):114859. https://doi.org/10.1016/j.diagmicrobio.2019.06.011.
44. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology. 2013;80(15):1430–8. https://doi.org/10.1212/WNL.0b013e31828c2fa1.
45. Kappos L, Bates D, Edan G, Eraksoy M, Garcia-Merino A, Grigoriadis N, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol. 2011;10(8):745–58. https://doi.org/10.1016/S1474-4422(11)70149-1.
46. Clerico M, Artusi CA, Di Liberto A, Rolla S, Bardina V, Barbero P, et al. Long-term safety evaluation of natalizumab for the treatment of multiple sclerosis. Expert Opin Drug Saf. 2017;16(8):963–72. https://doi.org/10.1080/14740338.2017.1346082.
47. Dahlhaus S, Hoepner R, Chan A, Kleiter I, Adams O, Lukas C, et al. Disease course and outcome of 15 monocentrically treated natalizumab-associated progressive multifocal leukoencephalopathy patients. J Neurol Neurosurg Psychiatry. 2013;84(10):1068–74. https://doi.org/10.1136/jnnp-2013-304897.
48. Cortese I, Muranski P, Enose-Akahata Y, Ha SK, Smith B, Monaco M, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. N Engl J Med. 2019;380(17):1597–605. https://doi.org/10.1056/NEJMoa1815039.
49. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. Clin Infect Dis. 2013;57(6):849–52. https://doi.org/10.1093/cid/cit376.
50. Fragoso YD, Brooks JB, Gomes S, de Oliveira FT, da Gama PD. Report of three cases of herpes zoster during treatment with natalizumab. CNS Neurosci Ther. 2013;19(4):280–1. https://doi.org/10.1111/cns.12067.
51. Kwiatkowski A, Gallois J, Bilbault N, Calais G, Mackowiak A, Hautecoeur P. Herpes encephalitis during natalizumab treatment in multiple sclerosis. Mult Scler. 2012;18(6):909–11. https://doi.org/10.1177/1352458511428082.
52. Dahdaleh D, Altmann DM, Malik O, Nicholas RS. Breathlessness, night sweats, and weight loss on natalizumab. Lancet. 2012;380(9843):726–7. https://doi.org/10.1016/S0140-6736(12)61401-9.
53. Loftus EV Jr, Feagan BG, Panaccione R, Colombel JF, Sandborn WJ, Sands BE, et al. Long-term safety of vedolizumab for inflammatory bowel disease. Aliment Pharmacol Ther. 2020;52(8):1353–65. https://doi.org/10.1111/apt.16060.

54. Colombel JF, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66(5):839–51. https://doi.org/10.1136/gutjnl-2015-311079.
55. McAuliffe ME, Lanes S, Leach T, Parikh A, Faich G, Porter J, et al. Occurrence of adverse events among patients with inflammatory bowel disease in the HealthCore integrated research database. Curr Med Res Opin. 2015;31(9):1655–64. https://doi.org/10.1185/03007995.2015.1065242.
56. Card T, Xu J, Liang H, Bhayat F. What is the risk of progressive multifocal leukoencephalopathy in patients with ulcerative colitis or Crohn's disease treated with vedolizumab? Inflamm Bowel Dis. 2018;24(5):953–9. https://doi.org/10.1093/ibd/izx097.
57. Langley RG, Carey WP, Rafal ES, Tyring SK, Caro I, Wang X, et al. Incidence of infection during efalizumab therapy for psoriasis: analysis of the clinical trial experience. Clin Ther. 2005;27(9):1317–28. https://doi.org/10.1016/j.clinthera.2005.09.007.
58. Scheinfeld N. Efalizumab: a review of events reported during clinical trials and side effects. Expert Opin Drug Saf. 2006;5(2):197–209. https://doi.org/10.1517/14740338.5.2.197.
59. McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, Molyneux P, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry. 2016;87(2):117–25. https://doi.org/10.1136/jnnp-2015-311100.
60. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366(20):1870–80. https://doi.org/10.1056/NEJMoa1107829.
61. Redelman-Sidi G, Michielin O, Cervera C, Ribi C, Aguado JM, Fernandez-Ruiz M, et al. ESCMID study Group for Infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). Clin Microbiol Infect. 2018;24(Suppl 2):S95–S107. https://doi.org/10.1016/j.cmi.2018.01.030.
62. Wattjes MP, Killestein J. Progressive multifocal leukoencephalopathy after natalizumab discontinuation: few and true? Ann Neurol. 2014;75(3):462. https://doi.org/10.1002/ana.24110.
63. Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2014;76(6):802–12. https://doi.org/10.1002/ana.24286.
64. Schwab N, Schneider-Hohendorf T, Melzer N, Cutter G, Wiendl H. Natalizumab-associated PML: challenges with incidence, resulting risk, and risk stratification. Neurology. 2017;88(12):1197–205. https://doi.org/10.1212/WNL.0000000000003739.
65. Vennegoor A, van Rossum JA, Leurs C, Wattjes MP, Rispens T, Murk JL, et al. High cumulative JC virus seroconversion rate during long-term use of natalizumab. Eur J Neurol. 2016;23(6):1079–85. https://doi.org/10.1111/ene.12988.
66. Gorelik L, Lerner M, Bixler S, Crossman M, Schlain B, Simon K, et al. Anti-JC virus antibodies: implications for PML risk stratification. Ann Neurol. 2010;68(3):295–303. https://doi.org/10.1002/ana.22128.
67. Lee P, Plavina T, Castro A, Berman M, Jaiswal D, Rivas S, et al. A second-generation ELISA (STRATIFY JCV DxSelect) for detection of JC virus antibodies in human serum and plasma to support progressive multifocal leukoencephalopathy risk stratification. J Clin Virol. 2013;57(2):141–6. https://doi.org/10.1016/j.jcv.2013.02.002.
68. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol. 2021;17(1):37–51. https://doi.org/10.1038/s41582-020-00427-y.
69. Antoniol C, Stankoff B. Immunological markers for PML prediction in MS patients treated with natalizumab. Front Immunol. 2014;5:668. https://doi.org/10.3389/fimmu.2014.00668.

70. Schwab N, Schneider-Hohendorf T, Pignolet B, Spadaro M, Gorlich D, Meinl I, et al. PML risk stratification using anti-JCV antibody index and L-selectin. Mult Scler. 2016;22(8):1048–60. https://doi.org/10.1177/1352458515607651.
71. Villar LM, Costa-Frossard L, Masterman T, Fernandez O, Montalban X, Casanova B, et al. Lipid-specific immunoglobulin M bands in cerebrospinal fluid are associated with a reduced risk of developing progressive multifocal leukoencephalopathy during treatment with natalizumab. Ann Neurol. 2015;77(3):447–57. https://doi.org/10.1002/ana.24345.
72. Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open forum. Infect Dis. 2018;5(8):ofy174. https://doi.org/10.1093/ofid/ofy174.
73. Ng SC, Hilmi IN, Blake A, Bhayat F, Adsul S, Khan QR, et al. Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. Inflamm Bowel Dis. 2018;24(11):2431–41. https://doi.org/10.1093/ibd/izy153.
74. Hillen ME, Cook SD, Samanta A, Grant E, Quinless JR, Rajasingham JK. Fatal acute liver failure with hepatitis B virus infection during natalizumab treatment in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm. 2015;2(2):e72. https://doi.org/10.1212/NXI.0000000000000072.
75. Kaufman M, Pardo G, Rossman H, Sweetser MT, Forrestal F, Duda P. Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis. J Neurol Sci. 2014;341(1–2):22–7. https://doi.org/10.1016/j.jns.2014.03.035.
76. Wyant T, Leach T, Sankoh S, Wang Y, Paolino J, Pasetti MF, et al. Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. Gut. 2015;64(1):77–83. https://doi.org/10.1136/gutjnl-2014-307127.