Progressive Multifocal Leukoencephalopathy

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Introduction

The John Cunningham virus (JCV) is a neurotropic DNA virus belonging to the polyomavirus family that binds to N-linked glycoproteins and serotonergic 5-HT receptors presented on the surface of many human cells including kidney epithelial cells, B-cells, platelets, glial cells, and neurons [1].

JCV infection is common, with seroprevalence rates increasing with age from 10% in children to more than 80% in adulthood [2]. Primary infection is usually asymptomatic, and JCV usually remains quiescent in the kidneys, bone marrow, and lymphoid tissues. Through intermittent episodes of viremia, JCV may reach the brain [1]. Nevertheless, adequate humoral and, more importantly, cellular immunity are capable of controlling viral replication in glial tissue and therefore avoid tissue damage [3].

Progressive multifocal leukoencephalopathy (PML) is a rare disease related to JCV infection-derived pathogenic lesions on oligodendrocytes, and, to a lesser extent, astrocytes, that trigger the development of areas of demyelination sparing spinal cord and optical nerves, clinically expressed by muscle weakness, sensory

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deficit, cognitive dysfunction, confusion, aphasia, coordination, or gait difficulties [1]. Replication and cytopathic effects of JCV in myelin-producing cells occur in situations of failure of immunological control by CD4+ and CD8+ T-cells, which hampers clearance of the virus from the cerebrospinal fluid [4]. Therefore, PML had been reported as a rare disease restricted to immunosuppressed hosts with hematological malignancies, organ transplant recipients, and with chronic inflammatory disorders. Since the emergence of the human immunodeficiency virus (HIV) epidemic, the prevalence of PML substantially increased so that more than 80% of cases of PML reported in the USA between 1998 and 2005 were AIDS-related [5].

More recently, PML has been increasingly reported as a rare, serious adverse event related with some new targeted and biological therapies. The first monoclonal antibodies (mAbs) approved for the treatment of cancer or autoimmune diseases that have been reported to incur an increased risk of PML included natalizumab, efalizumab, rituximab, and alemtuzumab [6]. Nevertheless, novel therapies approved for B-cell hematologic malignancies and autoimmune diseases as brentuximab vedotin, alemtuzumab, ofatumumab, ibrutinib, obinutuzumab, belimumab, and idelalisib had also been reported as potentially of risk in view of data from passive FDA pharmacovigilance surveillance program in the USA (Table 22.1).

With exception of α4-integrin-targeting agents natalizumab and efalizumab, in which the underlying mechanisms behind the development of PML have been clearly demonstrated, drug-related cases of PML are mostly based on statistical relationship and confusion by other potential risk factors are usually difficult to discard.

In the present chapter, we will revise currently available data on PML in patients receiving targeted and biological therapy, focusing on the underlying mechanisms and potential preventive management of natalizumab-related PML. Nevertheless, we will also discuss current information regarding drug-related PML by other targeted biological drugs with the most established statistical relationships and as is the case of alemtuzumab, anti-CD20 mAbs, brentuximab, and novel intracellular signaling pathway inhibitors.

Table 22.1 Cases of PML associated with the use of immune-targeted therapies (2009–2016) with significant signal detection results included in the FDA adverse event reporting system (FAERS)

Drug	PML cases	Drug courses	% PML	PRR (CI 95%)
Brentuximab vedotin[a]	15	1017	1.47	24.49 (14.79–40.56)
Ofatumumab[a]	14	1478	0.95	16.26 (9.64–27.42)
Alemtuzumab[a]	15	3038	0.49	9.87 (5.95–6.38)
Obinutuzumab[a]	3	655	0.46	7.36 (2.38–22.8)
Ibrutinib[a]	10	2860	0.35	5.63 (3.02–10.49)
Belimumab[a]	8	2985	0.27	4.5 (2.25–9)
Idelalisib	3	1089	0.46	4.05 (1.31–12.58)

Adapted from [7]
Only drugs with more than two PML cases and PRR (proportional reporting ratios with respect to other drugs) greater than 2.0 are included
PML progressive multifocal leukoencephalopathy, *FAERS* FDA Adverse Event Reporting System
[a] PML risk included in labeling

PML Related with α4-Integrin-Targeted Agents

Natalizumab (Tysabri®, Elan Pharmaceuticals and Biogen Idec) is a humanized IgG4 mAb targeting the α4 integrin subunit that constituted the first anti-integrin agent approved for clinical use. The α4 chain forms two different integrins, α4β1 (also known as very late antigen [VLA]-4) and α4β7, respectively [8]. VLA-4 is expressed on practically all leukocytes (except mature granulocytes) and mediates binding to endothelial cell layers, including the blood-brain barrier (BBB), via vascular cell adhesion molecule (VCAM)-1. The VLA-4/VCAM-1 interaction is required for immune cell trafficking into the central nervous system (CNS). Through blockade of α4β1 integrin (VLA-4), natalizumab inhibits T-cell migration across the BBB, thereby reducing CNS inflammation [9, 10]. This drug received FDA regulatory approval to treat relapsing-remitting multiple sclerosis (MS) in 2004 [11] and for moderate-to-severe Crohn's disease (CD) in 2008 [12].

Efalizumab (Raptiva®, Genentech) is also a recombinant humanized mAb targeted against CD11a, one of the two subunits of the αLβ2 integrin (also known as leukocyte function antigen-1 [LFA-1]) and prevents binding of T-cells to the intercellular adhesion molecule-1 (ICAM-1), found on antigen-presenting cells (endothelial cells and keratinocytes), interfering with inflammatory mechanisms involved in the formation of the psoriatic plaque. After approval for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis, the high number of cases of PML under this treatment led to drug withdrawn from the market, so it is no longer available [10]. Vedolizumab (Entyvio®, Millennium Pharmaceuticals) is the other currently approved α-integrin-targeted drug that selectively targets the α4β7 integrin, which binds to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) mediating T-cell migration to the lamina propria of the small intestine [10]. This drug has been approved for the treatment of moderately to severely active ulcerative colitis and Crohn's disease in adults who have failed at least one conventional therapy. Unlike natalizumab or efalizumab, vedolizumab does not affect CNS immune modulation as α4β7 integrin acts exclusively on intestinal lymphocytes and no cases of vedolizumab-induced PML have been reported to date [13–15]. We therefore will focus the present section on natalizumab-related PML.

Underlying Mechanisms of Natalizumab-Related PML

PML is the result of the infection (and subsequent degeneration) of oligodendrocytes in the white matter due to the JCV [16]. The archetypal form of JCV is the cause for primary infection and latency. In patients receiving natalizumab, several subtypes of mononuclear cells (central memory T-cells, effector memory T-cells, and activated monocytes) that express α4β1 and α4β7 on their surface are affected, and inhibition of their migration into the CNS is described [8]. This leads to a decrease in the CD4+/CD8+ T-cell ratio and B-cell and CD138+ plasma cell counts in the cerebrospinal fluid (CSF) [17, 18] and in the number of dendritic cells and CD4+ T-cells in cerebral perivascular spaces [19] allowing asymptomatic

reactivation of JCV in plasma and urine in parallel with a decrease in JCV-specific cellular immune responses [20]. Natalizumab treatment also induces rearrangements in the noncoding control region (NCCR) of the JCV genome [21] promoting replication of the so-called prototypical form (or PML-type) of the virus capable of promoting replication and pathogenic effect of JCV in oligodendrocytes.

Epidemiology and Risk Factors for Natalizumab-Related PML

Natalizumab initially seemed to be well tolerated in phase 3 randomized clinical trials (RCTs) leading to approval. However, the first cases of PML in natalizumab-treated patients recruited in pivotal trials were early reported through extended follow-up [12, 22, 23]. This circumstance led to a voluntary suspension of marketing in February 2005. Natalizumab was reintroduced in the US market in 2006 with a black box warning for PML and under a restricted distribution program (Tysabri® Outreach: Unified Commitment to Health [TOUCH]) [24]. The European Medicines Agency (EMA) furtherly approved natalizumab as monotherapy only for patients with highly active or rapidly evolving forms of relapsing-remitting MS despite an adequate course with at least one disease-modifying agent. On the basis of more than 150,000 patients treated with natalizumab worldwide, the overall current incidence of PML has been currently estimated in 4.22 cases per 1000 patients [24].

Three major clinical risk factors have been identified to stratify the risk of PML in patients receiving natalizumab [25]:

– *Treatment duration.* The annualized seroconversion rate among JCV-seronegative patients exposed to natalizumab has been estimated in 7.1% [26], reaching an incidence of two cases per 1000 treated patients beyond 48 months of therapy. However, although the incidence increases abruptly after 72 months, more information is needed to delineate the risk of PML after prolonged treatment courses [27, 28].
– *Exposure to JCV* (as assessed by a positive status for anti-JCV IgG antibodies). The risk of early natalizumab-induced PML seems to be negligible if pretreatment JCV-specific IgG antibodies are negative. The incidence among JCV-seropositive patients was estimated at 3.87 cases per 1000 natalizumab-treated patients, as compared to zero cases per 1000 in seronegative individuals [27]. Among JCV-seropositive subjects, those with an IgG index ≤1.5 have a lower incidence of PML compared to the remaining population of anti-JCV antibody-positive patients [29].
– *Previous or even remote history of immunosuppressive therapy* (including relatively mild agents such as methotrexate) double the incidence of PML among natalizumab-exposed patients [27], an observation likely explained by the higher risk of having latent infection due to the prototype form of JCV at therapy initiation.

By combining these variables into a risk stratification algorithm, different categories may be established, with expected PML incidences ranging from less than 0.09 cases per 1000 patients in the lowest-risk subgroup to 11.1 cases per 1000 patients in the highest-risk category [27]. The quantification of anti-JCV IgG titers by enzyme-linked immunosorbent assay (ELISA) has been proven to provide further refinement in risk prediction. The anti-JCV antibody index is the normalized ratio between the signal (in optical densities) obtained from the patient's serum and that from a cutoff calibrator prepared with pooled sera collected from JCV-seropositive healthy volunteers. Patients not previously treated with immunosuppressive agents with an index value ≤0.9 carried a risk of 0.1 cases per 1000 during the first 24 months of therapy, which gradually increased up to 0.4 per 1000 with 49 to 72 months of exposure. In contrast, the expected incidence during the first 24 months among patients with an index >1.5 was of 1.0 cases per 1000, reaching 10.12 per 1000 between months 49 and 72 [30]. An FDA-cleared second-generation ELISA test (STRATIFY JCV™, Focus Diagnostics) is now commercially available [31]. Other biomarkers that are being evaluated to stratify the risk of PML include decreased CD4+ T-cell expression of ʟ-selectin CD62L [32] and lipid-specific immunoglobulin M bands in CSF [33].

Clinical Features and Management

The prognosis of natalizumab-associated PML critically depends on early recognition [24]. Typical clinical and radiological characteristics are detailed in Table 22.2. The clinical presentation of natalizumab-induced PML includes motor weakness, cognitive deficits, dysarthria, and ataxia [34]. Cranial magnetic resonance imaging

Table 22.2 Main clinical and radiological features of PML in patients treated with natalizumab (modified from McGuigan et al.) [29]

Clinical presentation
• Subacute (weeks) onset and progressive course
• Aphasia, behavioral, and neuropsychological alterations, visual deficits, hemiparesis, and seizures
MRI features
• Large (>3 cm) lesions with unifocal, multifocal, or widespread distribution
• Subcortical location rather than periventricular
• Frequent involvement of cortical gray matter (50% of cases), posterior fossa less commonly affected
• No mass effect even in large lesions
• T2-weighted sequences: Diffuse hyperintensity (often with punctate microcystic appearance) within the lesions
• T1-weighted sequences: Lightly hypointensity at onset, with signal intensity decreasing over time
• Paramagnetic contrast enhancement in <50% of cases at the time of presentation (often patchy or punctate appearance)
• Diffusion-weighted imaging: Hyperintense appearance of acute lesions

MRI magnetic resonance imaging

(MRI) typically shows T2-weighted hyperintense lesions in subcortical white matter without gadolinium enhancement [35]. The detection of viral DNA in the CSF or brain biopsy is required for the definitive diagnosis [35]. JCV PCR on CSF has a high sensitivity and even higher specificity, but a negative result does not rule out the diagnosis of PML, and testing should be repeated in case of high clinical suspicion. Early discontinuation of natalizumab is the first step in the management of PML [4], whereas antiviral therapy has not shown clear benefit. Early removal of natalizumab from the bloodstream via plasma exchange or immunoadsorption is also indicated [35, 36], although such approach has been associated with the subsequent development of immune reconstitution inflammatory syndrome [37, 38].

Preventive Algorithms

In order to minimize the risk of PML under natalizumab treatment, different preventive algorithms have been developed based on pre-treatment serological risk stratification of patients and active clinical and virological surveillance in high-risk patients [38, 39] which is represented in Fig. 22.1:

- **Test for anti-JCV IgG antibodies** is recommended before starting treatment in natalizumab-*naïve* MS patients [29, 38]. An index cutoff value of >1.5 constitutes a reasonable threshold to guide the clinical decision process. Patients with an index >1.5 are to be already considered at high risk and no further testing is required. JCV-seronegative patients and those with IgG antibody index ≤1.5 should be retested every 6 months after the first year of treatment.
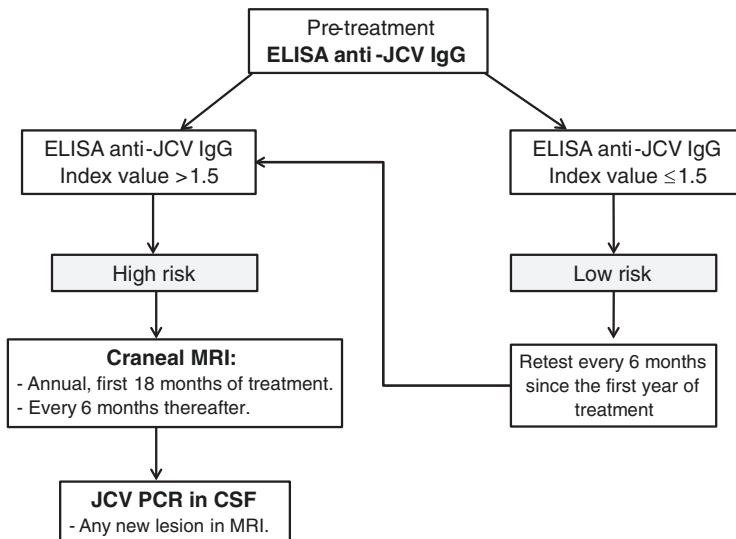

Fig. 22.1 Natalizumab-related PML risk stratification algorithm

- **Cerebral MRI** with diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) should be performed at baseline and repeated at scheduled intervals in seropositive patients:
  - Annual MRI scans during the first 18 months of therapy.
  - After the first 18 months of treatment at least 6-month intervals for patients with an index ≤1.5 and 3- to 4-month intervals for those with index >1.5.
- **PCR testing on cerebrospinal fluid specimens**. Should be performed whenever any new lesion on subsequent MRI [29].

A recent study from France found an annual reduction of 23.0% in the crude incidence of natalizumab-associated PML since 2013 (in contrast to the steady increase observed before that year), supporting the efficacy of this risk minimization strategy [40]. The decision of discontinuing therapy with natalizumab in patients at high risk of PML (positive anti-JCV serology with an IgG antibody index >1.5 and therapy duration of 48 months or more) is difficult and should be shared by the MS specialist and the patient [38].

PML Related to Monoclonal Antibodies Against Lymphoma and Leukemia Surface Antigens

Anti-CD20 Monoclonal Antibodies

In 1997, rituximab was the first anti-cancer mAb approved for clinical use. Since June 2017, there are six different anti-CD20 mAbs authorized for clinical use. In the European Union, a PML warning was added to the prescribing information of rituximab in 2007 based on pharmacovigilance signaling. In 2009, the Research on Adverse Drug Events and Reports (RADAR) group published the first case series of rituximab-related PML [41]. Although PML is still nowadays considered as a "very rare" complication of rituximab therapy, with current incidence rates estimation ranging from 0.2 to 2.56 per 10,000 exposed patients [42, 43], most experts take into consideration the risk of this serious complication in patients receiving anti-CD20 mAbs [44–46]. In spite of isolated cases of PML reported with other anti-CD20 antibodies as obinutuzumab [47] or ofatumumab [48], the possibility that PML could be a class effect of all anti-CD20 antibodies is currently debated as no conclusive evidence is yet available. However, as for cautionary approach, obinutuzumab, ofatumumab, and ocrelizumab labels included PML among potential adverse reactions since the first day of marketing and probably deserve similar precaution and surveillance than with rituximab [45].

About 65% of PML cases are diagnosed within the first 2 years after the first rituximab dose, and more than 70% of cases were reported during remission induction therapy for non-Hodgkin's lymphoma [46]. In contrast to what has been established with natalizumab-related PML, no cumulative dose-effect relationship has been demonstrated for rituximab, and concurrent drug analysis in PML cases has suggested potential confusion or synergies with other drugs which inhibit cellular

immunity as fludarabine or bendamustine [46]. Indeed, in a recent global post-marketing safety and clinical trial, all rituximab-related cases of PML had at least one additional potential risk factor [49].

The mechanisms underlying the increased risk of PML in patients receiving anti-CD20 mAbs are incompletely understood. Whereas rituximab has shown quantitative impact on other cell lines apart from CD20+ B-cells clinically expressed as neutropenia and thrombocytopenia, the impact on T-cell immunity has been more difficult to ascertain. A drop in CD4+ T-cell counts intensified through repeated treatment cycles has been reported in some series including rheumatoid arthritis patients treated with rituximab [43, 50, 51]. Nevertheless, available databases of post-marketing surveillance argue against the role of rituximab at causing severe CD4+ T-cell lymphopenia (with most of the cases providing alternative explanation, mainly concurrent use of bendamustine) and no definite conclusion whether rituximab induces a clinically relevant deleterious effect on the cell-mediated immunity in patients with normal T-cell counts at baseline can be made [46].

Regarding potential functional effect on T-cells, whereas animal models could not demonstrate that B-cells affect secondary T-cell responses against viral pathogens, B-cell depletion before or during primary viral infection significantly impairs cytokine production and generation of new memory CD4+ T-cells, thus increasing the risk of systemic primary infections [52]. In addition to B-cell-dependent mechanism, direct effect on T-cells of CD20-targeted agents could be suggested in view of efficacy data for graft rejection treatment after solid organ transplantation and graft versus host disease following allogenic hematopoietic stem cell transplantation. Finally, there is a population of 3%–5% of T-cells represented in different cell compartments, including the CNS, that express CD20 (CD3+ CD20+ T-cells) and are selectively depleted by CD20-targeted agents [53]. Although the natural function of this T-cell subset is currently unclear, their depletion seems to be crucial in the efficacy of anti-CD20 mAbs in the treatment of multiple sclerosis [53].

Unfortunately, there is no validated risk stratification strategy directed to the prevention of potential PML cases in patients under anti-CD20 treatments. CD4+ T-cell counts appear to be a reasonable marker for the risk of PML and possibly more cost-effective than using JCV detection techniques in contrast to what occurs with drugs with a higher and more clearly established risk such as natalizumab.

Antibodies Against Lymphoma and Leukemia Cell Surface Antigens

Alemtuzumab

Alemtuzumab is a humanized IgG1 mAb that binds to CD52 and leads to the lysis of targeted cells by means of complement-dependent cytotoxicity. CD52 is expressed on most mature lymphocytes, monocytes, and macrophages, thereby inducing severe depletion of peripheral blood lymphocytes (both T- and B-cells, especially CD4+), an effect that is more profound and long-lasting with repeated infusions. Even with the lower doses of alemtuzumab used in multiple sclerosis,

decreased CD4+ T-cell counts (<200 cells/μL) have been reported to persist months after the completion of therapy [54]. Lymphodepletion is evident by 2–4 weeks from the first dose with the lowest values typically found after 1 month [55] and remains below 25% from baseline levels beyond 9 months [56]. Recovery to the normal range can take 8 months for B-cells and up to 3 years for CD4+ and CD8+ T-cells, although lymphocyte counts rarely return to baseline values [54]. In view of the notable impact on the CD4+ T-cell subset, the expected infection risk is similar to the spectrum observed in advanced HIV infection, with increased incidence of classic opportunistic infections, including scattered cases of PML, that have been reported mostly in patients with hematological malignancy treated with this drug [57–59]. In spite of the potential risk of this complication under this treatment, no specific preventive recommendations are currently available [45].

Brentuximab

Brentuximab vedotin (Adcetris®, Takeda) is an antibody-drug conjugate composed of a human/murine chimeric anti-CD30 IgG1 mAb approved in 2011 by the FDA and in 2012 by EMA for the treatment of relapsed/refractory Hodgkin's lymphoma (HL) and anaplastic large T-cell lymphoma. CD30 is expressed in various cellular types, including T-cells, B-cells, monocytes, and activated natural killer cells. Taking into account that CD30 has been implied in the regulation of the balance between Th1 and Th2 responses and in the generation of memory and effector T-cells [60, 61], CD30-targeted agents may affect antibody-dependent cell-mediated cytotoxicity and exert a deleterious impact on humoral immunity.

PML has been described in patients receiving brentuximab vedotin, although the concomitant use of other cytostatic and immunosuppressive agents administered in affected patients makes it difficult to establish causality [62–65]. Time from initiation of therapy to symptom onset (second or third dose) has been reported as much shorter than PML cases related with anti-CD20 mAbs or natalizumab, and the case fatality rate among reported cases was 80% [62–65]. These clinical observations prompted the FDA to launch a Risk Evaluation and Mitigation Strategy (REMS) program including appropriate label warning [7, 65].

Clinical monitoring of neurological symptoms of new onset among brentuximab-treated patients in order to achieve prompt suspicion of PML and early drug discontinuation with appropriate diagnostic work-up is currently recommended [45].

Drugs Targeted to Intracellular Signaling Pathways

Several cases of fatal PML have been reported following the use of Bruton's tyrosine kinase inhibitor ibrutinib, although in the context of multiple prior treatment lines, including rituximab [7, 66–68]. In the same line, Janus kinase inhibitor ruxolitinib has also been recently associated with PML even in the absence of lymphopenia [69].

As cases of PML derived from these targeted therapies are currently emerging, there is still scant epidemiological data and little information on the underlying

pathophysiological mechanisms causing increased risk. Therefore, preventive algorithms have not yet been developed. As discussed for other targeted biological drugs potentially associated to PML, specific clinical surveillance of new onset of neurological symptoms in patients treated with ibrutinib or ruxolitinib seems to be advisable [70].

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