Cancer Control
2017, Vol. 24(4) 1–9

DOI: 10.1177/1073274817729901
journals.sagepub.com/home/ccx
SAGE

Progressive Multifocal Leukoencephalopathy and Monoclonal Antibodies: A Review

Chandrashekar Bohra, MD[1,2,3], Lubomir Sokol, MD, PhD[1,2,3], and Samir Dalia, MD[1,2,3]

Abstract

Progressive multifocal leukoencephalopathy (PML) is a viral infection predominantly seen in patients with HIV infection. However, with the increased use of monoclonal antibodies (MAB) for various lymphoproliferative disorders, we are now seeing this infection in non-HIV patients on drugs such as natalizumab, rituximab, and so on. The aim of this article is to review the relationship between the occurrence of PML and MAB used in the treatment of hematological malignancies and autoimmune diseases. Review of articles from PubMed-indexed journals which study PML in relation to the use of MAB. Relevant literature demonstrated an increased risk of reactivation of latent John Cunningham polyomavirus (JCV) resulting in development of PML in patients on long-term therapy with MAB. The highest incidence of 1 PML case per 1000 treated patients and 1 case per 32 000 was observed in patients treated with natalizumab and rituximab, respectively. Serological and polymerase chain reaction tests for the detection of JCV can be helpful in risk stratification of patients for the development of PML before and during therapy with MAB. Treatment with MAB can result in development of PML. Clinicians should include PML in differential diagnosis in patients treated with these agents if they manifest central nervous system symptoms.

Keywords

progressive multifocal leukoencephalopathy, monoclonal antibodies, JCV

Received February 21, 2017. Accepted for publication July 3, 2017.

Introduction

Progressive multifocal leukoencephalopathy (PML) was first described in 1958 by Astrom et al.[1] In 1965, ZuRhein and Chou suggested that a papovavirus was the cause of PML.[2] In the largest review of PML to that date published in 1984, Brooks and Walker identified 230 cases that were published in the English-written literature or from their own experience.[3] Of these, 69 patients were pathologically confirmed and only 40 tested positive with viral tests and pathology.[3] Ninety-five percent of patients had an underlying condition that predisposed them to PML, of which nearly two-thirds had an underlying B-cell lymphoproliferative disorder (LPD) while an underlying primary immunodeficiency was evident in 16% of cases.[4-6] With the concern of association of PML and B-cell LPD, the risk of developing PML in patients on therapies that alter the B-cell function became an important issue. As the use of monoclonal antibodies (MAB) such as natalizumab, rituximab, and efalizumab increased, there was also a rise in the literature of PML cases in patients treated with these antibodies. Due to a life-threatening clinical course of PML, it is important for clinicians to gain a better understanding of the pathogenesis of the John Cunningham polyomavirus (JCV), risk of JCV reactivation, and how different anti-CD20-directed MAB may play a role in this reactivation. This review aims to educate clinicians on these issues.

[1] Internal Medicine Program, University of South Florida, Tampa, FL, USA
[2] Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA
[3] Mercy Oncology and Hematology–Joplin, Joplin, MO, USA

Corresponding Author:
Samir Dalia, Mercy Oncology and Hematology–Joplin, 100 Mercy Way, Joplin, MO 64804, USA.
Emails: sdalia@gmail.com; samir.dalia@mercy.net

A search of PubMed-indexed journals was used to find articles related to JCV, PML, and MAB. The search was limited to the last 20 years to get the most recent information on these agents and risk of developing PML.

The JCV

The JCV is a DNA virus of the human polyomavirus family.[2] Serum antibodies to JCV are found in 50% to 70% of the healthy general population, indicating that JCV is ubiquitous in humans. The JCV encodes the large T antigen (TAg), small T antigen, 3 virus capsid proteins, and an agnoprotein in its genome. The JCV-encoded TAg plays an important role in virus replication by binding to the viral origin of replication through a DNA-binding domain. The nuclear localization signal in TAg recruits TAg to the nucleus, and the helicase domain in TAg unwinds the DNA double helix and promotes viral DNA replication.[7]

The passage of the JCV through the body can be stratified into several steps including primary viremia, latency, and reactivation. Two portals of entry for JCV into the body have been suggested: the tonsils and the gastrointestinal tract.[7,8] Primary viremia is usually asymptomatic and occurs in childhood. After primary infection, the virus remains in the body in a latent state in the kidneys, tonsils, bone marrow, spleen, brain, lymph nodes, and lungs.[7,8] Reactivation can occur following immunosuppression or after elimination of the B cells with drugs targeting B cells such as rituximab.

It has been suggested that after the initial infection the virus transforms into a neurotropic form by gene rearrangement and replicates in glial tissues. B cells have the capacity to harbor JCV with diverse regulatory regions, including neurotropic JCV.[7,9,10] The gene rearrangement in the noncoding control region of the neurotropic JCV permits binding to the NF-1X binding protein that glial cells share with B cells.[11-14] Therefore, B cells are the logical, though not proven, site of the mutation as they have a unique genetic machinery that facilitates gene rearrangements through the addition and deletion of nucleotides and somatic hypermutation. The cellular immune response is most important in preventing and controlling JCV.[15-16] There is no evidence that the presence of antibody offers any protection from future infection. On the other hand, the importance of cell-mediated immunity is indicated by the correlation between an impaired Th1-type T helper function and clinical manifestation of PML.[16] The significant role of cytotoxic T lymphocytes directed against JCV in controlling the disease has been established.[17,18] Given the large number of individuals in general population infected with JCV, rarity of PML indicates that substantial barriers to its development must exist in immunocompetent individuals.

Diagnosis of PML

Progressive multifocal leukoencephalopathy is suspected in patients who have subcortical white matter lesions. Berger et al[19] found that hemiparesis, visual impairment, and altered mentation were the 3 most common initial manifestations as well as the most frequent signs during the course of AIDS-related PML. A small number of patients present with signs and symptoms referable to the posterior fossa, that is, ataxia, dysmetria, and dysarthria, which is usually indicative of involvement of the cerebellum and brain stem.[20,21] Other signs and symptoms associated with PML include headache, vertigo, seizures, sensory deficits, parkinsonism, aphasia, and neglect syndromes.[3,19]

Progressive multifocal leukoencephalopathy has been identified in association with conditions affecting the immune system. The most common diseases associated with PML are HIV, hematological malignancies, and MAB treatment. In the setting of hematological malignancies, a population-based study estimated the PML incidence at 0.07%.[22] These results were based on only 3 cases of PML identified over a period of 11 years in a single Canadian province.[23] Accurate calculation of the risk of PML attributable to the underlying malignancy as opposed to treatment-related immunosuppression is complicated by a rarity of this disease and a few larger clinical. Among the MAB that increase the risk of PML, the most common are natalizumab, an $\alpha 4\beta 7$ integrin antagonist, and rituximab.

Table 1 summarizes clinical and pathological features of PML. When PML is suspected, neurological examination is the first important step followed by both laboratory testing and imaging. Brain magnetic resonance imaging shows characteristic findings of subcortical lesions. Electroencephalogram can show focal slowing of brain waves but is nonspecific. Cerebrospinal fluid (CSF) can reveal elevation of protein and an increased cell count. The JCV polymerase chain reaction (PCR) test can be done on CSF, which can confirm a diagnosis. Brain biopsy is the gold standard for diagnosis, and the microscopic hallmark of PML is intranuclear basophilic or eosinophilic inclusions within the swollen nuclei of oligodendrocytes, often at the periphery of lesions. Large, occasionally multinucleated astrocytes with prominent processes are another characteristic feature.

Pathogenesis of JCV Reactivation in Patients Treated With MAB

Natalizumab

Natalizumab is a MAB against $\alpha 4$ integrin that prevents entry of inflammatory cells into brain and other tissues that use $\alpha 4$ integrin very late atnigen - 4 (VLA-4) to bind with vascular cell adhesion molecule (VCAM).[24] This agent is mainly used in multiple sclerosis (MS) to prevent acute relapse. The current estimate of the incidence of PML due to natalizumab use is 1 in 1000 patients.[25]

The 3 main mechanisms by which natalizumab predisposes patients to PML have been described. First, natalizumab has an effect on the T cells which react against the active and dormant JCV. The JCV-specific cytotoxic T lymphocytes are critical for containing PML.[26,27] These cells are most likely important not only in the brain but also in other sites such as bone marrow and spleen. It is anticipated that administration of natalizumab may prevent the entry of these cytotoxic T cells into the brain tissue

Table 1. Clinical and Pathological Features of PML.

Clinical features
• Hemiparesis, visual impairment, and altered mentation
• Headache, vertigo, and seizures
• Parkinson's and aphasia
• Others depending on site of lesion
Radiological features
• Most likely subcortical lesion
• No ring enhancing
• CT scan demonstrates nonenhancing, subcortical hypodensities; MRI scan shows altered signal from the subcortical lesions
Laboratory features of PML
• EEG shows focal slowing; CSF may show mild elevation of protein or an increased cell count, viral antigen detection, viral DNA detection, and demonstration of viral pathogens in the lymphocytic cells
Pathological features
• The microscopic hallmark of the disease is intranuclear basophilic or eosinophilic inclusions within the swollen nuclei of oligodendrocytes, often at the periphery of lesions. Large, occasionally multinucleated astrocytes with prominent processes are another characteristic feature

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy.

or other sites where JCV may be dormant, preventing JCV suppression. Second, α4β1 VCAM mediates the homing and retention of lymphocytes in the bone marrow and spleen.[28] Blocking α4β1 integrin could result in a release of B cells from the bone marrow and spleen,[28] which are the common sites of JCV latency. Coupled with diminished immunosurveillance for JCV at these sites, this might increase the load of JCV in the peripheral blood. Peripheral blood, supporting the premise that B cells are mobilized by natalizumab and reports of increased numbers of circulating lymphocytes[29] following the administration of natalizumab. Another aspect of natalizumab therapy–induced PML is that all previous reports of PML after natalizumab therapy involved patients who had undergone concurrent treatment with either interferon βor other immunosuppressive agents suggesting that a suppressed immune state is needed for the development of PML in patients treated with natalizumab.[24] According to Gorelik et al,[30] the development of PML in patients on natalizumab is an interplay of 3 factors including duration of natalizumab treatment, the presence of anti-JCV antibodies, and concomitant use of other immunosuppressants. The highest risk was observed in patients treated with natalizumab for more than 24 months, positive for anti-JCV antibodies, and concurrent use of immunosuppressive agents.

Since anti-JCV antibodies have been implicated as a factor in the development of PML in patients on natalizumab, further research is being done to develop an assay to help reduce PML infections in these patients.[30] Currently, an enzyme-linked immunosorbent assay–based test that allows for the detection of anti-JCV antibodies, indicating past infection, has been developed and is offered for patient groups who have risk factors for PML such as treatment with natalizumab and rituximab and developing central nervous system (CNS) symptoms or have a history of hematological malignancy.[31,32] However, it cannot distinguish between antibody against wild-type and mutated viruses and is still being investigated at this time. Other methods to detect JCV infection may not be sufficient because of poor sensitivity (assays for JCV DNA in blood) or only intermittent presence of virus in urine (assays for viral DNA in urine). Urine viral DNA test is being tested to stratify the risk for the development of PML in patients on natalizumab. Currently, there are no guidelines or recommendations about testing for PML prior to treating with natalizumab in the United States.

Rituximab

Rituximab is an agent that is Food and Drug Administration (FDA) approved for the treatment of non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis with methotrexate, granulomatosis with polyangiitis, and microscopic polyangiitis in combination with glucocorticoids. The drug has also been used in non-FDA-approved treatment of immune thrombocytopenia, hemolytic anemias, other autoimmune disorders, and Epstein–Barr virus reactivation. Rituximab treatment has been associated with viral infectious complications. In February 2006, 9 years after the drug received its initial FDA approval, the labeling for rituximab was changed to include information about patients with NHL who had developed serious viral infections after treatment with the drug. Infections included hepatitis B, cytomegalovirus, herpes simplex virus, varicella zoster virus, West Nile virus, and JCV.[11,33] The pathophysiology of rituximab-associated PML is unclear. The mechanism underlying viral reactivation after rituximab treatment is hypothesized to be more complex than simple B-cell depletion.[11,34] Stasi et al[34] demonstrated changes in T-lymphocyte cytokine profiles among patients with immune thrombocytopenic purpura who responded to rituximab, suggesting that changes in T-lymphocyte activity after B-lymphocyte depletion frequently occur. A role of B lymphocytes in JCV immune responses is supported by JCV reactivation and development of PML in patients with congenital disorders of humoral immunity.[35-37] Experimental studies also suggested that hematopoietic progenitor cells might be a site of viral latency.[38] Three patients in a cohort study demonstrated JCV in paraffin-embedded bone marrow biopsy samples obtained years before rituximab administration. Hematopoietic progenitor cells mobilized into the peripheral blood during chemotherapy may have been infected with latent JCV and may have facilitated hematogeneous spread of JCV into the CNS.[39-41] As seen in natalizumab, PML associated with rituximab is also more frequently seen in immunocompromised patients, which again suggests that patients at risk are those who have greater immunosuppression. Carson et al reviewed PML cases among patients treated with rituximab included in the FDA database, the manufacturer, physicians, and literature reviews between 1997 and 2008. Overall, 52 patients with LPD, 2 patients with systemic lupus

erythematosus, 1 patient with rheumatoid arthritis, 1 patient with an idiopathic autoimmune pancytopenia, and 1 patient with immune thrombocytopenia developed PML after treatment with rituximab and other agents. Median time to death after PML diagnosis was 2.0 months. The case fatality rate is 90%.

Due to the high case fatality rate, it is important for clinicians to keep in mind that patients on rituximab can develop PML, and if relevant symptoms are present, discontinuation of therapy and urgent workup are necessary to try to decrease morbidity and mortality.[41] A review of literature suggested 2 possible rituximab-associated PML syndromes. The first one is associated with short interval between last rituximab dose and PML diagnosis among patients with low $CD4^+$ lymphocyte counts and occasionally low immunoglobulin G (IgG) levels. The second syndrome is associated with longer interval between the last rituximab dose and PML diagnosis among patients with higher $CD4^+$ lymphocyte counts.[42] At this time, there are no recommendations to screen patients for JCV prior to administration of rituximab and there is no evidence that either type of rituximab-associated PML syndrome can be prevented with currently available therapeutic measures.

The incidence of PML with natalizumab and rituximab in HIV-negative patients is 1 in 1000 and 1 in 32 000, respectively. Incidence rates of PML in patients on rituximab and natalizumab are similar to those in the HIV population, suggesting that better screening tools are needed to try to prevent JCV reactivation in patients on these medications.

Other MAB and Risk of PML

Alemtuzumab

Alemtuzumab is a humanized MAB that targets the CD52 receptor on B, T, and natural killer lymphocytes and monocytes.[43] It is FDA approved for uses in B-cell CLL. The drug has been tested in acute graft-versus-host disease and autoimmune hemolytic anemias but is not approved for use in these diseases. Clinical trials indicated that alemtuzumab has efficacy in the treatment of malignancies, such as NHL, B-cell CLL, and T-cell prolymphocytic leukemia.[44-46] It has also been used in other diseases mediated by the immune system, such as acute rejection of solid organ transplants,[47] rheumatoid arthritis,[48] and graft-versus-host disease.[49] Because of its ability to deplete T-cell populations, alemtuzumab has also been used as a conditioning agent in solid organ transplantation and hematopoietic stem cell transplantation (HSCT).[50-52] Martin et al conducted a follow-up study on 27 patients on alemtuzumab and described 1 case which developed PML.[52] Another study reported PML development in a few patients who were on alemtuzumab.[53,54] The mechanism responsible for PML is due to depletion of cytotoxic T cells that kill or suppress the latent JCV-infected cells. Rates of PML in patients with alemtuzumab remain low, but clinicians should think about this disease in patients on the medication with PML-like symptoms.

Efalizumab

Efalizumab is another immunomodulatory agent that acts by binding to CD11a, the α subunit of leukocyte function antigen-1, which is expressed on all leukocytes and decreases cell surface expression of CD11a. Kothary et al[54] described a study with 72 patients with psoriasis who were on treatment with efalizumab and 13 of these developed PML after an average treatment duration of 3 years. This medication has also been tested in CLL with limited studies at this time. The FDA-approved uses of efalizumab include severe plaque psoriasis and antirejection therapy in certain transplants. The drug was tested in patients with CLL but did not receive an FDA approval for this use. The risk of PML in patients with efalizumab is higher than most other medications and PML should also be considered in these patients with appropriate symptoms.

Brentuximab Vedotin

Brentuximab vedotin (BV) is an anti-CD30 MAB–drug conjugate that was approved in 2011 for the treatment of patients with anaplastic large-cell and relapsed classical Hodgkin lymphomas. It is also FDA approved to be as a consolidation therapy after autologous HSCT in patients with classical Hodgkin lymphoma. It has been used in non-FDA-approved trials in other $CD30^+$ lymphomas and is being studied in the upfront setting in classical Hodgkin lymphoma. CD30 is a membrane glycoprotein and a member of the tumor necrosis factor (TNF) receptor family, and signaling through CD30 can have pleiotropic effects, depending on the type and activation state of the cell. The cytoplasmic CD30 domain interacts with multiple members of the TNF receptor-associated factor family and is capable of inducing apoptosis through the c-Jun N-terminal kinase np38. It also mediates cell activation via nuclear factor kappa B as well as effector functions via Fas-associated protein with death domain.[55-57]

The ligand for CD30 is CD30L (CD153), a type 2 membrane protein with structural homology to TNF-α, TNF-β, and CD40 ligand. Signaling mediated by CD30 promotes cell proliferation and survival but can also induce antiproliferative responses and trigger cell death. Whether CD30 activation results in proliferation of cells or reduced viability depends on the cell type receiving the signal and the environment in which the signal is delivered.[58] Brentuximab is a very important drug that has shown high remission rates in Hodgkin lymphoma especially in people older than 60 years and has shown remission rates of greater than >50%. Treatment with BV is currently a standard of care for patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) and for patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplantation or at least 2 prior combination chemotherapy regimens. This agent is now being tested in combination with standard chemotherapy in both the first-line and relapsed setting, and the results are very promising.[59]

The BV is another MAB associated with the development of PML. There are important clinical differences among patients who developed PML after BV when compared with PML after exposure to the MAB such as rituximab, efalizumab, and natalizumab.[60] Time to the onset of symptoms and duration of BV therapy before PML were much shorter in 5 patients reported by Carson et al.[60] The proposed mechanism resulting in PML secondary to BV was a depletion of CD30-positive activated T cells involved in JCV immune surveillance in the CNS. Clinicians should think about PML in patients on BV who present with symptoms associated with the disease. Currently, no screening recommendations have been made.

Obinutuzumab

Obinutuzumab is a recently approved MAB against CD20 that has shown efficacy in B-cell malignancies and CLL. It is FDA approved to be used with chlorambucil in CLL and with bendamustine in patients with relapsed follicular lymphoma after rituximab use. The drug has also been tested in other lymphomas and autoimmune diseases. Obinutuzumab binds target cells both directly and together with the other immune cells.[61]

B-cell lysis is caused by 2 main mechanisms upon binding to CD20 including direct activation of intracellular death signaling pathways and/or activation of the complement cascade.[62] Progressive multifocal leukoencephalopathy has not been reported in patients on obinutuzumab.

Oftumumab

Oftumumab is human IgG1-type anti-CD20 MAB.[63] This agent targets a different epitope of CD20 than rituximab, and this may explain some of the difference between rituximab and ofatumumab.[64] This medication is FDA approved in combination with chlorambucil in untreated CLL and in refractory CLL in patients who are refractory to fludarabine and alemtuzumab. It is has been tested in other B-cell malignancies but has not gained approval in other settings.

Progressive multifocal leukoencephalopathy was seen as one of the complications of therapy with ofatumumab but is not seen as commonly as in patients treated with natalizumab or rituximab. Obinutuzumab and ofatumumab likely have lower reported rates of PML than rituximab due to the paucity of literature on complications of these 2 newer medications.

As more data are presented, one will be able to see whether there is a difference in PML rates between different anti-CD20 antibodies, and research will be needed to figure out why this occurs. One reason may be because rituximab redistributes CD20 into detergent-resistant lipid rafts. This clustering promotes association with other complexes such as the B-cell receptor, and binding to C1q, resulting in potent complement-dependent cytotoxicity, and it binds to all available CD 20 sites. In contrast, the newer agents trigger potent homotypic adhesion and lysosomal cell death and they bind to only a half of all the available CD20 sites. The immunosuppression caused by rituximab is thought to be greater than of obinutuzumab and ofatumumab which is likely why there are increased risk of PML in patients with rituximab.[65-68]

Table 2. Incidence of PML in Different Populations.

Clinical Entity	Incidence (Post 1996)
General population	1 per 200 000
HIV	1.3 per 1000
Natalizumab (HIV negative)	1 per 1000
Rituximab (HIV negative)	1 per 32 000

Abbreviation: PML, progressive multifocal leukoencephalopathy.

JAK 1 and 2 Inhibitors

Although not considered traditional MAB, Janus Kinase (JAK) inhibitors have been reported to have PML reactivation. The FDA-approved uses of JAK inhibitors currently are limited to primary polycythemia vera and primary myelofibrosis. They are being studied in other myeloproliferative disorders and other hematological malignancies. The mechanism by which these medications may cause reactivation of PML is due to the fact that the JAK–signal transducer and activator of transcription (STAT) pathway have a very important role in host defense and autoimmunity. The JAK mutations are associated with primary immunodeficiency and complete STAT-1 deficiency, block interferon signaling, and can lead to lethal viral and bacterial infection including PML. The literature shows that the progression of the neurologic features of PML continues after withdrawing these drugs. This may be due to immune reconstitution. More data are needed to truly know whether PML reactivation is as common with JAK inhibitors as some classical MABs targeting B cells.[69]

Clinical Importance of PML

We have discussed the PML incidence with the use of rituximab and natalizumab in Table 2, and to highlight its importance, we have also mentioned the incidence of PML with HIV in the same table. We see that the incidence of PML in patients on natalizumab therapy is very comparable to that in HIV-positive population. From a clinical perspective, it is important to know how to prevent PML reactivation. For this, we have to understand the main risk factors for the development of PML for patients on MAB. The presence of immunosuppression, anti-JCV antibodies, and duration of immunosuppression are the 3 most important reasons for PML reactivation. At this time, a quantitative anti-JCV antibody index is currently being investigated to determine its predictive value in detecting PML and to show whether increasing titers could reflect an increasing risk.[70] Initial interpretations of this serological test suggested that a negative status could be used to reassure patients as the probability of developing PML is very low at <1/10 000. Long-term studies like the AFFIRM and STRATIFY-1 suggest that the serological status could change

Table 3. Worldwide Guidelines for Monitoring Patients With Multiple Sclerosis Started on Natalizumab for Risk of PML.

Region	United States	United Kingdom[73]	Middle East and Africa[74]	Spain[75]
Pretreatment	No consensus guidelines	Anti-JCV index at the beginning of treatment and then every 6 months	Anti-JCV antibody test at the beginning and then every 6 months	MRI 3 months before treatment
During treatment	No consensus guidelines	Serology and radiology Anti-JCV test every 6 months <1.5—MRI every 6 months >1.5—MRI every 3 months	Serology—Every 6 months Anti-JCV antibody Radiology—If JCV is positive, then MRI every year from that point on	Serology—None Radiology—MRI based on clinical suspicion

Abbreviations: JCV, John Cunningham polyomavirus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy.

during MAB treatment and thus needed continuous monitoring every 6 months.[71]

Leukocyte markers have also been evaluated as a new way of determining risk of PML reactivation in patients on natalizumab. One of the proposed mechanism is downregulation of CD49d and CD29 (subunit of VLA-4) expressions on both $CD4^+$ and $CD8^+$ T cells has been shown in patients treated with natalizumab[72]. This test is currently being evaluated and is not ready for clinical use. Finally, a new test called the ELISPOT test for effector memory T cells (T-effector memory cells) has been suggested as test for evaluating the risk of PML development in patients on natalizumab.[72] From a clinical perspective, PML should be considered in any patient who is on long-term MAB such as natalizumab or rituximab for cancer or other medical problems such as Crohn disease and MS and testing should be done if clinical suspicion is high for PML.

Given the frequency of PML with natalizumab, different societies around the world have guidelines in place to assist clinicians during natalizumab therapy to monitor for PML. Table 3[73-75] summarizes guidelines from various regions of the world for monitoring patients with MS started on natalizumab to assist physicians with possible early diagnosis and even prevention of PML. To date, there are no guidelines for testing patients for PML prior to the start of therapy for any other MAB including rituximab.

Treatment of PML

Various antiviral drugs, including cidofovir, have been used in addition to highly active antiretroviral therapy for the treatment of PML in patients with HIV but have not been effective. Mefloquine, a drug approved for malaria therapy, has recently shown to have an effect on the activity of JCV in a screening bioassay when it is applied on a human glial cell line infected with JCV.[76] Mirtazapine, an inhibitor of 5-HT2a receptor, which may be used by JCV for cell entry, has also been shown to inhibit the infection of a human astroglial cell line.[77] Recently, an anecdotal report has shown the efficacy of mirtazapine in a patient with PML, although many experts doubt that this therapeutic agent has substantial efficacy. At the present time, if PML is discovered in a patient and due to discontinuation of MAB, the medication is the most appropriate action. The use of other medications to try to aid in the treatment of PML reactivation is currently experimental and patients should be referred to tertiary care centers for care or be placed on clinical trials.

Conclusion

Several distinct MABs employed in the treatment of various lymphoproliferative and autoimmune disorders including natalizumab, rituximab, alemtuzumab, BV, efalizumab, ofatumumab, and obinutuzumab were associated with the development of PML. The most important pathogenic mechanisms involved in PML evolution secondary to the use of MAB include immunosuppression due to elimination/suppression of B cells, cytotoxic T cells, natural killer cells, or T helper cells.

All patients treated with the above MAB should be monitored for CNS symptoms, and if any new symptoms occur, appropriate workup to rule out PML should be considered. Further research will be necessary to better understand pathobiology of JCV in order to predict high-risk patients for the development of PML prior to starting MAB therapy. Modern laboratory serology and PCR-based tests might become a standard for JCV monitoring in near future but cannot currently be recommended for use unless on a clinical trial.

Authors' Note

There are no significant relationships exist between the authors and the companies/organizations whose products or services may be referenced in this article. The authors have disclosed that this article discusses unlabeled/unapproved uses of drugs like rituximab for the treatment of immune thrombocytopenia, hemolytic anemias, other autoimmune disorders, and Epstein-Barr virus reactivation; alemtuzumab for the treatment of acute graft-versus-host disease and autoimmune hemolytic anemias; efalizumab for the treatment of CLL; brentuximab vedotin for the treatment of $CD30^+$ lymphomas and classical Hodgkin lymphoma other than anaplastic large cell and relapsed classical Hodgkin lymphomas; obinutuzumab for treatment of various lymphomas and autoimmune diseases; ofatumumab for the treatment of various B-cell malignancies other than untreated and refractory CLL; and JAK inhibitors for the treatment of myeloproliferative disorders and hematological malignancies other than primary polycythemia vera and primary myelofibrosis.

Declaration of Conflicting Interests

The author(s) declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukemia and Hodgkin's disease. *Brain*. 1958;81(1):93-111.
2. ZuRhein G, Chou S. Particles resembling papovavirons in human cerebral demyelinating disease. *Science*. 1965;148(3676):1477-1479.
3. Brooks BR, Walker DL. Progressive multifocal leukoencephalopathy. *Neurol Clin*. 1984;2(2):299-313.
4. Bernick C, Gregorios JB. Progressive multifocal leukoencephalopathy in a patient with acquired immune deficiency syndrome. *Arch Neurol*. 1984;41(7):780-782.
5. Miller JR, Barrett RE, Britton CB, et al. Progressive multifocal leukoencephalopathy in a male heterosexual with T cell immunodeficiency. *N Engl J Med*. 1982;307(23):1436-1438.
6. Snider WD, Simpson DM, Neilsen S, Gold JW, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol*. 1983; 14(4):403-418.
7. Caldarelli-Stefano R, Vago L, Omodeo-Zorini E, et al. Detection and typing of JC virus in autopsy brains and extraneural organs of AIDS patients and non-immunocompromised individuals. *J Neurovirol*. 1999;5(2):125-133.
8. Jensen PN, Major EO. Viral variant nucleotide sequences help expose leukocytic positioning in the JC virus pathway to the CNS. *J Leukoc Biol*. 1999;65(4):428-438.
9. Perez-Liz G, Del Valle L, Gentilella A, Croul S, Khalili K. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol*. 2008;64(4):379-387.
10. Delbue S, Branchetti E, Boldorini R, et al. Presence and expression of JCV early gene large T Antigen in the brains of immunocompromised and immunocompetent individuals. *J Med Virol*. 2008;80(12):2147-2152.
11. Houff SA, Major EO, Katz DA, et al. Involvement of JC virus-infected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy. *N Engl J Med*. 1988;318(5):301-305.
12. Major EO, Amemiya K, Elder G, Houff SA. Glial cells of the human developing brain and B cells of the immune system share a common DNA binding factor for recognition of the regulatory sequences of the human polyomavirus, JCV. *J Neurosci Res*. 1990;27(4):461-471.
13. Atwood WJ, Amemiya K, Traub R, Harms J, Major EO. Interactions of the human polyomavirus, JCV, with human B lymphocytes. *Virology*. 1992;190(2):716-723.
14. Monaco MC, Atwood WJ, Gravell M, Tornatore CS, Major EO. JC virus infection of hematopoietic progenitor cells, primary B lymphocytes, and tonsillar stromal cells: implications for viral latency. *J Virol*. 1996;70(10):7004-7012.
15. Willoughby E, Price RW, Padgett BL, Walker DL, Dupont B. Progressive multifocal leukoencephalopathy(PML): in vitro cell-mediated immune responses to mitogens and JC virus. *Neurology*. 1980;30(3):256-262.
16. Weber F, Goldmann C, Kramer M, et al. Cellular and humoral immune response in progressive multifocal leukoencephalopathy. *Ann Neurol*. 2001;49(5):636-642.
17. Du Pasquier RA, Clark KW, Smith PS, et al. JCV-specific cellular immune response correlates with a favorable clinical outcome in HIV-infected individuals with progressive multifocal leukoencephalopathy. *J Neurovirol*. 2001;7(4):318-322.
18. O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res*. 2008;132(1-2):97-103.
19. Berger JR, Kaszovitz B, Post MJ, Dickinson G. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. A review of the literature with a report of sixteen cases. *Ann Intern Med*. 107(1):78-87.
20. Jones HR Jr, Hedley-Whyte ET, Freidberg SR, Kelleher JE Jr, Krolikowski J. Primary cerebellopontine progressive multifocal leukoencephalopathy diagnosed premortem by cerebellar biopsy. *Ann Neurol*. 1982;11(2):199-202.
21. Parr J, Horoupian DS, Winkelman AC. Cerebellar form of progressive multifocal leukoencephalopathy (PML). *Can J Neurol Sci*. 1979;6(2):123-128.
22. Major EO, Amemiya K, Tornatore CS, Houff SA, Berger JR. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC Virus induced demyelinating disease of the human brain. *Clin Microbiol Rev*. 1992;5(1):49-73.
23. Power C, Gladden JG, Halliday W, et al. AIDS and non-AIDS-related PML association with distinct p53 polymorphism. *Neurology*. 2000;54(3):743-746.
24. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2006;354(9):924-933.
25. Rudick RA, Sandrock A. Natalizumab: alpha4-integrin antagonist selective adhesion molecule inhibitors for MS. *Expert Rev Neurother*. 2004;4(4):571-580.
26. Koralnik IJ. Overview of the cellular immunity against JC virus in progressive multifocal leukoencephalopathy. *J Neurovirol*. 2002; 8(suppl 2):59-65.
27. Koralnik IJ, Du Pasquier RA, Letvin NL. JC virus-specific cytotoxic T lymphocytes in individuals with progressive multifocal leukoencephalopathy. *J Virol*. 2001;75(7):3483-3487.
28. von Andrian UH, Engelhardt B. Alpha4 integrins as therapeutic targets in autoimmune disease. *N Engl J Med*. 2003;348(1):68-72.
29. Tysabri [package insert]. Biogenidec. Retrieved from https://www.tysabri.com.
30. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*. 2010;68(3):295-303.
31. Aksoy S, Harputluoglu H, Kilickap S, et al. Rituximab-related viral infections in lymphoma patients. *Leuk Lymphoma*. 2007; 48(7):1307-1312.
32. Weber F, Goldmann C, Krämer M, et al. Cellular and humoral immune response in progressive multifocal leukoencephalopathy. *Ann Neurol*. 2001;49(5):636-642.
33. Steurer M, Clausen J, Gotwald T, et al. Progressive multifocal leukoencephalopathy after allogeneic stem cell transplantation

and post transplantation rituximab. *Transplantation*. 2003;76(2): 435-436.
34. Stasi R, Del Poeta G, Stipa E, et al. Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. *Blood*. 2007;110(8):2924-2930.
35. Narula S, LaRosa DF, Kamoun M, Dalmau J, Levinson AI. Progressive multifocal leukoencephalopathy in a patient with common variable immunodeficiency and abnormal CD8+ T-cell subset distribution. *Ann Allergy Asthma Immunol*. 2007; 98(5)483-489.
36. Teramoto T, Kaneko H, Funato M, et al. Progressive multifocal leukoencephalopathy in a patient with X-linked agammaglobulinemia. *Scand J Infect Dis*. 2003;35(11-12):909-910.
37. Sabath BF, Major EO. Traffic of JC virus from sites of initial infection to the brain: the path to progressive multifocal leukoencephalopathy. *J Infect Dis*. 2002;186 (suppl 2):S180-S186.
38. Bonig H, Wundes A, Chang KH, Lucas S, Papayannopoulou T. Increased numbers of circulating hematopoietic stem/progenitor cells are chronically maintained in patients treated with the CD49d blocking antibody natalizumab. *Blood*. 2008;111(7): 3439-3441.
39. Lindberg RL, Achtnichts L, Hoffmann F, Kuhle J, Kappos L. Natalizumab alters transcriptional expression profiles of blood cell subpopulations of multiple sclerosis patients. *J Neuroimmunol*. 2008;194(1-2):153-164.
40. Zohren F, Toutzaris D, Klarner V, Hartung HP, Kieseier B, Haas R. The monoclonal anti-VLA-4 antibody natalizumab mobilizes CD34+ hematopoietic progenitor cells in humans. *Blood*. 2008; 111(7):3893-3895.
41. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood*. 2009; 113(20):4834-4840.
42. Waldmann TA. Immunotherapy: past, present and future. *Nat Med*. 2003;9(3):269-277.
43. Lundin J, Österborg A, Brittinger G, et al. CAMPATH-1H monoclonal antibody in therapy for previously treated low-grade non-Hodgkin's lymphomas: a phase II multicenter study. European Study Group of CAMPATH-1H Treatment in Low-Grade Non-Hodgkin's Lymphoma. *J Clin Oncol*. 1998;16(10):3257-3263.
44. Ferrajoli A, O'Brien SM, Cortes JE, et al. Phase II study of alemtuzumab in chronic lymphoproliferative disorders. *Cancer*. 2003; 98(4):773-778.
45. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. 2002;99(10): 3554-3561.
46. Calne R, Moffatt SD, Friend PJ, et al. Campath 1H allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. *Transplantation*. 1999;68(10):1613-1616.
47. Kyle V, Roddy J, Hale G, Hazleman BL, Waldmann H. Humanized monoclonal antibody treatment in rheumatoid arthritis. *J Rheumatol*. 1991;18(1):1737-1738.
48. Hale G, Jacobs P, Wood L, et al. CD52 antibodies for prevention of graft-versus-host disease and graft rejection following transplantation of allogeneic peripheral blood stem cells. *Bone Marrow Transplant*. 2000;26(1):69-76.
49. Kirk AD, Hale DA, Mannon RB, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). *Transplantation*. 2003;76(1):120-129.
50. Cull GM, Haynes AP, Byrne JL, et al. Preliminary experience of allogeneic stem cell transplantation for lymphoproliferative disorders using BEAM-CAMPATH conditioning: an effective regimen with low procedure-related toxicity. *Br J Haematol*. 2000; 108(4):754-760.
51. Ho AY, Pagliuca A, Kenyon M, et al. Reduced-intensity allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab conditioning. *Blood*. 2004;104(6):1616-1623.
52. Martin SI, Marty FM, Fiumara K, Treon SP, Gribben JG, Baden LR. Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. *Clin Infect Dis*. 2006;43(1): 16-24.
53. Uppenkamp M, Engert A, Diehl V, Bunjes D, Huhn D, Brittinger G. Monoclonal antibody therapy with Campath-1H in patients with relapsed high- and low-grade non-Hodgkin's lymphomas: a multicenter phase I/II study. *Ann Hematol*. 2002;81(1):26-32.
54. Kothary N, Diak IL, Brinker A, Bezabeh S, Avigan M, Dal Pan G. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *J Am Acad Dermatol*. 2011; 65(3):546-551.
55. Duckett CS, Gedrich RW, Gilfillan MC, Thompson CB. Induction of nuclear factor kappaB by the CD30 receptor is mediated by TRAF1 and TRAF2. *Mol Cell Biol*. 1997;17(3):1535-1542.
56. Lee SY, Park CG, Choi Y. T cell receptor-dependent cell death of T cell hybridomas mediated by the CD30 cytoplasmic domain in association with tumor necrosis factor receptor-associated factors. *J Exp Med*. 1996;183(2):669-674.
57. Gruss HJ, Boiani N, Williams DE, Armitage RJ, Smith CA, Goodwin RG. Pleiotropic effects of the CD30 ligand on CD30-expressing cells and lymphoma cell lines. *Blood*. 1994;83(8): 2045-2056.
58. Ansell SM. Brentuximab vedotin. *Blood*. 2014;124(22): 3197-3200.
59. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy 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):816-824.
60. Carson KR, Newsome SD, Kim EJ, et al. Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. *Cancer*. 2014;120(16):2464-2471.
61. Owen C, Stewart DA. Obinutuzumab for the treatment of lymphoproliferative disorders. *Expert Opin Biol Ther*. 2012;12(3):343-351.

62. Teeling JL, French RR, Cragg MS, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood*. 2004;104(6):1793-1800.
63. Teeling JL, Mackus WJ, Wiegman LJ, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol*. 2006;177(1):362-371.
64. Glennie MJ, French RR, Cragg MS, Taylor RP. Mechanisms of killing by anti-CD20 monoclonal antibodies. *Mol Immunol*. 2007; 44(16):3823-3837.
65. Alduaij W, Ivanov A, Honeychurch J, et al. Novel type II anti-CD20 monoclonal antibody(GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. *Blood*. 2011;117(17):4519-4529.
66. Ivanov A, Beers SA, Walshe CA, et al. Homotypic adhesion and lysosome-mediated cell death evoked by anti-CD20 (tositumomab) and HLA DR monoclonal antibodies. *J Clin Invest*. 2009; 119(8):2143-2159.
67. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today*. 1994;15(9):450-454.
68. Plavina T, Subramanyam M, Bloomgren G, 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):802-812.
69. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. *N Engl J Med*. 2013;368(2): 161-170.
70. Tur C, Montalban X. Natalizumab: risk stratification of individual patients with multiple sclerosis. *CNS Drugs*. 2014;28(7):641-648.
71. Jilek S, Mathias A, Canales M, et al. Natalizumab treatment alters the expression of T-cell trafficking marker LFA-1 α-chain(CD11a) in MS patients. *Mult Scler*. 2014;20(7):837-842.
72. Hendel-Chavez H, de Goër de Herve MG, Giannesini C, et al. Immunological hallmarks of JC virus replication in multiple sclerosis patients on long-term natalizumab therapy. *J Virol*. 2013;87(10):6055-6059.
73. McGuigan C, Craner M, Guadagno J, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. *J Neurol Neurosurg Psychiatry*. 2016;87(2):117-125.
74. Alroughani RA, Aref HM, Bohlega SA, et al. Natalizumab treatment for multiple sclerosis: Middle East and North Africa regional recommendations for patient selection and monitoring. *BMC Neurol*. 2014;14:27.
75. Fernández O, García-Merino JA, Arroyo R, et al. Spanish consensus on the use of natalizumab (Tysabri®)-2013 [in English, Spanish]. *Neurologia*. 2015;30(5):302-314.
76. Brickelmaier M, Allaire N, Gorelik L. Identification and characterization of Mefloquine efficacy against JC Virus in vitro. *Mult Scler*. 2008;14(suppl 1):S44-S44.
77. Verma S, Cikurel K, Koralnik IJ, et al. Mirtazapine in progressive multifocal leukoencephalopathy associated with polycythemia vera. *J Infect Dis*. 2007;196(5):709-711.