Progressive Multifocal Leukoencephalopathy and Monoclonal Antibodies: A Review

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Abstract
Progressive multifocal leucoencephalopathy (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 leucoencephalopathy, monoclonal antibodies, JCV

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Introduction
Progressive multifocal leucoencephalopathy (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.

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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. 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.

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. 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; 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. 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. 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. 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. The significant role of cytotoxic T lymphocytes directed against JCV in controlling the disease has been established. 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. 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. Other signs and symptoms associated with PML include headache, vertigo, seizures, sensory deficits, parkinsonism, aphasia, and neglect syndromes.

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%. These results were based on only 3 cases of PML identified over a period of 11 years in a single Canadian province. 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 α4β7 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 α4 integrin that prevents entry of inflammatory cells into brain and other tissues that use α4 integrin very late antigen - 4 (VLA-4) to bind with vascular cell adhesion molecule (VCAM). 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.

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. 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. Blocking α4β1 integrin could result in a release of B cells from the bone marrow and spleen, 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 following 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 β or other immunosuppressive agents suggesting that a suppressed immune state is needed for the development of PML in patients treated with natalizumab. According to Gorelik et al, 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. 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. 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. 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. Stasi et al 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. Experimental studies also suggested that hematopoietic progenitor cells might be a site of viral latency. 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 hematogenous spread of JCV into the CNS. 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...
erythematous, 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. 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. 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. 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. It has also been used in other diseases mediated by the immune system, such as acute rejection of solid organ transplants, and rheumatoid arthritis, and graft-versus-host disease. 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). Martin et al conducted a follow-up study on 27 patients on alemtuzumab and described 1 case which developed PML. Another study reported PML development in a few patients who were on alemtuzumab. 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 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 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 n338. It also mediates cell activation via nuclear factor kappa B as well as effector functions via Fas-associated protein with death domain.

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 anti proliferative 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. 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.
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.

**Ofatumumab**

Ofatumumab 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

**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

| 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.
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 mechanisms 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 natalizumab72. 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 373-75 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, eflizumab, 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; eflizumab 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.

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