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

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Rituximab improves outcomes for persons with lymphoproliferative disorders and is increasingly used to treat immune-mediated illnesses. Recent reports describe 2 patients with systemic lupus erythematosus and 1 with rheumatoid arthritis who developed progressive multifocal leukoencephalopathy (PML) after rituximab treatment. We reviewed PML case descriptions among patients treated with rituximab from the Food and Drug Administration, the manufacturer, physicians, and a literature review from 1997 to 2008. Overall, 52 patients with lymphoproliferative disorders, 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. Other treatments included hematopoietic stem cell transplantation (7 patients), purine analogs (26 patients), or alkylating agents (39 patients). One patient with an autoimmune hemolytic anemia developed PML after treatment with corticosteroids and rituximab, and 1 patient with an autoimmune pancytopenia developed PML after treatment with corticosteroids, azathioprine, and rituximab. Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2.0 months. The case-fatality rate was 90%. Awareness is needed of the potential for PML among rituximab-treated persons. (Blood. 2009;113:4834-4840)

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system that results from reactivation of latent JC polyoma virus (JCV). The disease was first described 50 years ago in patients with chronic lymphocytic leukemia and Hodgkin lymphoma.1 Up to 92% of the adult population is JCV-seropositive.2 PML typically occurs in persons with suppressed cellular immunity, particularly those with HIV infection.2 In clinical studies conducted by Koralnik et al, 80% of reported PML patients have AIDS, 13% have hematologic malignancies, 5% are transplant recipients, and 2% have chronic inflammatory diseases.3 Before the HIV epidemic, more than 60% of cases were seen in patients with lymphoproliferative disorders. The risk of PML in persons with hematologic malignancies is estimated to be 0.07%, with the highest incidence (0.5%) being reported in persons with chronic lymphocytic leukemia.4,5 JC viral reactivation with PML is a rare complication recently reported among 7 patients after treatment with natalizumab, a monoclonal antibody that interferes with T-lymphocyte trafficking and intercellular adhesion. In 2005, 3 cases of natalizumab-associated PML were described. All 3 patients had received more than 2 years of natalizumab before PML was diagnosed.6-8 Since then, 5 additional multiple sclerosis patients with natalizumab monotherapy have developed PML.9,10

Rituximab treatment has been associated with viral infectious complications. In February 2006, 9 years after the drug received its initial Food and Drug Administration (FDA) approval, the labeling.
for rituximab was changed to include information about patients with non-Hodgkin lymphoma (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 JC virus.11 In 2006 and 2007, the FDA, the European Medicines Agency, the World Health Organization, and the manufacturer disseminated safety alerts describing 2 patients with systemic lupus erythematosus (SLE) who developed PML after treatment with rituximab and other immunosuppressive medications.12-15 In September 2008, the FDA and rituximab manufacturers issued “Dear Health Care Professional” letters describing a third patient with rheumatoid arthritis who died of PML 18 months after receiving rituximab, corticosteroids, and methotrexate therapy.16,17 Herein, we describe 52 patients with lymphoid malignancies, 2 patients with SLE, 1 patient with rheumatoid arthritis, 1 patient with idiopathic autoimmune pancytopenia, and 1 patient with immune thrombocytopenia purpura who developed PML after rituximab treatment.

Methods
Cases were identified among rituximab-treated patients by clinicians from 12 cancer centers or academic hospitals (22 cases) or by reviewing FDA reports (11 cases), the manufacturer’s database (30 cases), and publications (18 cases; MeSH search terms: leukoencephalopathy, rituximab, immunosuppressed, lymphoma, and leukemia).18-31 The search covered the period from 1997, the date of the first FDA approval granted for rituximab, to December 31, 2008. Duplicate reports were identified based on age, sex, and underlying illness. Inclusion criteria were receipt of rituximab therapy before PML diagnosis or symptoms; PML confirmation based on histologic examination of brain tissue (histology-confirmed) or magnetic resonance imaging showing lesions consistent with a demyelinating process and documentation of cerebrospinal fluid (CSF) JCV DNA by polymerase chain reaction (PCR; laboratory-confirmed); and no evidence of HIV infection.32

Results
The median patient age was 61 years (range, 30-89 years). Underlying diagnoses included B-cell lymphoproliferative disorders (52 patients), SLE (2 patients), rheumatoid arthritis (1 patient), autoimmune pancytopenia (1 patient), and immune thrombocytopenic purpura (1 patient). Autoimmune hemolytic anemia had developed in 2 patients with B-cell lymphoproliferative disorders. Seven patients with lymphoproliferative disorders had received prior hematopoietic stem cell transplantation (3 allogeneic and 4 autologous). One patient had developed a postrenal transplantation lymphoproliferative disorder. Among 7 patients who had undergone prior hematopoietic stem cell transplantation, 14% had received purine analog therapy and 100% had received both alkylating agents and corticosteroids. Of 49 PML patients who had not undergone transplantation procedures, prior medications included purine analogs (46%), alkylating agents (81%), and corticosteroids (75%). One NHL patient with an autoimmune hemolytic anemia had previously received only corticosteroids and rituximab; 1 patient with an idiopathic autoimmune pancytopenia had previously received corticosteroids, azathioprine, and rituximab; and 1 patient with immune thrombocytopenic purpura had received corticosteroids, danazol, intravenous immunoglobulin, azathioprine, and romiplostim. Prior therapies for the 2 patients with SLE included corticosteroids and alkylating agents and for the patient with rheumatoid arthritis therapy included corticosteroids, methotrexate, a platinum-containing chemotherapy regimen, and a tumor necrosis factor-α inhibitor. A median of 6 rituximab doses (range, 1-28 doses) preceded PML diagnosis. Median time from first rituximab dose to PML diagnosis was 16.0 months (range, 1.0-90.0 months) and from last rituximab dose to PML diagnosis was 5.5 months (range, 0.3-66.0 months; Table 1).

Presenting findings included confusion/disorientation (54% of patients), motor weakness/hemiparesis (33%), poor motor coordination (25%), speech changes (21%), or vision changes (18%). Symptoms progressed over weeks to months. The diagnosis was primarily confirmed by magnetic resonance imaging and JCV detection in the CSF (54%) and by brain biopsy or autopsy in the remaining patients. Quantitative T-cell studies, available for 14 patients, identified CD4 lymphopenia (CD4+ lymphocyte counts < 500 cells/μL; 9 patients) or decreased CD4/CD8 ratios (9 patients; Table 2). Median duration between last rituximab dose and PML diagnosis was shorter among patients who had CD4+ lymphocyte counts < 500 cells/μL (3 months vs 17 months for patients with CD4+ lymphocyte counts > 500 cells/μL). One rituximab-treated patient who had not previously received a hematopoietic stem cell transplantation, purine analog, or alkylating agent had a normal CD4+ cell count and normal CD4/CD8 ratio. Paraffin-fixed bone marrow core specimens from 3 patients obtained before rituximab treatment had JCV detectable by PCR.

The case-fatality rate was 90%: 100% among PML cases diagnosed within 3 months of the last rituximab dose versus 84% among PML cases diagnosed more than 3 months after the last rituximab dose. PML treatments included cytarabine or antiviral or immunologic therapies. Of 5 patients who did not die of PML, 2 received no therapy, 1 received cytarabine, another mirtazapine, and the last received cidofovir, donor lymphocyte infusions, cytarabine, and risperidone. These patients had residual neurologic deficits including motor aphasia, hemiparesis, and visual defects.

Discussion
This is the first large case series of PML cases occurring among HIV-negative patients treated with rituximab. Fifty-two of the patients had a diagnosis of hematologic malignancies and 5 had autoimmune illnesses. Presenting findings were primarily neuropsychiatric. All patients had received prior therapies that affect immune function, including alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid organ graft rejection. The case-fatality rate was 90%. In interpreting our findings, several factors should be considered.

The pathophysiology of rituximab-associated PML is unclear, particularly with respect to the role of rituximab. The mechanism underlying viral reactivation after rituximab treatment is probably more complex than simple B-cell depletion.11,33 Pre-B cells that harbor JCV in a latent state may be released into circulation to reestablish JCV latent infection after rituximab treatment and to reactivate JCV in patients with congenital or acquired immune deficiencies.29,34 Stasi et al demonstrated changes in T-lymphocyte cytokine profiles among immune thrombocytopenic purpura patients who responded to rituximab, suggesting changes in T-lymphocyte activity after B-lymphocyte depletion.35 A role for B lymphocytes in JCV immune responses is supported by JCV reactivation identification and PML in patients with congenital disorders of humoral immunity.36,37 Our findings also suggest that hematopoietic progenitor cells may be a site of viral latency38; 3 patients in our cohort had JCV detected in paraffin-fixed bone
marrow 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 central nervous system. However, JCV latency may be more relevant for natalizumab-treated patients because CD34+/H11001 cells have been shown to mobilize into the peripheral circulation upon initiation of treatment.39-41

A high degree of awareness for PML facilitated case identification. This could account for the observation that most of the reported PML cases were from referral centers. At these centers, clinicians probably include PML in the differential diagnosis of hematologic malignancy patients who experience neuropsychiatric disturbances. One case of a rituximab-treated patient with rheumatoid arthritis was diagnosed as part of a long-term postmarketing safety study conducted by the manufacturer. It should be noted that recognition of PML in the general medical community probably has improved recently because of the widely publicized association of PML with natalizumab use.

A definitive diagnosis of PML can be based on compatible clinical findings, neuroimaging results, and characteristic histopathologic features with JCV detection in the brain tissue.42 However, brain biopsy is an invasive method with considerable risks. Others have proposed less invasive diagnostic methods based on amplification of the JCV-target DNA from CSF by PCR. Fong et al showed that the sensitivity and specificity of JCV DNA by PCR were 74% and 96%, respectively, and positive and negative predictive values were 89.5% and 88.5%, respectively (before the highly active antiretroviral therapy era).43 Persistent JC viremia in serum occurs in approximately 18% of HIV-positive patients without PML and 48% of HIV-infected patients with PML.44 Given the rarity of PML and the high incidence of transient JC viremia,
the positive predictive value of this test as a PML screening tool for rituximab-treated patients with NHL or autoimmune diseases is probably low.44,45

Risk factors for development of PML include having CD4⁺ lymphocyte counts less than 200 cells/µL among HIV-infected persons, whereas risk factors among HIV-negative persons have not been reported.46 One case report describes an HIV-seronegative patient with diffuse large B-cell lymphoma and an absolute CD4⁺ T-lymphocyte count of 68 cells/µL who developed PML and pneumocystis pneumonia 3 months after rituximab-containing chemotherapy treatment.50 Of note, PML has been reported in HIV-negative persons who have CD4⁺ lymphocytes counts in excess of 200 cells/µL.47 In our cohort, 9 of 14 rituximab-treated patients for whom CD4 cells were reported had CD4 cell levels less than 500 cells/µL. Two rituximab-associated PML patients with higher CD4⁺ lymphocyte counts had underlying B-cell disorders. Our data suggest 2 possible rituximab-associated PML syndromes. One syndrome is associated with short intervals between last rituximab dose and PML diagnosis among patients with low CD4⁺ lymphocyte counts and occasionally low IgG levels. The second syndrome is associated with longer intervals between last rituximab dose and PML diagnosis among patients with higher CD4⁺ lymphocyte counts. Laszlo et al reported that CD4⁺ lymphocyte cell counts decreased to a median of 216 CD4⁺ T cells/µL among 25 low-grade lymphoma patients who received rituximab and chlorambucil; 2 of these patients developed cutaneous herpes zoster infections, 1 developed reactivation of hepatitis B-viral infection, and none developed PML or other opportunistic infections.48 More information on CD4⁺ lymphocyte counts and immunoglobulin levels among rituximab-treated persons is needed.

Historically, treatment of PML rarely has been successful in the absence of immune system reconstitution, as was the case in this report as well.49 Cytarabine has been the most commonly administered PML therapy, although clinical benefit is infrequent. Among HIV-infected patients, mean survival after a diagnosis of PML was only 0.4 years before the introduction of highly active antiretroviral therapy versus 1.8 years more recently.46 Factors associated with increased rates of PML survival include having CD4⁺ cell counts more than 50 cells/µL at diagnosis among HIV-infected patients46 and among non–HIV-infected patients, after hematopoietic stem cell transplantation procedures where immune reconstitution frequently occurs.50 In our study, survival rates were 29% among the NHL patients who developed PML after hematopoietic stem cell transplantation procedures versus 7% among the NHL patients who did not undergo hematopoietic stem cell transplantation procedures. Similarly, Garcia-Suarez reported survival rates of 38% among NHL patients who developed PML after hematopoietic stem cell transplantation procedures versus 10% for NHL patients who did not undergo hematopoietic stem cell transplantation procedures.50 With close monitoring and early discontinuation of natalizumab, 2 of the 5 most recently diagnosed patients with natalizumab-associated PML have recovered.51

With increasing concern over PML occurring among persons who receive rituximab or natalizumab antibody therapies, focused risk management efforts have been developed. For natalizumab, the manufacturer implemented a Risk Minimization Action Plan (RiskMAP) in the United States called Tysabri Outreach: Unified Commitment to Health (TOUCH). This program is designed to prospectively assess the risk of PML associated with natalizumab, minimize PML risk, minimize death and disability resulting from PML, and promote informed risk-benefit decisions.52,53 Risks of natalizumab are addressed through educational efforts describing risks of PML associated with natalizumab, restricted distribution, and mandatory registration of prescribing clinicians, pharmacists, infusion center staff, and patients. The FDA has advised healthcare professionals that natalizumab monotherapy may confer a lower risk of PML than when natalizumab is administered with other immunomodulatory medications.54 Prospective follow-up of 5000 natalizumab-treated patients facilitates epidemiologic assessments.

Risk management related to rituximab-associated PML differs. Primary efforts involve educating physicians who prescribe rituximab and patients who receive the drug about PML.12,16,55 In addition, as part of an enhanced pharmacovigilance plan, the manufacturer will report to the FDA information on all rituximab-treated patients with PML and provide annual estimates of PML incidence rates among populations where cases have been reported. The risk management efforts do not include restricting rituximab distribution to certain prescribers as this would adversely affect drug access for large numbers of persons. It should be noted that risk-benefit assessments take into consideration observations that rituximab added to chemotherapy prolongs progression-free survival for persons with follicular non-Hodgkin lymphoma and prolongs survival and can be curative for patients with diffuse large B-cell lymphoma.56-58 Rituximab is proving to have benefit for a wide range of immunologic syndromes, including autoimmune hemolytic anemia, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, and rheumatoid arthritis.56,61-64

Table 2. T-lymphocyte studies for a subset of 14 rituximab-related PML cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Indication</th>
<th>CD4⁺ cells/µL</th>
<th>CD8⁺ cells/µL</th>
<th>CD4/CD8 ratio</th>
<th>Hematopoietic transplantation</th>
<th>Purine analog exposure</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse large B-cell lymphoma</td>
<td>68</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Systemic lupus erythematosus</td>
<td>71</td>
<td>57</td>
<td>1.25</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Non-Hodgkin lymphoma</td>
<td>89</td>
<td>41</td>
<td>2.17</td>
<td>Autologous</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse large B-cell lymphoma</td>
<td>94</td>
<td>243</td>
<td>0.39</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Mantle cell lymphoma</td>
<td>110</td>
<td>310</td>
<td>0.35</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Follicular lymphoma</td>
<td>152</td>
<td>532</td>
<td>0.29</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Follicular lymphoma</td>
<td>234</td>
<td>1015</td>
<td>0.23</td>
<td>Autologous</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Chronic lymphocytic leukemia</td>
<td>287</td>
<td>31</td>
<td>9.9</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Mantle cell lymphoma</td>
<td>403</td>
<td>1309</td>
<td>0.31</td>
<td>Allogeneic</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Marginal zone B-cell lymphoma</td>
<td>551</td>
<td>2596</td>
<td>0.21</td>
<td>Autologous</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Autoimmune hemolytic anemia</td>
<td>562</td>
<td>382</td>
<td>1.47</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Follicular lymphoma</td>
<td>570</td>
<td>1871</td>
<td>0.30</td>
<td>None</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Autoimmune hemolytic anemia</td>
<td>1059</td>
<td>3453</td>
<td>0.31</td>
<td>Allogeneic</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>Waldenstrom macroglobulinemia</td>
<td>2100</td>
<td>6200</td>
<td>0.34</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

The normal CD4⁺ range is 500 to 1600 cells/µL; the normal CD8⁺ range is 400 to 1100 cells/µL; the normal CD4/CD8 ratio is 0.8 to 2.7. NA indicates not applicable.
Queries of medical directors of lymphoma referral centers about cases of rituximab-associated PML facilitated obtaining unique detailed case descriptions for 22 cases of PML. Very few of these patients had been spontaneously reported previously to the FDA’s MedWatch program or to the manufacturer, and the completeness of the case reports was markedly greater in reports provided by these persons in comparison to reports submitted directly to the FDA or the manufacturer. Follow-up information was frequently provided by these clinicians in response to queries from investigators affiliated with the Research on Adverse Drug Events and Reports (RADAR) project. The RADAR project is an National Institutes of Health–funded, multidisciplinary team, led by a hematologist/oncologist/health services researcher, and consists of 25 core investigators with training in clinical pharmacology, pharmacy, epidemiology, statistics, internal medicine, and various medical subspecialties, including hematology, oncology, cardiology, infectious disease, and neurology. RADAR focuses on identification, evaluation, and dissemination of information describing rare and potentially fatal adverse drug events. As reported with our prior studies, close communication between clinicians and our pharmacovigilance project facilitates compilation of reports that are more complete than those reported spontaneously to the manufacturer or to the FDA. An important benefit of the collaboration was that RADAR, rather than the clinicians, responded to all follow-up queries from the FDA and the manufacturer.

Some study limitations should be noted. Epidemiologic estimates of PML incidence are difficult to derive. In the general population, PML is estimated to occur at 1 case per 200 000 persons. Among HIV-infected populations, incidence rates decreased from 3.3 cases per 1000 person-years at risk in 1995 to 1996 to 1.3 cases per 1000 person-years at risk in 2000 to 2006, after the introduction of highly active antiretroviral therapy. Among persons with multiple sclerosis or Crohn disease, the estimated incidence of natalizumab-associated PML is 1 PML case per 1000 natalizumab-treated patients. For PML-associated with rituximab, Kavanaugh and Matteson reported 2 PML cases per 8000 rituximab-treated SLE patients. It is not possible to accurately estimate the incidence of rituximab-associated PML among persons with hematologic malignancies because of incomplete reporting of PML cases among rituximab-treated patients and incomplete data on the number of unique patients with lymphoid malignancies who have received rituximab. It should also be noted that the epidemiology of PML in the setting of lymphoid malignancies has changed over time. Before 1990, most PML cases occurred among persons with Hodgkin disease, whereas in recent years, with the development of purine analogs, hematopoietic stem cell transplantation procedures, and rituximab, most PML cases occur among non–HIV-infected persons with NHL or chronic lymphocytic leukemia. Consideration should be given to conducting epidemiologic studies to prospectively evaluate incidence rates and risk factors for PML among cohorts of rituximab-treated patients with NHL, autoimmune diseases, SLE, rheumatoid arthritis, and multiple sclerosis. Finally, causation assessment is more difficult when PML occurs among rituximab- versus natalizumab-treated persons because PML occurs in the absence of rituximab therapy among persons with NHL or autoimmune diseases, whereas it has not been reported in the absence of natalizumab therapy among persons with multiple sclerosis or Crohn disease.

In conclusion, rituximab administration may increase risks of developing PML, although the absolute risk of developing PML is probably low. As use of rituximab expands to diverse clinical settings, clinicians and patients should be aware of the potential for PML after rituximab therapy. Awareness and reporting of rituximab-associated PML cases to the FDA are essential to improve our understanding of risk factors, natural course, and alternative therapeutic approaches. Despite widespread public health advisories describing 2 patients with SLE and 1 patient with rheumatoid arthritis who were diagnosed with rituximab-associated PML, we identified 22 previously unreported cases associated with lymphoid malignancies and immunologically mediated cytopenias. Early diagnosis of PML will prompt efforts at immune reconstitution, which may be beneficial in improving survival rates. Finally, early diagnosis before irreversible neurologic damage has occurred will be crucial for evaluation of the efficacy of new antiviral treatments.

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Authorship

Contribution: K.R.C. conceptualized and designed the research, analyzed data, and wrote and edited manuscript; A.M.E. helped conceptualize and design the research, and edited the manuscript; E.A.R. managed and analyzed the data and wrote and edited the manuscript; T.M.H., J.M.V., S.D.B., R.R.F., J.N.W., J.L., R.M., K.M., and R.L.T. provided vital data for this research; D.F. participated in the conception and interpretation of data and edited the manuscript; J.E.S. participated in the conception, design, and editing of the manuscript; L.I.G. participated in the design of the study and editing of the manuscript; J.N.W. participated in the conception and design of the study and editing of the manuscript; A.D.Z. participated in the design of the study and interpretation of the data; D.W.R. participated in the analysis and interpretation of the data; G.W.D. contributed data and participated in the interpretation and analysis of the data; S.T.R. participated in the conception and design of the study; N.R.G.-L. participated in the design of the study and edited the manuscript; O.S. interpreted the data and edited the manuscript; D.G. and E.O.M. conceptualized and designed the study and edited the manuscript; and C.L.B. conceptualized, designed, and analyzed the study, and wrote and edited the manuscript.

Conflict-of-interest disclosure: A.M.E. and S.T.R. serve on the Genentech speakers’ bureau. All other authors declare no competing financial interests.

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