Published in final edited form as:
Arthritis Care Res (Hoboken). 2012 April ; 64(4): 612–615. doi:10.1002/acr.21564.

Incidence and Risk Factors for Progressive Multifocal Leukoencephalopathy among Patients with Selected Rheumatic Diseases

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Abstract

We conducted a large, population-based study to describe the incidence and risk factors for progressive multifocal leukoencephalopathy (PML) among patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (PsO), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and ankylosing spondylitis (AS) using national inpatient and outpatient administrative data from the entire Center for Medicare and Medicaid Services (CMS) from 2000–2009. Suspected PML cases were identified using hospital discharge diagnosis codes. Risk factors for PML were evaluated using outpatient data >= 6 months prior to PML diagnosis.

Among 2,030,578 patients with autoimmune diseases of interest, a total of 53 PML cases were identified (2.6/100,000 patients). Most PML cases had HIV and/or cancer. Nine PML cases had evidence for biologic use prior to PML hospitalization, of which 3 had neither HIV nor malignancy and were exposed to biologics within 12 (rituximab) or 6 months(all other biologics) prior to PML diagnosis. PML occurred at an estimated incidence of 0.2/100,000 patients with autoimmune diseases who did not have HIV or malignancy. PML occurs at a very low incidence among patients with rheumatic diseases but can occur even in the absence of HIV or malignancy.

Keywords

rheumatoid arthritis; infliximab; progressive multifocal leukoencephalopathy; JC virus

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Disclosures:
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Kevin Winthrop, MD: Consultant for Genentech, Pfizer, Amgen.
John W Baddley, MD: Consultant for Merck.
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Elizabeth Delzell, ScD: Portion of Salary funded by a contract from Amgen.
Kenneth G Saag, MD MSc: Consultant for Amgen, AstraZeneca, Eli Lilly, Genentech, Horizon, Sanofi Aventis, Merck, Novartis, Pfizer.

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare and serious infection caused by the JC virus[1–2] and characterized by progressive inflammation and demyelination of the white matter of the brain at multiple locations. Most humans have been exposed to JC virus during their lifetimes, and infection typically occurs during the first several decades of life; approximately 50–80% of adults have serologic evidence of prior exposure. Following initial infection, the virus remains latent in multiple tissues in healthy individuals, with reactivation and clinical disease occurring in severely immunosuppressed states. PML has been most commonly observed among patients infected with human immunodeficiency virus (HIV), those with malignancies, and in organ transplant recipients. PML has also been reported rarely in patients with inflammatory autoimmune disorders including rheumatoid arthritis (RA)[3–4] and other rheumatic conditions[5–9], particularly in those using cytotoxic and biologic therapies including rituximab[10–13], natalizumab[14], efalizumab[15] and less commonly tumor necrosis factor (TNF) inhibitors[16–17]. At present, the contribution of biologic therapies to the development of PML is unclear, and the epidemiology of PML has been poorly characterized among patients with rheumatic diseases. Case series and data from spontaneous reports suggest that PML may occur more commonly in systemic lupus erythematosus (SLE) than in other rheumatic diseases[6], but little population-based data exist evaluating PML incidence and risk factors in the rheumatic disease setting.

Accordingly, we conducted a large, population-based study to ascertain the incidence of PML in patients with selected rheumatic diseases, to describe the characteristics of PML cases occurring in this setting, and to evaluate the extent to which such cases occurred in the context of biologic therapies such as rituximab or TNF antagonists.

Methods

We used person-level inpatient and outpatient administrative data from the Center for Medicare and Medicaid Services (CMS) for the period 2000–2009 and for the entire United States. Medicaid-only and ‘dual-eligible’ (Medicare + Medicaid) individuals with ≥ 1 physician diagnosis of RA, psoriatic arthritis (PsA), psoriasis (PsO), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and ankylosing spondylitis (AS) were identified. Suspected, hospitalized cases of PML were identified amongst these patients using hospital discharge diagnosis codes (ICD9-CM 046.3). The date of hospital admission was considered the PML ‘case date’.

Risk factors for PML were evaluated using inpatient and outpatient data prior to the case date. Thus, patients hospitalized with a diagnosis of PML were required to be observable (e.g. enrolled in Medicare part A + part B, but not enrolled in a Medicare Advantage plan) in the month of hospitalization and for at least the previous 6 months. Relevant comorbidities and medication exposures were determined using healthcare encounter coded-diagnoses, procedures and pharmacy fill records. Additionally, we described mortality within 4 months following the case date. Two study investigators (JC and AB) manually reviewed the claims data to ascertain the validity and features of each suspected PML case with a history of exposure to biologic therapies and without other risk factors such as HIV or malignancy. Because the data available in this report were not derived from review of medical records but only from inpatient physician diagnoses/hospital discharge diagnoses, all identified cases of PML were therefore considered as ‘suspected PML’. Written clearance was obtained from Center for Medicare and Medicaid Services (CMS) to describe the data, and the study was approved by the local Institutional Review Board at UAB.

Results

A total of 2,030,578 rheumatic disease patients with at least 6 months of observability (median 40 months, range 6–120 months) in the claims data were included. Among these individuals, 53 patients were hospitalized with a PML diagnosis, yielding an estimated incidence proportion of 2.6 PML cases per 100,000 rheumatic disease patients.

Among these 53 cases, and using all the data prior to hospitalization available (median 38 months, range 8–105 months), 35 (66%) had an HIV diagnosis, and 16(30%) had at least one cancer diagnosis (with or without HIV). Only 11 (21%) PML cases had neither HIV nor cancer diagnoses; all these individuals were observable in the CMS data for more than 1 year (median 36 months, range 14–85 months) prior to the case date. Among patients without any HIV or cancer diagnosis, the estimated incidence proportion was 0.2 PML cases per 100,000 rheumatic disease patients.

Among biologic users, we identified nine cases with evidence for use of a biologic prior to PML hospitalization; Of these 9 cases, 4 had no HIV or malignancy diagnoses. Next, we describe the 3 PML cases which had evidence of biologic use within 6 months prior to PML hospitalization. We also searched the 1 year prior to PML hospitalization for rituximab use given its more prolonged period of effect.

The first case was a Caucasian man in the 7th decade of life who had a history of inflammatory bowel disease diagnosed for at least three years prior to the date of PML hospitalization. He had frequent episodes of upper respiratory tract infection and renal calculi and a diagnosis of peptic ulcer disease. He had been on infliximab at a dose of 300–350 mg per infusion every 8 weeks for at least 3 years. The most recent dose of infliximab was administered 6 weeks before the PML hospitalization. He was not receiving oral glucocorticoids at the time of the hospitalization for PML (most recent dose 32 months prior to hospitalization). At the time of admission with PML, the coded diagnoses submitted by his physicians included loss of coordination, abnormal gait, dizziness, cerebellar ataxia, autonomic neuropathy and encephalopathy. Magnetic resonance imaging (MRI) of the brain (plain & with contrast) was performed; although the results of the MRI were not available in the data source. A search of the procedure codes during the hospitalization revealed no evidence of a brain biopsy being performed. PML was listed as the primary diagnosis code on hospital discharge. Subsequently, the patient expired at twelve days from the date of hospital admission.

We identified two additional patients hospitalized with PML with prior use of rituximab. One was a Caucasian woman in her early seventies with RA for at least 2.5 years before PML diagnosis. The patient had a history of diabetes, ileus, and hypertension. The patient manifested altered consciousness, lack of coordination, abnormal gait and peripheral neuropathy as an outpatient. She had received a total of 10 infusions of 1000mg IV rituximab. MRI of the brain and a lumbar puncture were performed; the patient was diagnosed with PML. The last dose of Rituximab was administered 2 months before PML was diagnosed. She was hospitalized 3 months after the outpatient PML diagnosis for 2 weeks with primary diagnosis of PML and secondary diagnoses of sepsis and heart failure. Three months later, she died of cardiac arrest and pulmonary embolism. In total, from the date of first PML diagnosis till the patient’s death, the diagnosis code for PML was reported 22 times by a physician.

The other rituximab user was a Caucasian woman in her early seventies who had been diagnosed with rheumatoid arthritis at least 3 years before PML diagnosis. She had a history of leflunomide use, colonic polyps, and stroke. Within 1 month prior to PML diagnosis, she had symptoms of speech disorder and aphasia, idiopathic peripheral neuropathy, abnormal

gait, lack of coordination and hemiplegia. The patient had used prednisone for at least 2.5 years. A total of 2 infusions of 1000mg IV Rituximab at 2 weeks interval were given 8 months before PML diagnosis. When she presented to the hospital, she underwent a lumbar puncture, was diagnosed with PML, and was discharged 11 days after admission to the hospital. Within 4 days of discharge, the patient was hospitalized again for 9 days with diagnosis codes for urinary tract infection, esophageal reflux, cerebrovascular accident and PML. The patient died 50 days after the date of first PML diagnosis. The diagnosis code for PML was recorded 24 times (both inpatient and outpatient diagnoses) from the day of first PML diagnosis to the patient's death.

Discussion

Among hospitalized cases of suspected PML occurring among individuals with selected rheumatic and autoimmune diseases, we identified three patients with RA or inflammatory bowel disease that had been exposed to either infliximab or rituximab within the several months prior to hospitalization for PML. The overall estimated incidence of PML was 0.2 per 100,000 persons for rheumatic disease patients without HIV or cancer.

While our data suggest that PML occurs very rarely in autoimmune disease patients without HIV, our three reported cases occurring in non-HIV patients join at least seven other published cases occurring in autoimmune or rheumatic disease patients use biologic therapy. Most of these have occurred while rituximab therapy was being given in the context of other immunosuppressive therapies[18]. Besides the case we reported here, the only other PML case receiving infliximab that has been previously reported[16] was a 72 year old Caucasian male with RA and sub-acute neurological and psychiatric symptoms that developed after 3 years of infliximab, prednisone and methotrexate. The PML diagnosis for this case was established and confirmed by MRI of the brain and a brain biopsy respectively. Discontinuation of anti-rheumatic drugs and supportive therapy led to stabilization of PML with continuation of neurological and cognitive deficits. Given a lack of other risk factors, it was suggested that infliximab might have been casually associated with the development of PML. At least 6 additional PML cases have occurred in those using rituximab[19–20]; however, in only one instance was such a patient lacking other risk factors for PML (e.g. previous history of other cytotoxic drugs, other biologics or documented cancer).

We were limited in not being able to review the medical records of our reported cases, making it difficult to judge whether other explanatory factors existed beyond biologic or other immunosuppressive therapy. Additionally, while the data contained evidence of multiple neurologic deficits compatible with PML, provided by physicians who cared for the patient during the hospitalization, we lacked detailed clinical information (e.g. laboratory or MRI results) that would further confirm the PML diagnosis. Finally, although most of the 53 cases of suspected PML had much more than 8 months of data available prior to hospitalization for PML, the differential availability of information prior to the case date could favor ascertainment of risk factors in patients with longer observable periods. Additionally, all of the PML cases without HIV or cancer were observable in the data for more than 2 years prior to hospitalization, making it unlikely that we missed relevant risk factors for these individuals.

In summary, we report population-based estimates of PML incidence using longitudinal inpatient and outpatient data among patients with selected autoimmune and rheumatic diseases (albeit not including SLE) who do not have HIV or cancer. Our findings suggest that PML occurs exceedingly rarely among such individuals, less than 1 per 100,000 patients during the study period. However rare, such catastrophic cases do occur, and our study and

others suggest that they can occur in the context of biologic therapies such as infliximab and rituximab, although a causal role for biologic agents remains uncertain.

Acknowledgments

This work was supported by Agency for Healthcare Research and Quality grant U18 HS17919. Dr. Curtis receives support from the National Institutes of Health (AR053351) and AHRQ (R01HS018517). Dr. Grijalva was supported by NIH grant 5P60AR56116. Dr Beukelman was supported by NIH grant 5KL2 RR025776-03 via the University of Alabama at Birmingham Center for Clinical and Translational Science.

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