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Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA's adverse event reporting system

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Abstract

Objective—To identify and summarize FDA's Adverse Event Reporting System (FAERS) cases of progressive multifocal leukoencephalopathy (PML) associated with biological and targeted cancer therapies (BTCT) that were approved between 2009 and 2015.

Methods—FAERS was searched using each BTCT name as primary or secondary suspect drug and the adverse reaction of PML. Among BTCTs with >2 case reports of PML, proportional reporting ratios (PRR) and 95% confidence intervals (CI) were calculated.

Results—Among 49 new BTCTs, 82 cases of PML were found for 16 drugs. Significant PRR signals were found among 7 (14.6%) BTCTs including: brentuximab (24.5, CI:14.8–40.6), ofatumumab (16.3, CI:9.6–27.4), alemtuzumab (9.9, CI:6.0–16.4), obinutuzumab (7.4, CI:2.4–22.8), ibrutinib (5.6 CI:3.0–10.5), belimumab (4.5 CI:2.3–9.0), and idelalisib (4.1, CI:1.3–12.6). Among the 82 cases among BTCTs with significant signals, confirmation of the diagnosis of PML using objective criteria was found in 56% of the cases. A limitation of FAERS data is that missing data are common.

Declaration of Interest

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Conclusions—When using BTCTs, clinicians and patients consider the risk of PML versus the therapeutic benefit, particularly when used in combination with other drugs which may cause PML, such as rituximab. It is important to recognize that PML may occur in some conditions, such as chronic lymphocytic leukemia, regardless of drug therapy.

Keywords

progressive multifocal leukoencephalopathy; biological drugs; targeted cancer therapies; FDA's Adverse Event Reporting System; data mining signal detection

1.0 Introduction

Progressive multifocal leukoencephalopathy (PML) can occur among immuno-compromised patients, such as those with human immunodeficiency virus (HIV) or hematologic cancer. PML is also associated with immunosuppressive therapies occurring as a rare, serious adverse event (SADE). Initial reports of PML in the literature go back to 1958.¹ The symptoms of PML involve a progressive loss of mental function that has an onset of confusion, loss of motor coordination, and visual and speech changes. The progression occurs, usually over weeks to months, with mortality as high as 90%.²

The incidence of PML associated with HIV has decreased with the adoption of highly active antiretroviral therapy, from 14.8/1000 in 1996 to 0.8/1,000 in 2011.³ A study of PML incidence in a large health insurer database (>60 million) found rates per person-year of 35.4/100,000 among bone marrow transplant (BMT) patients, compared to 11.1 for chronic lymphocytic leukemia (CLL), 10.8 for autoimmune vasculitis (AV), 8.3 for non-Hodgkin lymphoma (NHL), and 2.3 for systemic lupus erythematosus (SLE).⁴ Among 6 chart-confirmed cases in the study, one NHL patient had received rituximab and 3 patients had received mycophenolate (AV, BMT, SLE). For cohorts identified in the database, drug exposures within the past 183 days included rituximab (0.1%) for SLE to 7.6% for NHL, fludarabine (1.3%) for NHL to (4.3%) for CLL, or mycophenolate mofetil (7.4%) for BMT.⁴

The etiology of PML is re-activation of latent polyoma JC virus (JCV). Antibodies to JCV are present in 40 to 60% of the population, depending upon age.⁵ The pathogenesis of PML has been described as a sequence involving an initial infection which becomes a latent infection and then the virus evolves into a neurotropic JCV strain.⁵ The neurotropic JCV reactivates and enters the brain, but a defect in immune surveillance fails to eliminate neurotropic JCV.⁵ This defect may be associated with depletion or impaired function of specific T-cell and/or B-cell lymphocytes.⁶ Several immunosuppressive drugs, such as natalizumab, rituximab, efalizumab, and mycophenolate mofetil, deplete or impair T-cell or B-cell lymphocytes.⁶ Among multiple sclerosis patients treated for 2 to 3 years with natalizumab or efalizumab, PML incidence is as high as 1 in 1000.⁵

The FDA Adverse Event Reporting System (FAERS) is the FDA's passive pharmacovigilance surveillance program.⁷ Patients, practitioners, and pharmaceutical companies all contribute to the data through MedWatch reports of SADEs.⁸⁻¹² FAERS can be used to identify signals of a SADE/drug relationship by comparing reporting rates for the

SADE attributed to the drug versus reporting rates of the SADE for all drugs. It also serves as an early warning system for rare SADEs that were not identified during approval studies.

Since PML is a serious risk associated with certain immunosuppressive agents, it is important to identify treatments that carry this risk as quickly as possible. This will allow prescribers and patients an opportunity to consider it in risk/benefit assessment, as well help mitigate the impact of PML through early detection. The purpose of this paper was to summarize cases of PML in FAERS associated with recently approved biological drugs and targeted cancer therapies.

Our objectives were to:

1. Identify all biologicals and targeted cancer therapies that may cause immunosuppression and were approved from 2009 to 2015.
2. Search FAERS for cases of PML associated with these new drugs.
3. Apply signal detection algorithms to identify significant signals for PML associated with new drugs.
4. Summarize key features of FAERS PML cases reported for these new drugs. 2.0

2.0 Methods

Biological drugs approved since 2009 were identified by searching the FDA web site for all new drug approvals. This list was refined by assessing the mechanism of action and indication for each drug and selecting biologicals and targeted cancer therapies that cause immunosuppression.

2.1 PML cases in FAERS

We searched FAERS using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) preferred term of “progressive multifocal leukoencephalopathy” combined with each drug’s generic and brand names (US and non-US). For each drug, the time period included was from its approval date to July 2015. Duplicate cases were removed by screening cases by age, gender, date of event, and other criteria, such as concomitant drugs and reaction terms. Once the unique cases were identified, Freedom of Information Act requests were submitted to the FDA to obtain narratives of each MedWatch report. We extracted demographic and clinical information for each case and summarized these data for each drug in which 3 or more PML cases were found. In cases where date of initial treatment and date of event were available, we calculated the number of months to occurrence of PML. The specific diagnostic criteria of PML were tabulated, including detection of JCV by polymerase chain reaction (PCR) in brain tissue or cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) showing lesions consistent with the demyelinating process, and/or examination of brain tissue from biopsy. Cases that involved the administration of another drug known to be associated with PML were included, and the presence of the secondary suspect drug was noted. Since all cases were life threatening and required hospitalization, mortality was the only outcome summarized.

2.2 Data Mining Signal Detection

Signal detection consisted of determination of proportional reporting ratios (PRRs). PRRs reflect disproportionate reporting of an event (PML) for the drug of interest compared to all other reports of the event for all other drugs in FAERS. Specifically, PML was reported in approximately 0.04% of all MedWatch reports to the FDA for the time period of 2009 to 2015. PRR for PML is significant if a drug has: (1) more than 2 cases of PML, (2) the disproportionate reporting ratio (PRR) of PML is greater than 2.0, and (3) the chi-square value for the 2 x 2 comparison is greater than 4.0.¹³ The reporting rate for each drug was calculated based upon PML cases for the drug divided by all MedWatch cases for the drug. A significant data-mining signal indicated the possibility that the drug has an increased risk for PML. PRR and 95% confidence intervals (CIs) for each drug was based upon MedWatch cases reported after its approval date. PRR is a widely-accepted method for signal detection from voluntary reporting systems of adverse drug reactions.¹³

3.0 Results

The new biologicals and targeted cancer therapies approved since 2009 and selected for this study and number of PML FAERS reports are shown in Table 1. Of 49 new drug approvals, there were 82 cases of PML associated with 16 (32.6%) of the drugs. Table 2 displays results for each drug; specifically the number and percentage of FAERS cases of PML and the signal detection results (chi square values for drugs with 2 or more cases, PRR, and 95% confidence limits for each PRR). Significant signals were found for the following novel therapies approved for B-cell hematologic malignancies: brentuximab vedotin, alemtuzumab, ofatumumab, ibrutinib, obinutuzumab, and idelalisib. A significant signal was also found for belimumab, approved for SLE. For drugs with significant signals, the rates of PML versus all FAERS cases for each drug ranged from 0.27% (belimumab) to 1.47% (brentuximab).

Table 3 summarizes details of the cases of PML by drug. Brentuximab patients were youngest, with a mean age of 45.4 years. Belimumab patients were the next youngest and all cases were female, which probably relates to the indication of the drug (SLE) and demographic preponderance of SLE among females. Ibrutinib patients were also all female. Mortality was ranged from 25% of belimumab PML cases to 90% in ibrutinib PML cases. However, not all FAERS cases were complete regarding the ultimate outcome.

Presenting symptoms were consistent with previous reports of PML, with most cases listing confusion or altered mental state, motor weakness, loss of coordination, and/or visual and speech difficulties. For each drug, the majority of cases were diagnosed with magnetic resonance imaging (MRI) plus detection of JCV in the cerebral spinal fluid (CSF). However, in 44% of cases, the method of diagnosis was not specified. There were 2 cases where JCV was tested but not detected for alemtuzumab and information on whether a biopsy or autopsy was performed was not included in these case reports. Nondetection of JCV in the CSF among cases of PML has been previously reported, however in those cases JCV was detected when subsequent brain biopsies or autopsies were performed.¹⁴

It should be noted that rituximab, a monoclonal antibody with anti-CD20 activity, has been associated with PML.^{2,15,16} Rituximab was listed as a secondary suspect drug in 25 (30.5%) of the 82 FAERS cases (Table 1). Natalizumab, also associated with PML, was listed as a secondary suspect drug in one case.¹⁷ Data on secondary suspect drugs were missing in some FAERS reports. For golimumab, eculizumab, and obinutuzumab all cases included rituximab as a secondary suspect drug. Furthermore, rituximab was listed as a suspect drug in the following cases: denosumab (50% of cases), ibrutinib (50%), alemtuzumab (27%), ofatumumab (21%), and brentuximab (7%) (Table 1). The other drugs had no cases in which rituximab was listed. It is unclear whether the combination may increase risk of PML or if the reaction was primarily due to rituximab. Previous research has estimated the risk of PML associated with rituximab at 1 in 30,000.⁶ During the study period, there were 498 cases in FAERS of PML with rituximab listed as the primary suspect plus 203 cases where it was listed as a secondary suspect, accounting for 29.1% of 2412 cases. Other monoclonal antibodies with anti-CD20 activity found to have significant data mining signals in this review were obinutuzumab and ofatumumab. Ibritumomab tiuxetan and tositumomab also have anti-CD20 activity but were approved prior to 2009 and therefore not included in this study.

In cases where the onset of PML was soon after the start of therapy, the underlying condition or previous drug therapy may have been the cause of PML, rather than the new drug. The shortest mean duration of exposure was for ibrutinib. PML occurred 3 days after the first dose in one case and 8 days after the first dose for another case. We note that both of these cases included rituximab as a suspect drug. Brentuximab vedotin was also associated with a short duration from first dose to event, specifically in one case PML occurred after the 2nd dose and another after the 3rd dose. This has been previously reported regarding 5 PML cases associated with brentuximab vedotin.¹⁸

Times to PML events were longer for alemtuzumab and obinutuzumab. Mean numbers of months from first dose to event were 15.8 and 13.7 months, respectively (Table 3). One case occurred 4 years after beginning treatment. The time from start of therapy to PML event was available for only a portion of the cases, due to missing data or unavailability of narratives from the FDA.

4.0 Discussion

This paper is the first to review FAERS for PML cases associated with all new biologicals and targeted cancer therapies approved since 2009. Data mining of FAERS data is an established method to identify significant signals of rare, serious adverse events.^{13,19} Herein we summarize PML cases and report which drugs have disproportionate reporting signals. Among 7 products with significant signals, only one (idelalisib) did not include PML in the labeling. Our findings should increase awareness that PML should be considered in the differential diagnosis of persons receiving these drugs who present with speech disorders, confusion, gait alterations, hemiplegia, visual or hearing changes, and/or altered mental status. We note that none of the drugs approved in 2015 were found to have PML cases reported to FAERS. However, it is possible that this finding was a reflection of the short time of market availability.

Considering the many factors that influence voluntary reporting to FAERS, we note that the relative values of the data mining signals for these new drugs should not be compared directly. The higher PRR numbers in Table 2 indicate differences in disproportionality of reporting of PML between drugs but they should not be interpreted as equivalent to relative risk or odds ratios gathered from large epidemiologic studies. More appropriately, these results indicate signals for further study. Similarly, the indications listed in FAERS reports should not be interpreted as differences in risk or safety between different conditions. Those differences may be a reflection of relative utilization in certain populations or recognition of an adverse event in association with a specific treatment.

For the drugs with data mining signals (Table 2) we searched the literature for reports of PML and found 8 relevant articles for 4 of the drugs. There were 2 case reports for alemtuzumab, one in a lung transplant patient and another in a CLL patient. There were 2 case reports for belimumab, both in SLE patients.^{20,21} Brentuximab-associated PML was described in two articles.^{18,22} One study described 5 cases among patients with lymphoid malignancies.¹⁸ Another was a case report in a patient with Hodgkin lymphoma.²² For ofatumumab, there was a retrospective observational study of 103 poor-prognosis CLL patients that described 2 cases of PML.

Patients receiving immunosuppressive biologicals have increased risk of PML whether the treatment is for cancer or autoimmune diseases.²³ Among patients with rheumatic disease, concomitant HIV or cancer increases risk of PML.²⁴ A study of PML risk in rheumatic disease using the Center for Medicare and Medicaid Services (CMS) database identified 53 cases of PML (2.6 per 100,000). However, after removing patients with concomitant HIV or cancer, the estimated incidence rate dropped to 0.2 cases per 100,000 among rheumatic disease patients with exposure to biologicals.²⁴ Another study of risk of PML in rheumatic diseases in nearly 300 million hospital discharges, identified risk to be greater for SLE than for rheumatoid arthritis (4 vs. 0.4 per 100,000).²⁵

Risk factors for PML in patients with hematologic malignancies have been identified. A review of 46 published case reports among HIV-negative patients with lymphoproliferative diseases identified B-cell chronic lymphocytic leukemia, follicular lymphoma, and number of treatment cycles as risk factors.²⁶ In a recent study of Veterans Affairs (VA) patients, the relative risk of PML among non-NHL patients receiving rituximab was found to be 5.4 (CI: 1.9–15.4) compared to NHL patients not receiving rituximab.^{27,28}

The level of JCV in serum has not been shown to relate to risk of PML, but its presence in CSF using PCR is part of the diagnostic criteria for PML proposed by the American Academy of Neurology (AAN).²⁹ The AAN diagnostic algorithm for PML includes an alternative diagnostic branch if JCV is not detected in CSF, whereby it is confirmed through brain biopsy.²⁹ A marker of risk for PML is anti-JCV antibody level in serum/plasma.^{30,31} A PML risk stratification guideline, based on anti-JCV antibodies in multiple sclerosis (MS) patients receiving natalizumab has been proposed.¹⁷ Additional risk factors in MS, include prior use of immunosuppressants, underlying hematologic malignancy, and long duration of treatment with natalizumab.³¹ JCV antibody testing among rheumatoid arthritis patients

receiving biologics, however is not recommended due to the much lower risk of PML in these patients.³²

Regarding drug-specific mechanisms that might increase risk of PML, previous publications have suggested that monoclonal antibodies are more prone to cause the adverse effect, but PML is also associated with other immunosuppressant drugs.^{6,33} Zaheer and Berger classified drugs associated with PML into 3 classes⁶. Class 1 were drugs with inherent risk of PML, such as natalizumab and efalizumab (no longer marketed).⁶ Rituximab, mycophenolate mofetil, and brentuximab vedotin were considered Class 2; drugs that cause PML when given for diseases known to have increased risk of PML (hematologic malignancies, auto-immune diseases) or in combination with other immunosuppressive agents. Class 3 drugs (alemtuzumab, fludarabine, fumaric acid, and infliximab plus other tumor necrosis factor α inhibitors) were those in which PML has been reported rarely and the risk is still unknown.⁶ A common effect of all three classes is depletion or inactivation of B and/or T-cell lymphocytes. Of the 7 drugs identified in our study, 5 are monoclonal antibodies, one was a Bruton's tyrosine kinase inhibitor (ibrutinib) and one was a phosphoinositide 3-kinase delta kinase inhibitor (idelalisib). All 7 drugs have an effect of depletion or inactivation of B-cell lymphocytes,

In addition to stopping the drug suspected to have caused PML, a few studies have outlined potential treatments. A review of 28 post-marketing cases of PML associated with natalizumab therapy in MS patients summarized treatments.³⁴ Plasma exchange and/or immunoadsorption was performed in 27 cases and associated with survival in 19 cases. Additional therapies of the 19 surviving patients included mefloquine (n=9), mirtazapine (n=6), deflazacort (n=1), intravenous immunoglobulin (n=1), and cidofovir (n=1).³⁴ However, all surviving patients developed immune reconstitution inflammatory syndrome (IRIS), which required additional treatment with high dose intravenous or oral corticosteroids. Furthermore, after survival most patients had moderate to severe disability and only two had good recovery.³⁴ Immunoabsorption and plasma exchange was reported to improve PML in an MS patient.³⁵ The patient also developed IRIS, which is a worsening of PML after discontinuance of immunosuppression. It was successfully treated with steroid pulse therapy.³⁵ IRIS is rare in PML associated with hematological cancers but much more common in PML associated with natalizumab and HIV.^{36–38} Another study described treatment of IRIS with high dose corticosteroids and this treatment appears to be associated with improved survival.^{36–38}

The successful treatment of PML using pulsed steroid therapy (methylprednisolone) in a patient with HIV has also been reported.³⁹ Two case reports, from 1997 and 1999 demonstrated successful treatment of PML with interleukin 2.^{40,41} A more recent 2005 report demonstrated improvement, sustained over 5 years, in a PML patient treated with interleukin 2.⁴² Successful treatment of PML with interleukin 7 in a patient with idiopathic CD4+ T-cell lymphocytopenia has been described.⁴³ Another publication described successful treatment of PML in 2 patients with interleukin 7 in combination with vaccination with JCV capsid protein VP1.⁴⁴ Both patients had hereditary or acquired CD4 lymphopenia. A study summarizing published case reports of PML associated with lymphoproliferative diseases identified the following treatments among 4 surviving patients: intravenous

cytarabine, interleukin-2, intravenous immunoglobulins, and intrathecal cytarabine plus interleukin-2.²⁶ A fifth surviving patient had no treatment reported.²⁶ A recent review summarized the basis for treating PML, including use of antiviral agents to suppress JCV (e.g. cidofovir, mefloquine), immune response modulators (e.g. interleukin 7, corticosteroids) and passive or active immunization against JCV (still in development).³⁶

4.1 Recommendations

We note that only 1 to 10% of SADEs are reported to voluntary reporting systems.^{45–48} First, health care providers are encouraged to report drug-associated cases of PML to MedWatch or their country's voluntary adverse event reporting system. These reports are very valuable to further characterize PML and increase awareness in the medical community. Second, when PML is suspected, it is important to verify it using published diagnostic criteria, such as the decision tree developed by AAN.²⁹ Third, when reporting an SADE event to a voluntary reporting system, such as MedWatch, it is critical to include all relevant information to assure the data is complete. Furthermore, health care providers should consider applying a causation assessment algorithm when reporting an SADE.⁴⁹ This would clarify the strength of the drug/SADE association. Large database analyses are also crucial in describing these associations.^{4,24}

4.2 Limitations

Limitations of this study are inherent to FAERS data.^{8–12} It is unlikely that all occurrences of PML are reported to FAERS. Furthermore, relevant information, such as age, gender, diagnosis, and dosage information are sometimes missing from case reports. There is a potential for causal misrepresentation of FAERS cases. In this study, objective measures of diagnosis were not provided in 44% of the FAERS reports. Another limitation of FAERS is that there is a possibility for misattribution. It is possible that the underlying hematologic malignancy, rather than the drug, could be the primary causal factor. This is particularly apropos among persons with CLL, NHL, or other hematologic malignancies, as well as BMT patients.⁴ Several drugs identified here are treatments for hematologic malignancies. Therefore, there is need for further research to clarify the clinical course of development of PML, mitigating factors, and role of underlying malignancy.

5.0 Conclusions

In this study of new biologicals and targeted cancer therapies we found 82 suspected cases of PML that were reported to FAERS. This is the first study to report significant data mining signals for seven drugs approved since 2009. Additional research and follow-up of this study are needed to further clarify the development and treatment of PML. In the interim, physicians and patients should be vigilant in detecting and reporting this rare SADE.

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** of considerable interest

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Table 1

List of New Drug Biologic and Targeted Cancer Therapy Approvals (2009–2015) and Number of Progressive Multifocal Leukoencephalopathy (PML) Cases in FDA's Adverse Event Reporting System (FAERS)

Drug (Generic name); Company; Indication, Month Year approved	# of Cases of PML
2009 FDA Approved Drugs	
Simponi (golimumab); CentocorOrtho Biotech; For the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, Approved April 2009, For the treatment of ulcerative colitis, Approved May 2013	2 (2 with rituximab)
Ilaris (canakinumab); Novartis; For the treatment of cryopyrin-associated periodic syndromes (CAPS), Approved June 2009, For the treatment of Systemic Juvenile Idiopathic Arthritis, Approved May 2013	0
Votrient (pazopanib); GlaxoSmithKline; For the treatment of renal cell carcinoma, Approved October of 2009; also For the treatment of soft tissue sarcoma, Approved April 2012	2
Stelara (ustekinumab); Centocor Ortho Biotech; For the treatment of plaque psoriasis, Approved September 2009	0
Arzerra (ofatumumab); Glaxo; For the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab, Approved October 2009	14 (2 with rituximab)
2010 FDA Approved Drugs	
Actemra (tocilizumab); Genentech; For the treatment of rheumatoid arthritis, Approved January 2010, For the treatment of Polyarticular Juvenile Idiopathic Arthritis, Approved May 2013	1
Herceptin (trastuzumab); Genentech; Approved for the treatment of gastric cancer, Approved October 2010	1
Prolia (denosumab); Amgen; For the treatment of postmenopausal women with osteoporosis at high risk for fracture, Approved June 2010 Xgeva (denosumab); Amgen; For the prevention of skeletal-related events in patients with bone metastases from solid tumors, Approved November 2010	2 (2 with rituximab)
2011 FDA Approved Drugs	
Adcetris (brentuximab); Seattle Genetics; For the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen, Approved August 2011	15 (1 with rituximab)
Benlysta (belimumab); Human Genome Sciences; For the treatment of systemic lupus erythematosus, Approved March 2011	8
Nulojix (belatacept); Bristol Myers Squibb; For organ rejection in adult patients, Approved June 2011	1
Soliris (eculizumab); Alexion; For the treatment of atypical hemolytic uremic syndrome, Approved September 2011.	2 (2 with rituximab)
Sutent (sunitinib malate); Pfizer; For the treatment of pancreatic neuroendocrine tumors, Approved May 2011	0
Vandetanib (vandetanib); AstraZeneca; For the treatment of thyroid cancer, Approved April 2011	0
Xalkori (crizotinib); Pfizer; For the treatment of ALK+ non-small cell lung cancer, Approved August of 2011	0
Yervoy (ipilimumab); Bristol-Myers Squibb; For the treatment of metastatic melanoma, Approved March 2011	0
Zelboraf (vemurafenib); Roche; For the treatment of BRAF + melanoma, Approved August of 2011	0
2012 FDA Approved Drugs	
Bosulif (bosutinib); Pfizer; For the treatment of Ph+ chronic myelogenous leukemia, Approved September 2012	0
Cometriq (cabozantinib); Exelixis; For the treatment of metastatic medullary thyroid cancer, Approved November 2012	0
Erivedge (vismodegib); Genentech; For the treatment of basal cell carcinoma, Approved January 2012	0
Iclusig (ponatinib); Ariad Pharmaceuticals; For the treatment of chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia, Approved December 2012	2
Inlyta (axitinib); Pfizer; For the treatment of advanced renal cell carcinoma, Approved January 2012	0
Kyprolis (carfilzomib); Onyx Pharmaceuticals; For the treatment of multiple myeloma, Approved July 2012	0
Lucentis (ranibizumab injection); Genentech; For the treatment of diabetic macular edema, Approved August 2012	0
Perjeta (pertuzumab); Genentech; For the first-line treatment of HER2+ metastatic breast cancer, Approved June 2012	0

Drug (Generic name); Company; Indication, Month Year approved	# of Cases of PML
Stivarga (regorafenib); Bayer HealthCare Pharmaceuticals; For the treatment of previously treated patients with metastatic colorectal cancer, Approved September 2012, For the treatment of gastrointestinal stromal tumor, Approved February 2013	0
Xeljanz (tofacitinib); Pfizer; For the treatment of moderately to severely active rheumatoid arthritis, Approved November 2012	0
2013 FDA Approved Drugs	
Gazyva (obinutuzumab); Genentech; For the treatment of previously untreated chronic lymphocytic leukemia, Approved October of 2013	3 (3 with rituximab)
Gilotrif (afatinib); Boehringer Ingelheim; For the treatment of metastatic non- small cell lung cancer with EGFR mutations, Approved July 2013	0
Imbruvica (ibrutinib); Pharmacyclics; For the treatment of mantle cell lymphoma, Approved November of 2013 For the treatment of chronic lymphocytic leukemia, Approved February 2014	10 (5 with rituximab)
Tafinlar (dabrafenib); GlaxoSmithKline; For the treatment of unresectable or metastatic melanoma with BRAF V600E mutation, Approved May 2013	0
2014 FDA Approved Drugs	
Beleodaq (belinostat); Spectrum Pharmaceuticals; For the treatment of relapsed or refractory peripheral T-cell lymphoma, Approved July 2014	0
Blincyto (blinatumomab); Amgen; For the treatment of Philadelphia chromosome-negative relapsed /refractory B cell precursor acute lymphoblastic leukemia, Approved December 2014	0
Cyramza (ramucirumab); Eli Lilly; For the treatment of gastric cancer, Approved April 2014	0
Entyvio (vedolizumab); Millenium Pharmaceuticals; For the treatment of adults with ulcerative colitis and Crohn's disease, Approved May of 2014	0
Keytruda (pembrolizumab); Merck; For the treatment of unresectable or metastatic melanoma, Approved September 2014	1
Lemtrada (alemtuzumab); Genzyme; For the treatment of relapsing multiple sclerosis, Approved November 2014	15 (1 with natalizimab, 4 with rituximab)
Lynparza (olaparib); AstraZeneca; For the treatment of previously treated BRCA mutated advanced ovarian cancer, Approved December 2014	0
Ofev (nintedanib); Boehringer Ingelheim; For the treatment of idiopathic pulmonary fibrosis , Approved October 2014	0
Opdivo (nivolumab); Bristol-Myers Squibb; For the treatment of unresectable or metastatic melanoma, Approved December 2014, For the treatment of metastatic squamous non-small cell lung cancer, Approved March 2015	0
Plegridy (peginterferon beta-1a); Biogen IDEC.; For the treatment of relapsing multiple sclerosis, Approved August 2014	0
Sylvant (siltuximab); Janssen Biotech; For the treatment of multicentric Castleman's disease, Approved April 2014	0
Zydelig (idelalisib); Gilead; For the treatment of relapsed CLL, follicular B-cell NHL and small lymphocytic lymphoma, Approved July 2014	3 (3 with rituximab)
Zykadia (ceritinib); Novartis; For the treatment of ALK+ metastatic non-small cell lung cancer, Approved April 2014	0
2015 FDA Approved Drugs	
Cosentyx (secukinumab); Novartis; For the treatment of plaque psoriasis, Approved January 2015	0
Ibrance (palbociclib); Pfizer; For the treatment of ER-positive, HER2-negative breast cancer, Approved February 2015	0
Lenvima (lenvatinib); Eisai; For the treatment of thyroid cancer, Approved February 2015	0
Unituxin (dinutuximab); United Therapeutics; For the treatment of pediatrics with high-risk neuroblastoma, Approved March 2015	0

Table 2

Cases of Progressive Multifocal Leukoencephalopathy (PML) and Signal Detection Results by New Biological Product

Active Ingredient	PML Cases	Total cases for drug	% PML cases for drug	Chi square value	PRR	Lower Bound PRR	Upper Bound PRR
Alemtuzumab *	15	3038	0.49%	119.05	9.87	5.95	16.38
Belatacept *	1	527	0.19%	NC	3.19	0.45	22.59
Belimumab *	8	2985	0.27%	21.70	4.50	2.25	9.00
Brentuximab Vedotin *	15	1017	1.47%	335.48	24.49	14.79	40.56
Denosumab	2	28708	0.00%	NC	0.06	0.01	0.42
Eculizumab	2	14556	0.01%	4.81	0.24	0.06	0.96
Golimumab	2	8811	0.02%	1.93	0.39	0.10	1.55
Ibrutinib *	10	2860	0.35%	37.75	5.63	3.02	10.49
Idelalisib	3	1089	0.28%	6.88	4.05	1.31	12.58
Obinutuzumab *	3	655	0.46%	16.45	7.36	2.38	22.80
Ofatumumab *	14	1478	0.95%	199.37	16.26	9.64	27.42
Pazopanib	2	8609	0.02%	1.80	0.40	0.10	1.60
Pembrolizumab	1	1275	0.08%	NC	1.09	0.15	7.72
Ponatinib	2	1986	0.10%	0.64	1.75	0.44	7.01
Tocilizumab	2	9102	0.02%	2.06	0.38	0.09	1.51
Trastuzumab	1	9386	0.01%	NC	0.22	0.03	1.59

PRR = Proportional Reporting Ratios

* = PML included in labeling

NC = not calculated, too few cases to be a significant signal

Demographic and Clinical Characteristics of Cases of Progressive Multifocal Leukoencephalopathy (PML) among New Biological Products

Table 3

Characteristic	Alentuzumab (15)	Belinumab (8)	Brentuximab Vedotin (15)	Ibrutinib (10)	Idelalisib (3)	Obinutuzumab (3)	Ofatumumab (14)*
Age (mean ± SD)	58.4 ± 16.2	50.1 ± 8.3	45.4 ± 16.5	66.3 ± 7.7	74.3 ± 2.3	71.7 ± 11.0	70.9 ± 9.1
Male gender	50%	0	62%	30%	100%	0	71%
Diagnosis							
Immunosuppression /transplant	4	0	0	0	0	0	0
Oncologic	10	0	9	6	0	0	13
Rheumatologic	0	8	0	0	0	0	0
Multiple sclerosis	1+	0	0	0	0	0	0
Not reported	0	0	6	4	3	3	0
Months since first dose (mean, n of cases, range)	7.9	4.25	3.1	NA	NA	NA	13.7
Concomitant biological, previously associated with PML	n=5 2 to 22	n=2 3.5 to 5	n=5 1.4 to 5.4	n=7 0 to 47.5			
Presenting symptoms *							
Confusion	1	3	4	2	0	0	4
Focal motor weakness	2	1	4	1	0	0	5
Loss of coordination	0	2	2	1	0	0	1
Speech difficulties	0	2	2	0	0	0	0
Visual problems	0	0	1	0	2	0	3
Stroke, TIA	1	3	3	0	0	0	1
Seizure	1	1	2	0	0	0	2
None other than PML listed	6	1	3	4	1	3	5
Method of diagnosis	NA = 4	NA = 5	NA = 9	NA = 5		NA = 3	NA = 4
MRI + JCV in CSF	10	3	6	6	2	0	8
JCV	Positive = 9 Negative = 2	Positive = 3	Positive = 5 Negative = 1	Positive = 5	Positive = 2	0	Positive = 8
Brain biopsy	1	0	0	0	0	0	1
Deaths	12 (80%)	2 (25%)	5 (33.3%)	9 (90%)	2 (66.7%)	2 (66.7%)	6 (42.9%)

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= Number of cases varies from Table 2 due to lack of available summary data.
*
7 = The case included natalizumab as a secondary suspect drug.