

Monoclonal Antibodies and Progressive Multifocal Leukoencephalopathy

Daniel L. Keene, Carole Legare, Elaine Taylor, Jim Gallivan,
Gloria Mah Cawthorn, Duc Vu

ABSTRACT: Monoclonal antibodies have become an important treatment option for a number of serious conditions. Concerns have arisen about the potential association of these products with progressive multifocal leukoencephalopathy (PML). A list of monoclonal antibodies authorized for sale was derived from the Health Canada Drug Product Database. Case reports of PML after exposure to a monoclonal antibody authorized for use in Canada were retrieved by searching Canada Vigilance and WHO adverse event databases and through a Pub MED/Medline literature search. 182 adverse event case reports were retrieved (adalimumab -1 case, alemtuzumab-14, bevacizumab -3, cetuximab -1, efalizumab - 8, ibritumomab tiuxetan-5, infliximab-4, natalizumab-32, and rituximab-114). The Canadian Product Monographs for natalizumab and rituximab contain box warnings for PML. A natalizumab registry has been established.

RÉSUMÉ: Anticorps monoclonaux et leucoencéphalopathie multifocale progressive. Les anticorps monoclonaux font maintenant partie de l'arsenal thérapeutique de certaines maladies graves. Des inquiétudes ont été soulevées concernant une association potentielle de ces produits avec la leucoencéphalopathie multifocale progressive (LEMP). Nous avons compilé une liste des anticorps monoclonaux dont la vente est autorisée, selon la base de données des produits pharmaceutiques de Santé Canada. Des observations de LEMP après exposition à un anticorps monoclonal dont l'utilisation est autorisée au Canada ont été identifiées par une recherche des incidents thérapeutiques signalés dans la base de données de Vigilance Canada et de l'OMS et une recherche de littérature dans PubMed/Medline. Nous avons retrouvé 182 rapports d'incidents thérapeutiques (adalimumab - 1 cas, alemtuzumab - 14 cas, bevacizumab - 3 cas, cetuximab - 1 cas, efalizumab - 8 cas, ibritumomab tiuxetan - 5 cas, infliximab - 4 cas, natalizumab - 32 cas et rituximab - 114 cas). La monographie canadienne du natalizumab et du rituximab contiennent un encadré noir concernant la LEMP. Un registre a été établi pour le natalizumab.

Can. J. Neurol. Sci. 2011; 38: 565-571

The aim of a pharmacovigilance system is to detect, assess, understand and prevent adverse effects, or other possible problems related to administration of a drug throughout its life cycle¹⁻³. The possibility for an adverse event to occur remains throughout the life time of a drug. It can occur both in the period prior to market authorization, the pre-market phase, or after market authorization, the post market phase.

In the pre-market phase, safety data needed for pharmacovigilance is usually obtained from randomized controlled clinical trials which are designed to determine the efficacy of the agent. These trials often involve a limited number of subjects meeting specific pre-defined study entry criteria, with defined period of follow-up. The safety data obtained is usually limited to dose related safety issues, issues of tolerability, and adverse events that occur early after onset of administration. By design, these studies are limited in their ability to detect rare adverse events or adverse events that may occur in populations not studied (for example: the elderly, children, pregnant/ lactating females)². In contrast, in the post market phase, the length of time a person is exposed to the product can often be significantly

longer, and the number of persons exposed to the product is greatly increased. As well, its use is often extended to population groups that were not included in the pre-clinical trials. Safety data can come from post market clinical trials, but more commonly it comes from spontaneous reporting of an adverse event to a pharmaceutical company and/or from national regulatory bodies, published case reports, national registries and published observation case cohort studies^{2,4}.

The risk of developing progressive multifocal leukoencephalopathy after exposure to certain monoclonal antibodies is an example of why pharmacovigilance is needed throughout the life cycle of a product.

From the Marketed Biologicals, Biotechnology and Natural Health Products Bureau, Ottawa, Ontario, Canada.

RECEIVED NOVEMBER 22, 2010. FINAL REVISIONS SUBMITTED FEBRUARY 22, 2011.
Correspondence to: Daniel L Keene, Marketed Biologicals, Biotechnology and Natural Health Products Bureau, 200 Tunney's Pasture Driveway, Ottawa, Ontario, K1A 0K9, Canada.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder of the human brain caused by lytic infection of oligodendrocytes by the human polyomavirus, JC virus. The clinical diagnosis of PML is based on a constellation of clinical symptoms and signs, neuro-imaging findings and neuropathological findings. Clinically, the disorder presents with motor symptoms (i.e. hemiparesis, ataxia), visual field deficits and/or symptoms of cognitive impairment. In the vast majority of the cases, the disorder progresses to cortical blindness, quadriplegia, dementia, coma and death. Though the rate of progression is often rapid, it can be variable. There have been the occasional case reports in which the patient has survived, but not without significant neurological impairment⁵. Computerized tomography (CT) imaging of the brain demonstrates patchy or confluent areas of hypodense, non-enhancing lesions of the cerebral white matter without mass effect. Magnetic resonance imaging demonstrates bilateral, asymmetric lesions, usually in the subcortical white matter and often involving the U fibers, which are hypointense on T1-weighted images, and hyperintense on T2-weighted and fluid-attenuated inversion recovery images.

The lesions are usually non-enhancing, well demarcated and without evidence of the presence of oedema. Lesions have been reported to involve the posterior fossa, and the deep grey structures⁵.

A definite diagnosis of PML is established by the identification of the characteristic pathological changes of the disorder on histopathological examination of brain biopsy or autopsy specimens. These changes consist of multifocal demyelination, hyperchromatic and enlarged oligodendroglial nuclei, and enlarged, bizarre astrocytes with lobulated hyperchromatic nuclei^{5,6}. Demyelination begins microscopically and is asymmetric in space. As the areas of demyelination enlarge, foci coalesce. The areas are often periventricular, in keeping with a possible haematological spread of the virus. At the edges of areas of demyelination, the oligodendroglial cells are more prominent with larger nuclei and may contain inclusion bodies. Electron microscope examination of the intranuclear inclusions demonstrates a dense array of crystalline and filamentous JC virus particles. The astrocytes in the areas of demyelination are pleomorphic and bizarre. Though viral DNA can be detected in these bizarre astrocytes, late viral proteins are rarely found^{5,6}.

Though pathological diagnosis had been recommended in the past, the ability to detect the JC virus DNA in the cerebrospinal fluid of patients with the clinical symptoms/signs of the disorder using polymerase chain reaction (PCR) amplification has replaced the need for biopsy diagnosis in all cases. Brain biopsy is now considered only for cases in which the clinical picture and imaging findings on MRI are compatible with the diagnosis of progressive multifocal leukoencephalopathy, but PCR amplification for JC virus DNA in the cerebrospinal fluid is negative⁷.

It is difficult to accurately calculate the prevalence or incidence for progressive multifocal leukoencephalopathy. Prior to 1984, only 230 isolated cases involving patients with hematopathies, solid organ malignancies, inflammatory disorders, and organ transplant recipients had been reported with only five cases being associated with HIV infection⁸. Now, about 85% of the cases occur in persons with HIV (estimated incidence rate

being between 1.3 to 3.3 cases per person years at risk)⁸. More recently several case reports suggesting a possible relationship between the exposure to a monoclonal antibody and the development of progressive multifocal leukoencephalopathy have been reported⁹⁻¹².

JC Virus and Progressive Multifocal Leukoencephalopathy

The JC virus is a polyomavirus composed of a small, non-enveloped, icosahedral virion with a closed, circular, supercoiled double stranded DNA genome functionally divided into three regions—an early coding region, a late coding region and a regulatory (non-coding region). The early coding region encodes the T protein, which is required for the initiation of DNA replication. The late coding region contains the genes for the capsid proteins (VP1, VP2, VP3) and the non-structural agnoprotein. It also contains the epitopes for antibody induction and recognition¹³⁻¹⁷.

The JC virus is widespread in the human population. Seropositivity has been reported in 44-77% of the people in the United States and England and up to 85-92% in Brazil, Japan and Germany. The infection occurs in childhood with a 10% prevalence in persons between the ages of one and five years; whereas, 65% of the population are seropositive by the age of 17 years¹⁸.

Humans are the sole host for the JC virus¹⁹. The primary infection is typically subclinical or linked to a mild respiratory illness. The virus gains entry to the body through the respiratory tract. After initial mild or subclinical infection, the virus is disseminated by the tonsillar B lymphocytes to the kidneys, spleen and bone marrow²⁰. Viral persistence occurs in the kidneys and bone marrow¹³. As well, JC viral DNA has been isolated from brain tissue of persons dying from causes other than PML²¹⁻²⁴.

It has been postulated that PML is not the result of a primary brain infection or reactivation of the virus within the brain, but results from the entry into the brain of a mutated form of the virus after secondary peripheral reactivation. During reactivation, the virus mutates from the archetype JC virus (JC arch), which has a single copy of the promoter/enhancer; to the mutated form (JC MAD-1) found in patients with PML. This form has duplications and deletions in the codon in the promoter/enhancer region²⁰. In addition, polymorphisms have been reported in the late genomic region resulting in modifications to the outer loops of the major capsid protein (VP1 loops) – the region involved in cell receptor recognition²⁵. These changes allow for the virus to enter and replicate in the oligodendrocytes. In this model, during illness, reactivation and mutation of the latent virus occurs in the bone marrow. The virus then attaches to the mature B lymphocyte entering the circulation leading to viremia and urinary viral excretion. In the immune competent person, the virus is contained by the helper CD4+T cells and the cytolytic CD8+ cells²⁶. In the immune compromised person this does not occur enabling B lymphocytes to transport the virus across the blood brain barrier into the brain oligodendroglia and astrocytes where it replicates.

Monoclonal Antibodies

In October 1996, the first monoclonal antibody was authorized for market in Canada. Since then, twenty-one

Table 1: Monoclonal antibodies marketed in Canada with their authorized indication

Generic name (trade name)	Type of mono-clonal antibody	Action	Authorized indication for use in Canada ¹	Date marketed in Canada
Natalizumab (TYSABRI)	Humanized IgG1 κ	Anti-α4-integrin	Relapsing-remitting form of multiple sclerosis	2006.11.21
Rituximab (RITUXAN)	Chimeric IgG1 κ	Anti-CD20	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Rheumatoid arthritis	2000.03.30
Ibritumomab tiuxetan (ZEVALIN)	Murine IgG1 κ Radio-labelled(Y-90)	Anti-CD20	B cell non-Hodgkin lymphoma	2005.05.10
Tositumomab-I131 (BEXXAR)	Murine IgG2γ Radio-labelled (I131)	Anti-CD20	Relapsing or refractory low grade follicular non-Hodgkin's lymphoma	2006.04.10
Efalizumab (RAPTIVA)	Humanized IgG1 κ	Anti-CD11a	Chronic plaque psoriasis	2009.08.06 ²
Alemtuzumab (CAMPATH)	Humanized IgG1 κ	Anti-CD52	Progressive B cell chronic lymphocytic leukemia	2008.08.07
Daclizumab (ZENAPAX)	Chimeric IgG1 κ	Anti-CD25	Prevention of acute post transplant organ rejection	2000.03.02
Muromomab-CD3 (ORTHOCLONE OKT3)	Murine IgG2a	Anti-CD3	Prevention of acute post transplant organ rejection	2001.07.09*
Trastuzumab (HERCEPTIN)	Humanized IgG1 κ	Anti-HER2	Breast cancer with over-expression HER2	1999.08.23
Bevacizumab (AVASTIN)	Humanized IgG1 κ	Anti-VEGF	Metastatic colorectal cancer or breast cancer. Small cell lung cancer	2006.11.02
Ranibizumab (LUCENTIS)	Humanized IgG1 κ Fab	Anti-VEGF	Neovascular (wet) age-related macular degeneration	2007.07.26
Cetuximab (ERBITUX)	Chimeric IgG1 κ	Anti-EGF receptor	Colorectal cancer Squamous cell carcinoma of head and neck	2008.10.28
Panitumumab (VECTIVIX)	Human IgG2 κ	Anti-EGF receptor	Metastatic colorectal cancer	2008.05.27
Infliximab (REMICADE)	Chimeric IgG1	Anti-TNFα	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Chron's disease, ulcerative colitis, plaque psoriasis	2001.06.14
Adalimumab (HUMIRA)	Humanized IgG1 κ	Anti-TNFα	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis	2004.09.24
Abciximab (REOPRO)	Chimeric IgG1 κ Fab	Anti-GPIIb/IIIa	Prevention of cardiac ischemia during percutaneous coronary intervention	1996.10.30
Omalizumab (XOLAIR)	Humanized IgG1 κ	Anti-IgE	asthma	2005.02.03
Eculizumab (CETUXIMAB)	Humanized IgG2/4 κ	Anti-complement-5	Paroxysmal Nocturnal hemoglobinuria	2009.05.25
Golimumab (Simponi)	Humanized IgG1 κ	Anti-TNFα	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis	

¹The authorized indication for use in Canada as listed in Canadian Product Monograph <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>; ²Voluntarily removed from market in Canada

monoclonal antibodies have been authorized for therapeutic use in Canada (Table 1). Several, but not all, have been reported to be associated with a possible increased risk of developing PML. Except for natalizumab, the cases of PML had not been reported in the pre-market clinical trials, but rather occurred after the product had been marketed. The case reports were obtained through spontaneous reporting by health care professionals and/or consumers to regional national centres and/or to the pharmaceutical companies. In Canada, this information is submitted to Canada Vigilance, the national data base of adverse events operated by Health Canada. Internationally, the information is gathered together by the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring Adverse Event Data Bank, an international collaborative programme of all the participating national/regional adverse event reporting centres.

To obtain the cases of PML that had been reported after exposure to each of the monoclonal antibodies with market authorization in Canada, both the Canada Vigilance and the WHO Collaborating Centre for International Drug Monitoring Adverse Event Data Bank were searched using the following MedDRA (Medical Dictionary for Regulatory Authority Terminology) search terms: System Organ Classes (SOC) - infections and infestations; the High Level Group Term (HLGT) -viral infectious disorders; High Level Terms (HLT) - polyomavirus infections; and Preferred Term (PT) - progressive multifocal leukoencephalopathy. The time line for the search was January 01, 1965 to April 15, 2010.

No adverse event reports PML in association the therapeutic use of monoclonal antibodies in Canada were retrieved from the Canada Vigilance search.

Table 2: Monoclonal antibodies associated with case reports of progressive multifocal leukoencephalopathy

Generic name (trade name)	WHO	Canada Vigilance	Literature review
Natalizumab (TYSABRI)	32	0	28 ¹
Rituximab (RITUXAN)	114	0	58
Ibritumomab tiuxetan (ZEVALIN)	5	0	0
Bevacizumab (AVASTIN)	3	0	0
Efalizumab (RAPTIVA)	8	0	4
Alemtuzumab (CAMPATH)	14	0	3
Infliximab (REMICADE)	7 (4 duplicates)	0	2
Cetuximab (ERBITUX)	1	0	0
Adalimumab (HUMIRA)	1	0	0

The search of the WHO Collaborating Centre for International Drug Monitoring Adverse Event Data Bank, retrieved a total of 182 adverse case reports for the Preferred Term-progressive multifocal leukoencephalopathy associated with monoclonal antibody use (adalimumab -1, alemtuzumab-14, bevacizumab -3, cetuximab -1, efalizumab - 8, ibritumomab tiuxetan-5, infliximab-4, natalizumab-32, rituximab-114) (see Table 2). The median time, from starting the product to diagnosis of PML, was 48 months for efalizumab, 29 months for natalizumab, 18 months for rituximab, and 6.5 weeks for alemtuzumab (Table 3). The cases were confounded by indication and concomitant medications. As the information provided by the WHO Collaborating Centre for International Drug Monitoring Adverse Event Data Bank is limited to the source of the report, gender, list of medications taken at the time of the event, duration of therapy, and the suspected adverse reaction, detailed case descriptions were not available.

To investigate this possible association further, a search of the medical literature was done using PubMed/Medline. The following MeSH terms were used: JC virus, encephalitis, leukoencephalopathy, progressive multifocal leukoencephalopathy, and/or neurodegenerative disorder in combination with search term “monoclonal antibody” or individual generic / brand names for each of the monoclonal antibodies authorized for use in Canada. Ninety-five case reports were retrieved (natalizumab-28 cases^{9,10,27-36}, rituximab- 58 cases^{11,37-47}, alemtuzumab -3 cases^{12,48,49}, efalizumab- 4 cases^{50,51} and infliximab -2 cases⁵²).

Several reasons could account for the differences in the number of cases retrieved by each of the search methods. Searching data bases is biased by under reporting, notoriety and the length of time the drug has been marketed⁴. Though the number of cases retrieved from large database searches is usually greater than that obtained from a literature search, the

information is often insufficient to determine if a causal relationship is present. As well, under reporting is a significant concern. It has been reported that the spontaneous reporting of adverse events to national databases can miss up to 98% of the known cases⁴. In contrast, cases derived from a literature search do provide information needed to assess for causality. However, as previously stated, the number of cases retrieved is usually less. This reflects the preference of medical journal editors not to publish single or small case series reports related to known adverse reactions, and/or the lack of specificity or sensitivity of MeSH search terms.

The uncertainty about the completeness of case ascertainment, the rarity of the event, and the lack of exposure rates, results in inaccurate estimation of the true incidence of the adverse event. To obtain this information, well designed, mandatory registries or large comprehensive post-marketing observational studies are necessary, both of which are expensive and time consuming.

The latency time between exposure to the monoclonal antibody and the diagnosis of PML is longer than the product reported pharmacokinetic half-life profile (Table 3). The adverse event, therefore, cannot be explained by the product's pharmacokinetic properties (i.e. its blood concentration). It is more likely secondary to the pharmacodynamic (“down stream”) effects of the product (Table 3). The monoclonal antibodies in question interfere with B and/or T lymphocyte function, in particular CD4+ and CD 8+ lymphocytes. It is postulated that after reactivation of the JC (MAD-1) virus, the loss of the neurological immune surveillance provided by these lymphocytes puts the patient at risk of developing PML.

Risk Mitigation Strategies

As the safety profile of a drug can change over its life cycle, the review of case reports ascertained from searching adverse event databases can play an important role in risk mitigation. A series of well-documented case reports of a rare adverse event may be sufficient to question the benefit risk balance of the product and determine the need to develop strategies to minimize this risk. In other situations, data from pharmaco-epidemiological studies, for example registries, case cohort studies, or controlled post market clinical trials, might be necessary.

The risk mitigation strategy used needs to be responsive to the situation⁵³. When the risk of the adverse event is small or not serious, the strategy may only be the continued monitoring for the safety concern through routine analysis of further spontaneous case reports. As the risk increases, the risk mitigation strategy may include labelling changes to the product monograph, and/or the manufacturer might develop an education tool addressing ways to manage or avoid the event. The risk mitigation might require the addition of the need for informed consent, certification/ special training of practitioners using the product, and/or development of registries of patients on the product. In some circumstances, the access to the product is limited to certain practitioners and pharmacists under specific documented conditions. Rarely, is the risk such that withdrawal of market authorization is warranted.

The latter was the case for the therapeutic monoclonal antibody, efalizumab. Efalizumab was authorized for use in the

treatment of moderate to severe plaque psoriasis. Its action was directed against the CD11a antigen, thus, preventing T-lymphocyte activation, migration and reactivation. All the cases of PML reported in association with its use had received efalizumab as monotherapy for greater than three years. In 2009, the manufacturer announced a voluntary phased withdrawal of the product from the market⁵⁴.

The case was different for natalizumab. Natalizumab, a humanised IgG4 monoclonal antibody that binds to the α -subunit of the α -4 integrin, has been used, with good effect, in patients with relapsing multiple sclerosis. In 2005, during clinical trials, three cases of progressive multifocal leukoencephalopathy were reported^{31,32,37}. The total enrolment in studies was 3416 persons suggesting the overall occurrence rate of PML in this population to be 1 per 1000 treated persons (95%CI 0.2-2.8)³⁴. The sale of the product was suspended in the United States pending completion of a benefit risk analysis. As the product was beneficial in the treatment of the moderately severe relapsing form of multiple sclerosis, it was allowed to re-enter the market. When it was later authorized in Canada, the risk mitigation strategy put in place included enhanced labelling in the Canadian Product Monograph (i.e. drawing attention to the risk by placing it prominently within a box at the beginning of the monograph section titled Warnings and Precautions), the establishment of a central patient registry of treated persons, a patient and health care professional education program, a system of designated infusion centers, restricting prescription to certain qualified physicians, and the issuance of health care professional communications. As previously stated, rituximab has also been associated with the risk of developing progressive multifocal

leukoencephalopathy. This action of this monoclonal antibody is directed against the expression of anti-CD20 expressed by pre-B and B-cells, but not stem cells or plasma cells, resulting in depletion of B cells. It has been authorized for use in the treatment of non-Hodgkin's lymphoma, B-cell lymphoma, moderate to severe cases of rheumatoid arthritis which have inadequately responded to other disease modulation therapy and chronic lymphocytic leukemia. Since 2002, there have been over one hundred cases of PML described in association with its use.

The majority of the cases were reported with chronic lymphocytic leukemia and non-Hodgkin's lymphoma. For both these disorders, there is a baseline increased risk of developing PML without exposure to rituximab, particularly with exposure to purine analogue chemotherapy⁵⁵ and fludarabine⁵⁶. However, there have been six case reports of progressive multifocal leukoencephalopathy occurring in persons with rheumatoid arthritis. This is more frequent than expected. For this reason, a risk mitigation strategy was developed for rituximab that included enhanced product labelling for all indications (inclusion of a warning within a "box" in the Canadian Product Monograph), a "Dear Healthcare Professional" letter warning of the risk in patients with rheumatoid arthritis⁵⁷ and periodic review of safety data by the regulatory authority.

In Canada, alemtuzumab is authorized for use in the treatment of chronic lymphocytic leukemia, and non-Hodgkin's lymphoma. Its action is directed against the CD52 antigen, an antigen expressed on more than 95% of B and T-cells. As such, it depletes both B and T cells. After therapy, B-cells can, on average, take up to 27 +/- 15 months to return to baseline levels. The CD4 T-cells can be depleted for 61 months and CD8 cells

Table 3: Half-life⁵⁹ compared to median latency time to diagnosis of progressive multifocal leukoencephalopathy based on WHO data

Generic name (trade name)	Terminal half-life	Median latency from starting drug to diagnosis of PML	Mean age at time of diagnosis of PML	"down stream effects"
Efalizumab (RAPTIVA)	5.5-10.5 days	48 months	68 years	Inhibits T lymphocyte activation in node Inhibits T lymphocyte binding to endothelial cells
Natalizumab (TYSABRI)	10.5 days	29 months	43.5 years	Inhibits T lymphocyte transfer to brain ↓ C4, CD 8 in CSF (6months)
Rituximab (RITUXAN)	20.8 days	16 months	62.1 years	↓ B lymphocytes (3-12 months) ↓ C4, CD 8 (3years)
Alemtuzumab (CAMPATH)	12 days	1 month	58.2 years	↓ B lymphocytes (3-12 months) ↓ C4, CD 8 (3years)
Infliximab (REMICADE)	7.7 to 14.7 days	17 months	52 years	↓CD4+T cells, CD8+ T cells, macrophages, dendritic/natural killer cells (binding to membrane surface TNF α – cell death via CMC or ADC)
Adalimumab (HUMIRA)	10 to 20 days	7 months	71 years	↓CD4+T cells, CD8+ T cells, macrophages, dendritic/natural killer cells (binding to membrane surface TNF α – cell death via CMC or ADC)
Ibritumomab tuitexan (ZEVALIN)	1 day	36 months	61 years	↓ B lymphocytes (9 months)

for 30 months⁵⁸. As was the case with rituximab, this situation is confounded by its indication for use. Patients with chronic lymphocytic leukemia, not exposed alemtuzumab have an underlying increased risk of developing progressive multifocal leukoencephalopathy. This is reflected in the risk mitigation strategy adopted for alemtuzumab, which included the enhanced labelling of the risk in a “box warning” in the Canadian Product Monograph; however, a health care professional communication has not been issued.

CONCLUSIONS

Though there are inherent biases in the drug safety information obtained from literature reviews and from searching databases for spontaneously reported adverse events, the information found can be important in the assessment of rare adverse events. This method proved helpful in the identification of the association between the rare, adverse event -PML – and previous exposure to efalizumab, natalizumab, rituximab, alemtuzumab, and infliximab, but not for other monoclonal antibodies. It, also, became apparent that drug concentration at the time of the adverse event did not explain its occurrence. The therapeutic window had to be extended to look for possible “down stream effects” of the products. This information was useful in the development of the appropriate, risk mitigation strategy for each of the products at risk.

For pharmacovigilance to work well in Canada, it is imperative that all physicians continue to report all serious adverse events related to the use of a health product to Health Canada. (CanadaVigilance, phone 1-866-234-2345, fax 1-8660678-6789 or <http://hc-sc.gc.ca/dph-mps/medeff/index-eng.php>)

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