Strategy in Regulatory Decision-Making for Management of Progressive Multifocal Leukoencephalopathy

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Progressive multifocal leukoencephalopathy (PML) has been observed after the use of several medicines, including monoclonal antibodies. As these drugs play important roles in the therapeutic armamentarium, it is important to address the challenges that this severe adverse reaction poses to the safe use of medicines. Considering the need for consistent outcomes of regulatory decisions, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) used PML as an example to develop a systematic approach to labeling and risk minimization.

INTRODUCTION

PML and drug therapies

PML is a potentially fatal, demyelinating disease of the human brain caused by JC virus (JCV). It had previously been observed in severely immunosuppressed individuals with HIV infection, lymphoid malignancies, and after transplantation.[1] Diagnosis of drug-induced PML can be difficult and a need to harmonize case definitions has been expressed.[2] With the increasing clinical use of immunomodulatory biological therapies in the last decade, PML has emerged as an important serious adverse drug reaction, which may have an impact on benefit-risk balance that might lead to drug withdrawals. Where benefit-risk balance remains positive, in the context of the medicine's indication and efficacy, effective risk minimization is required. In addition, to ensure that healthcare professionals and patients are informed about the risks of medicinal products in a consistent way, guidance is needed on how to reflect PML in the product information based on the level of evidence, the level of risk, and opportunities for risk minimization. From the public health perspective, what is also important is the way marketing authorization holders address PML in their risk management plans (RMPs). RMPs are the central documents for planning of pharmacovigilance and risk minimization activities during the medicinal product life-cycle.

Learning from previous examples

An analysis of adverse drug reaction reports in the EudraVigilance database was performed, searching for all reports of suspected PML (including both spontaneous reports and reports from studies). A total of 1,363 reports of suspected PML (after screening for duplicates) were identified in the period up to 23 January 2013. Approximately half of the reports originated from the European Economic Area, 81% were spontaneous reports and 97% were reported by healthcare professionals. The majority of reports were received in association with antilymphocyte antibodies, cytostatics/antimetabolites, immunosuppressants, and HIV antivirals. Cases were reported most frequently in association with natalizumab and rituximab. A sharp increase in spontaneous reporting of PML was observed after 2007 (**Figure 1**). This increase can be attributed to increasing exposure and increased awareness of reporters, including retrospective reporting of previously occurring cases.[2]

All centrally authorized medicinal products with at least three reports of PML (n = 52) were included in an analysis to map the level of evidence in the database vs. the information included in the European Summary of Product Characteristics (SmPC) and in the European Union RMP. Information on approximate cumulative patient exposure per drug was obtained from the most recent Periodic Safety Update Report. This, together with further available evidence, formed the basis for development of decision-making diagrams on how to reflect future decisions after evaluation of new PML reports in regulatory documents.

Level of evidence

We used a two-step approach to classify the level of evidence of PML associated with different medicinal products. First, the level

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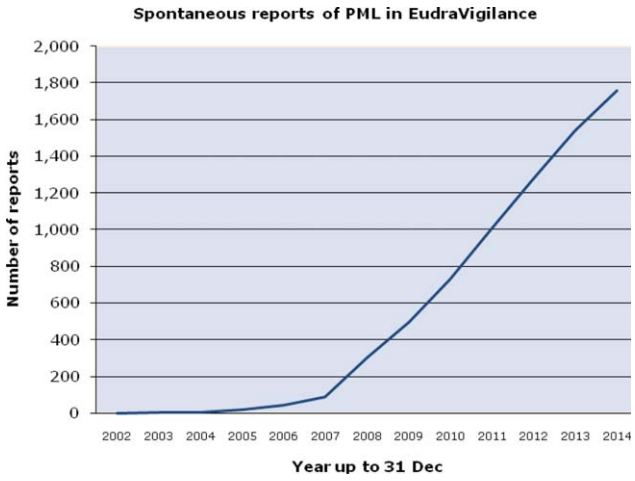

Figure 1 Cumulative number of spontaneous progressive multifocal leukoencephalopathy (PML) reports in EudraVigilance.

of diagnostic certainty of the individual PML reports submitted to EudraVigilance was assessed according to the PML case definition available at the time, as published by Mentzer *et al.*[3] This algorithm is based on clinical symptoms, polymerase chain reaction for JC virus DNA in cerebrospinal fluid, brain magnetic resonance imaging, and brain biopsy/autopsy. For the purpose of our analysis, a reported case was classified as PML suspicion "high" (diagnostic certainty 1), "intermediate" (diagnostic certainty 2), or "low" (diagnostic certainty 3), depending on the available diagnostic information. When insufficient information was available, a report was classified as level 4, if PML was excluded as a diagnosis, the report was classified as level 5. All cases of suspected PML were reviewed and categorized by one author (B.K.S.), and, in the absence of a second independent assessment, 5% of the assessed cases were selected at random and reviewed independently by a second author (C.M.).

Second, the integrated information of the assessed cases was used to derive the level of evidence on product level. HIV products were excluded for this analysis, as PML is most likely a consequence of the underlying disease. A second algorithm was applied to the remaining 35 products. The product level of evidence was categorized as at least moderate when there were more than three PML cases (diagnostic certainty level 1–3), and concomitant medication was not more likely to have caused PML based on an expert opinion (i.e., concomitant medication may also be associated with PML to an equal or lesser degree than the drug of interest). When, in addition, there was more than one PML case report (with diagnostic certainty level 1) without concomitant medication and/or underlying disease known to be associated with PML, product level of evidence was categorized as strong. If none of the above applied, the level of evidence was categorized as weak.

European SmPC and European Union RMP

The SmPC contains a standardized presentation of medicinal product information and is an integral part of the approval of new drugs in Europe.[4] Throughout the lifecycle of the medicinal product, the SmPC is updated as new information on benefits and risks becomes available over time. For each product, both the baseline SmPC (i.e., the adopted version at the time of approval), as well as the most recent version (data lock point: 1 March 2013) was retrieved from the European Medicines Agency website of European public assessment reports (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125).

We reviewed and documented whether information on PML was included. For the section on warnings and precautions for use (section 4.4), we assessed the availability of any information regarding the risk of PML, and extracted any provided wording. For the section on undesirable effects (section 4.8, Tabulated list of adverse reactions), we assessed whether PML was labeled as an adverse drug reaction and extracted any additional information pertaining to the PML risk. Information on the estimated frequency of PML was extracted according to the standardized terms: very common ($\geq$1/10); common ($\geq$1/100 to $<$1/10); uncommon ($\geq$1/1,000 to $<$1/100); rare ($\geq$1/10,000 to $<$1/1,000); very rare ($<$1/10,000); and not known. An obvious limitation of this classification is that it ignores a possible effect of time (i.e., length of treatment).

The RMP is a detailed description of the risk management system that includes a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions.[5] Risk management is applicable to medicinal products at any point in their lifecycle and RMPs can be continuously updated. For each product, the most recent version of the RMP (data lock point 1 March 2013) was retrieved from the European Medicines Agency.

We reviewed and documented whether PML was listed as a safety concern in the RMP and, if so, whether it was categorized as important identified risk, important potential risk, or as missing information. Pharmacovigilance activities for PML (routine pharmacovigilance or additional pharmacovigilance) were recorded and type of additional pharmacovigilance activities were characterized (i.e., active surveillance, observational study, clinical trial, drug utilization study, other, or multiple categories) when reported.

Listed risk minimization measures for PML were recorded (routine, additional, or both) as well. Finally, the type of routine risk minimization measures (i.e., SmPC, pack size, legal status, other, or multiple) and the type of additional risk minimization measures (i.e., educational program, patient alert card, controlled access, other, or multiple) was recorded, as appropriate.

Our analysis found that, among the 52 centrally authorized medicinal products with at least three reports of PML, three products had been withdrawn. The SmPC of nine products included information on PML (including six where this was added during the postauthorization phase) and 40 products had no mention of PML in their SmPC. Regarding RMPs, PML was included as an identified risk of three products and as a potential risk of seven products; further, 10 products had broader identified or potential risks of infections; 19 products did not include PML in their RMP and there was no RMP for 10 products. The

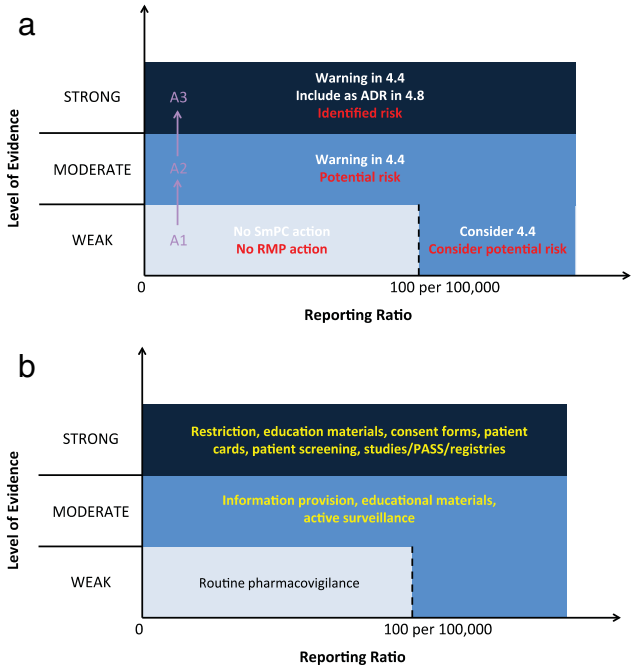

Figure 2 (**a**) Decision grid for SmPC (white) and RMP classification (red) of PML. (**b**) Decision grid for consideration of risk minimization activities for PML. Legend: 4.4 – SmPC section 4.4 on Special warnings and precautions for use; 4.8 – SmPC section 4.8 on Undesirable effects; ADR – adverse drug reaction. A1, A2, A3 – steps 1 to 3 of applying the strategy to a hypothetical product A (see **Table 1** for detailed steps).

10 products with PML included in the RMP had a mix of routine and additional pharmacovigilance and risk minimization activities. While the numbers were too low for statistical analyses, they formed an empirical basis for the labeling strategy.

Labeling PML after adverse drug reactions

To facilitate discussions and increase consistency of labeling decisions across medicinal products for PML, assuming that benefit-risk remains positive, we developed a decision diagram, illustrated in **Figures 2a and 2b**, and summarized in **Table 1**.

When new information on the risk of PML is reviewed for any reason (e.g., new case reports generating a safety signal), the totality of evidence available at the time should be assessed taking into account the drug's therapeutic benefits. Each known case of PML is analyzed according to an agreed case description.[3]

The number of PML cases is first put in the context of total patient exposure. Exposure data are often provided by the company but can also be extracted from other available sources (scientific publication, recent regulatory report, etc.). Products are located on the X-axis of the diagram according to the latest data on numbers of PML reports per 100,000 patients exposed to the drug (step 1). The time that the medicinal product has been on the market is a crucial element that should be taken into account together with the exposure. As a guide, we have chosen a mark for reporting ratio of 100/100,000 patients. This value will be reviewed as we gain experience and the number of patients exposed to these drugs over time evolves.

The location of the product on the Y-axis is decided after discussion at the Pharmacovigilance Risk Assessment Committee. Both the strength of evidence of individual cases and their number are key to the labeling decision and follow the two-step approach described in the section "Level of evidence" (step 2). Again, there are limits at the extremes: a single strong and unconfounded case can reach a maximum of moderate strength of evidence at product level; a cluster of confounded cases is considered weak overall evidence.

Any other relevant element that may have an impact on the evidence level of the product is considered next, including biological plausibility, class effects, related publications, etc. Final adjustments to the location in the diagram are implemented after the discussion of the impact and relevance of these additional pieces of information (step 3).

The suggested labeling practices for SmPC and RMP (**Figure 2a**, step 4) and for additional risk minimization activities (**Figure 2b**, step 5) are then followed. The committee then agrees on the period of time and/or trigger after which a review is needed.

The strategy presented here was discussed at the Pharmacovigilance Risk Assessment Committee in the summer of 2014. The committee agreed on the initiation of a pilot to test its validity and usefulness as a decision-making tool. It has been applied to a few cases originated by PML signals reviewed during late 2014 and the first half of 2015. As these procedures are still ongoing in the wider European Union regulatory environment, no details are included in the current publication. Pharmacovigilance Risk Assessment Committee meeting minutes can be accessed for publicly available details of ongoing procedures (http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf).

CONCLUSIONS AND FUTURE DIRECTIONS

PML cases associated with immunomodulating therapies will require ongoing assessment of the benefit-risk balance of these

Table 1 Summary of steps for applying the strategy to a hypothetical product A

Step 1	Locate reporting ratio on x-axis of **Figure 2a**. Example: position A1 in **Figure 2a** (assumed reporting ratio of 10 per 100,000).
Step 2	Locate level of evidence from reports of PML on y-axis of **Figure 2a**. Example: A2 in **Figure 2a** (1 well documented report = moderate evidence).
Step 3	Adjust position on y-axis after considering additional evidence (**Figure 2a**). Example: A3 in **Figure 2a** (extra cases with a possible association identified).
Step 4	The actions corresponding to the strong level of evidence in **Figure 2a** apply to the product. Example: SmPC update of 4.4 and 4.8 and inclusion in the RMP as an important identified risk.
Step 5	The risk minimization activities to be considered are included in the corresponding part of **Figure 2b**.

PML, progressive multifocal leukoencephalopathy; RMP, risk management plan; SmPC, Summary of Product Characteristics.

medicines to ensure that these important therapeutic agents are used to their best potential. Regulators will be faced with decisions regarding labeling and risk minimization activities across therapeutic indications and drug classes. Approaches and tools developed to facilitate regulatory decision-making and to increase consistency can be beneficial.

The strategy presented here is the starting point for a rational approach to methodically consider available evidence and to use it to better inform regulatory decisions. It should also result in an increased coordination of product labeling and risk management activities across Europe. This approach could potentially be extrapolated to other adverse drug reactions and other therapeutic areas.

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AUTHOR CONTRIBUTIONS

A.S., B.K.S., N.S.V., C.M., S.M.S., A.H.S., and M.L.D.B. designed the research. A.S., B.K.S, N.S.V., and C.M. performed the research, and A.S. analyzed the data. A.S., B.K.S., N.S.V., C.M., S.M.S., A.H.S., and M.L.D.B. interpreted the results and wrote the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest that are directly relevant to the content of this research.

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