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Transatlantic workshop on Drug-related Progressive Multifocal Leukoencephalopathy (PML): Workshop Proceedings

25-26 July 2011: European Medicines Agency, 7 Westferry Circus, Canary Wharf, London, UK

Executive summary

PML is a severe demyelinating disease of the central nervous system (CNS) caused by the JC virus (JCV). It is seen in many conditions that affect immune system function such as HIV-1/AIDS, certain cancers and organ transplant subject to immune suppressive therapies. Over the last 5 to 10 years, it has been increasingly reported as a serious adverse event of therapeutic monoclonal antibodies (MAbs) that modulate the immune system.

MAbs play a crucial role in the treatment of diseases in different therapeutic areas such as oncology, haematology, neurology and rheumatology and for some diseases, represent the most effective or sometimes the only effective treatment option.

To address the challenges of the benefit of such therapies with the risk of developing PML, the European Medicines Agency (EMA) hosted a two-day workshop on drug-related progressive multifocal leukoencephalopathy (PML), co-chaired by the US Food and Drug Administration (FDA). The workshop took place on 25th and 26th July 2011, and brought together European and US stakeholders, including patients, healthcare professionals, academia, industry and regulators.

The workshop's objectives were: map ongoing research, identify research gaps, find a common understanding of research priorities, foster funding and research partnerships and discuss the best mechanisms to ensure efficient information sharing. Each of the eight sessions focused on those topics, covering a wide range of relevant areas, including an overview of PML as a serious adverse event related to therapies with monoclonal antibodies, the role of regulators in a collaborative approach, the treatment of drug-induced PML, ongoing research and research agendas in PML, how to build collaboration and to fund PML research, and how to stay informed of progress in this topic for the benefit of public health. Perspectives on a PML research agenda were provided by patients, regulators, funders, academia, clinicians and industry.

For more information regarding the workshop, its participants, organization and meeting agenda, please see the Appendix I of these minutes.

The figure below shows a summary of the scientific concepts discussed at the workshop.



WHAT WE KNOW

THE DISEASE

- PML is a demyelinating disease, localised in the brain
- It is rare
- It is severe and can be lethal
- It is most frequently encountered in immunosuppression, and it is a complication seen in HIV and transplantation patients
- Sometimes, PML is diminished if the trigger can be eliminated
- PML can be induced by certain drugs, sometimes in combination with other risk factors

THE VIRUS

- PML is caused by a human polyomavirus, the JC virus (JCV)
- JCV infects only humans; no animal models exist
- JCV is common, present in around 50% of population
- It has one serotype but several different genotypes are known
- It grows very slowly in vitro
- It can replicate in the urinary tract asymptotically

THE PATIENT WITH PML

- Most patients report cognitive impairment, behavioural disturbances or personality changes. Hemi-paresis and focal paresis, dysarthria and aphasia are also frequently reported
- PML is usually less severe if the patient is young, when diagnosis and intervention take place early or it affects only one lobe of the brain
- Patients with immunosuppression or with a malfunction of the immune system are at higher risk to develop PML
- For drug-related PML, the risk increases with the duration of treatment, at least in the first few years
- The risk of drug-induced PML limits the use of some effective therapies

IRIS (*Immune reconstitution inflammatory syndrome*) is a life-threatening complication related to immune reconstitution that often occurs when an immunosuppressive medicine is stopped to address PML:

- IRIS is usually actively managed; the current treatment is high dose corticosteroids. It should be anticipated, by monitoring brain swelling using MRI starting a few weeks after withdrawal of immunosuppressive therapy.

THE FUTURE

- Benefit and risk should be presented together to inform decision making;
- PML challenges require collaboration on a global scale;
- Input from different disciplines/fields will benefit research progress;
- Sharing of information, best practice and resources between all stakeholders will produce results faster.

INITIATIVES THAT MAY CONTRIBUTE

- PML Consortium
 - IMI
 - ENCePP
- EU Seventh Framework Programme
 - Sentinel Initiative
 - Academic networks
 - Registries
 - NIH

WHAT WE DON'T KNOW

THE DISEASE:

- It is unclear how to best ascertain the number of drug-induced PML cases
- No universally accepted case definition exists
- No specific prophylaxis or treatment exists
- There is no animal model and no plaque assay
- We haven't predictive markers for PML
- There are limited data regarding the risk of drug-induced PML beyond 3 years of MAbs treatment
- The long-term impact of IRIS therapies is unclear

THE PATIENT:

- How best to communicate the benefit/risk of drugs causing PML?
- Which patients should not be treated with a PML-inducing drug?
- Which biomarkers should be monitored for drug-induced PML?
- How often should MRIs and CSF assessments be conducted?
- What is the value of a drug holiday? Should some drugs be stopped after 12 months, 18 months, two years?
- How can PML be distinguished from MS relapse?
- Which are the best type of information and communication tools to healthcare professionals and patients?

THERAPY WISH LIST:

- Early detection of PML
- Effective treatment for JCV
- Remyelination treatment
- Prediction of the risk of developing PML
- Prediction of the severity/ reversibility of PML
- Personalized treatment according to risk factors following assessment of the benefit/risk relationship in each patient

Transatlantic workshop: Drug-related Progressive Multifocal Leukoencephalopathy (PML)

The objectives of the workshop were to:

- Find a common understanding of the priorities for research in the area of drug-induced PML;
- Map ongoing research and identify gaps;
- Foster funding and partnerships to conduct research, in order to fill knowledge and research gaps;
- Build a mechanism to ensure the sharing of information and regular stocktaking on research results.

Proceedings

25th July 2011

Opening

Welcome to the participants

Presenters: Dr Hans-Georg Eichler (EMA) and Dr Gerald Dal Pan (FDA)

Dr Hans-Georg Eichler, Senior Medical Officer at the EMA, and Dr Gerald Dal Pan, Director of the FDA's Office of Surveillance and Epidemiology, welcomed the workshop participants and stressed the unique and pioneering nature of the gathering, bringing together patients, health care professionals, academia, industry and regulators.

PML is usually a fatal condition, and its prevention or treatment would bring about significant benefits to patients. PML is a classic complication of HIV and an AIDS-defining illness. Drug-induced PML limits the therapy of multiple sclerosis and raises the question how natalizumab and other PML inducing drugs can be used safely and effectively. To this end, risk management programs can help.

The aim of this workshop is to learn more about the disease. As a result, clinicians can be enabled to predict which patients are at higher risk of developing PML. In addition, clinical decision-making and risk management should be informed by the most up-to-date information. The know-how gained from drug-induced PML could also be applied to the management of other adverse drug reactions.

PML - Balancing risks and benefits - the patients' view

Presenter: Christoph Thalheim (European Multiple Sclerosis Platform)

Christoph Thalheim of the European Multiple Sclerosis Platform (EMSP) discussed the issue of drug-induced PML from a patient's perspective, explaining how MS patients perceive the risk of PML in relation to the benefits they derive from MS therapy.

The EMSP is an umbrella society of 38 national MS societies in 34 European countries representing more than half a million people with MS. Founded in 1989 to complement the work of its national member organisations on a European level, the organisation believes that it is important for patients and caregivers to play a role in healthcare debates because of the knowledge and expertise they bring through their personal and collective experience. Safety concerns of medical experts and regulators, for instance, are not necessarily identical to those of patients. MS patients accept a much higher risk

than medical experts assume they do when treatment benefit is probable and they are adequately informed of the likelihood of the risks, including worst-case scenarios.

Mr Thalheim explained that despite the 145 PML cases on natalizumab as at June 5, 2011, the majority of MS patients are still willing to accept the PML risk in exchange for the benefits of treatment. Many MS patients want treatment with monoclonal antibodies for aggressive relapsing-remitting MS even if the safety profiles of these new agents are uncertain and stringent risk management plans are required. Risk acceptability increases with disease severity, and MS patients, who are often severely debilitated, want to add 'life to their years, not necessarily years to their life'. Caregivers of MS patients with PML have a particular strong need for information on the latest research. They want to feel included and ask for support for internet-based networking.

Mr Thalheim also reported that patients are changing from people accepting therapeutic decisions made for them by others into people who are well informed, engaged and who want to be in control of their own situation. MS patients want to be regarded as equal partners in clinical decision-making. Objectivity and full transparency by the treating physician are basic requirements for this.

Session 1: Overview of PML as an adverse event of monoclonal antibodies (MAbs)

This session aimed to characterise the cases of drug-induced PML to date, describing the mechanisms of disease development, the drugs implicated and the established risk factors.

The possible mechanisms of the disease

Presenter: Dr Eugene Major (NIH)

Dr Eugene Major, Senior Investigator at the National Institutes of Health, US, gave an overview of the pathology of PML.

PML is a virus induced demyelinating disease, which differs markedly from non-viral demyelinating diseases like MS. Its prevalence classifies PML as a rare disease (fewer than 200,000 cases in the US). There is no known animal viral reservoir. PML is caused by a lytic infection of oligodendrocytes in the cerebral hemispheres and the cerebellum, without evidence for involvement of the spinal cord or the optic nerve. The disease is caused by the human polyomavirus JC virus (JCV), a common and widespread infection in humans. JCV is estimated to be present in 50-60 % of the adult population, usually in the kidney and the immune system. PML, which is a multifocal, acute and persistent condition, almost always occurs in individuals with immune system dysfunction (suppression/modulation). There are no effective therapies other than 'intact' immune clearance.

PML is an opportunistic infection. About 1 in 100 patients with HIV (it is an AIDS-defining illness), 1 in 1000 patients treated with natalizumab (and efalizumab) after at least 24 doses, and 1 to 5 in 100,000 patients treated with rituximab experience PML.

Outcomes in patients with drug-induced PML

Presenter: Prof Joseph Berger (Kentucky University)

Prof Joseph Berger of the University of Kentucky, USA, gave an overview of the outcomes in patients who developed drug-induced PML.

Prof Berger said that natalizumab and efalizumab cause PML independent of other risk factors, while rituximab and mycophenolate mofetil require an underlying disorder predisposing to PML. Natalizumab-induced PML causes death in 20% of cases and severe disability in 37%. Outcomes seem to be better

if PML is diagnosed early, if patients are young and less disabled before the occurrence of PML and if the PML is unilobar rather than multilobar. Outcomes appear to be independent of natalizumab treatment duration, viral load and plasma exchange (PLEX) treatment. Three cases of PML have been reported in patients treated with efalizumab. Rituximab-induced PML is fatal in 90% of the cases, with a median time to death of two months.

Prof Berger explained that the outcome of PML is, in large measure, predicted by the nature of the underlying immunological defect, i.e. whether it is reversible or irreversible. For PML due to reversible immunosuppression, i.e. by monoclonal antibodies, early detection of PML and immediate removal of the offending agent significantly improves results. The future calls for the development of an effective anti-JCV treatment and, if possible, remyelination therapy.

Natalizumab (Tysabri) and PML - the current figures, risks and particularities

Presenter: Dr Brigitte Keller-Stanislawski (PEI)

Dr Brigitte Keller-Stanislawski, who heads the Safety of Medicinal Products and Medical Devices unit at the Paul-Ehrlich-Institut (PEI), Germany, provided a description of the PML findings in patients treated with natalizumab in the US and EU.

Natalizumab is a recombinant humanized antibody directed against the $\alpha 4$ integrins, both $\alpha 4\beta 1$ and $\alpha 4\beta 7$, which are located on the surface of all leucocytes except neutrophils. $\alpha 4$ -integrins play an important role in leukocyte trafficking into tissue. Natalizumab blocks the transmigration of leukocytes into the inflammatory tissue. The drug was approved by the FDA for the treatment of relapsing forms of MS in November 2004. Because of the occurrence of PML, the use of natalizumab was suspended on February 28, 2005. After evaluation of the cases, the drug was re-introduced in February 2006 in the US and authorised in the EU the same year. Of the three reported PML cases, two occurred in MS patients and one in a Crohn's disease patient who was participating in a clinical trial.

The manufacturer of Tysabri offers an ELISA test which can identify anti-JCV-antibodies. In infected individuals, JCV can persist and replicate asymptotically in the urinary tract and possibly also in other organs. In severely immunosuppressed patients such as those who are HIV positive, the virus may cause a lytic infection of oligodendrocytes, leading to PML.

It is important to note that the natalizumab indication for MS in the US is different from the indication granted in the EU – there is a broader indication in the US – and this may explain some of the differences found in the EU and US.

As at July 2011, the MAH had confirmed 144 cases of PML, while confirmation for several suspected cases was still pending. The majority of cases occurred in the EEA, despite the fact that slightly more patients have been treated in the US than in the EEA. One PML case was reported in a Crohn's disease patient (Tysabri is authorised for the treatment of Crohn's Disease in the US but not in the EU). The age of patients ranges between 15 and 71 years, with a mean of 44.7 years. Of note, one female teenager developed PML in off-label use.

The mean treatment duration to onset of symptoms is 30.8 months and increasing, with the majority of cases from 21 months onwards. This may indicate that the PML incidence is still rising with the duration of treatment, as more patients are now exposed to natalizumab for longer periods. While there is a decline in incidence after 34 months of treatment, this may be due to the fact that only 25% of patients are treated for more than 3 years.

The estimated incidence of PML in the EU is apparently higher than that in the US. In the EU, the risk for PML is significantly higher in patients treated for 24 months and longer, while in the US this occurs even later. There are limited data about the risk of PML beyond three years.

The spectrum of first symptoms is broad and not pathognomonic, with many patients experiencing several symptoms. The majority of patients reported cognitive impairment, behavioural disturbances or personality changes. These symptoms may be very mild and difficult to detect. Hemiparesis and focal paresis have been reported quite frequently, too, as well as dysarthria and aphasia.

The outcomes of the PML cases so far are: 19% fatal, 3% recovered, 2% improving, 12% with sequelae, 25% not recovered and 39% unknown. A few patients were asymptomatic and only diagnosed upon routine NMR imaging. Survival is greatly enhanced by early diagnosis of PML. The existing risk management measures are still insufficient.

Dr Keller-Stanislawski also discussed immune reconstitution inflammatory syndrome (IRIS), a life-threatening complication related to immune reconstitution to address PML, characterised by an exacerbation of clinical MS symptoms and enlargement of lesions in the MRI after stopping treatment with natalizumab. The time interval may be shorter after PLEX or immunoadsorption.

The relationship between PML-Rituximab and other immunobiologicals - an overview

Presenter: Prof Renaud Du Pasquier (University of Lausanne)

Prof Renaud Du Pasquier of the University of Lausanne, Switzerland, discussed the risk of PML with rituximab and other MAbs in rheumatoid arthritis (RA) patients.

PML is a very rare complication of RA. No PML was reported in more than 72,000 RA patients in a study published in 2010 by Amend et al. in *Neurology*. There were 0.4 cases per 1,000,000 RA patients in an investigation published in 2009 by Calabrese and Molloy in *Arthritis Rheumatology*.

Five cases of PML have been reported in 129,000 RA patients exposed to rituximab, including one patient with minimal immunosuppression, resulting in a rate of one PML case for every 25,000 rituximab-exposed patients. Rituximab most probably confers an added risk of PML when administered to patients with PML-favouring diseases and/or with concomitant immunosuppressants. However, so far, there is little evidence that rituximab alone increases the risk of PML in RA patients significantly.

Efalizumab (withdrawn in 2009) had a high risk of PML. For alemtuzumab and anti-TNF-alpha agents, there is little evidence that they trigger PML.

The risk in transplanted patients

Presenter: Dr Marco Tuccori (University Hospital of Pisa)

Dr Marco Tuccori of the University Hospital of Pisa, Italy, gave a presentation on the risk of PML in patients undergoing transplantations, based on a search of cases from the scientific literature.

Dr Tuccori noted that PML has been reported both in hematopoietic stem cell transplantation (HSCT) and solid organ transplantations with different immunosuppressants but that the attribution and quantification of specific causative roles to single drugs remain a challenge. In patients receiving HSCT, the onset of PML following transplantation is earlier than in solid transplantation recipients and this is probably due to a high degree of immunosuppression caused by exposure to prior chemotherapy in the HSCT patients.

It appears that the risk of PML is increased in HSCT patients with reduced intensity conditioning by non-myeloablative regimens, developed to reduce the risk of adverse reactions to immunosuppressive drugs.

Treatment of PML by discontinuation of immunosuppressive therapy (probably the best available therapeutic approach) causes graft-versus-host disease and transplant rejection, although the extent of this risk remains undetermined.

Session 2: The regulatory role - a collaborative approach

This session aimed to discuss the role of regulatory bodies in dealing with drug-related PML (specifically the recent cases with MABs), the measures adopted by them, the need for a collaborative approach and the evidence to drive risk minimization

Activities in the US: The experience of FDA Neurology Division

Presenter: Dr Russel Katz (FDA)

Dr Russel Katz of FDA's Center for Drug Evaluation and Research presented the FDA experience with natalizumab (Tysabri)-induced PML.

Cases of natalizumab-induced PML were rapidly identified after initial marketing in 2004. The Tysabri Outreach Unified Commitment to Health (TOUCH) program was put in place to apply safeguards and minimize PML risk to the extent possible. Key elements are a registry of all patients, prescribers and infusion centres, as well as a patient checklist. A positive answer to any question on this checklist requires a call by the infusion centre to the prescriber to obtain specific permission for infusion. One of the goals of TOUCH is to diagnose PML and to stop Tysabri treatment earlier in case of PML. According to Dr Katz, the effectiveness of TOUCH is still unclear.

TOUCH enables real time incidence data of PML cases, which results in real time labelling changes and communications to the public via Drug Safety Communications.

Risk communication in EU

Presenter: Dr Rafe Suvarna (MHRA)

Dr Rafe Suvarna of the UK's Medicines and Healthcare products Regulatory Agency discussed the issue of communication with regard to the risk of PML.

Dr Suvarna, who is also a UK representative at the EMA's Committee for Medicinal Products for Human Use (CHMP), stressed that risk communication should always be benefit-risk communication. The communication needs to be targeted according to audience and purpose and should receive input from patient groups and professionals. He stated that valuable communication tools were in place, particularly for Tysabri (physician information leaflet, patient alert card, treatment initiation and continuation forms and a website) but that there were still some gaps in information and knowledge (outcomes, benefit-risk balance, risk uncertainties), and further work is needed on risk stratification.

As regards tools for communication, websites are considered helpful if the information is up to date, robust and provided in a useful and meaningful way. The regulatory Product Information (SmPC, labelling, package leaflet) for drugs other than natalizumab is generally limited. Dr Suvarna said that there is a need to think about testing the utility and success of all PML risk communication materials required by regulators in the EU, in particular by surveying the acceptability of the communications, and potentially by tracking PML outcomes and changes in the rates of PML infection. Changes to EU legislation regarding the Product Information, the Innovative Medicines Initiative (IMI) project, and

benefit-risk-assessment initiatives could support the use of graphical tools for risk communication and of new media and technologies to transmit the key messages, e.g. applications for smartphones.

Changes in the incidence: How to best communicate to patients and physicians? The FDA perspective

Presenter: Dr Alice Hughes (FDA)

Dr Alice Hughes's presentation focussed on the communication of the risk of PML to patients and physicians.

Dr Hughes, Supervisory Medical Officer at the FDA, said that it is still not known how to best communicate the incidence of drug induced PML to patients and physicians, in order to enable informed decision-making. What forum is the best? How much quantitative information is useful? How best to express incidence quantitatively? Over time the FDA has increased the transparency of information about the PML incidence on natalizumab via labelling changes, the Tysabri Medication Guide and Drug Safety Communications (three since 2006).

The FDA is now placing more granular incidence information in the label itself, presenting more quantitative information, describing the risk according to discrete intervals of exposure rather than cumulative durations and communicating the risk more in tabular than in free-text format. The distribution of up-to-date information in the label requires frequent updates, as the information becomes quickly outdated.

A common case definition for PML

Presenter: Dr Dirk Mentzer (PEI)

Dr Dirk Mentzer, who heads the pharmacovigilance unit at the Paul-Ehrlich-Institut (PEI), discussed the need for a case definition to adjudicate reports of suspected PML.

The confirmation of PML cases requires the presence of JCV DNA in the CSF, but such a presence without clinical symptoms and MRI features consistent with PML is insufficient to confirm PML. The presence of JCV DNA needs to be corroborated by a reference laboratory.

The PEI case definition includes five levels of diagnostic certainty. The highest level of certainty is defined by the presence of clinical symptoms consistent with PML and evidence of PML from a brain biopsy or an MRI compatible with PML, as well as a positive PCR test for JC virus DNA in the CSF. Based on this definition, about 150 PML cases on Tysabri have been confirmed so far and 150 cases have been ruled out.

National registry in Italy

Presenter: Prof Gioacchino Tedeschi (Seconda Università di Napoli)

Prof Gioacchino Tedeschi of the Seconda Università di Napoli (Second University of Naples) in Italy gave a presentation on the Italian national registry for Tysabri.

The Italian Medicines Agency (AIFA), in collaboration with the Italian Neurological Panel, adopted more restrictive criteria for dispensing and reimbursing Tysabri than the indication authorised by the European Commission. AIFA implemented a web-based Italian registry for access by 206 specialized MS centres. Tysabri treatment is authorised only for patients satisfying the AIFA criteria. Adverse reactions are promptly communicated through the registry.

According to Dr Tedeschi, so far more than 4,500 patients have been enrolled in the registry, 70% of them women. Eight PML cases have been reported. 18.8% of all patients discontinued treatment, after a mean of 16 drug administrations.

Only the 206 MS centres authorized on the basis of predetermined professional competence and organizational features have access to Tysabri treatment and the registry. Central authorization for Tysabri treatment is only provided for patients satisfying the AIFA criteria.

The TYSEDMUS Study

Presenter: Prof Christian Confavreux (European database for Multiple Sclerosis-FR)

Professor Christian Confavreux of the European Database for Multiple Sclerosis (EDMUS) in France spoke on TYSEDMUS (Tysabri in EDMUS), an observational, prospective, phase IV pharmacoepidemiological study of patients with MS treated with Tysabri in France.

Professor Confavreux said that MS patients in France are managed by a network of 63 MS centres with the help of EDMUS. This software, now used in 285 centres in 40 countries, includes electronic medical records of more than 32,000 patients with MS in France.

TYSEDMUS, which is sponsored by the French medicines agency, AFSSAPS, and funded by a public-private partnership, is based on the French network of neurologists using EDMUS. TYSEDMUS assesses relative and absolute benefit, risk and conditions of use of patients treated with or without Tysabri. So far, 2855 patients have been included in TYSEDMUS, with a median follow-up of 19.5 months. 16% of the patients have discontinued the drug. So far, eight definite and two possible cases of PML have been reported, one of which was fatal.

Professor Confavreux informed the workshop of another MS project that was underway in France: OFSEP (Observatoire Français de la Sclérose En Plaques), a permanent multi-drug pharmacoepidemiological surveillance system for MS, sponsored by the French government

Industry experience with PML

Presenter: Dr Carmen Bozic (PML-Consortium/Biogen)

Dr Carmen Bozic, Senior Vice President at Biogen Idec, the company that markets Tysabri in the US, gave an update of industry experience with Tysabri-induced PML.

Tysabri is approved in more than 50 countries for relapsing multiple sclerosis. As at 31 March 2011, more than 80,000 patients had been treated worldwide post-marketing for almost 150,000 patient years. In addition to the regular submission of information to the regulators, Biogen Idec and Elan (the marketing authorisation holder for Tysabri in the EU) provide PML adverse reaction data to physicians globally upon request.

Dr Bozic said that there is general agreement regarding the definition of confirmed PML, i.e. clinical and MRI findings consistent with PML and evidence of JCV DNA in CSF, preferably using an ultrasensitive, quantitative PCR assay; or brain biopsy with evidence of JCV based on immunohistochemistry or in situ hybridization. However, a consensus concerning the classification of suspect cases is lacking and may not be achievable. The PML risk in patients treated with Tysabri is increasingly well characterized. The majority of patients survive (80%), with disability sequelae ranging from mild to severe. The duration of Tysabri treatment, prior immunosuppressant treatment and the presence of anti-JCV antibodies are risk factors for PML, which enable personalized treatment.

Session 3: Treatment of drug-induced PML

This session aimed to present a critical appraisal of current treatments of (drug-related) PML, the difficulties in the development of such treatments, and the need for progress in this area.

Development of models for testing possible treatments

Presenter: Prof Igor Koralnik (Harvard University)

In his presentation, Igor Koralnik, Professor of Neurology at Harvard Medical School, spoke on the major obstacles in the development of models for testing PML treatment.

JCV grows very slowly in vitro, and there is no plaque assay. A low percentage of cells are in- or transfected. The effect of therapeutic candidates is difficult to evaluate in vitro, and JCV receptors are not fully characterized. JCV infects only humans, so there is no animal model of PML.

Professor Koralnik also touched on the rarity of PML and the need for multicenter studies to pool enough patients for treatment evaluation. Another major obstacle to research is the lack of funding. He said that streamlining information and access to funding for collaborative research studies should be a major goal of this workshop.

New drugs to treat JCV and PML: the current stage and the perspectives for the future

Presenter: Prof Teresa Compton (Biogen Idec)

Prof Teresa Compton, Vice President, Research and Development at Biogen Idec, described Biogen Idec's research for new drugs to treat JCV and PML.

Prof Compton stated that Biogen Idec has a comprehensive, collaborative research program for PML. Both biological and clinical challenges exist to identify and advance new therapies. Currently, immune reconstitution remains the standard approach to treat PML. This can be accelerated by active drug removal via PLEX. A number of existing drugs have been tested for anti-PML efficacy, so far unsuccessfully.

Biogen is currently working on two novel JCV treatment options. Significant challenges exist with regard to clinical trial design and pre-identification of sites which will receive drug-induced PML cases. Addressing these questions is a global challenge and requires collaboration and guidance from regulatory agencies.

Plasma exchange: What is the evidence about plasma exchange in natalizumab-related PML? Is plasma exchange beneficial?

Presenter: Prof Ralf Gold (Ruhr University Bochum)

Prof Ralf Gold, Chair of Neurology at Ruhr University Bochum, Germany, talked about the use of plasma exchange for managing patients with drug-induced PML.

Prof Gold explained that no controlled studies have been performed with plasma exchange for drug-induced PML, but that there is indirect evidence of efficacy (immune parameters, clinical outcome). A more specific removal of IgG4 could be achieved by immunoadsorption columns.

Prof Gold said that IRIS should be managed actively. MRI monitoring of brain swelling should start 3-4 weeks after removal of natalizumab. Repeated pulses of methylprednisolone (3 days with 1,000 mg) are indicated, even forced immunosuppression. Osmotherapeutic agents should be used, and anti-viral therapy with mefloquine and mirtazapine should be continued. These measures are critical determinants of the final outcome.

Immune Reconstitution Inflammatory Syndrome (IRIS), can the risk for developing IRIS be mitigated? How should IRIS be treated?

Presenter: Prof Joseph Berger (Kentucky University)

In his presentation on IRIS, Prof Berger said that there is no widely accepted standard definition, and that IRIS can be described as a 'paradoxical deterioration in clinical status attributable to recovery of the immune system'. It was first recognized with HIV infection after the introduction of highly active antiretroviral therapy. The pathogenesis of IRIS is poorly understood. This accounts for its clinical and pathological heterogeneity. The common therapeutic intervention is high-dose corticosteroids. The mortality rate of IRIS is 28.5%. There is no difference in IRIS incidence, and in the case of HIV - in IRIS survival, whether patients are treated with PLEX, immunoabsorption or not at all.

Session 4: Ongoing research in PML

This session aimed to provide an overview of the ongoing PML research and the possible directions to be followed in the future.

PML development: risk factors and predictive biomarkers - limitations and perspective

Presenter: Prof Heinz Wiendl (University of Münster)

Prof Heinz Wiendl of the University of Münster, Germany, gave a presentation on the risk factors and biomarkers for the development of PML.

Professor Wiendl said that the combination of duration of therapy, previous immunosuppression and presence of anti-JCV antibodies is predictive of PML, but that the weighing of each element is unclear.

The German Natalizumab Pharmacovigilance Study is investigating immune effects and PML risk factors of Tysabri treatment. Due to the multifactorial nature of this rare reaction, a 'dynamic' biomarker of the PML risk seems to be needed. A 'biosignature', including functional components, is probably more likely to reflect the complex nature of the PML pathogenesis. Some potential risk factors are highly difficult to standardize (e.g. migration and flow cytometry). Biological plausibility needs to be taken into account (e.g. dynamic aspects and reversibility). Larger consortia have to be established, in order to cooperate and to validate risk factors independently. The German disease-related competence network for multiple sclerosis has established a structure, an IT platform, several biorepositories and common SOPs to sample various PML biospecimens.

Diagnosis of PML: Available methodologies and improvements of the tools

Presenter: Prof Joseph Berger (Kentucky University)

Prof Joseph Berger, in his presentation on the diagnosis of PML, explained that the clinical diagnosis of PML is a combination of clinical manifestations (e.g. hemiparesis, sensory abnormalities, hemianopsia, aphasia, dysarthria, behaviour changes, while excluding such findings as optic neuritis and myelitis), MRI features compatible with PML, and spinal fluid positive for JCV by PCR.

It is important to consider that routine PCR is falsely negative in about 25% and ultrasensitive PCR is falsely negative in 5% of the cases. Up to 2.4% of the cases are falsely positive. Dr Berger listed other challenges: cases with radiographically monofocal PML, asymptomatic cases and signs and symptoms compatible with MS. The gold standard for PML diagnosis is brain histopathology.

Viral subtypes and the development of the disease, what is the evidence in the area

Presenter: Prof Igor Korolnik (Harvard University)

The JCV coding region is very conserved. One JCV serotype but three genotypes (based on point mutations of VP1 genes) are known. Lesser binding of JCV in the periphery may promote entry in the brain. The phenotypes of JCV granule cell neuropathy and JCV encephalopathy are characterized by alterations in the VP1 C terminus and a novel mutation in the agnogene, respectively. JCV in natalizumab-induced PML appears similar to JCV in other PML cases.

The research in the field: where to progress (translational medicine)

Presenter: Dr Eugene Major (NIH)

Dr Eugene Major highlighted the main areas of PML research such as disease incidence including a standard case definition, predictors of the disease, understanding the JCV, disease characteristics and safe and effective treatment. He announced that two data registries are planned in the US: a project by the Laboratory of Molecular Medicine and Neuroscience which will be developing standard diagnostic criteria for PML and registry data elements and a public-private PML consortium that will coordinate and advance PML research efforts.

26 July 2011

Session 5: Research agendas

This session aimed to discuss how drug-induced PML has led to important initiatives by different stakeholders (e.g. regulatory bodies and industry) and to identify key questions in research.

Regulators initiative, the PML research agenda

Presenter: Dr Ana Hidalgo-Simon (EMA)

Dr Ana Hidalgo-Simon of the EMA's Pharmacovigilance and Risk Management Sector presented the regulators agenda in the field of PML and drug-induced PML research.

Common challenges and needs across products and therapeutic areas and the features of rare and life-threatening ADRs like PML have led to the development of collaborative initiatives by the FDA and the EMA. The goal is to stimulate and to integrate PML research in order to improve risk minimisation and to optimise the benefit-risk-relationship of needed drugs.

The regulators have developed a research agenda which embraces basic biology, clinical aspects and risk management issues to provide a framework to manage the risk of drug-induced PML. It identifies key questions and the fastest way to obtain answers. The research questions around drug-induced PML concern the prediction, prevention and early identification of PML, the minimisation of PML severity and adverse outcomes, the treatment of PML including its efficacy and safety, and the assessment of the efficacy of PML risk minimisation.

According to Dr Hidalgo-Simon, the way forward is to secure funding and to foster collaboration among patients, academia, industry and regulators. This includes an alignment of research agendas and priorities and to establish a framework for regular communication and exchange among all stakeholders.

Academia

Presenter: Dr Eugene Major (NIH)

Dr Eugene Major discussed the challenges faced by academic researchers in the field. He said that the JC virus is a very difficult agent to work with and that research is likely to move slowly compared to more conventional agents. Currently, NIH funds JCV research at about 10 million USD per year. To advance research, the field needs more formal support, collaboration and infusion of new ideas. New research approaches may be needed, such as coordinated technologies and 'team' investigations that direct 'translational' work. Recruiting new principal investigators from different fields such as rheumatology, immunology, and basic neuroscience of (glial) cells, genetics and neuro-infectious diseases would help advancing the science that could inform medical research.

Interface Academia-Clinical Practice

Presenter: Prof Joseph Berger (Kentucky University)

Prof Joseph Berger elaborated that the research questions of clinicians for drug-induced PML are similar to the regulators'. They revolve around the topics of benefit-risk of natalizumab, the predictors of PML, the monitoring of natalizumab therapy, and the diagnosis and the treatment of PML. MS treatment is increasingly becoming restricted to dedicated MS centres, enabling easier collection of PML information like signs, symptoms, patient characteristics and treatment experiences.

PML consortium - industry

Presenter: Dr Susan Goelz (PML-Consortium/Biogen-ELAN)

Dr Susan Goelz, Director at Biogen Idec, explained the activities of the PML Consortium, whose current membership includes Biogen Idec, BMS, Elan, Pfizer and Roche.

Dr Goelz said that because PML occurs so rarely, research efforts will be accelerated through collaboration. The PML Consortium aims to find methods to predict, to prevent and to treat PML. It sponsors research to reduce the occurrence, morbidity and mortality of PML, using a multi-company, not-for-profit, collaborative approach, through sharing of research strategy, investment, data acquisition, data analysis and communication and by a multi-year commitment from member organizations. The Consortium can be reached by e-mail at pmlconsortium@dbr.com.

Ongoing projects are the creation of a clinical database of PML cases, the establishment of a repository of samples available for research sponsored by the consortium, and the funding of the Academic Collaborative Research Network for basic JCV and PML research. Dr Goelz said that future plans under consideration include the clinical validation of risk stratification assays and the clinical evaluation of emerging PML therapeutics. Near-term priorities are to collaborate with patients, including e.g. as members of the Scientific Advisory Board, to find new partners and to enrich the consortium website with educational material and information about PML research.

Session 6: Building collaboration

This session aimed to discuss the possible ways to build research partnerships in the area of PML.

Challenges and opportunities from public private partnerships as a way to build collaboration in research

Presenter: Dr Richard Bergström (EFPIA)

Dr Richard Bergström, Director-General of the European Federation of Pharmaceutical Industries and Associations (EFPIA) highlighted the public private partnership nature of drug development.

The European Union and the pharmaceutical industry have joined forces in the Innovative Medicines Initiative (IMI) to make drug R&D processes in Europe more efficient and effective and to enhance Europe's competitiveness in this sector. One of the reasons is the dramatic increase in drug development costs per approved compound. IMI includes pooling of industry resources and sharing precompetitive information.

Currently, the IMI research clusters consist of EU Medical Information System; Chemistry, Manufacturing, and Control; and Technology and Molecular Disease Understanding. About half of the IMI budget has been allocated. PML related topics could be proposed by academia in the next EU Framework Program.

The importance of clarity in relationships and transparency: the role of ENCePP

Presenter: Henry Fitt (EMA)

Henry Fitt, the EMA's Coordinator of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP), explained the role of ENCePP in bringing together the available expertise in the fields of pharmacovigilance (PhV) and pharmacoepidemiology (PhEpi) in a Network of Excellence.

ENCEPP, an EMA-led collaborative project with academia, facilitates the conduct of post authorisation studies and the collaboration between researchers. It promotes independence, transparency and standards throughout the whole research process by means of a code of conduct to regulate interaction between study funder and researchers, a checklist and a guide of methodological standards, and an e-register of PhEpi studies and their results. Its goal is to build capacity for quality research and to contribute to public health.

Mr Fitt also explained the PROTECT public-private consortium, which serves to strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods. Examples of work packages are a framework for pharmacoepidemiological studies, signal detection, data collection from consumers and benefit-risk integration and representation. The EMA prioritises funding for safety studies of class issues, studies with off-patent substances and studies with public health impact, including delivering comparative safety data.

Drug Safety Surveillance Initiatives

Presenter: Dr Gerald Dal Pan (FDA)

In his presentation on drug safety surveillance initiatives, Dr Gerald Dal Pan from the FDA stated that increasing knowledge about drug adverse reactions and drug use are the goals of the FDA's drug safety surveillance. It comprises active surveillance (e.g. the sentinel initiative), passive surveillance (the spontaneous ADR report database AERS), external health care databases (e.g. health insurance databases), drug utilisation data (e.g. drug utilisation studies) and pharmacoepidemiological studies (e.g. the Drug Liver Injury Network registry). Challenges for ADR research (e.g. drug-induced PML) are the quality of spontaneous reports, the underreporting of ADRs by spontaneous methods, the lack of

drug utilisation data on medicines administered by health care professionals and the low sensitivity and positive predictive value of ADR report codes.

How to facilitate the communications/data exchange?

Presenter: Dr Janice Soreth (FDA)

Dr Janice Soreth, the FDA's Liaison Official at the EMA, discussed how to facilitate communication and data exchange among the stakeholders.

Regulators communicate and collaborate with patients, caregivers, healthcare professionals, researchers, industry and other regulatory agencies. The EMA involves patients in public meetings, as committee and advisory group members or observers and as commentators on scientific guidelines and patient-oriented communication. The FDA informs, communicates and collaborates with the public in advisory committee hearings, "Part 15" hearings, public workshops and as commentators to the FDA docket.

The FDA has confidentiality agreements with many other regulatory agencies including the EMA. It learned intensive collaboration with other stakeholders in its search for an HIV treatment surrogate together with researchers, patients, public agencies and the industry in the 1980s. Since 2004, FDA's Critical Path Initiative consists of numerous projects and collaborations involving all stakeholders to facilitate drug development, support pre-clinical research and improve risk management. Examples are the frozen trial initiative, a specimen bank of samples and corresponding patient data obtained during clinical trials, and the DAPT Study, an independent study of large size and scope to determine the appropriate duration for dual antiplatelet therapy to protect patients from stent thrombosis and major adverse cardiovascular and cerebrovascular events following the implantation of drug-eluting coronary stents.

Dr Soreth concluded by explaining that emerging areas of science, evolving technologies, and globalization require the regulators to modernise their tools and processes. However, this cannot be done by one entity alone. Regulators must continue forging partnerships and collaborations, leveraging resources for research and laying the groundwork for transforming medical treatment to the benefit of patients.

Session 7: Funding of research

This session aimed to explore some of the key existing funding mechanisms for health research that are or could be relevant to drug-induced PML.

Public funding of research – EU perspective

Presenter: Dr Stefanie Prilla (EMA)

Stefanie Prilla, EMA Project Manager for IMI-PROTECT, outlined aspects of research funding in the EU.

Funding sources for medical research in Europe include public programmes of the European Commission with the Seventh Framework Programme (FP7) and the European Regional Development Fund (ERDF), public private partnerships such as the IMI Joint Undertaking, a FP7 Joint Technology Initiative, and numerous national funding schemes.

FP7, which runs until 2013, aims to strengthen the scientific and technological base of the European industry. The FP7 Health Theme provides 600,000 to 800,000 Euros per year of funding. Pertinent topics in 2012 are rare diseases and personalised medicine and in 2013 'the brain' and antimicrobial

resistance. Further FP7 information, including an automated e-mail alert subscription, is available at <http://cordis.europa.eu>.

Calls for proposals are fielded annually, and proposals are assessed for scientific and technologic excellence, implementation and management, as well as potential impact. In this context, the Commission consults the EMA in order to identify priority drug safety research topics.

Any research organisation worldwide can participate, including larger companies, as well as service-providers. Funding levels for research activities range from 50% to 75%. Proposals must include at least three partners from the EU or countries associated to FP7. Cooperation of multinational groups with broad representation of EU member states, involvement of third countries, involvement of small and medium enterprises and involvement of different stakeholder (academia, regulatory, patients, industry, etc) is advantageous.

As of 2014, after the end of FP7, the Commission will put in place a new, integrated funding system for research and innovation "Horizon 2020". One of the future priorities will be to reduce the time to market of the research results in order to achieve a short- and medium-term impact.

Public funding of research – US perspective

Presenter: Dr Eugene Major (NIH)

Dr Eugene Major of the NIH explained how NIH funding in the US works through various mechanisms such as Research Grants, Career Development awards, Research Training and Fellowships, Program Project/Centre Grants and Resources Grants.

Seventy awards have been given out for JCV/PML research in the last three years, totalling 31 million USD. Future PML research could be modelled on the HIV Latency Collaboration, bringing together industry, government (including NIH and the EMA), private foundations (e.g. the Gates foundation) and centres of excellence in academic institutions.

The role of the pharmaceutical industry funding research in this area

Presenter: Dr Sophie Banzet (PML Consortium/Roche)

Dr Sophie Banzet, Head of Safety Science CNS at Roche, used the PML Consortium as an example of how the pharmaceutical industry may fund research for drug-induced PML.

Dr Banzet explained that in the PML Consortium, member companies provide expertise, personnel and funding to advance the goals of the consortium. The budget is shared based on equity across all member companies, and decisions are made consensually. As the members have different corporate objectives, the activities in relation to the vision and mission of the consortium are prioritized. Long-term funding would benefit from additional partners.

Public Private Partnerships as funders

Presenter: Hugh Lavery (IMI JU)

Hugh Lavery, Scientific Project Manager for the Innovative Medicines Initiative (IMI) explained the role of IMI as a public private partnership.

While the IMI does not support research, it does support projects to reduce the time to market for efficacious and safe medicines. It is the largest public-private-partnership in life science R&D. It provides funding, an opportunity to address issues too 'big' to be addressed individually, and access to non-competitive data and resources not publicly available.

Organisations eligible for funding include those from academia, small and medium enterprises (SMEs as per EU definition), patient organisations, non-profit research organisations and intergovernmental organisations.

EFPIA companies, companies not falling within the EU definition of SMEs and entities not based in the EU and its affiliated neighbours are not eligible.

Funding rates range from 75% to 100%. Annual calls are extended, based on the EFPIA research agenda. So far, 453 million euros has been awarded to 23 projects of 298 academic teams, 47 SMEs and 11 patient organisations. An example is PROTECT, a project of 19 partners coordinated by the EMA with the goal of strengthening the monitoring of the benefit-risk of medicines in Europe.

Session 8: Keeping abreast of progress for the benefit of public health

This session aimed to identify mechanisms for information sharing and regular stocktaking of research in the area of drug-related PML.

EU Regulator's perspective

Presenter: Dr Peter Arlett (EMA)

Dr Peter Arlett, Head of the EMA's Pharmacovigilance and Risk Management Sector, outlined the EMA's position.

Dr Arlett mentioned that regulators can provide advice to industry for example in the areas of biomarker validation (joint procedure between FDA and EMA), clinical development, postmarketing pharmacovigilance and pharmacoepidemiology.

Improving the information provided to healthcare professionals and patients is also key for complex adverse reactions like PML. To this end, the EMA is increasing transparency in the areas of clinical trials and adverse reactions and is promoting information about and the conduct of non-interventional studies.

The EMA would like to foster capacity building through networking to share information and best practice and to tackle obstacles. The Agency also endorses a PML research agenda and supports the dissemination of this agenda to funding bodies. The EMA believes that the identification of the existing and missing knowledge about drug-induced PML and the proposal for a PML research agenda will eventually lead to the optimisation of the benefit-risk-balance of PML-inducing medicines and - by this - of public health.

US Regulators perspective

Presenter: Dr Russel Katz (FDA)

Dr Russel Katz, presenting the perspective of the FDA, said that it is important to ensure that the (perceived) burden of risk evaluation and mitigation strategies like TOUCH does not prevent the development and use of medicines addressing unmet medical needs. This calls for involvement of all stakeholders, including patients and healthcare professionals. Given their limited number, reporting all drug-induced PML cases with at least the minimum necessary information and managing all cases in a collaborative study would be helpful. An international PML registry like that for severe cutaneous reactions could support this. Recently, interaction and collaboration between the FDA and the EMA in neurology has increased substantially, supporting the regulators' ability to understand and manage drugs causing PML.

Current knowledge gaps are the predictors for drug-induced PML including its course and outcome, which drugs are effective and which are not against this infection including efficacy surrogates, and how to assess efficacy against PML. Grants for clinical trials of orphan diseases like PML may be an option to address these gaps. Finally, there is a need to establish what information each stakeholder needs and how to provide it to them most effectively.

Industry PML consortium view

Presenter: Dr Sophie Banzet (PML Consortium/Roche)

Dr Sophie Banzet presented the views of the PML Consortium. Dr Banzet said the consortium wants to accelerate PML research for the benefit of public health, using a new organizational model based on non-competitive collaboration focussing on risk and innovative use of tools for communication and education. The consortium is transparent about its activities, progress and accomplishments and shares best practices and approaches across companies and across therapeutic areas. It also aims to gather PML data to maximize its scientific utilization under a strong governance to ensure patient privacy and scientific integrity.

The PML Consortium fosters collaboration, communication and education through its research program and grants, workshops, publications, and through the identification of research topics for the PML Consortium website. The consortium's PML Clinical Database may allow the identification of broader trends across cases, including risk factors and variables that are associated with improved outcome. The consortium aims to collaborate (e.g. with regulators) to establish feasible clinical trial designs and endpoints for potential PML treatments. Experts can be made available to work with regulators and other stakeholders on the need for specific guidance (e.g. PML case definition). Dr Banzet also stressed that a fundamental component of tackling PML is the education of those concerned.

Clinical Researchers

Presenter: Prof Igor Koralnik (Harvard University)

Prof Igor Koralnik, giving a perspective of clinical researchers, said that clinical researchers provide direct contact and care for PML patients, access to MS patients treated with natalizumab and knowledge of basic science in house or in collaboration, making them ideal partners for clinical research. They are frequently consulted about management of PML patients worldwide and are kept abreast by monthly natalizumab PML statistics from Biogen. Better access to clinical information on natalizumab-PML via a website and an e-mail list of health carers of patients with drug-induced PML to share experiences and views on patient management could address existing knowledge gaps. Prof Koralnik said that research collaborations on a larger scale should be promoted, and access to funding for collaborative PML research by the EU, NIH, foundations, and philanthropic organisations should be supported and streamlined.

Researchers

Presenter: Dr Eugene Major (NIH)

Dr Eugene Major said that from a public health perspective, public education sites (e.g. the NINDS A-Z information page about neurological disorders which includes PML) seem helpful in providing current and accurate information to investigators, clinicians, and patients. Public liaison offices such as the INDS Office of Communications and Public Liaison can enhance communication strategies to promote research and utilization of new ways to stratify risk. Patient advocacy groups should continue to garner support for projects advancing knowledge and research. Interaction with the public by the PML stakeholder community should be increased and professional societies and organizations encouraged to

tackle PML-related research topics. In order to convince the CDC to designate PML as a reportable disease, it is important to better understand what makes a disease rare according to CDC standards, as well as when such a disease becomes a public health issue. Finally, larger research consortia could counter the issue of scarcity in PML cases and funding.

Physicians view

Presenter: Prof Ralf Gold (Ruhr University Bochum)

Prof Ralf Gold said that regulators should consider compulsory patient registries to ensure appropriate use of drugs causing PML ('license to infuse or prescribe'), and that standard treatment algorithms could help health carers achieve the best outcome for their patients. Immediate communication of new (putative) surrogate markers, as well as supporting independent studies, e.g. on natural clearance mechanisms against JCV, could be further measures to achieve better patient outcomes.

Patient view

Presenter: Christoph Thalheim (European Multiple Sclerosis Platform)

Christoph Thalheim explained the need for patients and care givers to have a final voice in risk-benefit assessments of new medicines, including e.g. CHMP representation. More frequent interactions on benefit-risk methods, research and decisions between patient groups, health professionals and regulators would be helpful. Patient organisations should be more involved in the dissemination of vital benefit-risk information to the individual patient. The capacity and limitations of blood tests on JCV antibodies as risk indicator should be clarified to Tysabri users. More studies on the – apparently decreasing – risk of developing PML after 3 years of Tysabri use seem warranted, just like public private partnerships to support development of effective anti JCV therapy. Internet based networking of PML patients and care givers should be supported and facilitated by all stakeholders, and a central database informing about PML cases worldwide should be made available to patients and families once a PML diagnosis is made. In general, the dissemination of PML information to the patients should be improved.

Next steps

Presenters: Dr Peter Arlett (EMA) and Dr Gerald Dal Pan (FDA)

At the end of the workshop, it was agreed that all stakeholders should play their part in treating, preventing, diagnosing, studying, collaborating, funding and sharing knowledge in regards to drug-induced PML to reduce the PML burden.

Workshop proceedings and research agendas will be published on the EMA website. Further publications will be arranged and communicated to funders for their consideration. Stakeholders are encouraged to support PML research collaborations and the identified research priorities. A mechanism to share information needs to be developed.

The big picture: Research priorities for drug-induced PML

Over the two days, the different stakeholders presented their agendas reflecting their different point of view. These research priorities were:

Patient priorities

- More involvement in benefit-risk methods and decisions

- Improve pathways to disseminate information
- Clarify role of anti-JCV-antibody as risk indicator
- Study risk of PML beyond three years
- Develop anti-JCV therapy

Regulatory priorities

- What is the best approach to ascertain the number of drug-induced cases of PML?
- Is it possible to identify populations at risk/not at risk prior to treatment initiation with a drug associated with PML?
- Are there early biomarkers of drug-induced PML that might be used to mitigate the severity of the clinical manifestation of PML?
- What is a suitable in vivo/animal model for PML?
- What are the best drugs or combination of drugs with anti-JCV activity?
- What are the best treatment strategies for both PML and Immune Reconstitution Inflammatory Syndrome?
- What is the long-term safety and effectiveness of plasma exchange/immunoadsorption in patients with drug-induced PML?
- What is the best tool to evaluate the effectiveness of risk minimisation activities in PML?

Industry priorities

- Better predict, prevent and treat PML
- Create of a clinical database with demographics, clinical information and MRI images
- Establish a repository of samples
- Fund an academic collaborative research network (basic biology of JCV, pathogenesis of PML; immune response to JCV; viral changes associated with PML; animal models of PML)
- Validate clinically a risk stratification assay
- Evaluate clinically emerging PML therapeutics

Academic priorities

Research approaches:

- Molecular genomics/proteomics, viral and host
- Viral gene regulation in specific cells, i.e. glia vs. neurone
- Immunology of therapies and host response to infection

Drug discovery:

- Small molecules to interrupt viral growth once identified; relevant cell model to screen molecules
- Vaccines, peptides, VLP (like papilloma) as prophylactic and/or therapeutic
- Pre-clinical/clinical studies based on a relevant animal model for pathogenesis and intervention

Clinical research priorities

- What is the risk/benefit ratio of drugs causing PML? Should my patient be treated with drug X?
- What are predictors for PML? Which patients should not be treated with the drug? Which biomarkers should I follow in my patients treated with drug X? How often should I use MRIs and CSF testing?
- What is the value of a drug holiday? Should I stop drug X after 12 months, 18 months, two years?
- My MS patient has experienced new neurological problems - does the patient have PML? How to distinguish PML from MS relapse?
- How to treat PML?
- How to mitigate the PML risk? e.g., through patient selection?

ANNEX I - Transatlantic workshop information

Title: Drug-related Progressive Multifocal Leukoencephalopathy (PML)

Host: European Medicines Agency, 7 Westferry Circus, Canary Wharf, London, UK

Date: 25-26 July 2011

General objectives

The objectives of the workshop were to:

- Find a common understanding of the priorities for research in the area of drug-induced PML;
- Map ongoing research and identify gaps;
- Foster funding and partnerships to conduct research, in order to fill knowledge and research gaps;
- Build a mechanism to ensure the sharing of information and regular stocktaking on research results.

Presenters

The speakers represented the following parties in Europe and the United States:

- Regulators: FDA, EMA, and EU national regulatory agencies
- Public funding bodies from EU (IMI, ENCEPP) and US (NIH)
- Academic researchers
- Clinical Researchers
- Patient organisations (EMSP)
- Pharmaceutical industry (Biogen Idec, Elan, PML Consortium, EFPIA)

Organising team

Programme coordination: Monica Vinhas de Souza (EMA, scientific lead), Gerald dal Pan (FDA), Peter Arlett (EMA), Janice Soreth (FDA), Henry Fitt (EMA).

EU programme committee (in alphabetical order): Eric Abadie (CHMP), Peter Arlett (EMA), Michael Berntgen (EMA), Hilde Boone (EMA), Henry Fitt (EMA), Manuel Haas (EMA), Brigitte Keller-Stanislawski (PhVWP), Bert Leufkens (CHMP), Luca Pani (CHMP), Christian Schneider (CHMP) Rafe Suvarna (CHMP), Monica Vinhas de Souza (EMA).