EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA and Progressive Multifocal Leukoencephalopathy.

ENCePP Plenary, London 23 November 2011

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In my presentation…

What is PML?

Why is EMA interested in PML?

What has EMA done regarding PML?

- PML research agenda
- Multi stakeholder workshop

How can EMA further help?

- Raising awareness
- Facilitate Funding?

What is PML?

- Progressive Multifocal Leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by JC virus (JCV)

- Devastating course (progressive neurological disabilities, behavioural changes, dementia, death)

- Knowledge of JCV and PML are limited.

- Different medicines tested for the treatment of JCV and PML, none have yet demonstrated efficacy.

What is PML?

- PML is a severe adverse reaction of several drugs that affect immunological functions, in particular monoclonal antibodies (MAbs).

- Reports of PML related to the use of MAbs are growing and have occurred in patients with cancer, HIV/AIDS, transplantation patients, and patients with immune disorders such as rheumatoid arthritis or multiple sclerosis.

Why is EMA interested in PML?

Confirmed cases of PML related to 4 EMA authorised MAbs (from both clinical trials and post marketing).

- Tysabri (**natalizumab**), disease modifying therapy in highly active relapsing remitting multiple sclerosis

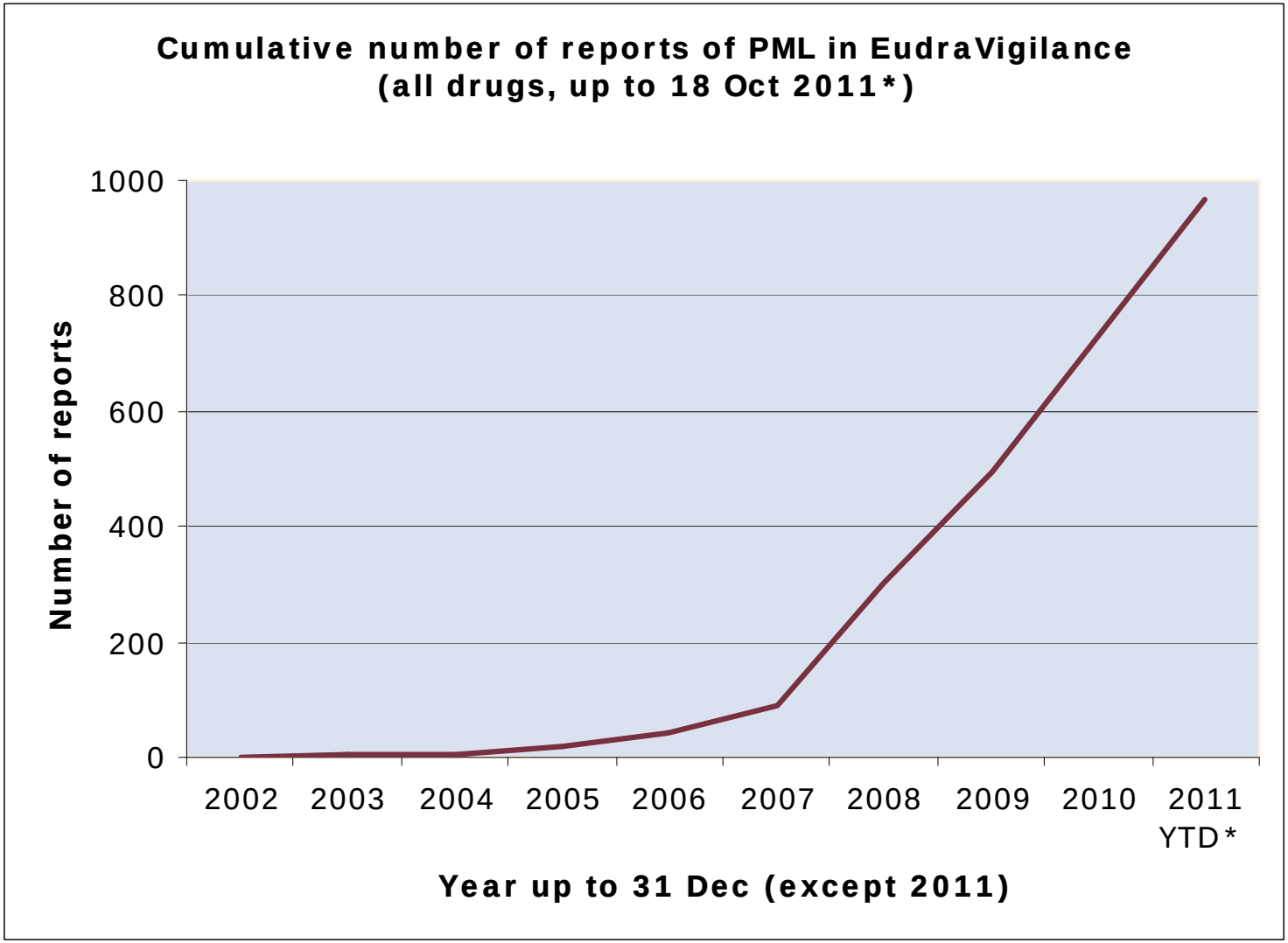
- Mabthera (**rituximab**), indicated in Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis

- Arzerra (**ofatumumab**) indicated for the treatment of chronic lymphocytic leukaemia (CLL)

- Raptiva (**efalizumab**) indicated for chronic plaque psoriasis (withdrawn)

Considering the mechanisms that link MAbs and PML, more drugs from this class could be associated with PML.

Why is EMA interested?



Why is EMA interested in PML?

From the public health protection perspective, considering

- PML is such a severe complication, and
- MAbs represent effective (or the only) treatment options for many serious diseases

it makes consideration of benefits and acceptable risks an issue of high interest.

PML research agenda project

- Different regulatory actions regarding drug-related PML (product specific) have been taken in recent years;
- Project to develop EMA “PML research agenda” (not product specific) since January 2010 in collaboration with FDA;
- An innovative approach to adverse events common to different medicines;
- Define researchable questions that would help regulatory agencies to protect public health;

- Endorsed by PhVWP and CHMP in June-July 2010.

Transatlantic PML Workshop (July 2011)

Brought together the experts and all the stakeholders on PML to a common purpose of reducing the burden of PML

General objectives

1. Common understanding of research priorities;
2. Map ongoing research and identify gaps
3. Foster partnerships and funding to conduct research to fill knowledge and research gaps;
4. Agree a mechanism to ensure information sharing and regular stocktaking of research results, knowledge, knowledge gaps.

Transatlantic PML workshop

- Meeting very well attended and well received;
- Proceedings are published on EMA website:

https://docs.eudra.org/webtop/drl/objectId/090142b281914a2c

- Follow-up TC with key stakeholders on-going

Scientific highlights I – **What we know**

The disease

• PML is a demyelinating disease, localised in the brain;

• It is rare, severe and can be lethal;

• Most frequently in immunosuppression;

• Diminished if trigger can be eliminated;

• PML can be induced by certain drugs.

The virus

• Caused by JC virus (JCV);

• JCV infects only humans; no animal models exist; grows very slowly in vitro;

• JCV is common, present in around 50% of population;

• It has one serotype but several different genotypes are known;

• It can replicate in the urinary tract asymptomatically.

The PML patient

• Clinical presentation known;

• Less severe if: young patient, early diagnosis and intervention, unilobar;

• Malfunction of the immune system leads to higher risk;

• For drug-related PML, risk increases with duration of treatment (in first few years);

• The PML risk limits the use of some effective therapies.

What we don't know

The disease:

- How to best ascertain the number of drug-induced PML cases;
- No universally accepted case definition exists;
- No specific prophylaxis or treatment exists;
- No animal model and no plaque assay;
- No predictive markers for PML;
- Limited data regarding the risk of drug-induced PML beyond 3 years of MAbs treatment;
- The long-term impact of IRIS therapies is unclear;

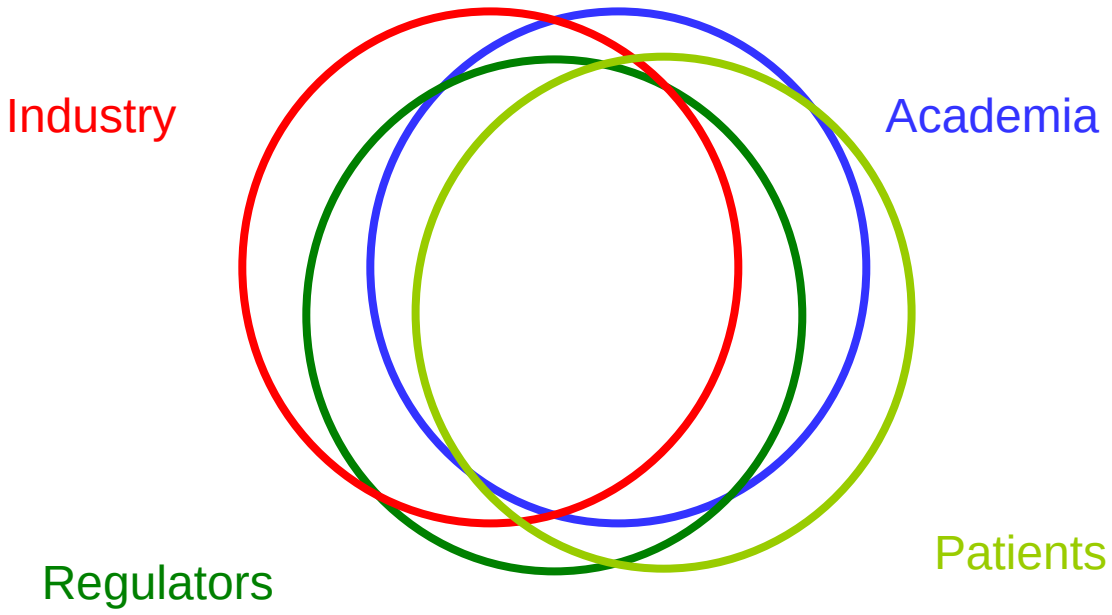
The patient:

- 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? • How can PML be distinguished from MS relapse?
- Which are the best type of information and communication tools to healthcare professionals and patients?

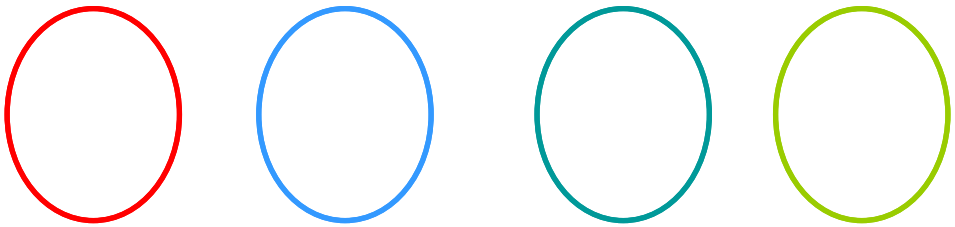
Transatlantic PML workshop - **The Future**

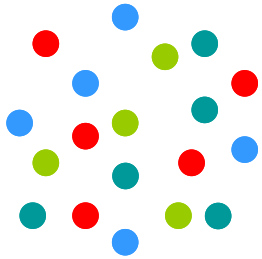
- Benefit and risk should be presented together to inform decision making;
- PML challenges require collaboration on a global scale;
- Input from different disciplines/fields will benefit research progress;
- Sharing of information, best practice and resources between all stakeholders will produce results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

Research Agendas I



Research Agendas II





Revised Agenda Post-PML Workshop

JCV

- Effective anti-viral therapy;
- Relevant animal model/cell culture model to test therapies;
- Viral gene regulation in specific cells;
- Develop small molecules to modulate viral growth and behaviour;
- Clinical studies for potential interventions;
- Investigate molecular genomics/proteomics (viral and host).

Prediction and Prevention

- How to identify populations at risk before treatment;
- Which patients should not be given specific drugs;
- Biomarkers;
- Anti-JCV antibodies as risks indicators;
- Risk of PML beyond 3 years;
- Develop vaccines, peptides and other prophylactic interventions;
- Repository of samples.

Benefit/Risk

- Which is the B/R ratio of PML-inducing drugs?
- Which patients should not take specific drugs?
- How to minimize the risk of PML?
- How to involve patients more in B/R methods and decisions?
- Which is the best way to evaluate effectiveness of risk minimization activities?
- Clinical validation of risk stratification assay.

Therapy

- How to treat PML?
- How to evaluate new therapies with risk of PML?
- Value of drug holidays;
- Best strategy for Immune Reconstitution Inflammatory syndrome (IRIS);
- Long-term value of plasma exchange/ immunoadsoption;
- Create a clinical database for research (demographics, clinical information, MRI images…).

Communication

- Improve pathways to collect information;
- Improve pathways to disseminate information (on disease, therapies, risks, safety, etc…);
- Improve communication between stakeholders;
- Establish collaborative research networks (PML Consortium).

PML research agenda

Drug-induced PML: A global agenda for a global challenge

Submitted for publication Nature's Clinical Pharmacology & Therapeutics

PML - **Initiatives that may contribute**

- Industry PML Consortium (EMA observer in the Consortium Advisory Board)
- IMI
- EU (7th) Framework Programme
- NIH
- ENCePP
- Academic networks
- Registries
- Sentinel Initiative

THANK YOU