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- Raptiva (efalizumab) indicated for chronic plaque psoriasis (withdrawn)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

**Cumulative number of reports of PML in EudraVigilance**
(all drugs, up to 18 Oct 2011*)

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<th>Year up to 31 Dec (except 2011)</th>
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*Year up to 31 Dec (except 2011)*

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**European Medicines Agency**
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.
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 asymptptomatically.

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

- Industry
- Academia
- Regulators
- Patients
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/immunoadsorption;
- 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