Safeguarding public health

PML: Risk Communication in the EU

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PML: Risk Communication in the EU
In this talk...

- **General observations on regulatory risk communication**
- **Particular challenges with PML**
- **What has been done to date:**
  - **What works, what could be better**
- **Measuring success?**
- **Future directions**

Aims of risk communication, for prescribers and patients

1. To help decide whether a medicine is the **right choice***
2. To advise on **safe and appropriate use**
3. To **describe possible risks** and how to minimise them
4. To advise on **what to do** in the event of a potential adverse effect (early detection)
5. To advise on **when/whether to stop*** taking the medicine

***To advise about starting and stopping:**
Need to put **risk in the context of benefit**

Risk communication should be benefit/risk communication!

Risks and benefits – difficult concepts and differing perspectives

Risk communication and drug regulation

At time of licensing

- Summary of Product Characteristics - SPC
- Patient information Leaflet - PIL
- Public assessment report - EPAR
- Risk Management plan - RMP

Post-licensing - emphasis is on risk as new information emerges

- Updated RMP, SPC, PIL
- 'DHPCs' (Dear Dr letters), 'Q&A' documents etc
- Press briefings/press releases

Additional materials

- Patient materials: reminder cards, information sheets etc
- Healthcare professional educational materials
- National communications: bulletins etc (e.g.UK *Drug Safety Update*)
- International publications: WHO bulletin

How good are SPCs & PILs for B/R communication?

Limitations of current documents/templates:

Benefit – very limited information
•SPCs – Indications and section 5.1 only (data)
•PILs – statement on indications
Usually no clear summary of expected benefits, magnitude and uncertainty

Risks
•Inadequate **qualitative** description of harm, seriousness/outcomes
•Potential confusion over **statistical probability**:
("rare", "common" vs absolute risks)
•Absence of information on **baseline risk**
•Lack of information on **uncertainty** or impression of risk estimate
•Lack of clear advice on what **action to take** in the event of problems

Future solutions: new templates, better guidance…?

EPARs – recently improved template:
•**Benefit and uncertainties**
•**Risks and uncertainties**
•**Benefit/Risk balance**.

Particular challenges to communicating on PML

- Putting risk in the **context of benefit**
- **Qualitative description of PML** (how to inform without being alarmist)
- **Quantitative description/stratification**:
  - Estimates using best evidence: studies vs ADR reports
  - Describing changing risk with duration of use
  - Consideration of Risk factors – **individualisation of risk**
- **Describing early symptoms**, and advice on action
- **Consequences**: Qualitative/quantitative description of **IRIS**
- Keeping benefit/risk information **up to date** (emerging data)
- **Consistency** of information between documents and products

Tysabri: wide range of communication tools

Targeted communications

- **SPC/PIL** – regular updates, benefit information in PIL
- **Physician information** – risk management/stratification
- **Patient Alert Card** – information on risk and symptoms
- **Treatment initiation and continuation forms** – benefit/risk
- **Website information for patients**

General communications

- Press releases
- Q&A documents
- National bulletins – PML in general, and Tysabri in particular

Tysabri: Patient information leaflet - Benefit information

"In clinical trials, TYSABRI **approximately halved the progression** of the disabling effects of MS and also **decreased the number of MS attacks by about two-thirds**. However, TYSABRI cannot repair the damage that has already been caused by MS. When you receive TYSABRI you might **not notice any improvement, but TYSABRI may still be working to prevent your MS becoming worse**."

Conveying uncertainties over benefit?

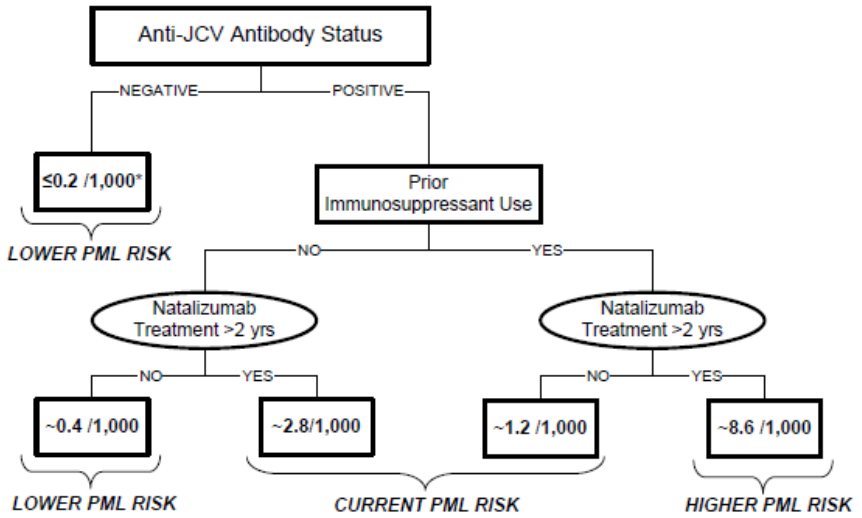
Detailed Patient Information Leaflet - still some knowledge/information gaps

“Take special care with TYSABRI
There have been cases of a **rare** brain infection called PML (progressive multifocal leukoencephalopathy) that have occurred in patients who have been given TYSABRI. PML **may lead to severe disability or death**. The risk of PML increases the longer that you are on treatment especially if you have been on treatment for more than two years. It is not known if the chance of getting PML continues to rise, remains the same, or falls after you have been on TYSABRI for more than three years. The risk of PML is also greater if you have previously taken a medicine that weakens your immune system. In patients with PML a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) **is likely to occur after treatment for PML**, as TYSABRI is removed from your body. **IRIS may lead to your condition getting worse, including worsening of brain function**. “

-What is overall expectation for outcomes (PML & IRIS)?
-What are the chances of death, serious disability, recovery?
-Balance this against benefit information – and uncertainties

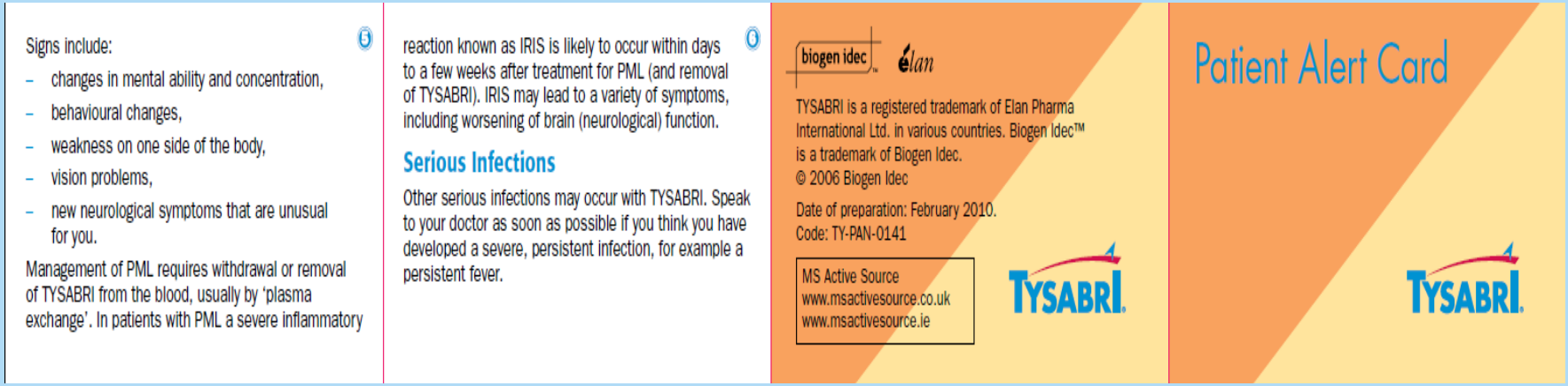
Better informed benefit/risk decisions - risk stratification helpful; some caveats

Figure 2: Anti-JCV Antibody Testing and Risk Stratification Algorithm using 104 PML cases



The prevalence of anti-JCV antibodies is 55% of the MS patient population and the incidence of PML in anti-JCV antibody positive patients is 1.8 fold higher than the overall Tysabri-treated population.
* Point estimate based on an assumption that 1 out of 23 PML patients tested anti-JCV antibody negative. PML incidence in anti-JCV antibody negative patients treated for 18 infusions or more is estimated at 0.21 per 1,000 patients while the incidence in JCV antibody negative patients treated for up to 18 infusions would be less than 0.2 per 1,000 patients. Additional data are needed to further quantify PML incidence in patients who are anti-JCV antibody negative.

Patient Alert Card
Warning on early symptoms



Signs include:

- changes in mental ability and concentration,
- behavioural changes,
- weakness on one side of the body,
- vision problems,
- new neurological symptoms that are unusual for you.

Management of PML requires withdrawal or removal of TYSABRI from the blood, usually by 'plasma exchange'. In patients with PML a severe inflammatory reaction known as IRIS is likely to occur within days to a few weeks after treatment for PML (and removal of TYSABRI). IRIS may lead to a variety of symptoms, including worsening of brain (neurological) function.

Serious Infections

Other serious infections may occur with TYSABRI. Speak to your doctor as soon as possible if you think you have developed a severe, persistent infection, for example a persistent fever.

biogen idec Elan

Date of preparation: February 2010.
Code: TY-PAN-0141

MS Active Source
www.msactivesource.co.uk
www.msactivesource.ie

TYSABRI

Patient Alert Card

TYSABRI

PML with other medicines
Drug Safety Update (March 2009)

Drugs associated with PML

The MHRA has previously identified an association between PML and use of some monoclonal antibodies such as natalizumab (Tysabri ▼, used to treat multiple sclerosis) and rituximab (MabThera, indicated for non-Hodgkin's lymphoma and severe active rheumatoid arthritis). An association has also been identified between PML and efalizumab (Raptiva ▼, a treatment for moderate to severe plaque psoriasis). A European review has concluded that the benefits of this drug do not outweigh its risks, and the European Medicines Agency has recommended the suspension of the marketing authorisation for efalizumab.

Warnings about PML are given in the product information for rituximab, alemtuzumab, natalizumab, fludarabine, nelarabine, and mycophenolate mofetil. There is currently insufficient evidence of a causal relation between cyclophosphamide or epirubicin and PML, and PML is not currently listed in the product safety information for these drugs. The risk of drug-induced PML continues to be monitored closely by the MHRA.

Product information for other drugs

•Wide range of indications…examples:

- **Rituximab (Mabthera)**: NHL, CLL, Rheumatoid Arthritis
- **Efalizumab (Raptiva)**: Moderate to severe psoriasis (second line)
- **Fludarabine (Fludara):** B-cell CLL

Communication challenges:

•Less known about absolute risk/risk stratification

•Implications for benefit/risk varies: Raptiva withdrawn

•Limited information provided

Limited patient information

Efalizumab

- You might get infections more easily. If you develop a new infection or notice any new or sudden change in thinking, balance, strength, talking, walking or vision, please contact your doctor. He/she will determine whether to monitor your treatment or whether it is necessary for you to stop using Raptiva.

Mabthera

[Patient card provides further information]

Take special care with MabThera

- tell your doctor if you are taking or have previously taken medicines which may affect your immune system, such as chemotherapy or immunosuppressive agents.

Very rarely, some patients taking MabThera have had a serious brain infection, which has been fatal. **Tell your doctor immediately** if you have memory loss, trouble thinking, difficulty with walking or loss of vision.

Websites/transparency/real-time data
A good principle, but needs to be thoughtful... not just a 'data dump'

Benefit/risk communication for PML
How should we measure success?

Success = ?

- **Better informed HCPs and Patients?**

User-testing of materials, surveys of value/understanding.

- **Better outcomes for PML?**

Is earlier recognition of symptoms leading to reduced mortality/morbidity.
Measure trends in mortality rates?

- **Reduction in PML rates?**

Is better risk stratification leading to better informed decisions on starting and stopping treatment?

Benefit risk communication for PML: Overall conclusions

- **Risk communication should be Benefit/Risk communication**
- **Communications need to be targeted for audience/purpose [involvement of patient groups, and professionals]**
- **Much good material been generated – especially Tysabri**
- **Still some gaps in knowledge and information [outcomes, balancing benefits versus risks, uncertainties]**
- **Websites/internet: up to date information – useful[?]**
- **Product information for other drugs generally limited…**
- **Need to think about testing the utility/success of all materials**

Future directions

- Possible further changes to EU legislation – SPC/PILs

- IMI, EMA and other initiatives on benefit/risk – graphical tools for communication (e.g. Multicriterion decision analysis?)

- Use of new media and technologies to transmit the messages updates– apps for smart phones?

Thank you for your attention

Benefit/Risk information: Clear, unambiguous , user-tested