Changes in the Incidence of PML in Tysabri-treated Patients: How best to communicate to patients and physicians

Division of Neurology Products' Perspective

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Background

- When Tysabri was re-introduced to the market in 2006, we did not know what the incidence of Progressive Multifocal Leukoencephalopathy (PML) would be in the post-marketing setting
  - Three cases in clinical trials (2/1869 patients with multiple sclerosis [MS] and 1/1043 patients with Crohn's disease [CD])
    - MS patients were on concomitant beta-interferon
    - CD patient had had recent immunosuppressive therapy (azathioprine) treatment
  - Risk of PML at that time roughly estimated to be 1/1000
  - Risk in monotherapy setting unknown
  - Risk with long term treatment unknown
    - MS trials: median duration 120 weeks

- Since marketing re-introduction, we have been getting expedited reports of all new cases and regular updates of PML incidence according to duration of exposure
  - TOUCH program places us in the unique position of having reliable numerator (PML cases) and denominator information (number of patients treated according to exposure duration)

Background

- What we've learned about PML incidence since 2006
  - Risk for PML not limited to patients receiving Tysabri with other immunomodulatory medications (or with very recent history of such)
  - Risk increases with increasing durations of exposure
  - Risk increased in patients with a history of immunosuppressant treatment

Background

- How do we best communicate what we've learned, and the latest incidence information, to patients and physicians?
  - Our overarching principle has been that it is important to communicate important new information related to PML incidence as we learn it so patients and physicians can make informed decisions about Tysabri treatment in the context of an individual patient's illness
    - But what forum/fora is best?
    - How much quantitative information is useful?
    - How best to express incidence quantitatively?

Outline

- History of our communications related to PML incidence over time
  - Key labeling changes
  - Drug safety communications
- Unanswered questions

History of Key Labeling Changes

- June 2006
  - Label approved when Tysabri was re-marketed for MS:
    - “Two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease after the patient received 8 doses. The absolute risk for PML in patients treated with Tysabri cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified.”
- August 2008
  - Label updated after we received the first postmarketing case reports
    - Stated that additional cases of PML had been reported in the postmarketing setting in MS patients not taking other immunomodulatory therapy
    - Number of cases not given
    - “The relationship between the risk of PML and the duration of treatment is unknown, but most cases of PML were in patients who received more than one year of treatment.”

History of Key Labeling Changes

- January 2010
  - Label updated with information about link between exposure duration and PML risk that we had concluded was present
    - At that time, risk in patients treated for two years or more was approximately 1/1000
    - "..the risk of developing PML increases with longer treatment duration, and for patients treated for 24 to 36 months is generally similar to the rates seen in clinical trials. There is limited experience beyond 3 years of treatment."
      - No precise quantification of risk added to label—just the reference to the clinical trial rate
- Developments after label change:
  - Additional data accrued showed that the PML risk in patients treated for two years or more was becoming greater than the rate of 1/1000 that we had estimated from clinical trials
  - We accumulated enough data for treatment beyond 3 years to give risk estimates for treatment beyond 3 years
  - Growing desire for transparency about PML incidence information—label seemed like the best repository for this information
    - Readily accessible to patients and physicians
  - Increasing need to give more quantitative risk information according to exposure duration as we accumulated more data
  - General statement comparing risk to rates observed in clinical trials no longer seemed sufficient

History of Key Labeling Changes

- April 2011
  - Label updated with:
    - "The risk of PML is also increased in patients who have been treated with an immunosuppressant (not including prior treatment with short courses of corticosteroids) prior to receiving TYSABRI."
      - No estimate of the magnitude of risk increase conferred by such prior treatment
    - A table providing incidence of PML according to duration of therapy/number of infusions:

Estimated Incidence of PML in the Postmarketing Setting

Duration of Therapy (Number of Infusions)	PML Incidence per 1000 Patients
Up to 24	0.3
25-36	1.5
37-48	0.9
Data as of January 2011 Data beyond 4 years of treatment are limited	

History of Key Labeling Changes

- Medication Guide
  - Part of approved label written directly to patients that presents key risk information
  - Medication Guide revisions have generally accompanied our other labeling changes
  - Given to the patient at every Tysabri infusion
  - Opportunity to communicate directly to patients
  - Information about PML incidence currently in the Medication Guide:
    - Your chance of getting PML increases:
      - With a longer period of Tysabri treatment
      - If you have received medicines that can weaken your immune system prior to starting Tysabri

History of Drug Safety Communications

- Primary FDA risk communication tool currently in use is the Drug Safety Communication
  - Provides information to patients and healthcare professionals in a standardized format (Summary, Additional Information for Patients, Additional Information for Healthcare Professionals, Data Summary)

- DSCs issued related to Tysabri since 2006:
  - August 2008: first postmarketing cases
    - Numerator and denominator information provided
  - February 2010: PML risk/exposure duration association discussed at length
    - Table provided showing cumulative risks above certain thresholds of exposure
  - April 2011: PML risk/prior immunosuppressant therapy association and new incidence table being added to label discussed
    - Explanation of our new data presentation format: “FDA believes that presenting PML incidence for discrete intervals of treatment instead of showing cumulative risks above certain thresholds of exposure will allow prescribers to better assess risk based on duration of treatment, and will aid healthcare professionals in discussing the risk of PML with their patients.”

- DSCs have generally paralleled our labeling changes
  - More detail and supportive data provided vs. label
  - Updated number of PML cases and number of patients treated given

Change in presentation of incidence information: Old vs. new formats using latest incidence data (through July 5, 2011)

Number of Tysabri Infusions received	Cumulative rate of PML per 1000 patients
≥ 1	1.6
≥ 12	2.4
≥ 24	3.0
≥ 30	2.5
≥ 36	1.8

Duration of therapy (number of infusions)	PML Incidence per 1000 Patients
Up to 24	0.4
25-36	1.9
37-48	1.3

- We decided that the presentation on the right is more clinically useful for assessing an individual patient's risk at a given point in time, and in discussing risk over time with patients
- Which presentation is more understandable to patients and physicians?
- We have limited the incidence presentation in label to one known risk factor
  - Risk over time is important for ongoing treatment decisions
  - As known risk factors accumulate, this table may grow more complex and unwieldy

Historical trends in our communications

- Move towards greater transparency regarding incidence information
- Move towards placing more granular incidence information in the label itself
- Move towards presentation of more quantitative information
  - Move from presentation of risk according to cumulative durations of exposure to presentation of risk according to discrete intervals of exposure
- Move toward tabular presentation of risk vs. descriptive text
  - Communication of up to date information leads to the need for updates; information becoming quickly outdated

Unanswered questions

- What does this information mean to patients and physicians? How do they integrate PML incidence information into their treatment decisions?
- What's a regulatory agency's role in disseminating real time incidence information for an adverse event?
- Are we overcommunicating? Undercommunicating? Providing necessary risk context?
  - We have not assessed the effect of our communications on patient or physician understanding of risk
    - Once TOUCH is approved as a Risk Evaluation and Mitigation Strategy, mandatory assessments of understanding will be included
- What else can we do? What other forms of communication should we be using?
- Who else can be productively involved?
- How much granularity should be in the label itself?
  - Is there another forum that should serve as a repository for up to date incidence information? Will patients and physicians think to look at the label for the latest incidence information?
    - Tysabri.com website?
- What is an acceptable level of risk?