Progressive Multifocal Leukoencephalopathy (PML) in Natalizumab-Treated Patients: Experience of the FDA Division of Neurology Products

M. Lisa Jones MD, MPH
Russell Katz, M.D.
Director
Division of Neurology Products)

Natalizumab Background

- Natalizumab (Tysabri®) is a recombinant humanized antibody directed against α_4 integrins ($\alpha_4\beta_1$ and $\alpha_4\beta_7$)
- Prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue
- Indicated as a monotherapy treatment for the relapsing forms of Multiple Sclerosis (MS) and for moderate to severe Crohn's disease (CD)
  - Less than 2% of natalizumab use in US in CD
- Administered as an infusion at 4 week intervals

Development Program Review

- The sponsor (Biogen Idec) submitted a Biologic License Application for natalizumab in May 2004
- The development program consisted of 5 Phase 3 studies involving ~4,000 patients
- Received accelerated approval for marketing in November 23, 2004
- At time of approval, ~1,100 MS patients had received natalizumab for one year or more
- No cases of PML were observed prior to marketing

Initial PML Cases

- Within weeks of approval, the first cases of PML were reported to the FDA by the sponsor
- Initially two cases in MS patients were identified:
  - Both patients were enrolled in a long-term clinical trial and had been taking natalizumab for more than 2 years
  - Both were receiving concomitant interferon beta-1a
  - One case was fatal
- Subsequent fatal case in a CD patient who had received 8 doses
  - One additional case in a CD patient in June 2011

Response to Initial PML Cases

- Due to the PML cases, in February 2005 the FDA issued a Public Health Advisory (PHA) announcing the suspension of natalizumab marketing. The PHA noted a potential relationship between PML and natalizumab, although the link was only verified as further data accrued
- The FDA also halted all clinical trials
- The sponsor reviewed all adverse events in the clinical trial database to determine if any of these could possibly represent cases of PML; attempts were made to obtain more data (e.g., MRI)
- No additional cases identified

Advisory Committee Consultation

- In March 2006, the FDA consulted its Peripheral and Central Nervous Systems Drugs Advisory Committee
- The FDA Advisory Committee:
  - Voted unanimously to re-introduce natalizumab to the market based on natalizumab's efficacy in treating MS clinical exacerbations
  - recommended a risk minimization program with mandatory patient registration and periodic follow-up to identify any further cases of PML as early as possible
  - Boxed Warning in label

Labeled Indication

- Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of disability and reduce the frequency of clinical exacerbations
- Because Tysabri increases the risk of [PML]…[it] is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, and alternative [MS] therapy

Return to Market

- Since 2006, natalizumab has only been available in the US through a risk minimization plan called Tysabri Outreach Unified Commitment to Health (the TOUCH™ Prescribing Program)
- TOUCH™ was developed by the FDA and the sponsor to ensure that patients and providers understand natalizumab's benefits and potential risks
- TOUCH™ allows the FDA to monitor both PML cases and the number of patients treated with natalizumab

The TOUCH™ Program

The TOUCH™ program requires:

1. Enrollment of all patients and prescribers
2. Prescribers must agree that patients have MS
3. A copy of a Medication Guide be given to patients prior to each infusion
4. Training and enrollment of infusion sites and affiliated central pharmacies
5. Completion of Pre-infusion Patient Checklists
6. Drug distribution to, and administration only in, authorized infusion sites
7. Prescriber authorization every 6 months

The TOUCH™ Program

- Critical Elements of TOUCH
  - A "positive" answer on any question on the pre-infusion checklist requires that the infusion not be given, and that the prescriber be called and specific permission obtained for the infusion to be given

The TOUCH™ Program

- Critical Elements of TOUCH
  - If the pre-infusion checklist is not returned to the sponsor (with some allowances), additional drug is not sent for that patient
  - This ensures that “no” patient receives drug without the checklist being employed

Other Risk Management Measures

- Healthcare professionals have been trained to monitor for signs and symptoms of PML
- Natalizumab labeling recommends baseline MRIs to assist in diagnosis of PML, especially in MS patients
- Patients treated with natalizumab must taper off any concomitant corticosteroids within 6 months of natalizumab treatment (CD indication only)

Subsequent actions/activities

- ***"Complete"*** follow-up has allowed examination of data that has led to identification of risk factors:
  - ***Duration of treatment:*** Risk increases with longer duration of treatment, especially with use for more than 2 years
  - ***Prior use of immunosuppressant drugs:*** Patients previously treated with other immunosuppressant drugs have a higher risk of PML
  - Currently examining ***JC Virus antibodies*** as a risk factor

Subsequent actions/activities

- Additional Labeling changes
- ***PLEX***
  - No known treatment of PML
  - PLEX accelerates clearance of Tysabri
  - Alpha-4 integrin binding remains high
- ***Immune Reconstitution Inflammatory Syndrome***
  - Occurs in majority of patients treated with PLEX

Subsequent actions/activities

- Multiple labeling changes have been made to describe risk factors, incidence of PML
- Multiple communications to the public to announce labeling changes, update incidence data
- Obviously, we keep a close watch on the incidence of PML; no regulatory action indicated at this time
- We are closely examining data on the patients with PML to learn about additional risk factors, response to treatment (plasmapheresis), cause of death, etc.
- Transforming the program to a Risk Evaluation and Mitigation Strategy (REMS)

Summary

- Cases of PML rapidly identified after initial marketing
- TOUCH program placed to apply safeguards and minimize risk to the extent possible
- TOUCH program allows real time incidence data, which results in real time labeling changes, communications to the public
- Does it really help?