PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

What's the big deal?

PML

- Disease of the white matter of the brain
- Polyomavirus JC (often called JC virus)
- Caused by a virus infection that targets cells that make myelin
- 50% population is antibody positive
- False negative (3-5%)
- Rare
- HIV population
- Treatment with biological therapies allow JC virus reactivation
SYMPTOMS

- Slow evolution
- Prominent symptoms:
  - Clumsiness
  - Progressive weakness
  - Visual changes
  - Speech changes
  - Personality changes
  - Seizures

DIAGNOSIS

- Abnormal magnetic resonance imaging (MRI)
  - Multifocal, bilateral, asymmetric, and predominantly subcortical lesions
- Detection of the JC virus in spinal fluid
- Brain biopsy
Reversal of the immune-deficient state

- Plasma exchange (PLEX) to accelerate the removal and enhances leukocyte transmigration

- Rapid correction in immunosuppression can lead to immune reconstitution inflammatory syndrome
  - 2–6 weeks later
  - Difficult to distinguish from progressive PML
  - Treated with high-dose corticosteroids
PROGNOSIS

- Mortality rate of 30-50 percent in the first few months
- Those who survive PML can be left with severe neurological disabilities

NATALIZUMAB

- Inhibits the influx of leukocytes into the central nervous system
- Blocks the [alpha]-4 subunit of very late activation antigen-4
- Prevents interaction of lymphocytes with endothelial ligand vascular cell adhesion molecule-1
- Induces a sustained decrease in T and B cells within the cerebrospinal fluid (CSF)
- Depletes dendritic cells in the perivascular spaces
- May influence natural killer cell immune surveillance in the CNS
- Inhibition of T cells is thought to be the main therapeutic benefit and toxicity
PML CASES IN MS PATIENTS TREATED WITH TYSABRI

- PML was first reported in patients treated with natalizumab (Tysabri) in 2005
- 588 confirmed cases were reported in over 142,000 patients (433,208 treatment years) who received at least 1 dose of natalizumab as of August 31, 2015
- Overall mortality associated with PML was 23% in December
- Estimated risk of PML = 4.1 / 1,000 patients
- Estimated rate of PML = 135.7 /100,000 patient years

RISK ASSESSMENT

- Anti-JCV serum antibodies
- Prior use of immunosuppressant medication
- Increased duration of treatment (25–49 infusions)
Natalizumab Risk Assessment

Anti-JCV Virus Antibody Status

- **Negativ**
  - Prior Immunosuppressant Use:
    - **No**
      - **1-24 months of Natalizumab exposure**
        - PML Cases (no.): 25
        - Patients Treated (no.): 11,625
        - PML Incidence per 100 Patients: 0.21 (0.07-0.63)
      - **25-48 months of Natalizumab exposure**
        - PML Cases (no.): 52
        - Patients Treated (no.): 44,711
        - PML Incidence per 100 Patients: 0.11 (0.03-0.31)
    - **Yes**
      - **1-24 months of Natalizumab exposure**
        - PML Cases (no.): 16
        - Patients Treated (no.): 20,382
        - PML Incidence per 100 Patients: 0.79 (0.1-2.6)
      - **25-48 months of Natalizumab exposure**
        - PML Cases (no.): 4,681
        - Patients Treated (no.): 16,043
        - PML Incidence per 100 Patients: 2.89 (0.9-8.3)

- **Positiv** (MS population < 50%)

Approx. every 90th patient develops PML.

The risk estimate for progressive multifocal leukoencephalopathy (PML) for patients on Natalizumab is based on data available until February 26, 2012. There were 211 confirmed cases of PML among 59,571 patients treated with Natalizumab (2.1 cases per 1000 patients). As of November 1, 2012, there have been 302 confirmed cases of PML worldwide.

The number of cases of PML represents the number of confirmed cases of PML with the characteristic of interest (i.e., positive or negative status with respect to anti-JCV virus antibodies, prior or no prior use of immunosuppressants, and duration of Natalizumab treatment). 1 to 24 months or 25 to 48 months in the postmarketing setting among patients treated with Natalizumab.

http://www.natalizumab.org

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RISK ASSESSMENT

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Negative</th>
<th>TYSABRI Exposure†</th>
<th>Anti-JCV Antibody Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prior Immunosuppressant Use</td>
<td>Prior Immunosuppressant Use</td>
</tr>
<tr>
<td>&lt;1/1,000</td>
<td>1/1,000</td>
<td>1/1,000</td>
</tr>
<tr>
<td>1-24 months</td>
<td>3/1,000</td>
<td>12/1,000</td>
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<tr>
<td>25-48 months</td>
<td>6/1,000</td>
<td>13/1,000</td>
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<tr>
<td>49-72 months</td>
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</tbody>
</table>

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.

†Data beyond 6 years of treatment are limited.

The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.
DIMETHYL FUMARATE

- Activates the nuclear erythroid 2-related factor 2 (NrF2) transcriptional pathway
- Brief period of oxidative stress results in the intraneuronal synthesis of the antioxidant glutathione (GSH) mediated through the Nrf2 pathway
- Proposed additional immunomodulatory actions mediated through nitric oxide, interleukins, tumor necrosis factor (TNF-α), or other cytokines

RISK ASSESSMENT

- JC virus seropositive
- Reduction of specific lymphocyte subpopulations
  + CD 4+
  + CD 8+
- Total lymphocyte below 800 cells per cubic millimeter
- Prolonged lymphopenia
PML IN TECFIDERA TREATED PATIENTS

- Cumulatively 4 cases of PML as of December 2015
- Patients exposed to dimethyl fumarate (Tecfidera) ~155,000 patients or 178,000 patient-years
- Estimated risk of PML = 0.019 / 1,000 patients
- Incidence rate of PML = 1.68 / 100,000 patient-years

PATIENT DETAILS: TECFIDERA

- Fatal case: 54yo female who received dimethyl fumarate for 4.5 years with prolonged lymphopenia <500 cells/mm3 for 3.5 years
- Non-fatal case: 64yo with PPMS treated with prolonged severe lymphopenia
- Non-fatal case: Patient with RRMS treated for 1.5 years and experienced prolonged lymphopenia
- Non-fatal case: 61yo 22 months of treatment had Grade 2 lymphopenia with 600 cells/mm3 for 6 months before developing symptoms
  + Patient had previously taken natalizumab for 6 years and 4 months
FINGOLIMOD

- Superagonist to sphingosine-1-phosphate receptors on the surface of thymocytes and lymphocytes
- Reduction of number of circulating lymphocytes
- Decreases available lymphocytes to mount immune response

RISK ASSESSMENT

- JC virus seropositive
- Perhaps lymphopenia
- 5 cases
SURVIVING PML

- Younger age at diagnosis
- Less functional disability prior to diagnosis
- Lower JC viral load at diagnosis
- More localized brain involvement by MRI at the time of diagnosis

CASE STUDY

- 36 y/o male
- Natalizumab monthly infusions- infusion #56
- Previous MS therapy includes interferon beta-1a (Rebif), glatiramer acetate (Copaxone)
- JCV antibody +
- Index 1.9
- Stable on current therapy
- Last MRI 3 months ago: no new lesions/no gad+ lesions
QUESTIONS

- What is his PML risk as we understand it?
- What would you tell the patient about PML?
- What is your experience with PML?
- What has PML presentation looked like in your practice?