Biologic Therapies in MS: Approved/Late-Stage Development

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Disclosures

Robert Fox has received personal consulting fees from Avanir, Allozyne, Biogen Idec, Novartis, Teva, and Xenoport.

In addition, research support, consultant and advisory committee fees from Biogen Idec and Novartis were paid to Cleveland Clinic.
**Multiple Sclerosis**

- MS is a chronic, inflammatory disorder of the brain and spinal cord

![MRI images of brain and spinal cord]

**Natural History of Relapsing MS**

- Relapses and Impairment
- MRI Activity
- Brain Atrophy

- Preclinical
- RR-MS
- SP-MS

10 FDA-approved therapies ~$12B/yr

No therapies with demonstrated efficacy

![Graph showing disease progression]

- Disease Duration (Years)
  - 0
  - 5-10
  - 15-20+

**MRI**
Biologic Therapies in MS
Approved/Late-Stage Development

- Natalizumab – FDA-approved
- Alemtuzumab – Phase III trials
- Dacluzumab – Phase III trials
- Rituximab – Phase II trial
  - Ocrelizumab – Phase III trials
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Selective Adhesion Molecule Inhibition

Blood Vessel → Endothelium → Brain Tissue

White blood cell

\[ \alpha^3\beta^1 \] (VLA-4)

Chemoattractant Signal

Reduced Brain Inflammation
Natalizumab and PML

As of April 2, 2013:

- 347 confirmed cases of natalizumab-related PML (among 112,200 patients exposed to natalizumab as of December 31, 2012)
  - Rate of 3.1 / 1000 natalizumab-treated patients
  - Total cases probably not helpful – incidence rate more important
- Overall incidence:
  - 4.81 / 1000 natalizumab-treated patients in EU
  - 2.03 / 1000 natalizumab-treated patients in US
- Presentation:
  - 21 cases (6.6%) were asymptomatic
- Outcome:
  - Symptomatic: 76.5% survival
  - Asymptomatic: 100% survival

Medical Information Services, Biogen Idec, 4-2013

Natalizumab and PML, post-re-approval

Incidence by Treatment Duration

As of April 2013

- Increasing incidence with cumulative exposure
- Plateau of risk after 24-36 infusions

Medical Information Services, Biogen Idec, 4-2013
**Natalizumab and PML**

**Incidence by Duration of Exposure**

**February 2010**

**April 2013**

PML incidence for each epoch of treatment exposure are more stable over time.

*Medical Information Services, Biogen Idec, 2-2010 & 4-2013*

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**Change in Incidence of Natalizumab-related PML over Time**

*Source: Medical Information Services, Biogen Idec, 2010-2013*
Natalizumab and PML

- Duration of natalizumab therapy: widely variable
- Prior treatment: 42% had prior chemotherapy treatment
  - ~25% with mitoxantrone
  - Comparison: ~12-20% of all natalizumab-treated MS patients have received chemotherapy prior to natalizumab
    - TYGRIS study: 13% in US; 24% in EU
  - Prior immunosuppressant therapy increases PML risk by about 2-4 fold
- Gadolinium-enhancement is quite common at presentation
- Cognitive, motor, language, and visual symptoms are most common
  - Seizures and paroxysmal events not uncommon at presentation
- About half have initial CSF viral load <500 copies
  - Need very sensitive PCR testing – Focus Lab’s “Ultrasensitive” JCV assay or NIH (Dr. Gene Major)
  - A “negative” JCV PCR isn’t always a negative
- Plasma exchange is standard treatment for natalizumab-related PML

D. Clifford, Lancet Neurology, 2010; Stangel et al, ECTRIMS 2009; Medical Information Services, Biogen Idec, 4-2013

Risk stratifying for PML

3 factors may predict risk of PML: JCV Ab status, prior chemotherapy, treatment duration

<table>
<thead>
<tr>
<th>JCV Ab negative</th>
<th>Prior Chemo-therapy?</th>
<th>Risk Before 24 mos therapy</th>
<th>Risk after 24 mos therapy</th>
<th>Lifetime Risk of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>~1:45,890*</td>
<td>~1:5,725*</td>
<td>Airplane crash 1:20,000</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>~1:16,184*</td>
<td>~1:2,019*</td>
<td>Drowning 1:8,942</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>JCV Ab positive</th>
<th>No</th>
<th>~1:1,147</th>
<th>~1:143</th>
<th>Fire/Smoke 1:1,116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>~1:405</td>
<td>~1:50</td>
<td>Car accident 1:100</td>
<td></td>
</tr>
</tbody>
</table>

* estimated; no cases yet reported

Clearly, natalizumab is a different therapy to different patients

Modified from Fox and Rudick, Neurol 2012;78:436-7
Natalizumab Summary

- Overall risk of PML has increased slightly to ~3:1000 overall
  - Risk of PML increases with cumulative exposure, but appears to plateau after 24-30 mos
  - Incidence will likely decrease over time with JCV serology testing
- 3 established risk factors:
  - JCV seropositivity
  - Previous immunosuppression
  - Duration of treatment (>2 years)
  - Possible risk factor: lower body weight?
- JCV serology testing has become standard-of-care
  - Start of therapy
  - Every six months during therapy
  - ? Possibly at MS diagnosis?
- FDA request is pending for first-line indication in JCV seronegative patients

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Alemtuzumab (Campath-1h)

- Humanized mab targeting CD52 cell surface antigen
  - CD52 - anonymous surface protein expressed by T-cells, B-cells, monocytes, and eosinophils
- Produces rapid, profound, and prolonged lymphocyte depletion
  - Followed by distinctive pattern of cell repopulation over time
- Approved for chronic lymphocytic leukemia (CLL)
  - Withdrawn from market by sponsor in preparation for MS approval; available from manufacturer through request
- Two Phase 3 clinical trials for relapsing-remitting multiple sclerosis (RRMS) vs SC IFNB-1a (Rebif)
  - CARE-MS I (treatment-naïve patients)
  - CARE-MS II (previously treated patients)

Alemtuzumab and Circulating Leukocytes

- Alemtuzumab rapidly and selectively depleted lymphocytes after each treatment course
- Other white blood cells, including neutrophils, monocytes, eosinophils and basophils were minimally or transiently affected

Lycke EFNS 2012
Alemtuzumab and Circulating Lymphocytes

- After alemtuzumab treatment, CD19 B-cells repopulate more rapidly than T-cells
- CD4 T-cells are particularly slow to repopulate
- Hypothetical autoimmune mechanism: “uneducated” B-cells, which lack T-cell training

Lycke EFNS 2012

CARE-MS I: Study Design and Enrollment

- Both treatment arms received 1 gm MP once daily x3 days at M0 and M12
- 97.6% of alemtuzumab and 92.5% of IFNB-1a patients completed the study
- Care-MS II had similar study design
  - initially included a 24 mg IV group, which was dropped

CARE-MS I: Relapse Rate

- 55% Rate Reduction
  - $p<0.0001$
  - $p<0.0001$

CARE-MS I & CARE-MS II

- **Efficacy - Relative to interferon-β1 (Rebif):**
  - 49-55% reduction in annualized relapse rate ($p<0.001$)
  - 42% reduction in sustained progression of disability ($p>0.01$)
    (CARE-MS II only)
  - 44% reduction in gadolinium-enhancing lesions ($p<0.001$) (CARE-MS II only)
  - 27% reduction in new or enlarging T2 lesions ($p=0.03$) (CARE-MS II only)
  - 23-42% reduction in progression of brain atrophy ($0=0.01$; $p<0.001$)

**CARE-MS I: Humoral Autoimmunity**

**Thyroid Disease**

- Increased rate of thyroid disorders
  - 18.1% alemtuzumab vs. 6.4% SC IFNB-1a
  - Hyperthyroidism most common

- Mostly mild-moderate in severity
  - 1.1% with serious alemtuzumab-associated thyroid events
    - 1 (0.3%) ophthalmopathy, 1 (0.3%) thyrotoxicosis (same patient)

- Detected through regular monitoring
  - Incidental findings of thyroid papillary carcinoma detected in 2 patients during thyroid screening; one had known nodule pre-treatment

- Most events managed by conventional oral medications

Coles et al, Lancet Neurology 2013

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**CARE-MS I: Thyroid Dysfunction**

<table>
<thead>
<tr>
<th>Patients with Events</th>
<th>IFNB-1a (N=187) n (%)</th>
<th>Alemtuzumab (N=376) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid AE based on clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>7 (3.7)</td>
<td>55 (14.6)</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>3 (1.6)</td>
<td>19 (5.1)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0 (0.0)</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>Thyroiditis*</td>
<td>4 (2.1)</td>
<td>18 (4.8)</td>
</tr>
<tr>
<td>Goiter</td>
<td>2 (1.0)</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>Thyroid mass</td>
<td>0 (0.0)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>Thyrotoxic crisis</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Thyroid AE based on laboratory findings</td>
<td>5 (2.7)</td>
<td>21 (5.6)</td>
</tr>
<tr>
<td>Thyroid SAE based on clinical findings</td>
<td>0 (0.0)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Thyroid SAE based on laboratory findings</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Onset month 3-24; peaked at month 24

Some patients were reported as having more than one thyroid event.

Coles et al, Lancet 2012
CARE-MS I: Humoral Autoimmunity
Immune Thrombocytopenic Purpura (ITP)

<table>
<thead>
<tr>
<th></th>
<th>IFNB-1a (N=187) n (%)</th>
<th>Alemtuzumab (N=376) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet-based* or SAE-based definition</td>
<td>3 (1.6)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Platelet-based* definition</td>
<td>3 (1.6)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>SAE-based definition</td>
<td>0</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

- Identified through routine monitoring and managed with medical treatment, including steroids, IVIg, rituximab
- No splenectomy required
- Patient and physician education, monthly questionnaires, and monthly CBC allowed early detection and intervention

*Confirmed platelet count ≥50,000/μL but <100,000/μL on at least 2 consecutive occasions over at least 1 month, or
Confirmed platelet count <50,000/μL without clumping documented on at least 2 consecutive occasions over any period of time

Coles et al, Lancet 2012

CARE-MS II: Autoimmune Adverse Events

<table>
<thead>
<tr>
<th>N (%)</th>
<th>IFNB-1a (n=202)</th>
<th>Alemtuzumab 12 mg/day (n=435)</th>
<th>Alemtuzumab 24 mg/day (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid AEs</td>
<td>10 (5.0)</td>
<td>69 (15.9)</td>
<td>31 (19.3)</td>
</tr>
<tr>
<td>Serious Thyroid AEs</td>
<td>0</td>
<td>2 (0.5)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>ITP AEs</td>
<td>0</td>
<td>4 (0.9)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Serious ITP AEs</td>
<td>0</td>
<td>3 (0.7)</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>

- Thyroid disorders
  - 94.3% mild or moderate in severity
  - Responded to standard treatment
  - No ophthalmopathy or thyrotoxicosis
- Immune thrombocytopenia
  - Detected through clinical and laboratory monitoring
  - Most responded to first-line treatment with prompt and sustained responses; 1 patient underwent splenectomy during the extension study

Cohen et al, Lancet 2012
Alemtuzumab Summary

- Anti-CD52 cell surface antibody, leading to profound lymphocyte depletion
- Clear efficacy in relapsing MS,
  - Perhaps somewhere between current oral therapies and natalizumab
- Humoral auto-immunity is main safety concern
  - Risk appears to continue several years after treatment
- It’s potential placement in MS treatment paradigm not yet clearly defined
- Status: under review by FDA
  - Risk MAP will be key focus

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Daclizumab Background

- Humanized MAb vs. IL-2Rα (CD25, Tac)
  - Mouse (~10%) CDR
  - Human (~90%) IgG1 constant and variable regions
- Biological activity
  - Binds at high affinity to IL-2Rα-chain blocking IL-2 binding and subsequent signaling
  - Inhibits T-cell and B-cell activation by IL-2
  - Down modulates IL-2Rα on activated T-cells
- Approved for prevention of renal allograft rejection by FDA (1997) and EMEA (1999)
  - Marketed as Zenapax® (Roche)
- Also studied in other transplants, lymphoproliferative disorders, HTLV-I associated myelopathy, uveitis, psoriasis, aplastic anemia, pure red cell aplasias

Daclizumab Mechanism of Action

- Binds at high affinity to IL-2Rα-chain blocking IL-2 binding and subsequent signaling
- Inhibits T-cell and B-cell activation by IL-2
- Down modulates IL-2Rα on activated T-cells
Daclizumab - Potential Mechanisms

- Inhibition of binding to high-affinity IL-2 receptor on T-cells
  -> blocks signaling, proliferation
- Antagonism of IL-2-driven B-cell proliferation and Ab production
- Down-modulation of IL-2Rα
- Depletion IL-2Rα-expressing cells via complement-fixation or ADCC
- Induction of regulatory mechanisms

SELECT Phase III RRMS Trial

621 patients randomly assigned

- Subcutaneous placebo every 4 weeks
- Subcutaneous daclizumab HYP 150 mg every 4 weeks
- Subcutaneous daclizumab HYP 300 mg every 4 weeks

52 week treatment period | 20 week follow-up or extension study

Gold et al, Lancet 2013 (epub ahead of print)
SELECT Phase III RRMS Trial

- **Efficacy - Relative to Placebo:**
  - 50-54% reduction in annualized relapse rate (p<0.001)
  - 43-57% reduction in sustained progression of disability (p=0.02 in lower dose group only)
  - 69-78% reduction in gadolinium enhancing lesions (p<0.001)
  - 70-79% reduction in new or enlarging T2 lesions (p<0.001)

- **Safety:**
  - 2% incidence of serious infections (vs none in placebo)
  - Single cases of serious adverse events: autoimmune thyroiditis, Crohn’s disease, hypersensitivity, lymphadenopathy
  - 1.4% incidence serious cutaneous events: rash, atopic dermatitis, allergic dermatitis, exfoliative dermatitis, erythema nodosum
    - One death from psoas abscess in patient with serious rash

Gold et al. Lancet 2013 (epub ahead of print)

Daclizumab Summary

- IL-2-receptor targeted therapy
- Clear efficacy in relapsing MS, although not clearly superior to current oral therapies
- Increased serious infections (Ph II, Ph III)
- Serious cutaneous events (Ph II, Ph III)
- It’s potential placement in MS treatment paradigm not yet clearly defined
- Status: not yet submitted to FDA
Summary
Biologic Therapies in MS

- Biologic therapies used in MS target various aspects of immune response
  - Immune cell ablation, cell trafficking, cytokines
- Efficacy varies between very good and excellent
- Safety concerns vary depending upon the therapy, but each have serious risks
  - Strong safety of current oral therapies presents a significant challenge for biologics
- Neutralizing antibodies can develop and (at least with some therapies) abrogate efficacy

Thank you for your attention!