Treatment of Multiple Sclerosis
Navigating the Unlit Path
Anna Scieglenka, PharmD

Multiple Sclerosis (MS)
~ A chronic, inflammatory, demyelinating disease of the central nervous system
~ Highly variable and unpredictable
~ Characteristics
  ~ Numerous affected brain/spinal cord areas
  ~ Plaques (sclerosed areas)

Etiology

- Geography
  • Higher rates with increasing distance from the Equator

- Environment
  • UV exposure/Vitamin D
  • Smoking
  • Infections

- Age
  • Onset: 15 – 50 years
  • Average: 29.1 years

- Genetics
  • Female:Male ~ 2:1
  • Monozygotic twins: 25%
  • Various genes

Immunopathophysiology

Pathophysiology

Presenting Symptoms

Weakness or Spasticity
Sensory Problems/Fatigue
Visual Disturbances
Balance Disturbances
Bladder/Bowel Problems
Pain
Cognitive/Behavioral Problems
Sexual Dysfunction

% Reported at Presentation

Tullman, 2013.

Aharoni, 2013.

Nerve fibers, 2013.

Guido, 2013.
Diagnosis
~ Diagnosis of exclusion
~ McDonald Criteria
  ~ Established in 2001; revised in 2005, 2010
  ~ Requires
    ~ 1+ episode of neurologic dysfunction
    ~ Absence of fever/infection x 24 hours
    ~ Objective evidence disseminated in time and space
      (clinically or MRI)
~ Physical exam, eye exam, history, MRI, and CSF evaluation help diagnose MS

Tullman, 2013.

Magnetic Resonance Imaging

T<sub>1</sub> gadolinium-enhanced

Lesions that enhance after injection of gadolinium
T<sub>2</sub> contrast reflect new lesions or changes

Types of MRI, 2013.

Clinical Classifications
~ Clinically isolated syndrome (CIS)
~ Radiologically isolated syndrome (RIS)
~ Relapsing-remitting MS (RRMS)
~ Secondary-progressive MS (SPMS)
~ Primary-progressive MS (PPMS)
~ Progressive-relapsing MS (PRMS)

Clinical Classifications

Time
RRMS
SPMS
PPMS
PRMS

Lublin and Reingold, 1996.

Favorable Prognosis Indicators
Age <40 years at onset
Female gender
Initial symptoms of optic neuritis or sensory symptoms
Low attack frequency in early disease
Relapsing-remitting MS

Tullman, 2013.

What’s his prognosis?
~ BR is a 30 year old male with an 8 year history of relapsing-remitting multiple sclerosis. His initial presentation included bilateral hand numbness. He has relapsed 13 times in the past 8 years. BR’s MS has progressed over the past 2 years, including onset of neurogenic bladder with urinary urgency and development of muscle spasms.
~ What factors contribute to a…
  … favorable prognosis?
  … poor prognosis?
Goals of Therapy

- Reduce Relapses
- Prevent Progression
- Minimize New MRI Lesions
- Manage Symptoms
- Restore Function
- Maintain or Improve Quality of Life

Therapeutic Considerations

- Management of Relapses
- Symptomatic Treatment
- Disease Modifying Therapy (DMT)

Disease Modifying Therapies

- Alter the natural course of MS
- Diminish progressive disability over time
- Effects seen in months to years
  - Fewer exacerbations/hospitalizations
  - Slowed disease progression/disability
  - Best evidence in relapsing-remitting MS
  - Little evidence for other classifications
- Consider initiation as soon as possible

Good Therapeutics, Good Safety, and Good Value in that order…

- Bruce Alexander

The path behind us…

1993 IFN β-1b
1996 IFN β-1a (IM)
1997 Glatiramer Acetate
1998 AAN Guidelines
2000 Mitoxantrone
2002 IFN β-1a (SC)
2004 '07 '01 '04 '10 '13

Interferon beta (IFNβ)

- Impairs lymphocyte egress
- Hinder activated T cell migration across BBB
- Decreases antigen-presenting cells
- Down-regulates inflammatory response pathways
- Apoptosis

Goverman and Ransohoff, 2013
Interferon beta (IFNβ)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>IFNβ-1b</th>
<th>IFNβ-1a</th>
<th>IFNβ-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaseron</td>
<td>Avonex</td>
<td>Rebif</td>
<td></td>
</tr>
<tr>
<td>Approval Date</td>
<td>1993</td>
<td>1996</td>
<td>2002</td>
</tr>
</tbody>
</table>

**Route of Administration**
- Subcutaneous (90° angle)
- Intramuscular
- Subcutaneous

**Dose**
- 0.25 mg every other day
- 30 mcg once weekly
- 22 or 44 mcg three times weekly

**Product**
- Vial
- Syringe
- Autoinjector

**Precautions**
- Myelosuppression, Hepatic injury, Depression/Suicide
- Pregnancy Category C

**Adverse Effects**
- Flu-like symptoms, Injection site reactions, Mood disturbances

**Financial Assistance**
- BETAPLUS: $0 monthly copay, $9,500/year limit
- Active/Access: $10/monthly copay, Income-based cap
- MS Lifelines: $0 monthly copay

---

Glatiramer Acetate (Copaxone)

**Mechanism of Action**
- Immunomodulation (periphery and CNS)
- Reduces CNS injury
- Involved in remyelination and neurogenesis

**Dose and Route**
- 20 mg subcutaneously daily

**Product**
- Prefilled syringe

**Precautions**
- Lipatrophy/Skin necrosis
- Chest pain
- Pregnancy Category B

**Adverse Effects**
- Immediate post-injection reactions

**Financial Assistance**
- Copaxone Shared Solutions: $35 per month copay after private insurance

---

Mitoxantrone (Novantrone)

**Indication**
- SPMS, PRMS, or worsening RRMS. Not for use in PPMS.

**Mechanism of Action**
- Inhibits B cell, T cell, and macrophage proliferation; impairs antigen presentation; inhibits secretion of IFNγ, TNFα, and IL-2

**Dose and Route**
- 12 mg/m² IV infusion (over 5-15 min) every 3 months
- Not to exceed a lifetime dose of 140 mg/m²

**Black Box Warnings**
- Congestive Heart Failure
- Secondary acute myeloid leukemia

**Precautions**
- Blue-green discoloration of urine and sclera
- Hepatic impairment
- Pregnancy Category D

**Adverse Effects**
- Nausea, Alopecia, Menstrual disorders, Depression

---

2002 AAN Guidelines

**Interferon (IFN) beta**
- Reduces attack rate in CIS and MS (A)
- Appropriate for RRMS or SPMS with relapses (A)
- Route of administration probably not important for efficacy (B), but side effect profiles differ
- Associated with production of neutralizing antibodies (A), but less commonly with INFβ-1a than with INFβ-1b (B)

**Glatiramer Acetate**
- Reduces attack rate in RRMS (A)
- Appropriate to consider for treatment (A)

**Mitoxantrone**
- Probably reduces attack rate in relapsing forms of MS (B)
- Potential toxicity may outweigh benefit

---

Outcome Measures

- Annualized Relapse Rate
- Expanded Disability Status Scale (EDSS)
- Lesions on MRI
Expanded Disability Status Scale (EDSS)

0 – normal neurologic examination
1 – no disability, minimal signs
2 – minimal disability
3 – moderate disability
4 – disability not preventing normal activities
5 – disability limiting walking to few blocks
6 – assistance required to walk
7 – restricted to wheelchair but self-moving
8 – restricted to bed or chair but with arm function
9 – confined to bed
10 – death due to MS


The path behind us...

1993 IFN β-1b
1997 Glatiramer Acetate
2002 IFN β-1a (SC)
2000 Mitoxantrone
2004 Natalizumab

Natalizumab (Tysabri)


AFFIRM

Design Randomized, double-blind, placebo-controlled, phase 3 clinical trial
Duration 2 years
Patients 942 patients diagnosed with RRMS, EDSS score between 0.0 and 5.0, and relapse documented within previous year
Intervention Natalizumab 300 mg IV every 4 weeks
Control Placebo
Objective To confirm the efficacy and safety of natalizumab in relapsing MS

Polman, et al. 2006.

AFFIRM – Efficacy

Primary end point at 2 years: cumulative probability of sustained disability progression

Polman, et al. 2006.

<table>
<thead>
<tr>
<th>End Points</th>
<th>1 Year</th>
<th>2 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Natalizumab (n = 627)</td>
<td>Placebo (n = 315)</td>
</tr>
<tr>
<td>Annualized Relapse Rate</td>
<td>0.23* (0.19 - 0.28)</td>
<td>0.73 (0.62 - 0.87)</td>
</tr>
<tr>
<td>Proportion of relapse-free patients</td>
<td>501 (80%)</td>
<td>189 (60%)</td>
</tr>
<tr>
<td>Mean number of new or enlarging T2 hyperintense lesions</td>
<td>1.2 ± 4.7</td>
<td>6.1 ± 9.0</td>
</tr>
<tr>
<td>Mean number of Gd-enhancing lesions</td>
<td>0.1 ± 1.3</td>
<td>1.3 ± 3.2</td>
</tr>
</tbody>
</table>

*Primary end point

Polman, et al. 2006.
**AFFIRM – Safety**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Natalizumab (n = 627) % of patients</th>
<th>Placebo (n = 312) % of patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>38</td>
<td>33</td>
<td>0.137</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>21</td>
<td>0.048</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>9</td>
<td>4</td>
<td>0.012</td>
</tr>
<tr>
<td>Infection</td>
<td>17</td>
<td>17</td>
<td>0.257</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>20</td>
<td>17</td>
<td>0.257</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>17</td>
<td>16</td>
<td>0.644</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>11</td>
<td>9</td>
<td>0.328</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>10</td>
<td>8</td>
<td>0.133</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>7</td>
<td>5</td>
<td>0.291</td>
</tr>
</tbody>
</table>

Polman, et al. 2006.

**Progressive Multifocal Leukoencephalopathy**

- Opportunistic infection caused by the JC virus
- Symptoms
  - Progressive weakness
  - Clumsiness in limbs
  - Vision disturbances
  - Confusion and personality changes
  - Severe disability leading to death
- Risks in natalizumab-treated patients
  - Longer treatment duration
  - Prior treatment with immunosuppressants
  - Presence of anti-JC virus antibodies

Tysabri, 2013.

**The TOUCH Program**

- Prescribers, pharmacies, and patients receiving natalizumab must be enrolled
- Helps patient locate an infusion center and coordinates follow-up appointments
- **Tysabri ActiveAccess**
  - $10/month copay for commercially insured
  - Plus $100/month allowance for infusion copays
  - Separate assistance for patients insured through a public payer

The Tysabri TOUCH Prescribing Program, 2013.

**Fingolimod (Gilenya)**

Pelletier and Hafer, 2012.

**TRANSFORMS**

**Design**
Randomized, double-blind, double-dummy, parallel-group, phase 3 trial

**Duration**
12 months

**Patients**
1292 patients diagnosed with RRMS with recent history of relapse

**Intervention**
- Fingolimod 0.5 mg PO daily
- Fingolimod 1.25 mg PO daily

**Control**
- Interferon β-1a (Avonex) 30 mcg IM weekly

**Objective**
To compare the efficacy and safety of fingolimod with Avonex

TRANSFORMS – Efficacy

Primary end point: annualized relapse rate

- Adjusted Annualized Relapse Rate
  - Avonex
  - Fingolimod 0.5 mg
  - Fingolimod 1.25 mg


---

TRANSFORMS – Safety

- Cardiovascular
  - Bradycardia
    - 2.4% in fingolimod 1.25 mg group (n = 420)
    - 0.5% in fingolimod 0.5 mg group (n = 429)
  - Atrioventricular block
    - 3 patients in fingolimod 1.25 mg group
    - 1 patient in fingolimod 0.5 mg group

- Macular edema
- Skin cancer
- Infections


---

TRANSFORMS – Efficacy

- Mean number of new or enlarged lesions on T2-weighted images:
  - Fingolimod 1.25 mg (n = 420): 1.5 ± 2.7 (p < 0.001)
  - Fingolimod 0.5 mg (n = 429): 1.7 ± 3.9 (p = 0.004)
  - Avonex (n = 431): 2.6 ± 5.8

- Mean number of Gd-enhancing lesions on T1-weighted images:
  - Fingolimod 1.25 mg (n = 420): 0.14 ± 0.58 (p < 0.001)
  - Fingolimod 0.5 mg (n = 429): 0.23 ± 0.97 (p < 0.001)
  - Avonex (n = 431): 0.51 ± 1.86

- % of patients with no confirmed disability progression:
  - Fingolimod 1.25 mg (n = 420): 93.3 (p = 0.50)
  - Fingolimod 0.5 mg (n = 429): 94.1 (p = 0.25)
  - Avonex (n = 431): 92.1

- Mean change in EDSS score from baseline:
  - Fingolimod 1.25 mg (n = 420): -0.11 ± 0.90 (p = 0.02)
  - Fingolimod 0.5 mg (n = 429): -0.08 ± 0.79 (p = 0.06)
  - Avonex (n = 431): 0.01±0.78


---

MJ is a 43 year old Caucasian woman with a 10 year history of relapsing-remitting multiple sclerosis. She currently uses Betaseron (interferon β-1b) 0.25 mg subcutaneously every other day.

MJ recently relapsed and is experiencing residual weakness in her hands, which makes it difficult for her to self-administer injections.

She would like to try a different disease modifying agent. MJ is positive for anti-JC virus antibody. Which disease modifying agent would be most appropriate for MJ?

A. Natalizumab (Tysabri)
B. Fingolimod (Gilenya)
C. Glatiramer acetate (Copaxone)
D. Continue her current regimen

---

**Gilene Go Program**

1. Physician faxes paperwork
2. Benefit investigation is conducted
   - Insurance company chooses specialty pharmacy
   - Potential $0 monthly copay
   - Up to $12,000/year in drug copay assistance
3. Patient completes baseline labs, ECG, and eye exam
   - Up to $600 medical copay reimbursement
4. Patient is instructed to receive the first dose at an outpatient urgent care clinic or a doctor’s office
   - Must be monitored for 6 hours post-administration
5. Specialty pharmacy mails fingolimod to patient
6. “Just one pill, once a day.”

GileneGo-Program, 2013.

---

**The path behind us...**

- 1993 INF β-1b
- 2002 INF β-1a (SC)
- 2006 Natalizumab
- 2012 Teriflunomide

- 1996 INF β-1a (IM)
- 2000 Mitoxantrone
- 2004 Natalizumab
- 2010 Fingolimod

- 1997 Glatiramer Acetate
- 2007 Natalizumab
- 1998 INF β-1b
- 2013 Teriflunomide

- 1995 INF β-1b

---

**MJ is a 43 year old Caucasian woman with a 10 year history of relapsing-remitting multiple sclerosis. She currently uses Betaseron (interferon β-1b) 0.25 mg subcutaneously every other day. MJ recently relapsed and is experiencing residual weakness in her hands, which makes it difficult for her to self-administer injections. She would like to try a different disease modifying agent. MJ is positive for anti-JC virus antibody. Which disease modifying agent would be most appropriate for MJ?**

A. Natalizumab (Tysabri)
B. Fingolimod (Gilenya)
C. Glatiramer acetate (Copaxone)
D. Continue her current regimen
Teriflunomide (Aubagio)

- TERiflunomide is TE RATogenic!
  - Pregnancy category X
  - Males and females should avoid teriflunomide use if pregnancy is possible

- Accelerated Elimination Procedure
  - Cholestyramine or activated charcoal x 11 days
  - If not utilized, teriflunomide is detectable for 8 months to 2 years after discontinuation!

TENERE

**Design**  Randomized, rater-blinded, parallel-group, phase 3 trial

**Duration**  48 weeks

**Patients**  324 adult patients diagnosed with relapsing MS and EDSS ≤5.5 at time of screening

**Intervention**  Teriflunomide 7 mg PO daily
Teriflunomide 14 mg PO daily

**Control**  Interferon β-1a (Rebif) 44 mcg SC three times weekly after initial titration

**Objective**  To compare efficacy, safety, and tolerability of teriflunomide to Rebif in patients with RMS

### TENERE – Efficacy

**Primary end point: time to failure**

<table>
<thead>
<tr>
<th></th>
<th>IFNβ-1a (n = 104)</th>
<th>Teriflunomide 7mg (n = 109)</th>
<th>Teriflunomide 14mg (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure, n (%)</td>
<td>44 (42.3)</td>
<td>53 (48.6)</td>
<td>42 (37.8)</td>
</tr>
<tr>
<td>Confirmed relapse</td>
<td>16 (15.4)</td>
<td>46 (42.2)</td>
<td>26 (23.4)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>25 (24.0)</td>
<td>7 (6.4)</td>
<td>15 (13.5)</td>
</tr>
</tbody>
</table>

### TENERE – Safety

<table>
<thead>
<tr>
<th></th>
<th>Teriflunomide 7mg (n = 110)</th>
<th>Teriflunomide 14mg (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>103 (93.6%)</td>
<td>102 (92.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25 (22.7)</td>
<td>23 (20.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>28 (25.5)</td>
<td>22 (20.0)</td>
</tr>
<tr>
<td>Hair Thinning</td>
<td>6 (5.5)</td>
<td>22 (20.0)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>14 (12.7)</td>
<td>11 (10.0)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>10 (9.1)</td>
<td>11 (10.0)</td>
</tr>
</tbody>
</table>

Teriflunomide, 2012.

Aubagio One to One Program

- **Financial Assistance**
  - First 3 prescription fills at no charge
  - $10 copay per 28-day supply, if eligible
  - Mailed from specialty pharmacy
  - May renew participation every 12 months

- **Baseline**
  - Pregnancy test, liver function tests, CBC, TB test, blood pressure

- **Liver function tests monthly x 6 months**
The path behind us...

1993 IFN β-1b  
1997 Glatiramer Acetate  
2002 IFN β-1a (SC)  
2006 Natalizumab  
2012 Teriflunomide

1996 IFN β-1a (IM)  
2000 Miloxantrone  
2004 Natalizumab  
2009 Fingolimod  
2013 Dimethyl Fumarate

Dimethyl Fumarate (Tecfidera)

Dimethyl Fumarate

Monomethyl Fumarate

CONFIRM

Design  Randomized, double-blind, placebo-controlled, phase 3 study
Duration  96 weeks
Patients  1430 adult patients diagnosed with relapsing MS and EDSS ≤5.5 at time of screening
Intervention  Dimethyl fumarate 240 mg PO BID  
Dimethyl fumarate 240 mg PO TID
Control  Placebo  
Glatiramer acetate (reference comparator)
Objective  To evaluate the efficacy and safety of dimethyl fumarate in patients with relapsing-remitting multiple sclerosis

CONFIRM – Efficacy

Primary end point: annualized relapse rate at 2 years

<table>
<thead>
<tr>
<th>Placebo (n = 363)</th>
<th>BID DF (n = 359)</th>
<th>TID DF (n = 345)</th>
<th>GA (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Relapse Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.40</td>
<td>0.22</td>
<td>0.20</td>
<td>0.29</td>
</tr>
</tbody>
</table>

CONFIRM – Safety

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n = 363)</th>
<th>BID RG-12 (n = 359)</th>
<th>TID RG-12 (n = 344)</th>
<th>Glatiramer (n = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>333 (92%)</td>
<td>338 (94%)</td>
<td>316 (92%)</td>
<td>304 (87%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>13 (4)</td>
<td>110 (31)</td>
<td>85 (25)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (8)</td>
<td>45 (13)</td>
<td>50 (15)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (8)</td>
<td>40 (11)</td>
<td>51 (15)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Upper Abdominal Pain</td>
<td>17 (5)</td>
<td>36 (10)</td>
<td>33 (10)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>38 (10)</td>
<td>44 (12)</td>
<td>41 (12)</td>
<td>35 (10)</td>
</tr>
</tbody>
</table>
**Tecfidera ActiveAccess**

~ $10 monthly drug copay for eligible patients with private insurance
~ No limits on duration
~ Prescriptions mailed from specialty pharmacy
~ Store in original container!
~ Peer mentors and nurses

**MATCH FACT THAT**

<table>
<thead>
<tr>
<th>Accelerated Elimination Procedure</th>
<th>Natalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML</td>
<td>Fingolimod</td>
</tr>
<tr>
<td>Flushing</td>
<td>Teriflunomide</td>
</tr>
<tr>
<td>AV Block</td>
<td>Dimethyl Fumarate</td>
</tr>
</tbody>
</table>

**Illuminating the Path Ahead**

Alemtuzumab (Lemtrada)
Laquinimod
Daclizumab
Firategrast
Ocrelizumab
Siponimod
Mastinib

**Illuminating the Path**

Disease modifying therapies diminish progression and disability
Relapsing-remitting is the most common classification of MS
There are no known DMTs approved for primary-progressive MS
Parenteral DMTs include IFNβ-1a and -1b, glatiramer acetate, mitoxantrone, and natalizumab
Oral DMTs include fingolimod, teriflunomide, and dimethyl fumarate
New DMTs are in phase II and III trials – keep an eye out for these agents in the coming years!