Integrating New Treatments: A Case Based Approach

JILL CONWAY, MD, MA, MSCE
DIRECTOR, MS CENTER
DIRECTOR, NEUROLOGY CLERKSHIP AT UNCSOM-CHARLOTTE CAMPUS
CAROLINAS HEALTHCARE CENTER
Objectives

- Provide a context for balancing risk and benefit
- Review comparative data among various MS therapies
- Examine cases that cover the MS spectrum
Current and Emerging Therapies

**FDA-Approved Therapies**

- **Injectable/Infusion Therapy**
  - Copaxone®
  - Avonex®
  - Novantrone®
  - Rebif®
  - Extavia®
  - Plegridy
  - PegIFN B-1a
  - Lemtrada
  - Alemtuzumab

- **Oral Therapy**
  - Gilenya™
  - Aucabio®

**Coming Soon?**

- Generic Glatiramer Acetate
- Laquinimod
- Ocrelizumab
- Daclizumab
## Choices and More Choices

<table>
<thead>
<tr>
<th>Injections</th>
<th>Oral Medications</th>
<th>Infusion Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferons</td>
<td>Fingolimod</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>Teriflunomide</td>
<td>Natalizumab</td>
</tr>
<tr>
<td></td>
<td>Dimethyl Fumarate</td>
<td>Alemtuzumab</td>
</tr>
</tbody>
</table>
How to Navigate These Choices?

- Do the medications all have the same efficacy?
- How does safety balance with efficacy?
- How much disease breakthrough is too much?
- Are we doing the best we can for our patients in terms of efficacy? Quality of life? Prevention of disability?
Relapse Rates from Pivotal Trials

** Compared to Interferon, Not Placebo
## Relapse Rates in Placebo Groups

<table>
<thead>
<tr>
<th>RRMS placebo group</th>
<th>Recruitment start date</th>
<th>Annualized relapse rate (2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal IFN beta-1b study(^{11})</td>
<td>Jun 1988</td>
<td>1.27</td>
</tr>
<tr>
<td>Pivotal GA study(^{13})</td>
<td>Oct 1991</td>
<td>0.84</td>
</tr>
<tr>
<td>MSCRG(^{12*})</td>
<td>Nov 1990</td>
<td>0.90</td>
</tr>
<tr>
<td>PRISMS(^{14})</td>
<td>May 1994</td>
<td>1.28(^{†})</td>
</tr>
<tr>
<td>AFFIRM(^{6})</td>
<td>Nov 2001</td>
<td>0.73</td>
</tr>
<tr>
<td>CLARITY(^{7})</td>
<td>Apr 2005</td>
<td>0.33</td>
</tr>
<tr>
<td>FREEDOMS(^{8})</td>
<td>Jun 2006</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Interferon High Dose (Rebif) Relapse Rates

- PRISMS (1994): 0.88
- EVIDENCE (1999): 0.53
- CAMMS (2002): 0.34
- REGARD (2004): 0.30
Case I: RRMS

- 46 yo male
  - Noted red desaturation 8 years ago
  - Diagnosed 6 years ago after vertigo
  - One C spine lesion at diagnosis
- Started a DMT, platform high-dose interferon
- Full recovery from initial symptoms
- No further relapses
- No change on MRI
Case I: Stability

- No change on MRI over 6 years
- No relapses
- No change in exam
- Tolerates therapy well
Long-Term Efficacy of Interferon B-1b

Long-term Efficacy of Glatiramer Acetate

Ford, C et al. Multiple Sclerosis. 16(3) 342-350.
MS and Mortality

- MS usually not thought of as fatal
- Few mortality studies
- Original Betaseron trial cohort was
  - Followed for 21 years
  - 98.4% (366 of 372) identified
  - Original cohort on DMT vs placebo for 5 years before open label
  - Death increased in placebo group
  - With hazard ratio of 0.532
MS and Mortality

**Proportion of patients who are still alive (%)**

- **IFNβ-1b 250 µg**: Black line
- **Placebo**: Red line

**HR = 0.532 (95% CI 0.314-0.902)**

- 46.8% reduction in hazard rate
- Log-rank, $p = 0.0173$

**At risk (n):**
- IFNβ-1b 250 µg: 124, 124, 121, 118, 104
- Placebo: 123, 120, 117, 109, 88

*Goodin et al, Neurology® 2012;78:1315–1322*
Multiple studies examined and average shows life expectancy reduction of 7 to 14 years in MS patients compared to healthy controls.

At least 50% of patients die from MS related causes.

MS can be devastating with impacts on mortality and morbidity:
- Risks of therapy need to be taken in context.

Case I: RRMS - Stability

- Male
- Spinal cord lesions at diagnosis and diagnosed with brainstem syndrome
- Older at diagnosis
- Despite some risk factors, no progression or relapses, or changes on MRI on first-line therapy
- Alternatives for quality of life issues?
- If it’s not broken, no need to fix it
Case II: RRMS - More Complicated

- 30 yo male

- Diagnosed after one week of bilateral hand weakness and numbness in his feet with L’hermitte’s sign

- History of blurry vision in the right eye 5 years previously
Initial MRI at diagnosis
Initial spinal cord MRI
Case II: Treatment history

- Started on a platform DMT but multiple steroid courses in the first year
- Initially changed to another platform therapy, with continued disease progression and relapses
Disease activity while on therapy
Disease activity while on therapy
Relapse Rates from Pivotal Trials

** Compared to Interferon, Not Placebo
Teriflunomide and IFN B-1a SC

Dimethyl Fumarate and Glatiramer

CONFIRM trial

Alemtuzumab and Interferon B-1a subq

**ARR: Years 0–2**

- **IFNB-1a SC 44 µg** (n=202): 0.52
- **LEMTRADA 12 mg** (n=426): 0.26

49% reduction, P<0.0001

**Time to 6-month SAD**

- **IFNB-1a SC 44 µg**:
  - HR: 0.58
  - 42% reduction, P=0.0084

- **LEMTRADA 12 mg**:
  - 21%

Care MS II, 55% ARR reduction for Care MS I

DMT Safety and Efficacy

Comparative Safety

- PML cases on natalizumab, dimethyl fumarate, and fingolimod
  - 514 PML cases on natalizumab through December, 2014
    - (255/258 with JCV antibody samples were positive)
    - Total treated patient > 132,000, overall incidence 3.78/1000
  - 1 confirmed PML case on Tecfidera with others on DMF
  - 1 PML case reports on fingolimod in February, 2015

- Autoimmunity with alemtuzumab
- Other infections – herpes, shingles
- Does JCV antibody index matter for fingolimod or DMF? Lymphocyte counts? CD4/CD8 subsets?
Comparative Efficacy

- Alemtuzumab reduced relapses more than high-dose interferon

- Fingolimod reduced relapses more than IM interferon

- Looking across trials, there appears to be differential efficacy among therapies
  - Experience with natalizumab and fingolimod supports the significant ARR reduction and MRI findings in the trials
More Risk – More Reward

A

![Graph showing EDSS scores for Interferon beta 1a and Alemtuzumab 12 mg over time.]

Number of observations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta 1a</td>
<td>202</td>
</tr>
<tr>
<td>Alemtuzumab 12 mg</td>
<td>426</td>
</tr>
</tbody>
</table>

EDSS score over time:

- Interferon beta 1a: 198, 194, 190, 185, 180, 176, 172, 174
- Alemtuzumab 12 mg: 419, 419, 419, 422, 415, 410, 413, 413
Case II: Treatment History

- Successfully treated with natalizumab for 18 months, but has high JCV antibody index

- Tried two oral therapies, with MRI changes and relapses on each

- Plans to start alemtuzumab

- More aggressive therapy needed in more aggressive disease
Case III: Just a little badness

- 32 yo female diagnosed with MS at age 26
  - Initial episode of numbness in her toes for one month
  - Two years later, optic neuritis leads to diagnosis
  - Initial MRI shows few brain lesions and one T spine lesion
  - Started on a platform DMT but developed L’hermitte’s sign and MRI showed enhancing C spine lesion
  - She changed to another DMT
Case III: Just a little badness

- She felt well on her therapy
- She had no clear relapses or changes on MRI for two years
- After two years, repeat MRI revealed two new lesions
MRI on second DMT
MRI on second DMT
Natural Progression of MS

- **Subclinical**
  - Initial demyelinating event

- **Monosymptomatic**
  - Clinically definite MS

- **Relapsing–Remitting**

- **Secondary Progressive**
  - Relapse

- **Time**
  - Increasing disability

- **Level of disability**
- Accumulated MRI lesion burden
- Cognitive dysfunction
- Brain volume
- Acute (new and Gd+) MRI activity
Relapses and Disability


Effect of relapses on development of residual deficit in multiple sclerosis.
More lesions, More Disability

Lesions predict later disability

<table>
<thead>
<tr>
<th>No. of New Lesions</th>
<th>Patients with Worsening Disability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>1</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>73%</td>
</tr>
<tr>
<td>≥3</td>
<td>83%</td>
</tr>
</tbody>
</table>

Most lesions are clinically silent but MRI change predicts disability.

Should NEDA be our standard?

- No Evidence of Disease Activity
  - No changes on MRI
  - No relapses
  - No evidence of disability progression
  - Perhaps to include measure of cognition, mood, QOL

- Is this too difficult?

Rotstein et al. JAMA Neurol. 2015 Feb 1;72(2):152-8.
Clinical Disability and MRI

Positive indicates disease activity; negative indicates no disease activity.

Case III: Just a little badness

- Two new lesions on MRI predicts worse outcome
- She has been on two DMTs and there are many, many others
- With many choices available, MRI changes can indicate need for treatment change
MRI in monitoring

- Gd+ lesions and new T2 lesions predict poor outcome
- MRI lesions 5-10 times more common than symptoms
- MRI 6 months after change of therapy to assess effectiveness
- Consider alternatives if active disease
New and Exciting

- Pipeline: ocrelizumab

- Progressive MS
  - Recent disappointments, still seeking options and ongoing trials
General Thoughts, Personal Thoughts

- **Safer Medications:**
  - Interferons, Glatiramer acetate

- **Stronger Medications:**
  - Natalizumab, Fingolimod, Alemtuzumab

- **Better Tolerated Medications:**
  - Natalilzumab, Fingolimod, Teriflunomide

- **Personal Experience vs Trial Experience**
  - The plural of anecdote is not data, but different populations
Summary

- No need to change a good thing
  - But make sure it really is a good thing

- Do change what doesn’t work
  - So many choices, so many variables, but mostly, the new therapies have manageable safety concerns and safety monitoring

- In the absence of all the desirable data for comparisons, generally the newer medications have better efficacy and more safety concerns, with variable tolerability
Thank You