EMERGING THERAPEUTIC ADVANCES IN MULTIPLE SCLEROSIS

POWERPOINT PRESENTATIONS
January 23, 2015
1:00 p.m. – 4:00 p.m.
Pointe Hilton Tapatio Cliffs Resort
Highland 3

January 23–25, 2015 • Phoenix, AZ

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Breakthroughs in Neurology Conference
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3. Fill out the evaluation(s) and select the “Next” button.
4. All evaluations have been submitted when you see the Thank You screen.

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1. Enter your AAN ID. This can be found in the upper right-hand corner of your badge.
2. Fill out the evaluation and select the “Next” button.
3. Your evaluation has been submitted when you see the Thank You screen.

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- Attendees must be registered and badged to attend the individual programs.
- CME Category 1 Credit is awarded to persons registering for and participating in the AAN Regional Programs and submitting an evaluation form. Evaluation instructions are found at the beginning of each syllabus. Evaluations must be submitted online.
- CME Credits/Certificates of Attendance will be sent to attendees four to six weeks following the Regional Conference.

Program Director
Eric Klawiter, MD
Boston, MA

Program Schedule and Faculty
1:00 p.m. – 1:45 p.m. Treating Relapsing MS: Choosing Among the Options
Myla Goldman, MD
Charlottesville, VA

1:45 p.m. – 2:30 p.m. Treating Relapsing MS: Risk Stratification and Mitigation
Bruce A. C. Cree, MD, PhD, MCR
San Francisco, CA

2:30 p.m. – 2:45 p.m. Break

2:45 p.m. – 3:15 p.m. Is No Evidence of MS Disease Activity an Achievable Goal?
Robert A. Bermel, MD
Cleveland, OH

3:15 p.m. – 4:00 p.m. Advances in Understanding and Treating Progressive MS
Robert J. Fox, MD, FAAN
Cleveland, OH

Program Description:
In recent years, the FDA has approved three new oral therapies for relapsing remitting multiple sclerosis. There are several other treatments for MS that are in the midst of or have completed phase III clinical trials. Additional emerging therapeutics are currently at varying stages of the drug development pipeline. Faculty will discuss the current treatment options, focusing on clinical trial efficacy, side effect profiles and risk stratification and monitoring. In a case-based interactive format, faculty will discuss how treatment selection is made in individual patients. Additionally, the session will cover treatment of progressive MS.

Learning Objectives:
Participant should become familiar with new and emerging therapeutics for MS. They should be equipped to improve their management of patients with MS.

Recommended Audience:
Neurologists and other healthcare professionals responsible for the diagnosis, treatment or management of patients with multiple sclerosis.

2015 AAN Breakthroughs in Neurology Conference
January 23-25, 2015
Emerging Therapeutic Advances in Multiple Sclerosis
Friday, January 23, 2015
1:00 p.m. – 4:00 p.m.
CME Credits: 3
Accreditation
The American Academy of Neurology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AMA PRA Credit

The AAN designates these educational activities for a maximum number of hours in category 1 credit toward the AMA Physician's Recognition Award. The number of credits assigned to each individual program is outlined in the program's description. Each physician should only claim those hours of credit that he/she actually spent in the activity.

Certificates for Non-Physicians
Non-physician participating in the programs will receive a certificate of attendance indicating attendance at an activity designated for AMA PRA category 1 credit.

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The primary purpose of the AAN Regional Conference is to provide educational programs. Information presented, as well as publications, technologies, products and/or services discussed, are intended to inform attendees about the knowledge, techniques, and experiences of physicians who are willing to share such information with colleagues. A diversity of opinions exists in the medical field, and the view of the program’s faculty is offered solely for educational purposes. Faculty members' views represent neither those of the AAN nor constitute endorsement by the AAN. The AAN disclaims any and all liability for all claims which may result from the use of information, publications, products, and/or services discussed at the AAN Regional Conference.

Faculty's Disclosure of Commercial Relationships
Consistent with the AAN and ACCME policies, faculty must disclose any significant financial or other relationship with the manufacture(s) of any commercial product(s) or service(s) discussed in their presentations. This policy is intended to make participants aware of all speakers' financial or other relationship(s), so that attendees may form their own judgments about material discussed during the educational activity. Full disclosure of faculty's commercial relationships will appear in the individual program materials. All faculty must sign a letter of agreement stating explicitly that they understand and will adhere to AAN and ACCME guidelines that require full disclosure of commercial relationships, unlabeled use of products, and identification of data sources.

Faculty Commercial Relationship Disclosures
- Dr. Klawiter has received personal compensation for activities with Biogen Idec and Mallinkrodt Pharmaceuticals as a consultant.
- Dr. Goldman has received personal compensation for activities with Concert Pharmaceuticals.
- Dr. Cree has received personal compensation for activities with Abbvie, Biogen Idec, EMD Serono, Genzyme, Medimmune, Novartis, Sanofi Aventis, and Teva Neuroscience. Dr. Cree has received research support from Acorda, Avanir, Hoffman La Roche, and Novartis.
- Dr. Bermel has received personal compensation for activities with Biogen Idec, Novartis, Genzyme, Questcor, and Teva. Dr. Bermel has received research support from Novartis.
- Dr. Fox has received personal compensation for activities with Biogen Idec, GlaxoSmithKline, Novartis, Questcor, Teva, and Xenon as a consultant. Dr. Fox received research support from Novartis.

Unlabeled Use of Product Disclosure
The AAN, as an ACCME accredited provider, requires all faculty members to disclose if a product is not labeled for the use being discussed or that the product is still investigational.

Faculty Unlabeled Use of Product Disclosures
- Dr. Goldman will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Cree will discuss the use of alemtuzumab, daclizumab, rituximab, ocrelizumab, RPC-1063, sponimod, poniesimod, mycophenolate mofetil, azathioprine, cyclophosphamide, and IVIg which are off-label.
- Dr. Bermel will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Fox will discuss various therapies in clinical development for progressive MS, all of which are off-label.
TREATING RELAPSING MS: CHOOSING AMONG THE OPTIONS

Myla D. Goldman, M.D., M.Sc.
Director, James Q. Miller MS Clinic
University of Virginia
MDG3N@Virginia.edu

Disclosure

- Consulting: Concert Pharmaceuticals & Questcor
- UVA Institutional Contracts
  - Consulting: Acorda Pharmaceuticals, Biogen Idec, Novartis Pharmaceuticals
  - Research: NIH NINDS, NMSS, Biogen Idec, & Novartis Pharmaceuticals
30,000 Foot View

Jan 2010: Dalfampridine
<table>
<thead>
<tr>
<th>Name</th>
<th>Administration</th>
<th>Approval</th>
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</thead>
<tbody>
<tr>
<td>Interferon-beta 1b (Betaseron/Extavia)</td>
<td>250 mcg SQ every other day</td>
<td>1993</td>
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<tr>
<td>Interferon-beta 1a (Avonex)</td>
<td>30 mcg IM weekly</td>
<td>1996</td>
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<tr>
<td>Peg-IFN-beta 1a (Plegridy)</td>
<td>125 mcg SQ every 14 days</td>
<td>2014</td>
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<tr>
<td>Glatiramer Acetate (Copaxone)</td>
<td>20 mg SQ daily</td>
<td>1996/1997</td>
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<tr>
<td></td>
<td>40 mg SQ three times week</td>
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<tr>
<td>Interferon-beta 1a (Rebif)</td>
<td>22 or 44 mcg SQ three times wk</td>
<td>2002</td>
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<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>12 mg/m² IV q3M</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Max dose 140 mg/m²</td>
<td></td>
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<tr>
<td>Natalizumab (Tysabri)</td>
<td>300 mg IV every 4 wks</td>
<td>2004/2006</td>
</tr>
<tr>
<td>Alemtuzumab (Lemtrada)</td>
<td>60 mg/5days &amp; 36 mg/3days</td>
<td>2014</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>0.5 mg PO daily</td>
<td>2010</td>
</tr>
<tr>
<td>Teriflunomod (Aubagio)</td>
<td>7 or 14 mg PO daily</td>
<td>2012</td>
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<tr>
<td>Dimethyl Fumarate (Tecfidera)</td>
<td>240 mg PO twice daily</td>
<td>2013</td>
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</tbody>
</table>

Treatment Goal

No Evidence of Disease Activity (NEDA)

- Clinical Relapse
- MRI Progression
- Disability Progression (Independent of Relapse)
Figure 2. Proportion of Patients With and Without Magnetic Resonance Imaging (MRI) or Clinical Disease Activity During 7 Years in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women’s Hospital Cohort.

NEDA’s PPV
7-yr No Progression

Therapy Selection: A Balancing Act

Drug A

Drug J
Survey of Neurologists

- Efficacy
- Safety
- Tolerability
- Patient Preference
- Convenience

Hanson, KA, et al.; Patient Pref & Adherence 2014

Survey of Neurologists

- **Efficacy** -- 86.3%
- Safety
- Tolerability
- Patient Preference
- Convenience
Phase III Placebo Trials: ARR Reduction

Relative Reduction (%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Relative Reduction</th>
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</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>68</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>54</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>54</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>53</td>
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<tr>
<td>Dimethyl Fumarate</td>
<td>44</td>
</tr>
<tr>
<td>Teriflunomide 14 mg</td>
<td>36</td>
</tr>
<tr>
<td>Teriflunomide 7 mg</td>
<td>22</td>
</tr>
<tr>
<td>GA TIW</td>
<td>34</td>
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<tr>
<td>GA OD</td>
<td>29</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>33</td>
</tr>
</tbody>
</table>

Therapy Selection: A Balancing Act

1993 – 2014

Low Efficacy

High Efficacy
Placebo Annualized Relapse Rates

Figure 1. Pre-trial ARR and on-trial placebo ARR observed in the 56 MS trials that were identified by our literature search against the calendar year in which the papers were published. The size of the circles indicates the size of the trial and is inversely proportional to the SE of the ARR. The solid lines show the model values and the dashed lines indicate the 95% CI. ARR: annualized relapse rate; CI: confidence interval; MS: multiple sclerosis; SE: standard error.

Steinworth SM; Mult Scler. 2013
### Head-to-Head Studies

<table>
<thead>
<tr>
<th>IFNβ-1b IM</th>
<th>IFNβ-1b SQ</th>
<th>GA</th>
<th>IFNβ-1b SQ</th>
<th>NTZ</th>
<th>Fingo</th>
<th>Teri</th>
<th>DMF</th>
<th>GA TIW</th>
<th>PEG-IFNβ</th>
<th>Aelmtuz</th>
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</table>

**8 of 55 Possible Head-to-Head Studies**
### Head-to-Head: ARR at 24 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Fingolimod</th>
<th>INF (Rebif)</th>
<th>Teriflunimod</th>
<th>INF (Rebif)2</th>
<th>Alemtuzumab</th>
<th>Teriflunimod 7mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE-MS I</td>
<td>0.39</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TENERE (NS)</td>
<td>2.22</td>
<td>0.26</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONFIRM (NS)</td>
<td>0.29</td>
<td></td>
<td>0.22</td>
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<tr>
<td>TRANSFORMS (Sig)</td>
<td>0.33</td>
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<td></td>
<td>0.16</td>
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</tr>
</tbody>
</table>


### Therapy Selection: A Balancing Act

Safety/Risk

Low Efficacy

High Efficacy
Therapy Selection: A Balancing Act

Safety/Risk
Low Efficacy

Safety/Risk
High Efficacy

Natalizumab: Safety & Risk Tolerance

JC Virus Positive Patients

<table>
<thead>
<tr>
<th>NTZ Exposure</th>
<th>No Prior IS</th>
<th>Prior IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-24 months</td>
<td>&lt; 1:1000</td>
<td>1:1000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>~ 1:330</td>
<td>~ 1:77</td>
</tr>
<tr>
<td>49-72 months</td>
<td>~ 1:142</td>
<td>~1:111</td>
</tr>
</tbody>
</table>

modified from Tysabri PI, updated 12/2013
NTZ Risk Tolerance: Patients & Physicians

![Bar chart showing NTZ risk tolerance for patients and physicians.]

Figure 1. Putative progressive multifocal leukoencephalopathy risk making patients and physicians stop natalizumab.

Heesen, C, et.al.; Mult Sci 2010

Natalizumab: Safety & Risk Tolerance

<table>
<thead>
<tr>
<th>NTZ Exposure</th>
<th>No Prior IS</th>
<th>Prior IS</th>
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<td>~ 1:77</td>
</tr>
<tr>
<td>49-72 months</td>
<td>~ 1:142</td>
<td>~ 1:111</td>
</tr>
</tbody>
</table>

modified from Tysabri PI, updated 12/2013
Risk Tolerance to MS Therapies: Survey Results from the NARCOMS Registry

High Risk Tolerance
- Disability
- Tysabri Use

Low Risk Tolerance
- Female
- Care for Dependents
- Seat Belt Use

Fox, RJ et al. Submitted
Therapy Selection: A Balancing Act

MS Disease Severity

Safety/Risk

Low Efficacy

High Efficacy

Disease Severity: Lessons from Epilepsy

Abou-Khalil, et.al.; Seizure 2003
Disease Severity: Lessons from Epilepsy

![Figure: Therapeutic plasma concentrations of phenytoin, phenobarbital, and carbamazepine in 64 patients receiving single-drug treatment. Complete cessation of all seizures occurred at these therapeutic plasma concentrations.](image)

Schmidt & Haenel, Neurology 1984

---

Articles

Multiple sclerosis unrelated to dog exposure

*SHOW AFFILIATIONS*

doi: 10.1212/01.WNL.34.9.1149

Neurology September 1984 vol. 34 no. 9 1149
Therapy Selection: A Balancing Act

MS Disease Severity

Safety
Lowest Effective Dose

Safety
Highest Effective Dose

MS Disease Severity & Level of Concern

Table 1: Recommendations for determining the level of concern when considering treatment modification based on relapses.\textsuperscript{6}

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Level of concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>B ≤ 1</td>
<td>Low</td>
</tr>
<tr>
<td>1 &lt; B ≤ 2</td>
<td>Medium</td>
</tr>
<tr>
<td>B &gt; 2</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 2: Recommendations for determining the level of concern when considering treatment modification based on disability progression

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Level of concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS score</td>
<td>Low</td>
</tr>
<tr>
<td>≤ 3</td>
<td>Low</td>
</tr>
<tr>
<td>4.0</td>
<td>Low</td>
</tr>
<tr>
<td>≥ 6</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 3: Recommendations for determining the level of concern when considering treatment modification based on annual MRI findings

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Level of concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active on MRI\textsuperscript{*}</td>
<td>Low</td>
</tr>
<tr>
<td>New Gd-enhancing lesions OR Accumulation of new T2 lesions per year</td>
<td>1 lesion</td>
</tr>
</tbody>
</table>

*Note: Routine follow-up MRI with gadolinium (Gd) is recommended 6–12 months after initiating therapy for RRMS (or in CIS if therapy is not initiated). Note: New T2 lesions that are also enhancing on the same scan are only counted once as unique active lesions. The presence of Gd-enhancing lesions is more reliable than new T2 lesion counts. New T2 lesion counts require high-quality comparable MRI scans and interpretation by highly qualified individuals.\textsuperscript{7}.

Freedman, MS Canadian Work Group, 2013
Drug of Choice

- Efficacy & Safety
- Disease Severity
- Risk Tolerance

One-size-fits-all does not fit all.
Therapy Selection: A Balancing Act

MS Disease Severity

Safety

Lowest Effective Dose

Tolerance
Pregnancy Comorbidity

Safety

Highest Effective Dose

MS Medications and Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer Acetate</td>
<td>B</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>C</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>C</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>C</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>C</td>
</tr>
<tr>
<td>Teriflunimide</td>
<td>X</td>
</tr>
</tbody>
</table>
Therapy Selection: A Balancing Act

MS Disease Severity

Lowest Effective Dose

Safety

Tolerance

Pregnancy Comorbidity

Safety

Highest Effective Dose

Treatment Selection: Balancing Act

- Efficacy
- Safety
- Tolerability
- Patient Preference
- Convenience
- Risk Tolerance (Pt & HCP)
- Geographic Parameters
- Pt Specific Characteristics
  - Disease Severity
  - Pregnancy Plans
  - Medical Comorbidities
- Cost (3rd Party Payers)
At The Bedside
Treating Relapsing Multiple Sclerosis: Risk Stratification and Mitigation

Bruce Cree, MD, PhD, MCR
University of California San Francisco

Disclosures

- Dr. Cree has received personal compensation for consulting from Abbvie, Biogen Idec, EMD Serono, Genzyme/sanofi aventis, MedImmune, Novartis and Teva Neurosciences.
- Dr. Cree has performed contracted research studies (including clinical trials) with Acorda, Avanir, Biogen Idec, Hoffman La Roche and Novartis.
Existing and Emerging MS Therapies

**Approved therapies**

- Betaseron® (IFNβ-1b)
- Avonex® (IFNβ-1a)
- Copaxone® (glatiramer acetate)
- Novantron® (mitoxantrone)
- Rebif® (IFNβ-1a)
- Extavia® (IFNβ-1b)
- Gilenya® (fingolimod)
- Tysabri® (natalizumab)
- Laquinimod
- Cladribine®
- Teriflunomide
- Dimethyl Fumarate (BG-12)
- RPC-1063
- Ofatumumab
- Daclizumab
- Siponimod
- Laquinimod

**Phase III completed**

- Ampyra® (4-aminopyridine)
- Nuedexta® (Dextromethorphan Quinidine)
- Daclizumab
- Ocrelizumab
- Ofatumumab
- Siponimod
- Ampyra®
- Nuedexta®
- Quinidine
- Lemtrada® (alemtuzumab)

**In Phase III**

- Cladribine®
- Daclizumab
- Ocrelizumab
- Ofatumumab
- Siponimod
- RPC-1063

*In March 2011, the FDA did not approve cladribine and requested Merck KGaA provide an improved understanding of its safety risks and overall benefit-risk profile.*

The Challenges of MS Management

- Little-to-no guidance for treatment selection
- Current guidelines recommend1-3
  - **First-line therapy:** IFN βs, glatiramer acetate, fingolimod, dimethyl fumarate or teriflunomide
  - **Second-line therapy:** natalizumab, fingolimod, alemtuzumab or mitoxantrone
- No single therapy is recommended over another
- Dearth of well-designed, controlled “switch” studies
  - Many patients are treated with multiple therapies during the course of their illness
  - Decision of which therapy to switch to is often made by considering a patient’s disease course, efficacy, tolerability, potential adverse effects, proposed mechanism of action and the risk a patient is willing to accept
- No proven options for PPMS patients or for RRMS who convert to SPMS

DMT: disease-modifying therapy; IFN: interferon; MOA: mechanism of action.
DMTs Approved for RMS

<table>
<thead>
<tr>
<th>First-line Agents (lower risk)</th>
<th>Second-line Agents (higher risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>Natalizumab</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td><strong>Oral therapies:</strong></td>
<td><strong>Oral therapies:</strong></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Fingolimod</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td></td>
</tr>
</tbody>
</table>

Tiered Treatment

- Begin with safer, but possibly less efficacious, medications
- Monitor for treatment response
  - Clinical: relapses, disability progression
  - Radiographic: new gadolinium enhancing lesions or new T2 lesions, brain volume loss
- Switch to potentially more efficacious therapies for so-called “breakthrough disease”
- Established efficacy and excellent long-term safety of interferons and glatiramer acetate, “first-line”
- So-called second line treatments are less safe than “first-line” therapies, e.g. alemtuzumab and natalizumab
Overview of Safety Considerations for IFN βs and GA

Common adverse effects associated with IFN βs

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>IFN β-1a IM (30 µg)</th>
<th>IFN β-1b SC (250 µg)</th>
<th>IFN β-1a SC (44 µg)</th>
<th>PEG-IFN β-1a SC (125 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Depression</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Summary of GA-associated adverse events

- Injection site/systemic reactions
- Immediate post-injection reaction:
  - Pain, flushing, chest pain, rapid heartbeat, non-cardiac shortness of breath, anxiety, tightness in throat (symptoms typically remit in about 15 minutes)
- Lipoatrophy

GA, glatiramer acetate; IFN, interferon.


Tiered Treatment Approach

- Advantages
  - Easy to understand
  - Utilizes therapies with proven long term safety
  - Can apply a treat-to-target approach (to be discussed later)

- Disadvantages
  - May not take into account individual patient needs that may influence choice of therapy
  - Does not account for the potential to stratify individual patient risk
Natalizumab as a “Second Line” Therapy

- Indicated for relapsing MS
- Blocks lymphocyte entry into the CNS
- Proven efficacy
  - 68-70% relative reduction in relapses
  - 42-54% reduction in hazard ratio for disability
- Once monthly infusion
- Generally well tolerated
- Progressive multifocal leukoencephalopathy risk
  - Risk is influenced by duration of treatment, prior use of immune suppression and prior exposure to the JC virus

Global Natalizumab PML Risk Estimates by Treatment Epoch

Incidence estimates by treatment epoch are calculated based on natalizumab exposure through December 31, 2013 and 430 (428 MS, 2 Chron Disease) confirmed PML cases as of January 6, 2014 (141 USA, 252 Europe Economic Area, 37 rest of world). Data Courtesy of Biogen Idec and provided for professional use upon provider request.

http://medinfo.biogenidec.com
Estimated Incidence of Natalizumab-Associated PML Risk Factors

JCV Antibody Status

Prior IS Use?

<table>
<thead>
<tr>
<th>JCV Antibody Status</th>
<th>No Prior IS Use</th>
<th>Prior IS Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.56/1,000 (95% CI, 0.36-0.83)</td>
<td>1.6/1,000 (95% CI, 0.91-2.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>4.6/1,000 (95% CI, 3.7-5.6)</td>
<td>13/1,000 (95% CI, 8.3-14.5)</td>
</tr>
</tbody>
</table>

- Label change that identifies JCV antibody status as a risk factor for developing PML recently approved by US FDA

Lipid-specific IgM bands and Natalizumab

- Lipid-specific IgM bands (LSMB) in the CSF were previously associated with suboptimal response to IFN
- European study of 367 natalizumab treated patients, 23 of whom developed PML
- The presence of these bands in the CSF appeared to be protective for PML. JCV seropositive patients with LSMB showed similar risk to JCV seronegative patients
- LSMB (−) patients appear to carry most (but not all) of the PML risk, O.R.=58.2
- It may be possible to further stratify risk of PML in JCV seropositive patients by assessing LSMB from the CSF in natalizumab treated patients
- Needs replication in larger cohort
Alemtuzumab Phase III CARE MS-1

Results of CARE MS-1 Study

ARR years 0-2

% pts w sustained disability at 6 mos

Significant

Non-Significant

p<0.0001 0.39

p=0.22 0.28

Alemtuzumab: Secondary Autoimmunity

- Thyroid disorder
  - Cumulative incidence 36%
  - Onset 12–48 months
  - Peak incidence at Years 2, 3
- ITP
  - Cumulative incidence 1.1%
  - Onset 14–36 months (may occur several years after dose)
  - Characterized by:
    - Delayed onset
    - Responsiveness to standard therapy
    - Durable remission
- Nephropathies
  - Glomerular disease types observed in trials: anti-GBM (2 cases) and membranous nephropathy (1 case)
  - Onset months after last dose
  - Early detection crucial for prognosis
- Serum IL-21 levels: potential predictive marker for autoimmunity

Alemtuzumab

- Alemtuzumab
  - Highly efficacious (similar to natalizumab)
  - Problematic safety profile with *de novo* autoimmunity
  - Likely relegated to rescue therapy
  - Biomarkers in development might stratify risk for patients (somewhat akin to JCV serology)
  - Cumbersome REMS program
    - Q month platelets, creatinine and U/A for 5 years
  - Annual therapy, but uncertain when to retreat
  - Possible “induction therapy”
  - Will some US patients travel abroad to be treated?
  - Typical patient: JCV seropositive with disease activity on fingolimod or DMF

Fingolimod as a “second-line therapy”

- Indicated for relapsing MS
- Traps lymphocytes in lymph nodes and spleen
- Proven efficacy 1
  - 54% relative reduction in relapses
  - 30% reduction in hazard ratio for disability (3 month sustained change)
- Single once daily pill
- Generally well tolerated but associated with bradyarrythmia among other side effects
- No clear PML risk 2, can be used in JCV seropositive patients
- Single reported PML case with >100,000 patients treated
  - now believed to be a neuromyelitis optica spectrum disorder patient

### Potential AE or Risk Mitigation Strategy

<table>
<thead>
<tr>
<th>Potential AE or Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia/AV block</td>
<td>• All pts must be observed for 6 h after initial dose for signs and symptoms of bradycardia. ECG pre and post- first dose</td>
</tr>
<tr>
<td></td>
<td>• If pts go off medication for prolonged time period, they must be observed when restarting therapy</td>
</tr>
<tr>
<td>Macular edema</td>
<td>Ophthalmologic exam at baseline and 3-4 mo after treatment initiation</td>
</tr>
<tr>
<td>Infection</td>
<td>• Patients should be vaccinated for varicella zoster virus</td>
</tr>
<tr>
<td></td>
<td>• Risk of VZV reactivation, especially with corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• Consider stopping therapy if serious infection develops</td>
</tr>
<tr>
<td></td>
<td>• Avoid live attenuated vaccines for at least 2 months after stopping therapy</td>
</tr>
<tr>
<td>↓FEV₁ and ↓DLCO</td>
<td>Spirometric evaluation when indicated</td>
</tr>
<tr>
<td>LFT elevations</td>
<td>Monitor regularly, as needed</td>
</tr>
<tr>
<td>Pregnancy risk category C</td>
<td>• Counsel patients about fetal risks</td>
</tr>
<tr>
<td></td>
<td>• Use effective contraception on treatment and for at least 2 mo after stopping therapy</td>
</tr>
</tbody>
</table>

*AV: atrioventricular; DLCO: diffusion capacity of the lung for carbon monoxide; FEV₁: forced expiratory volume over 1 second.


### Fingolimod: Issues for Consideration Before Initiating Treatment

- **Avoid with:**
  - Antiarrhythmics (Ia or III)
  - Antineoplastic agents
  - Immunosomodulating or immunosuppressive therapies
- **Caution with:**
  - Heart rate lowering medications
    - β-blockers
    - Calcium channel blockers
  - CYP450 3A4 inhibitors
    - May ↑ fingolimod levels
- **Additional considerations:**
  - > 4 weeks for WBC to return to normal after discontinuation
  - In the US, 3rd party payers often restrict use to second, or even third line, therapy (step edits)
Oral Therapies Are Changing the Picture

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN β-1a</td>
<td>30 µg</td>
<td>IM</td>
<td>QW</td>
</tr>
<tr>
<td>IFN β-1a</td>
<td>44 µg</td>
<td>subcutaneous (SC)</td>
<td>TIW</td>
</tr>
<tr>
<td>IFN β-1b (2 formulations)</td>
<td>250 µg</td>
<td>SC</td>
<td>QOD</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>20 mg</td>
<td>SC</td>
<td>QD</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12 mg/m²</td>
<td>IV</td>
<td>Q3M</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>300 mg</td>
<td>IV</td>
<td>Q4W</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>0.5 mg</td>
<td>PO</td>
<td>QD</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>7 mg, 14 mg</td>
<td>PO</td>
<td>QD</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>240 mg</td>
<td>PO</td>
<td>2XD</td>
</tr>
</tbody>
</table>

- Dalfampridine is also approved to improve walking in patients with MS
- Dextromethorphan/quinidine is approved for pseudobulbar affect in MS and ALS

Novel options offer the chance for improvements in patient outcomes, but it remains uncertain how these therapies will fit into the current MS treatment paradigm.

Teriflunomide

- Indicated for relapsing MS
- Anti-metabolite, inhibits dihydroorotate dehydrogenase thereby inhibiting de novo DNA synthesis in proliferating lymphocytes
- Proven efficacy
  - 32% relative reduction in relapses (14 mg)
  - 30% reduction in hazard ratio for disability
- Single once daily pill
- Generally well tolerated, but with black box warnings
- No known PML risk

Teriflunomide Risk Stratification

- Parent compound leflunomide is associated with severe and fatal liver injury in rheumatoid arthritis patients
  - similar risk to MS patients is assumed
- Based on animal studies, teriflunomide could cause fetal death and malformations
- Additional risks include tuberculosis reactivation, nephropathy, peripheral neuropathy, alopecia, hypertension
- Pre-treatment: screen for tuberculosis, infection, pregnancy, renal failure, peripheral neuropathy, interstitial pulmonary disease, hypertension; assess WBC, renal function, and LFTs
- During treatment: blood pressure monitoring; serum transaminase determinations, renal function
- Women of childbearing age should not be started on therapy until pregnancy is excluded and confirmation of reliable contraception (category X)

Pregnancies Reported in Teriflunomide Clinical Trial Database

- Pregnancies in patients exposed to teriflunomide, in unblinded data:
  - 63 pregnancies in women
  - 16 pregnancies in partners of men
- Pregnancy outcomes
  - No structural defects in newborns
  - No functional deficits in newborns
  - Birth weight range: 2,780–4,150 grams (6–9 pounds)
  - Rate of miscarriage: 19%
    - Similar to previous reports for GA and IFN
- Elimination procedure
  - Discontinue treatment
  - Undergo elimination procedure
    - Cholestyramine or activated charcoal until plasma drug levels < 0.02 mcg/mL
  - Male patients are advised the same
Dimethyl Fumarate

- Indicated for relapsing MS \(^1\)
- Mechanism unclear, may induce anti-oxidative genes through Keap1 inhibition that allows NRF2 to translocate to nucleus and induce antioxidative response
- Proven efficacy \(^2\)
  - 53% relative reduction in relapses
  - 38% reduction in hazard ratio for disability (3 month sustained change in EDSS)
- Twice daily capsule
- Generally well tolerated
- Hypothetical risk of PML and possibly RCC based on dimethyl fumarate used for psoriasis (Fumaderm)

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Risk Mitigation with DMF

- GI symptoms and flushing are common
- May cause lymphopenia: recent complete blood cell count (< 6 months) before starting treatment and annually or as clinically indicated
- Liver function tests at baseline
- Administration with food may decrease flushing
  - Co-treatment with aspirin can reduce flushing
- Withholding treatment should be considered in patients with severe infections
- Check JCV serology?, no cases of PML reported in MS patients treated with DMF
Is Tiered Treatment Still Applicable?

- New therapies are changing the way relapsing MS is managed
- Oral treatment options are likely to be better tolerated and therefore associated with better adherence compared to auto-injectable medications
- Some oral DMTs may be more effective than injectable therapies in reducing relapses
  - Fingolimod was compared to interferon beta-1a IM and showed superior efficacy\(^1\)
  - Dimethyl fumarate was compared to glatiramer acetate and showed apparent superior efficacy (post-hoc analysis)\(^2\)
- Natalizumab individual risk stratification spans from ~1/10,000 to ~1:100 (2 orders of magnitude)

Maximal Efficacy Approach

- Treat CIS/RMS from onset with the most efficacious therapy possible
  - leverages ability to stratify individual patient risk
- For example:
  - Natalizumab in JC virus (JCV) seronegative patients
  - Fingolimod or dimethyl fumarate in JCV seropositive patients
  - Alemtuzumab as “induction” therapy in high risk patients

2. Fox et al, NEJM 367:1087-1097; 2012
Maximal Efficacy Approach

- Advantages
  - Provides more efficacious treatment for patients who would have experienced a more severe disease course

- Disadvantages
  - Assumes validity of certain cross-trial comparisons
  - Options for switching for breakthrough disease are less obvious
  - Limited ability to forecast patients at high risk for severe disease
  - Stratification by JCV serology is imperfect
    - Seronegative patients still carry a small but real risk of PML
    - False negative rate of JCV serology is as high as 2.2%
    - 2 cases of PML so far reported in JCV seronegative patients
    - Therefore additional cases will likely follow

Tiered Treatment versus Maximum Efficacy?

- Clinical trials are unlikely to answer this question
  - Comparing tiered treatment to maximum efficacy strategies would require lengthy durations of observation, e.g. > 5 years (or perhaps even longer)
    - Need to wait for enough patients to develop clinically important outcomes such as disability milestones or development of secondary progressive MS
  - Methods for assessment of efficacy following switching and criteria for when to switch are not well defined

- Very limited existent long term outcome data from trials or observational cohorts
“Induction” Therapy, a variant of Maximal Efficacy Approach

- Conceptually similar to oncology focusing on aggressive suppression of inflammation with high potency medications
- Induction is followed by “maintenance” with other medications whose safety profiles are more conducive to ongoing use
- Proposed examples of induction agents could include: lymphocytotoxic medications such as alemtuzumab, ocrelizumab (rituximab), cladribine, mitoxantrone
- Maintenance medications could include the so-called first line therapies
- No data available as yet that strongly supports this strategy

A Proposed Treatment Algorithm

New therapies offer improvements in tolerability and efficacy

Each therapy has a unique risk/benefit profile

Tiered approach may be appropriate for patients with better prognostic features and a maximal therapeutic strategy may be useful in patients with more aggressive disease at onset

Selection of treatment involves assessing treatment options in the setting of individual risk

Optimization of treatment may involve switching therapies based on clinical and/or radiographic assessments
Is No Evidence of MS Disease Activity an Achievable Goal?

Robert Bermel, MD
Staff Neurologist and Medical Director
Mellen Center for Multiple Sclerosis
Cleveland, OH, USA

Objectives of this talk:

• Describe the rationale for a “Treat to Target” initiative in MS
• Explore existing clinical trial data on “No Evidence of Disease Activity” (NEDA) as an outcome
• Discuss opportunities and challenges to implementing NEDA as a treatment target in the MS clinic
The clinical situation in RRMS

- We are well-equipped to treat and monitor the inflammatory component of RRMS
  - 10 (11) approved therapies
  - Widespread availability of MRI for monitoring
- DMTs are variably effective in individuals
- No biomarker to prospectively predict efficacy of specific treatments in individual patients
- Monitoring on therapy (clinically and with MRI) is common, though there are no standards or defined targets in the clinic

Rheumatoid Arthritis as an Example

A change over time in mortality from RA:

- Use of early DMARDs (MTX, AZA), targeting remission, was attributed as a major contributor.
Treating to Target: RA as an example

TICORA trial: Patients with RA randomized to systematic intensive treatment regimen vs. routine office care (same treatment options available to both groups)

An Opportunity in MS

- Could targeting tight control of the disease, using existing therapies, improve outcomes in the MS clinic?
- Could a composite remission measure help to evaluate the efficacy of more highly effective therapies in clinical trials?
“Disease-Free Status” in AFFIRM- The First Report of the Concept in MS

“Our aim was to develop composite measures that can be applied in clinical practice and used as a measure of disease remission in clinical studies. Therefore, relapses, progression of disability (sustained for 12 weeks), Gad+ lesions, and new or enlarging T2-hyperintense lesions were taken into account.”


Nomenclature

• “Disease-Free Status” is commonly used, but is discouraged, because we lack methodology to fully evaluate ongoing pathology

• “Disease-Activity Free Status” (DAFS) is better, but we lack methodology to assert that we have eliminated all disease activity (e.g. what about triple-dose gad?)

• “No Evidence of Disease Activity” (NEDA) is a reasonable term for this concept. It implies that the neurologist has monitored the patient for disease activity
Definition from Clinical Trials

- No new or enlarging T2 lesions
- No new Gad+ lesions
- No relapses
- No confirmed EDSS worsening

No Evidence of Disease Activity

NEDA in the AFFIRM trial (natalizumab vs. plc)

Havrdova et al. Lancet Neurology 2009;8:254-60
NEDA in Placebo-controlled Trials

- Natalizumab
- Fingolimod
- Cladribine
- BG-12
- Teriflunomide
- Daclizumab
- Peg IFN

NEDA in FREEDOMS (fingolimod)

Kappos et al., AAN 2011
NEDA in DEFINE (DMF vs. placebo)

Giovannoni et al., AAN 2012

Proportion NEDA: Placebo-controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Active Arm</th>
<th>Fold ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>natalizumab (AFFIRM)</td>
<td>15</td>
<td>47</td>
<td>3.0</td>
</tr>
<tr>
<td>Daclizumab-HYP</td>
<td>11</td>
<td>39</td>
<td>3.5</td>
</tr>
<tr>
<td>Peginterferon beta-1a Q2W</td>
<td>15</td>
<td>34</td>
<td>2.2</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>natalizumab (AFFIRM)</td>
<td>7</td>
<td>37</td>
<td>5.3</td>
</tr>
<tr>
<td>cladribine (CLARITY)</td>
<td>16</td>
<td>44</td>
<td>2.8</td>
</tr>
<tr>
<td>Fingolimod (FREEDOMS)</td>
<td>13</td>
<td>38</td>
<td>2.9</td>
</tr>
<tr>
<td>BG-12 (DEFINE)</td>
<td>15</td>
<td>28</td>
<td>1.9</td>
</tr>
</tbody>
</table>
NEDA in CARE-MS I
(alemtuzumab vs IFNβ-1a SC)

![Bar chart showing NEDA at 2 years: IFNβ-1a (SC) 27%, Alemtuzumab 39%, Fold-Increase 1.4]

Giovannoni et al. ENS 2012

NEDA in CARE-MS II
(alemtuzumab vs IFNβ-1a SC)

![Bar chart showing NEDA at 2 years: IFNβ-1a (SC) 13%, Alemtuzumab 32%, Fold-Increase 3.0]

Hartung et al. AAN 2013- P 07.093
Common Concerns:

1. Is achieving NEDA clinically meaningful?
2. Is achieving NEDA a realistic goal given the percentages achieved in clinical trials?
3. What is the evidence that achieving short-term disease control has long-term benefit?
4. Implementing in the clinic seems complex
Is NEDA clinically meaningful?

- NEDA Correlates from AFFIRM - 2 years
  - Brain atrophy
  - Cognition
  - Ambulation
  - Vision
  - Disability improvement
  - Patient reported outcomes

- NEDA Correlates - longer term
  - Data from STRATA
  - Data from CLIMB

Brain Atrophy (BPF) in AFFIRM by NEDA status

\[ p=0.0055 \]

\[ \text{Percent change in BPF Y1-Y2} \]
PASAT-3 in AFFIRM by NEDA status

Long-term follow-up of AFFIRM patients in STRATA
Mean EDSS Score

Rudick et al. PS13-ECTRIMS 2011
Common Concerns:

1. Is achieving NEDA clinically meaningful?
2. Is achieving NEDA a realistic goal given the percentages achieved in clinical trials?
3. What is the evidence that achieving short-term disease control has long-term benefit?
4. Implementing in the clinic seems complex

Disease Activity While on Rx

<table>
<thead>
<tr>
<th>Study</th>
<th>NEDA in Active Arm</th>
<th>Disease Activity in Active Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>natalizumab (AFFIRM)</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Daclizumab-HYP</td>
<td>39%</td>
<td>61%</td>
</tr>
<tr>
<td>Peginterferon beta-1a Q2W</td>
<td>34%</td>
<td>66%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>NEDA in Active Arm</th>
<th>Disease Activity in Active Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>natalizumab (AFFIRM)</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>cladribine (CLARITY)</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>Fingolimod (FREEDOMS)</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>BG-12 (DEFINE)</td>
<td>28%</td>
<td>72%</td>
</tr>
</tbody>
</table>
NEDA in the CLIMB registry

- 7-year follow-up in Brigham and Women’s CLIMB registry
- 99 of 215 had NEDA at 1 year (46%)
- 17 of 216 at 7 years (7.9%)

Rotstein et al. JAMA Neurol 2014

NEDA in the HALT-MS experience

- 25 patients selected after 36 screened
- 78.4% NEDA after 3 years in patients receiving immunoablation and autologous hematopoetic stem cell transplantation
- Highest reported rate of NEDA to date

Nash et al. JAMA Neurol 2015
Common Concerns:

1. Is achieving NEDA clinically meaningful?
2. Is achieving NEDA a realistic goal given the percentages achieved in clinical trials?
3. What is the evidence that achieving short-term disease control has long-term benefit?
4. Implementing in the clinic seems complex

Early MRI activity on IFN predicts poor long-term outcome

ASSURANCE Study (15-year f/u of IM IFN beta1a): Results:

MRI activity and relapses predicted future disability in patients treated with IFNβ

Bermel RA et al, Ann Neurol 2013
**Modified Rio Score**

- Based on PRISMS-4 data (IFN)
- Composite score integrating new T2 lesions and relapses
- Disease activity over first year to predicts disability progression in subsequent 3 years

\[
score = \begin{cases} 
0 & \text{if new T2 lesions } \leq 5 \text{ and relapses } = 0; \\
1 & \text{if new T2 lesions } \leq 5 \text{ and relapses } = 1; \\
2 & \text{if new T2 lesions } > 5 \text{ and relapses } = 0; \\
3 & \text{if new T2 lesions } \leq 5 \text{ and relapses } = 2; \\
4 & \text{if new T2 lesions } > 5 \text{ and relapses } = 1; \\
5 & \text{if new T2 lesions } > 5 \text{ and relapses } \geq 2.
\end{cases}
\]

**Figure 3.** Probability of disability progression from the first year 1 follow-up period (4 years, (b)), according to application of the mod

---

**MRI activity on IFN: The dominant factor predicting EDSS worsening**

<table>
<thead>
<tr>
<th>New T2-hypointense lesions at 1 year</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
<th>All patients (n = 394)</th>
<th>Ref</th>
<th>95% CI</th>
<th>p-value</th>
<th>Patients with subclinical disease only* (n = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One new lesion</td>
<td>0.6</td>
<td>3.9–21.7</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.1</td>
<td>3.8–60.1</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Two new lesions</td>
<td>1.2</td>
<td>0.8–5.1</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.1</td>
<td>0.6–2.2</td>
<td>&lt; 0.001</td>
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<tr>
<td>Three or more new lesions</td>
<td>2.0</td>
<td>1.2–3.7</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.4</td>
<td>1.0–1.9</td>
<td>0.03</td>
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<tr>
<td>Occurrence of 2 or more relapses</td>
<td>1.5</td>
<td>1.2–1.9</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.4</td>
<td>1.0–1.9</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Efficacy at IFN/B (each month)</td>
<td>0.5</td>
<td>0.6–0.8</td>
<td>&lt; 0.001</td>
<td></td>
<td>0.7</td>
<td>0.6–0.8</td>
<td>&lt; 0.001</td>
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<td>Active MRI scan at baseline*</td>
<td>1.7</td>
<td>1.1–2.8</td>
<td>0.03</td>
<td></td>
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*Patients without clinical relapse during the 1st year of IFN treatment. *not included in the analysis of patients with subclinical disease because it did not improve the goodness of fit of the model (Likelihood ratio test \( P = 0.123 \)).

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Prosperini et al. *Eur J Neurol* 2009
NEDA predicts stability in CLIMB

- BWH CLIMB registry experience
- NEDA at 2 years predicted EDSS stability at 7 years
- PPV=78.3%

Complexities: Monitoring

- Even monitoring the core components is complex
  - Reestablishing the baseline for MRI monitoring
  - How to appropriately analyze MRI
  - No easy way to track the components of NEDA in most electronic medical records
  - Threshold to act (and what to do) is unclear
- Should we include other/additional measures?
- Implementing in the clinic may be facilitated by enlisting radiology colleagues, and using technology
Moving forward:

1. Is achieving NEDA clinically meaningful?
   – Evidence is developing, pointing toward yes
2. Is it a realistic goal given the percentages achieved in clinical trials?
   – A comprehensive strategy remains untested
3. What is the evidence that achieving short-term disease control has long-term benefit?
   – Data are best for interferons, can we extrapolate to other DMTs?
4. Implementing in the clinic seems complex
   – Technology and cooperation may help
Advances in Understanding and Treating Progressive MS

Robert J. Fox, MD
Staff Neurologist
Mellen Center for Multiple Sclerosis

Vice-Chair for Research
Neurological Institute

Cleveland Clinic, Cleveland, OH

Disclosures

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In addition, research support, consultant and advisory committee fees from Biogen Idec and Novartis were paid to Cleveland Clinic.
Natural History of Relapsing MS

- Relapses and Impairment
- MRI Activity
- Brain Atrophy

Preclinical

RR-MS

12 FDA-approved therapies

15-20+

Disease Duration (Years)

Why such failure with PMS?

SP-MS

SPMS (and PPMS) represents a significant unmet clinical need.

Advances in Understanding and Treating Progressive MS

- Overview of the challenges of progressive MS
- Clinical trials in progressive MS
- Current treatment approaches
Defining Terms: Progressive MS

- **Neurologist:**
  - Progressive myelopathy (ambulation, arms)
  - Cognitive impairment
- **Imager:**
  - Progressive atrophy
  - Decreasing MTR, NAA, fractional anisotropy
- **Pathologist:**
  - Axonal pathology
  - Oligodendrocyte pathology
- **Physiatrist:**
  - Loss of function; worsening symptoms
- **Patient:**
  - Loss of independence
  - Inability to work
  - Worsening symptoms – i.e. pain

Progressive MS is defined differently from different perspectives

---

Defining Progressive MS – Case 1

- 27 yo male develops optic neuritis
  - MRI shows a few periventricular lesions
  - Follow-up MRI: two new lesions
  - Dx: Relapsing remitting MS
- He remains stable for next 15 years – no relapses and no new lesions . . .
- What is his diagnosis? Stable RRMS
- Except that he’s a long-distance runner:
  - 33 yo - “foot slapping” at end of marathons
  - 38 yo - right leg dragging after 10-15 miles
  - 40 yo – can only run 3-4 miles
  - When not running: asymptomatic
- What’s his diagnosis now? SPMS
- When did it start?
- What if he weren’t a runner?
Defining Progressive MS – Case 2

- 53 yo women with a 2-year history of progressive myelopathy and typical demyelinating lesions
  - Denies previous episodes of neurologic dysfunction
- Diagnosis: Primary progressive MS

- At follow-up: she remembers one month of left eye blurry vision and soreness with eye movements 5 years previously
  - VEP and OCT are consistent with previous left optic neuritis
- Diagnosis: Secondary Progressive MS
- Patient recollection can re-classify her diagnosis?
MS Phenotypes: The 2013 Revisions
Core Phenotypes and Modifiers

◊ The core MS phenotypes (relapsing and progressive disease) should be retained (with some modification)
◊ Assessment of disease activity is an important modifier of the core phenotypes, as measured by
  - clinical relapses or
  - CNS lesion activity
◊ Assessment of ongoing progression of disability is an important modifier of the core phenotypes

Lublin et al, Neurol Neurology 2014;83:278-286
MS Phenotypes: 2013 Revisions

PR MS, PP MS, CIS and RIS

- The Progressive-Relapsing MS (PRMS) phenotype is eliminated
  - Such patients would be categorized as Primary Progressive MS (PPMS) with activity
- Primary Progressive MS (PPMS) is part of the spectrum of progressive disease
  - Differences from other forms are relative rather than absolute.
- Clinically Isolated Syndrome (CIS) is part of the spectrum of MS phenotypes
- Radiologically Isolated Syndrome (RIS) should not be considered an MS phenotype, as patients lack clinical signs and symptoms

Lublin et al, Neurol. Neurology 2014;83:278-286

MS Phenotypes: 2013 Revisions

Terminology and Biological Markers

- The term “worsening” is preferable to “progressing” to describe patients with relapsing disease whose disease is advancing due to frequent relapses or incomplete relapse recovery,
  - Reserve the term “disease progression” for those in a progressive phase with evidence of gradual worsening over time.
- The term “confirmed worsening” in EDSS, over a defined period of time, is preferable to “sustained worsening”
- “Benign” and “malignant” disease are often misused and should be used with caution

Lublin et al, Neurol. Neurology 2014;83:278-286
Do relapses matter in Progressive MS?

Time from onset of progressive MS to walking with a cane

Defining Progressive MS

- It’s defined differently from different perspectives
- Disease sub-types are inherently fuzzy
- Re-conceptualization of MS:
  - Progressive vs. non-progressive
  - Active inflammation vs. no active inflammation
- Relapses still matter in progressive MS
Natural History of Relapsing MS

- Relapses and Impairment
- MRI Activity
- Brain Atrophy

SP-MS (and PPMS) represents a significant unmet clinical need.

Why such failure with PMS?

Preclinical  RR-MS

12 FDA-approved therapies

1 FDA-approved therapy (mitoxantrone - rarely used)

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

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Disease Duration (Years)
Classical Drug Development

**Benchtop Model**

**Phase I Safety**

**Phase II Proof of Concept**

**Phase III Efficacy**

**Market Approval**

#### Classical RRMS Drug Development

**EAE Model**

**Phase I, 10-20 pts**

**Phase II, 100-200 pts, Outcome: Gad, T2 lesions**

**Phase III, 500-1300 pts, Outcome: relapses and EDSS**

**Market Approval**

- natalizumab, teriflunomide, fingolimod, daclizumab, laquinimod, glat. acet.
- BG12, alemtuzumab
- rituximab
- IFN
**Natalizumab Phase II Trial**

Mean Number of New Gd-enhancing Lesions


* p < 0.01 different from placebo
** p < 0.001 different from placebo

**Natalizumab Phase III Trial**

C Polman et al. *NEJM* 2005

Annualized Relapse Rate (95% CI)
Natalizumab Phase III Trial

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Natalizumab</th>
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<td>200</td>
</tr>
<tr>
<td>199</td>
<td>199</td>
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</tbody>
</table>

Proportion With Sustained Progression

Hazard Ratio (HR) = 0.58 (95% CI: 0.43, 0.77)
P = 0.0002

Placebo 29%
Natalizumab 17%

MRI Predicting Clinical Outcomes in RRMS

N = 54 studies

R² = 0.76

Sormani et al, Lancet Neurol 2013
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Pathologic Mechanisms in Early vs. Late MS

Inflammation

Something Else

Years After MS Onset
Classical Drug Development - PMS

- What model?
- What human pathophysiology?
- How to identify potential drugs?
- What outcome?
- What to replace EDSS?
- Market Approval

- Benchtop Model
- Phase I Safety
- Phase II Proof of Concept
- Phase III Efficacy

International Progressive MS Alliance

Five Key Areas of Unmet Need:
- Experimental Models
- Pathway Identification and Repurposing
- Proof of Concept Trial Design
- Clinical Outcome Metrics
- Symptom Management and Rehabilitation

Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS

Efforts Underway

2012 Global Progressive MS Portfolio

$85.5 M USD

19.9
13.4
51.4

 Targets-Pathways
 Symptoms-Rehabilitation
 POC-Clinical Outcomes
 Experimental models

Plus ~45 interventional clinical trials currently recruiting patients (www.clinicaltrials.gov)

Previous Progressive MS Trials

Ontaneda, Lancet Neurol, in press
Progressive MS Efforts Underway

- Progressive MS Trials:
  - Phenytoin Optic Neuritis Study (Phase II)
  - PROXIMUS Trial - oxcarbazepine in SPMS (Phase II)
  - ASCEND – natalizumab in SPMS (Phase III)
  - ORATORIO – ocrelizumab (rituximab cousin) in PPMS (Phase III)
  - EXPAND – siponimod (fingolimod cousin) in SPMS (Phase III)
  - MS Smart Trial – riluzole, amiloride, ibudilast in SPMS (Phase II)
  - SPRINT-MS – ibudilast in PPMS/SPMS (Phase II)
  - rituximab, mesenchymal stem cells, mastitinib, lipoic acid, erythropoietin, hydroxyurea, idebenone, rehabilitation

www.clinicaltrials.gov
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www.clinicaltrials.gov

Secondary and Primary pRgressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

- 96-week, 250-subject, randomized, placebo-controlled phase II trial of ibudilast (PDE- and MIF-inhibitor) in SPMS/PPMS
- Concurrent treatment with IFN-β1 or GA is allowed
- Primary Outcome: whole brain atrophy (BPF)
  - Secondary Outcomes:
    - DTI (descending pyramidal tracts)
    - MTR (whole brain)
    - OCT (retinal nerve fiber layer)
    - Cortical atrophy (CLADA)
- Standardized 3T imaging at all sites
- EDSS, MSFC-4, PROs
- Utilizing NeuroNEXT, a US-based, NIH-funded Phase II clinical trial network
- Head-to-head comparison of imaging measures
  - Longitudinal validation to clinical outcomes
Treatment Approach to Progressive MS

- Differentiate between:
  - Disease activity (relapses, new MRI lesions)
  - Disease progression (gradual, insidious disability progression)
- Use immunomodulating therapies if there is disease activity
  - Consider continuing immunomodulating therapy if patient tolerating it well
- Main management focuses on symptoms:
  - Spasticity, pain, fatigue, sphincter dysfunction, mood disruption, etc
  - Optimizing function – PT, OT, braces, stretching program
  - Adjustment challenges – family, professional, disability
- Consider clinical trials of new therapies
Summary – Progressive MS

- Disease classification has been revised
  - Relapsing disease and progressive disease often overlap
    - “Does the patient have active inflammation?”
    - “Does the patient have gradual progression”
- There are many challenges in developing effective therapies for progressive MS
  - Targeted efforts are underway to address these barriers
- There are management approaches
  - Consider immunomodulating therapy if active inflammation
  - Symptomatic management is typically focus of management
- Many trials are enrolling and need patients

*Thank you for your attention!*