Recent Advances in Neurology
Multiple sclerosis: how will recent clinical trials change our practice?
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Faculty Disclosure
Bruce Cree, MD, PhD, MCR has received personal compensation for consulting from Abbott Pharmaceuticals, EMD Serono Inc, Genzyme, Novartis Pharmaceuticals Corporation, sanofi-aventis and has received grant/research support from Hoffman La-Roche.

MS Epidemiology and Natural History\textsuperscript{1,2}

- Affects approximately 400,000 individuals in the US
  - Other countries/regions with high MS prevalence include Canada, Northern Europe, and Southern Australia
- Most patients exhibit progressive neurologic deterioration without treatment
- More common in women than in men; men more likely to have a worse clinical course
- Approximately 20 years after diagnosis without treatment
  - 50% of patients require a cane to ambulate
  - More than half of patients with RRMS convert to SPMS

Impact of MS on Mortality

- Data from Danish MS Registry\textsuperscript{1}
  - Compared with general population, mortality approximately 3 times higher in patients with MS
  - Life expectancy approximately 10 years less among patients with MS compared with general population
  - However, excess mortality declined significantly since 1950
- Recent population-based study cohort\textsuperscript{2}
  - British patients with MS have a 3.5-fold increased mortality rate compared with general population
  - Smoking and respiratory diseases are major and potentially preventable factors related to increased mortality rate in patients with MS

16-Year Follow-Up Study of Pivotal IFN β-1b Trial in MS

- Original trial included 372 patients with MS
  - Randomized to IFN β-1b 50 µg, IFN β-1b 250 µg, or placebo
  - Unequivocal benefit seen with 250 µg dose in terms of relapse rate, relapse-free interval, time to first relapse, T2 disease burden, new active T2 lesions, and EDSS change ≥ 1 point at end of study

Impact of Treatment on Mortality

<table>
<thead>
<tr>
<th>Mortality Rate, %</th>
<th>Placebo</th>
<th>IFN β-1b 50 µg</th>
<th>IFN β-1b 250 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.3%</td>
<td>8.3%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale

The Challenges of MS Management

Little-to-no guidance for treatment selection
- Current guidelines recommend1-3
  - First-line therapy: IFN βs, glatiramer acetate, or fingolimod
  - Second-line therapy: natalizumab, fingolimod, or mitoxantrone
  - No single therapy is recommended over another

Dearth of well-designed, controlled “switch” studies
- Most patients are treated with multiple lines of therapy throughout course of their disease
- Decision of which therapy to switch to is often made by considering a patient’s disease course, DMT MOA, efficacy, tolerability, potential adverse effects, and the risk a patient is willing to accept
- Few treatment options for patients with RRMS who convert to SPMS

Available 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>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>Mitoxantrone</td>
<td>12 mg/m²</td>
<td>IV</td>
<td>Q3M</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

2013 and Beyond

Oral Therapies: dimethyl fumarate, laquinimod
Monoclonal antibodies: alemtuzumab, daclizumab, and ocrelizumab

Major Themes for This Afternoon

From the neurologist’s perspective: How will my practice change based on latest advances?
- How to apply recent data on established therapies to your patients with MS
- How to integrate novel therapies into standard care
  - What are the best ways to safely administer and assess the efficacy of emerging oral agents and monoclonal antibodies?
- Understanding the practicalities of risk assessment, stratification, and mitigation
  - In which patients with MS do the potential risks of available DMTs outweigh the benefits?
  - How can we deal with unique adverse effects of available and emerging DMTs?
What have we learned from recent trials on available therapies?

**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>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Depression</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Summary of GA-associated adverse events

- Injection site/systemic reactions
  - Pain, flushing, chest pain, rapid heartbeat, noncardiac shortness of breath, anxiety, tightness in throat (symptoms typically remit in about 15 minutes)
  - Lipoatrophy

**REFLEX: A Phase 3 Trial of IFN β-1a Efficacy in Patients After First Clinical Demyelinating Event**

- N = 517
- First clinical demyelinating event (ie, CIS)
- ≥ 2 clinically silent T2 brain lesions

**Endpoints**

- Time to McDonald MS 2005
- Time to CDMS
- MRI parameters

CDMS: clinically definite MS; CIS: clinically isolated syndrome.

1. Kappos L et al. 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS 2011). Abstract P91.
**REFLEX: Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>IFN β-1α 44 µg TIW</th>
<th>IFN β-1α 44 µg QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of McDonald MS 2005 at 2 y</td>
<td>85.8%</td>
<td>62.5%</td>
<td>75.5%</td>
</tr>
<tr>
<td>Median time to McDonald MS 2005</td>
<td>97 d</td>
<td>310 d</td>
<td>182 d</td>
</tr>
<tr>
<td>Cumulative incidence of CDMS</td>
<td>37.5%</td>
<td>20.6%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Mean # CUA lesions/patient/scan (vs placebo)(^a)</td>
<td>↓ 81% (( P &lt; .001 ))</td>
<td>↓ 63% (( P &lt; .001 ))</td>
<td></td>
</tr>
</tbody>
</table>

- MRI lesion volumes decreased or remained stable for both active treatment groups, but increased in placebo group
- No new or unexpected adverse events were reported

\(^a\) Reduction in CUA lesions was also significantly greater with TIW vs QW dosing.

CUA: combined unique active


**Glatiramer Acetate: Current Status and Future Directions**

**FORTE Trial**
- N = 1,155 patients with MS
- Randomized to either 20 mg/day or 40 mg/day GA
- Primary endpoint = rate of confirmed relapse during 12-mo study period
- Primary endpoint similar in both groups: RR = 1.07, 95% CI 0.88-1.31; \( P = .486 \)

**Daily vs Twice Weekly Administration**
- N = 48 patients with MS treated with GA for ≥1 year
- Randomized to GA 20 mg either once daily or twice weekly
- Efficacy in terms of ARR, T2 and T1 lesions, and EDSS similar between dosing schedules at 2 years
- Compared with once daily group, twice weekly group had:
  - Less lipoatrophy at injection site
  - Fewer local injection site reactions
  - Fewer post-injection systemic reactions

**GALA Trial**
- N = 1,350 patients with MS
- Comparing GA 40 mg SC TIW with placebo

ARR: annualized relapse rate; RR: relative risk.


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**GALA Study Design: 40 mg TIW versus Placebo**

**Eligible patients**

- Aged 18–55 years RRMS (revised McDonald criteria)\(^1\)
- EDSS score of ≤5.5
- Relapse free ≤30 days

**Screening**

- Placebo-controlled phase\(^*,†\)
  - Open-label phase: 40 mg tiw (all subjects)

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Khan O., et al. Presented at Late Breaking News, October 13, ECTRIMS 2012 Abstract 166

**Significantly Greater Reduction in ARR for GA 40 mg tiw vs. Placebo**

ARR: annualized relapse rate; RR: relative risk.

Khan O., et al. Presented at Late Breaking News, October 13, ECTRIMS 2012 Abstract 166
is this 95% CI? please check and add as appropriate

Michael Craig, 8/27/2012
CombiRX Trial: Comparison of Combined IFN β-1a and GA to Either Agent Alone in RRMS

- **N = 1,008**
- **Age: 18-60 years**
- **RRMS**
- **EDSS ≤ 5.5**
- ≥2 relapses in prior 3 years
- No prior treatment with either IFN β-1a or GA

**Endpoints**
- Relapse rate at 3 years
- MRI parameters
- Time to confirmed disability

CombiRX Trial: Outcomes

- **ARR at 3 Years**
- IFN β-1a: 0.16
- GA: 0.11
- IFN β-1a + GA: 0.12

- **Free of Relapse at 3 Years**
- IFN β-1a: 74.0%
- GA: 79.5%
- IFN β-1a + GA: 76.9%

- Time to first relapse and disability progression measures showed no benefit to the combination over either agent alone
- However, significant benefits in favor of combination observed in some MRI metrics


RESTORE Trial: Rationale

- Natalizumab efficacy in RRMS based on phase 3 SENTINEL and AFFIRM trials
- Associated with PML caused by JC virus
- Risk increases with anti-JC virus antibody (+) status, prior immunosuppressant use, and duration of natalizumab treatment
- RESTORE study evaluated effect of 24-week natalizumab treatment interruption on immune parameters and disease activity
- Study not designed or powered to determine effect on development of PML

Natalizumab PML Risk Estimates by Treatment Epoch

The observed clinical trial PML incidence in patients who received a mean of 17.9 monthly doses of natalizumab was 1.00 per 1000 natalizumab treated patients (95% CI 0.20–2.80). Yousry TA. El al. N Engl J Med. 2006;354:924–933. The post-marketing rate is calculated using an incidence rate based on the number of PML cases diagnosed during the period from the last dose of natalizumab through November 30, 2012 and 312 confirmed cases as of December 5, 2012. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed ever exposed to at least25 infusions and therefore having risk of developing PML during this time.


PML: progressive multifocal leukoencephalopathy; RRMS: relapsing-remitting MS.

1. Biogen Idec: Global Natalizumab Safety Update December 5, 2012
RESTORE Trial: Design

- N = 175
- MS
- Relapse free ≥ 12 mo during treatment with natalizumab
- No GdE lesions on screening MRI

24 weeks

• Natazumab continuation

Switch to placebo

Open-label switch to GA, IFN β-1a, or MP

24-week follow-up

• Open-label natalizumab

Rescue Therapy

- High-dose corticosteroids and/or
- Natalizumab

If

- Clinical disease activity or
- 1 GdE lesion >0.8 cm³ or
- ≥ 2 GdE lesions


2. Cree B et al. AAN 2012. Abstract P06.168

RESTORE: Results

- Interruption of natalizumab resulted in a high rate of recurrence of MRI and clinical MS disease activity (starting at ~week 12)
- Return of MRI disease activity to pre-natalizumab levels around week 16 after natalizumab cessation corresponded with immune parameters returning to levels expected for non-natalizumab treated patients
- IFN β-1a IM appeared to suppress MRI activity more than other open-label treatments, although this group had lower disease activity prior to start of natalizumab (data not shown)
- Monthly MP (1 g IV, started 3 months after last natalizumab dose) did not appear to be effective in disease suppression


Fingolimod: The First Orally Administered DMT for Patients With MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSFORMS¹</td>
<td>(1) Fingolimod 0.5 mg (2) Fingolimod 1.25 mg (3) IFN β-1a 30 µg</td>
<td>Outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARR -52% (P &lt; .001) -38% (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active T2 -35% (P &lt; .001) -42% (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GdE lesions -55% (P &lt; .001) -73% (P &lt; .001)</td>
</tr>
<tr>
<td>FREEDOMS²</td>
<td>(1) Fingolimod 0.5 mg (2) Fingolimod 1.25 mg (3) Placebo</td>
<td>Outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARR -54% (P &lt; .001) -60% (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enlarging T2 -74% (P &lt; .001) -74% (P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GdE lesions -82% (P &lt; .001) -82% (P &lt; .001)</td>
</tr>
</tbody>
</table>


Current Strategies for Mitigating the Potential Risks Associated With Fingolimod

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

Fingolimod: Potential Cardiovascular Risks and Their Impact\(^1,2\)

- More than 30,000 patients have been treated with fingolimod worldwide since its approval; no cases of sudden or explained death reported in studies with this agent
- An unexplained death of a patient within 24 h of first fingolimod dose occurred on December 12, 2011
- 6 other cases of unexplained death have been reported; 3 were sudden
- Additional other reports include 3 deaths due to heart attack and 1 due to heart rhythm disruption
- Currently, US FDA recommends:\(^3\):
  - Practitioners to follow the recommendations in the approved drug label
  - Patients with MS should not stop taking fingolimod without talking to their healthcare professional
- EMA now recommends:\(^4\):
  - Heart activity should be monitored by ECG before first dose is given and continuously for first 6 hours, although this may need to be extended if heart rate is still low
  - Continual monitoring throughout the night may be necessary if heart problems such as bradycardia or AV block do not resolve

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Teriflunomide: Clinical Program

**Monotherapy**
- TEMSO: Phase 3 RMS / placebo study
- TOWER: Phase 3 RMS / placebo study
- TENERE: Phase 3 RMS / vs. IFN
- TOPC: Phase 3 CIS-early MS / placebo study

**Adjunctive therapy**
- Phase 2: RMS, IFN
- Phase 2: RMS GA
- TERACLES: Ph 3 RMS adjunct to IFN / PBO study

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**Teriflunomide: Potential Cardiovascular Risks and Their Impact**


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**Teriflunomide**

- Two doses 7 and 14 mg approved for relapsing forms of MS
- Hepatotoxicity? Q month monitoring x 6
- Pregnancy Category X
- Other less common adverse events:
  - CBC (lymphocytes and neutrophils)
  - Hair thinning
  - Peripheral neuropathy
- Where does it fit?
  - Treatment naïve newly diagnosed RRMS?
  - Only Treatment failures?
  - Injection fatigue
  - Post-Tysabri
  - Select populations

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**TEMSE: Phase 3 Placebo-Controlled Trial of Teriflunomide in MS**

- \(N = 1,088\)
- RRMS
- Placebo
- Teriflunomide 7 mg/day
- Teriflunomide 14 mg/day

**Additional Outcomes**

- Both teriflunomide doses superior to placebo in terms of MRI outcomes
- ~30% in 12-wk CDP with 14 mg teriflunomide dose (\(P = .03\) vs placebo)
- Both doses were well tolerated; diarrhea, nausea, and alopecia were more common with teriflunomide than with placebo
- Incidence of liver enzyme elevations higher in teriflunomide groups

Summary

- Long-term follow-up study has shown treatment with IFN beta-1b has a positive impact on patient mortality.
- The results of the GALA trial might offer patients with MS with an alternative to the standard GA dosing schedule.
- An unexpected death of a patient within 24 hours after the first dose of fingolimod triggered a safety review by regulatory agencies with new treatment guidelines for cardiac monitoring.
- Teriflunomide is now US FDA approved as the second oral MS DMT.

Emerging Therapies for MS: What is their potential role in patient management?

Emerging DMTs for MS: Mechanisms of Action

- BG-12: Oral fumarate derivative; Th2 shift and detoxification.
- Teriflunomide: Inhibits pyrimidine synthesis; cytostatic effect on B and T cells.
- Laquinimod: Quinoline derivative; Th2 shift; decreased leukocyte infiltration into CNS.
- Alemtuzumab: Anti-CD52 mAb; depletes lymphocytes and monocytes.
- Ocrelizumab: Anti-CD20 mAb; depletes B cells.
- Daclizumab: Anti-CD25 mAb; arrests activated lymphocytes; expansion of NK cells.

DEFINE: A Phase 3 Placebo-Controlled Trial of BG-12 in MS

- N = 1,231 RRMS
- Cumulative Probability of Relapse:
  - BG-12 BID: HR = 0.51 (P < .0001)
  - BG-12 TID: HR = 0.50 (P < .0001)
- Time to Confirmed 12-Wk CDP:
  - BG-12 BID: HR = 0.62 (P = .005)
  - BG-12 TID: HR = 0.66 (P = .012)
- Compared with placebo, both BG-12 schedules significantly reduced the number of GdE lesions and new or enlarging T2 lesions.
- Adverse event incidence similar between all three treatment groups.
- Incidence of flushing and GI events (e.g., nausea, vomiting, diarrhea) higher in BG-12 treated patients.

DMT: disease-modifying therapy; mAb: monoclonal antibody


RRMS: relapsing-remitting MS.
CONFIRM: A Phase 3 Trial of BG-12 With an Active Comparator in Patients With MS

- N = 1,417
- Ages 18-55 years
- RRMS
- EDSS 0.0 to 5.0
- 2-year study

BG-12 240 mg BID
BG-12 240 mg TID
Placebo
GA 20 mg/day

EDSS: Expanded Disability Status Scale; GA: glatiramer acetate.

ARR 44% Reduction vs placebo (P < .0001)
51% Reduction vs placebo (P < .0001)
29% Reduction vs placebo (P = .0128)

Placebo BG-12 BID BG-12 TID GA

ARR 44% Reduction vs placebo (P < .0001)
51% Reduction vs placebo (P < .0001)
29% Reduction vs placebo (P = .0128)

CONFIRM: Additional Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>BG-12 BID (vs Placebo)</th>
<th>BG-12 TID (vs Placebo)</th>
<th>GA (vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of relapse</td>
<td>~34% (P = .002)</td>
<td>~45% (P &lt; .0001)</td>
<td>~29% (P &lt; .0007)</td>
</tr>
<tr>
<td>New/enlarging T2 lesions</td>
<td>~71% (P &lt; .0001)</td>
<td>~73% (P &lt; .0001)</td>
<td>~54% (P &lt; .0001)</td>
</tr>
<tr>
<td>New T1 hypointense lesions</td>
<td>~57% (P &lt; .0001)</td>
<td>~65% (P &lt; .0001)</td>
<td>~41% (P &lt; .0021)</td>
</tr>
<tr>
<td>T1-GdE lesions</td>
<td>~74% (P &lt; .0001)</td>
<td>~65% (P &lt; .0001)</td>
<td>~61% (P &lt; .0001)</td>
</tr>
<tr>
<td>12-Wk CDP</td>
<td>~21% (P = .2536)</td>
<td>~24% (P = .2041)</td>
<td>~7% (P = .7036)</td>
</tr>
</tbody>
</table>

• Similar to the DEFINE trial, incidence of flushing and GI events (ie, nausea, vomiting, diarrhea) higher in BG-12–treated patients vs patients on placebo, as well as vs patients on GA

CONFIRM: Additional Outcomes

ALLEGRO: Phase 3, Placebo-Controlled Trial of Laquinimod in Patients With MS

N = 1,106
RRMS

Recent Efficacy Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Laquinimod 0.6 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS progression after 2 years, %</td>
<td>14.0</td>
<td>9.8</td>
</tr>
<tr>
<td>ARR requiring IV steroids</td>
<td>0.358</td>
<td>0.263</td>
</tr>
<tr>
<td>ARR requiring hospitalization</td>
<td>0.114</td>
<td>0.071</td>
</tr>
<tr>
<td>Relapse-free during study, %</td>
<td>52.2</td>
<td>62.9</td>
</tr>
<tr>
<td>Risk of EDSS score progression</td>
<td>36% ↓ in laquinimod group (P = .0122)</td>
<td>48% ↓ in laquinimod group (P = .0023)</td>
</tr>
</tbody>
</table>


ALLEGRO: Phase 3, Placebo-Controlled Trial of Laquinimod in Patients With MS (Cont’d)

Safety

- Frequency of adverse events in laquinimod group comparable to placebo group
- Headache, nasopharyngitis, and back pain most common AEs associated with laquinimod
- Incidence of liver enzyme elevation higher in laquinimod group, but were transient, asymptomatic, and reversible

Phase 3 BRAVO trial yielded similar results compared with placebo as ALLEGRO after correction for baseline characteristic imbalances

Pooled analysis of ALLEGRO and BRAVO trials showed laquinimod significantly reduced ARR, slowed disability progression and brain atrophy, with a good safety profile compared with placebo

CARE-MS-1: A Phase 3 Trial of Alemtuzumab in Previously Untreated Patients With MS

- N = 581
- RRMS
- ≥2 relapses in previous 2 years
- or
- <2 relapse in previous year

Alemtuzumab
12 mg IV d1-d5 → d1-d3 at 12 mo

IFN β-1a
44 µg SC
TIW

Outcome

<table>
<thead>
<tr>
<th>Year</th>
<th>Alemtuzumab</th>
<th>IFN β-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.46</td>
<td>0.22</td>
</tr>
<tr>
<td>1-2</td>
<td>0.29</td>
<td>0.13</td>
</tr>
<tr>
<td>0-2</td>
<td>0.39</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Adjusted ARR

- 55% Reduction
- P < .0001

No significant difference between treatment groups in time to 6-month sustained accumulation of disability

CARE-MS-1: Safety Issues

Autoimmune Thyroid Disease
- Thyroid disorders more common with alemtuzumab treatment
  - 18.1% alemtuzumab vs 6.4% IFN β-1a SC
  - Hyperthyroidism most common
  - Mostly mild-moderate in severity
  - 1.1% with serious alemtuzumab-associated thyroid events
    - 1 (0.3%) ophthalmopathy, 1 (0.3%) thyrotoxicosis in same patient

Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>IFN β-1a SC</th>
<th>n = 187 n (%)</th>
<th>Alemtuzumab</th>
<th>n = 376 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet-based or AE-based definition</td>
<td>3 (1.6)</td>
<td>3 (0.8)</td>
<td></td>
</tr>
<tr>
<td>AE-based definition</td>
<td>1 (0.5)</td>
<td>3 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

SELECT: A Phase 2 Study Comparing Daclizumab HYP With Placebo in RRMS

Daclizumab HYP
- Humanized monoclonal antibody directed against a-subunit (CD25) of IL-receptor
- Modulates IL-2 signaling and causes CD-56 natural killer cell expansion

SELECT Trial

- N = 600
- RRMS
- EDSS 0.0-5.0
- ≥1 relapse (with positive MRI) within 12 months
  - or
- Brain GdE lesion in previous 6 weeks

Daclizumab HYP
150 mg SC Q4W

Placebo

SELECT: A Phase 2 Study Comparing Daclizumab HYP With Placebo in RRMS

Daclizumab HYP
150 mg SC Q4W

Placebo
### SELECT: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DAC 150 mg</th>
<th>DAC 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR*</td>
<td>0.46</td>
<td>0.21*</td>
<td>0.23*</td>
</tr>
<tr>
<td>Relapse-free patients*</td>
<td>64%</td>
<td>81%*</td>
<td>80%*</td>
</tr>
<tr>
<td>New or newly enlarging T2 lesions (1 year)*</td>
<td>8.1</td>
<td>2.4*</td>
<td>1.7*</td>
</tr>
<tr>
<td>New GdE lesions (weeks 8-24)*</td>
<td>4.8</td>
<td>1.5*</td>
<td>1.0*</td>
</tr>
<tr>
<td>Risk of 3-month sustained disability progression at 1-year vs placebo</td>
<td>–</td>
<td>57% ↓ (P = .02)</td>
<td>43% ↓ (P = .09)</td>
</tr>
</tbody>
</table>

* \(P < .001\) for both doses of DAC compared with placebo.

DAC: daclizumab.


- Adverse event incidence similar between treatment groups
- Incidence of serious infection and cutaneous events higher in daclizumab groups
- 1 death in DAC 150-mg group; patient who was recovering from a serious cutaneous event died due to complication of a psoas abscess
- A phase 3 trial comparing daclizumab with IFN β-1a 30 mg QW is ongoing

---

### Update on Ocrelizumab for the Treatment of MS

- Humanized version of rituximab (chimeric anti-CD20 monoclonal antibody active in patients with RRMS and subgroups of PPMS)
- Phase 2 study comparing 600 mg and 2,000 mg ocrelizumab vs placebo
  - Significant ↓ in new GdE lesions and ARR observed with both doses at 24 weeks
  - Benefits maintained at 96 weeks
  - Common adverse effects included systemic inflammatory response syndrome, hypersensitivity, oral herpes infection, and anxiety
  - Serious infection rates were similar for both ocrelizumab groups; rates did not increase over time
  - No opportunistic infections reported among all groups during entire trial
  - 1 death attributed to systemic acute inflammatory reaction observed in high-dose ocrelizumab group (at week 14)

- Currently being tested in phase 3 clinical trials in RRMS

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### Conclusions

- Placebo-controlled trials of BG-12 have shown this agent is efficacious with a good tolerability profile in patients with MS
- Laquinimod has been shown to be superior to placebo in patients with MS; however, further study is necessary to determine whether the 0.6 mg/day dose is optimal
- Alemtuzumab produced robust results compared with IFN β-1a SC in previously untreated and treated patients with MS and provides clinicians with an additional option for individuals with an aggressive disease course
  - However, due to the potential risk of autoimmune thyroid disorders, clinicians will need to carefully determine whether benefits are greater than risks in some patients
- Ocrelizumab and daclizumab have produced positive results in phase 2 trials of patients with MS; phase 3 trials are currently under way to validate the efficacy, safety, and tolerability of these agents in patients with MS

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### CASE DISCUSSIONS

PPMS: primary progressive MS.

Patient Scenario: V.N.

- 28-year-old woman is referred by her PCP

Initial Presentation and Workup

- Signs and symptoms consistent with partial myelitis; improved following short-course IVMP; EDSS=1
- MRI findings by CNS region:
  - Periventricular: 4 T2/FLAIR lesions; 1 T1-GdE lesion
  - Juxtacortical: 3 T2/FLAIR lesions
  - Posterior fossa: 1 T2/FLAIR lesions
  - Spinal cord: 2 T2/FLAIR lesions

Diagnosis

- MS; 2010 International Panel Criteria

Notable History

- BMI = 27
- Hyperlipidemia; currently being treated with statin therapy
- Episode of major depressive disorder 3 years ago; is remission of depressive symptoms taking a SSRI
- Migraine headaches

Additional Information

- JC virus seronegative

Question

How would you proceed with the management of this patient?

- a. Commence therapy with an IFN β
- b. Commence therapy with glatiramer acetate
- c. Commence therapy with fingolimod
- d. Commence therapy with teriflunomide
- e. Commence therapy with natalizumab
- f. Commence therapy with mitoxantrone

Patient V.N.: Summary

- Patient currently on class of medication for hyperlipidemia known to increase LFTs; IFN β, fingolimod, teriflunomide may not be best option
- Patient is thinking about pregnancy at some point, teriflunomide may not be the best option
- Patient selects glatiramer acetate because of long-term safety record
- Wants to hold off on treatment with natalizumab because of fear of PML association, despite testing negative for JCV
How Do You Handle This?

- 28 year old woman with baseline EDSS of 1.
- She has been on glatiramer acetate for 2 years and has been stable with stable annual MRIs.
- She has had no new relapses.
- A surveillance MRI reveals a single new, non-enhancing T2 lesion in the right parietal lobe.

Do you recommend switching therapy?
1. Yes
2. No

Okay, how about this?

- 28 year old woman with baseline EDSS of 1.
- She has been on glatiramer acetate for 2 years and has been stable with stable annual MRIs.
- She has had no new relapses.
- A surveillance MRI reveals a new, T2 lesion that enhances after the administration of gadolinium in the right parietal lobe.

Do you recommend switching therapy?
1. Yes
2. No

Okay, how about this?

- 28 year old woman with baseline EDSS of 1.
- She has been on glatiramer acetate for 2 years and has been stable with stable annual MRIs.
- She has had no new relapses.
- A surveillance MRI reveals three new T2 lesions and a lesion that enhances after the administration of gadolinium in the right parietal lobe.

Do you recommend switching therapy?
1. Yes
2. No

Now how about this?

- 28 year old woman with baseline EDSS of 1.
- She has been on glatiramer acetate for 2 years and has been stable with stable annual MRIs.
- She has had a relapse of right hemiparesis, treated with IVMP.
- A surveillance MRI reveals a single new, non-enhancing T2 lesion in the right parietal lobe.

Do you recommend switching therapy?
1. Yes
2. No
And this?

- 28 year old woman with baseline EDSS of 1.
- She has been on glatiramer acetate for 2 years and has been stable with stable annual MRIs.
- She has had two relapses a right hemiparesis and an optic neuritis during years 3 and 4 of treatment with GA.
- Brain MRI reveals three new T2 lesions in the right parietal lobe.

Do you recommend switching therapy?
1. Yes
2. No

Switching Therapy: What to do next?

The patient tests seronegative for JC virus antibodies
a. Switch to interferon
b. Switch to natalizumab
c. Switch to fingolimod
d. Switch to teriflunomide
e. Continue glatiramer acetate until dimethyl fumarate becomes available
f. Continue glatiramer acetate until alemtuzumab becomes available
g. Add interferon beta-1a to glatiramer acetate

Switching Therapy: What to do next?

The patient tests seropositive for JC virus antibodies
a. Switch to interferon
b. Switch to natalizumab
c. Switch to fingolimod
d. Switch to teriflunomide
e. Switch to natalizumab for ≤2 years, then switch to another therapy
f. Continue glatiramer acetate until dimethyl fumarate becomes available
g. Continue glatiramer acetate until alemtuzumab becomes available
h. Add interferon beta-1a to glatiramer acetate
Switching Therapies

- Does switching classes of medications with similar efficacy make sense?
- Does escalating to treatments that appear to be of greater efficacy but have more potential side effects make sense?
- Is there a role for combination therapy?

Patient D.T.: Continued

- The patient is JCV seropositive, VZV seropositive and has normal ECG, LFTs and CBC
- The patient decides on treatment with fingolimod
- While waiting 6 months for approval from her 3rd party payer for treatment the patient is switched from fluoxetine to citalopram for treatment of depression by her PCP due to sexual side effects from fluoxetine
- During first dose observation, the patient’s heart rate drops from 72 bpm to 48 bpm. The patient is otherwise asymptomatic.

ECG at 6 hours of FDO

Patient D.T.: Continued

- The patient
- Because the patient has insurance, the patient cannot be admitted to the county hospital that serves only Medicaid or uninsured patients.
- The patient is transferred by ambulance to a university medical center where the patient is admitted to cardiology and observed overnight on the telemetry unit.
- The patient remains asymptomatic; 2:1 AV block resolves; the patient is in sinus bradycardia with heart rate of 54 bpm and wants to go home
- What next?
How Do You Handle This?

- 32 year old woman with EDSS of 2.5
- Initially on glatiramer acetate for 2 years but relapsed with new brain lesions during years 3-4
- JCV seropositive
- On fingolimod but developed bradycardia
- After 6 months of treatment a surveillance brain MRI shows a **new ponto-cerebellar junction lesion and a new corpus callosum lesion.**

Do you recommend switching therapy?
1. Yes
2. No

What next?

The patient is seronegative for JC virus antibodies

a. Switch to interferon
b. Switch to natalizumab
c. Switch to teriflunomide
d. Continue fingolimod until dimethyl fumarate becomes available
e. Continue fingolimod until alemtuzumab becomes available

Should there be a MS treatment algorithm?

- Should MRI disease activity be used to switch therapies?
- Is the new gold standard of treatment “freedom from disease activity”?
- Is this not the same thing as treating the MRI scan?
- How long should a course of treatment be given before concluding that it is sub-optimal?
- Are trials that establish treatment algorithms feasible?