Treating Relapsing Multiple Sclerosis: Risk Stratification and Mitigation

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

Existing and Emerging MS Therapies

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

**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.

DMT: disease-modifying therapy; IFN: interferon; MOA: mechanism of action.

*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.*
DMTs Approved for RMS

<table>
<thead>
<tr>
<th>First-line Agents (lower risk)</th>
<th>Second-line Agents (higher risk)</th>
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<tbody>
<tr>
<td>Interferon beta-1a</td>
<td>Mitoxantrone</td>
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<tr>
<td>Interferon beta-1b</td>
<td>Natalizumab</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Alemtuzumab</td>
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<tr>
<td>Oral therapies:</td>
<td>Oral therapies:</td>
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<tr>
<td>Fingolimod</td>
<td>Fingolimod</td>
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<tr>
<td>Teriflunomide</td>
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<tr>
<td>Dimethyl fumarate</td>
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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
  - Pain, flushing, chest pain, rapid heartbeat, non-cardiac shortness of breath, anxiety, tightness in throat (symptoms typically remit in about 15 minutes)
  - Lipoatrophy

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
Lipid-specific IgM bands (LSMB) in the CSF were previously
associated with suboptimal response to IFN

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

- 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
- JCV (+) LSMB (–) patients appear to carry most (but not all) of the PML
risk, O.R.=59.7
- It may be possible to further stratify risk of PML in JCV seropositive
patients by assessing LSMB from the CSF in natalizumab treated
patients
- Proposed to counter immune suppression risk of natalizumab
- Needs replication in larger cohort

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

Lipid-specific IgM bands and Natalizumab
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Estimated Incidence of Natalizumab-Associated PML Risk Factors

Global Natalizumab PML Risk

<table>
<thead>
<tr>
<th>JCV Antibody Status</th>
<th>Negative</th>
<th>Positive</th>
<th>Prior IS Use?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>≤0.09/1,000</td>
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<tr>
<td>(95% CI, 0-0.48)</td>
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<tr>
<td>Based on 1 hypothetical JCV antibody-negative PML case</td>
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<table>
<thead>
<tr>
<th>Natalizumab Exposure</th>
<th>No Prior IS Use</th>
<th>Prior IS Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-24 months</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>25-48 months</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>

Incidence estimates by treatment epoch are calculated based on natalizumab exposure through December 31, 2013 and 430 (438 MS, 2 IBD) 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://www.biogenidec.com


3. Immunosuppressants. JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy
Alemtuzumab versus IFN beta-1a
TIW Phase III CARE MS-1 and 2

- 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"
  - Typical patient: JCV seropositive with disease activity on fingolimod or DMF

- Fingolimod
  - Indicated for relapsing MS
  - Traps lymphocytes in lymph nodes and spleen
  - Proven efficacy
    - 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 bradyarrhythmia among other side effects
  - No clear PML risk, 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 with prior IS
    - 13 confirmed/suspected cases with prior natalizumab exposure

1. Kappos et al. NEJM 362:387-401; 2010
**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)

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**Fingolimod: Issues for Consideration**

- Avoid with:
  - Antiarrhythmics (Ia or III)
  - Antineoplastic agents
  - Immunomodulating 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 therapy (step edits)

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**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>
<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. • All 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. • Risk of VZV reactivation, especially with corticosteroids. • Consider stopping therapy if serious infection develops. • 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. • Use effective contraception on treatment and for at least 2 mo after stopping therapy.</td>
</tr>
</tbody>
</table>

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**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

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**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

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**Dimethyl Fumarate**

- Indicated for relapsing MS
- Mechanism unclear, may induce anti-oxidative genes through Keap1 inhibition that allows NRF2 to translocate to nucleus and induce antioxidative response
- Proven efficacy
  - 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 every 6 months thereafter 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?, 1 case of PML reported in MS patients treated with DMF

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**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
  - Dimethyl fumarate was compared to glatiramer acetate and showed apparent superior efficacy (post-hoc analysis)
- Natalizumab individual risk stratification spans from ~1/10,000 to ~1:100 (2 orders of magnitude)

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

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

Disadvantages
- Assumes validity of certain cross-trial comparisons
- For example:
  - Options for switching for breakthrough disease are less obvious
- 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

- Treatment with disease-modifying agents commences
- MRI and clinical assessments at 6 to 12 months
- Relapse and/or observed progression
- Consider change in therapy
- Relapses and/or disease progression
- No relapses and no disease progression
- Active MRI result
- Periodic clinical and MRI assessment
- Negative MRI result
- Close clinical and MRI monitoring
- Consider change of therapy

Summary

- 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