Current & Emerging Treatment & Novel Strategies in the Management of MS

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Objectives

1. Discuss safety and efficacy profiles of new and emerging DMTs/DMDs & their effect on staging, sequencing, and combination treatment for patients with MS
2. Review recent clinical data surrounding emerging agents for the treatment of MS
3. Evaluate what constitutes optimal utilization of MS DMTs & patient adherence to DMTs **
4. Analyze the role of MRI in the evaluation of MS diagnosis & progression and the effect of such data on treatment planning and monitoring patient outcomes
5. Discuss strategies to address AEs associated with DMTs in order to improve patient adherence **

Composite Approach

Natural History of MS: Summary

Adapted from Goodkin DE. UCSF MS Curriculum. 1999.
Immune Steps Leading to Neurological Problems

“Activated” T cells, B cells and monocytes... **Immunemodulation/Immunesuppression**

...cross the blood-brain barrier...

...launch attacks on myelin & nerve fibers...

...to obstruct nerve signals.

**Neuroprotection** **Remyelination**

Diagnosis of Relapsing Remitting (RR) MS

“Episodic demyelinating disorder with dissemination in space and time...”

→ demonstrate clinically or by MRI

Increased attention to early diagnosis due to known benefit of early disease-modifying therapy (DMT)

MRI ± other ancillary tests (lumbar puncture, evoked potentials) may be helpful
2010 MAGNIMS MRI Criteria

- **Dissemination in Space**

  ≥ 1 lesion in two of the following:
  Periventricular, juxtacortical, posterior fossa, spinal cord

- **Dissemination in Time**

  Simultaneous asymptomatic enhancing lesion at the time of the first attack
  OR
  ≥ 1 new T2 lesion (on any follow-up MRI)

**Diagnosis of Progressive MS**

- One year of progressive symptoms, plus

- 2 of 3 of the following:
  - ≥ 1 T2 lesion in one of the following brain regions: periventricular, juxtacortical, infratentorial
  - ≥ 2 cord lesions
  - Oligoclonal bands or elevated IgG index in cerebrospinal fluid
**Imaging Characteristics of MS**

- **Classic lesions:** T2/FLAIR-hyperintense periventricular lesions

![Sagittal FLAIR](image1)  ![Axial T2](image2)  ![Axial T1 GAD](image3)

- New lesion → Contrast enhancing → May become persistently black on T1
- New lesion → Often remain T2 bright
- Therefore new T2 lesions & contrast enhancing lesions used to monitor disease activity

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**MS Therapy Approval Dates in US**

- IFNbeta-1b (Betaseron) 1993
- IFNbeta-1a (Avonex) 1996
- Glatiramer Acetate (Copaxone) 1996
- Mitoxantrone (Novantrone) 2000
- IFN-1a (Rebif) 2002
- Natalizumab (Tysabri) 2004/2006
- IFNbeta-1b (Extavia) 2009
- Dalfampridine (Ampyra) 2010
- Fingolimod (Gilenya) 2010
- Teriflunomide (Aubagio) 2012
- Dimethyl fumarate (Tecfidera) 2013
Interferon β

- **Basic MoA:** reduce T-cell activation/proliferation

Copaxone

- **Basic MoA:** Th1 to Th2 shift

Natalizumab

- **Basic MoA:** Humanized monoclonal antibody against alpha-4 (α4) integrin


Updates and Advances with Existing Drugs

- Long-term follow up of patients on IFN & GA suggest these drugs are safe & in some patients effective for decades.
- The risks associated with mitoxantrone appear greater than first thought (cardiac toxicity and leukemia).
- Oral formulations of interferon and Copaxone do not work.
- CombiRx trial: 1008 patients. Double blind 3 year RCT of IFN-β1a weekly plus GA vs. either alone; No benefit combination
- Strategy to make interferon longer acting, called PEGylation, looks promising (Year 1: PEG-IFN 125μg SQ every 2 weeks vs every 4 weeks (vs placebo); 1,516 patients)

- Natalizumab → PML update
Is there a way to predetermine PML risk?

Natalizumab PML Incidence Estimates by Treatment Duration

Calculations based on exposure through 28 February 2013 and 343 confirmed cases as of 5 March 2013

Biogen Idec; data on file.
**Oral Therapies in MS: Fingolimod (FTY-720)**

1. **FTY720**-P signaling of S1P receptor
2. Enhanced response to gradient of lymphocyte homing chemokines
3. Sequestration in secondary lymphoid organs, inhibiting egress of naive and effector lymphocytes from LN into the circulation
4. Restriction of lymphocyte recruitment to target tissues and inflammatory sites

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**JCV Index Titer**

- **Index result**
  - ≤0.9
  - >0.9

<table>
<thead>
<tr>
<th>Index result</th>
<th>1-24 months (CIs)</th>
<th>25-48 months (CIs)</th>
<th>49-72 months (CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.9</td>
<td>0.1 (0.04-0.41)</td>
<td>0.3 (0.03-1.38)</td>
<td>0.4 (0.01-3.12)</td>
</tr>
<tr>
<td>0.11-1.0</td>
<td>0.7 (0.35-1.33)</td>
<td>1.0 (0.51-2.34)</td>
<td></td>
</tr>
<tr>
<td>1.01-2.0</td>
<td>1.0 (0.61-1.98)</td>
<td>1.2 (0.71-2.42)</td>
<td></td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>1.2 (0.76-2.10)</td>
<td>1.3 (0.83-2.69)</td>
<td></td>
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**PML risk estimates per 1000 patients (no prior IFU use)**

- **PL values** calculated based on the current PML risk stratification algorithm (effective September 2008) and patient characteristics where P values of the Kaplan-Meier estimate of the survival function for patients with PML risk index (PML risk index [PRI]) and for the population allows an index of 0.5. For PML risk index (PRI) values below 0.5, patient numbers were insufficient to allow for calculation of risk estimates.
Primary End Point: Annualized Relapse Rate

**TRANSFORMS**

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Annualized relapse rate</th>
<th>Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a IM (n=431)</td>
<td>0.33</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fingolimod 0.5 mg (n=429)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod 1.25 mg (n=420)</td>
<td>0.20</td>
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**FREEDOMS**

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Annualized relapse rate</th>
<th>Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=418)</td>
<td>0.40</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fingolimod 0.5 mg (n=425)</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod 1.25 mg (n=429)</td>
<td>0.16</td>
<td></td>
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</table>

Fingolimod 0.5 mg vs placebo: HR=0.70, p=0.02
Fingolimod 1.25 mg vs placebo: HR=0.68, p=0.02

FREEDOMS
Percentage of Patients With 3-month Confirmed Disability Progression

ITT population, Kaplan-Meier (KM) estimate
EDSS, Expanded Disability Status Scale; HR, hazard ratio
Analysis performed using a negative binomial regression model adjusted for treatment group and country.

Analysis performed using rank ANCOVA adjusted for treatment group, country and number of lesions at baseline.

Fingolimod
Fingolimod 0.5 mg (n=370)
Fingolimod 1.25 mg (n=337)

Placebo (n=339)

Number of new/enlarging T2 lesions at month 24 from baseline:

- Placebo: 9.8 (13.2)
- Fingolimod 0.5 mg: 2.5 (7.2)
- Fingolimod 1.25 mg: 2.5 (5.5)

Number of T1 Gd+ lesions at month 24:

- Placebo: 1.1 (2.4)
- Fingolimod 0.5 mg: 0.2 (0.8)
- Fingolimod 1.25 mg: 0.2 (1.1)

FREEDOMS
MRI Lesion Activity

Mean (SD) lesion number:

p<0.001

74% reduction

82% reduction

Fingolimod General Safety

- Increased risk of infection
  - Fatal disseminated VZV and HSV encephalitis cases in clinical trials
  - Though rate of total and serious infections was the same in the fingolimod and placebo groups
- First-dose bradycardia (1:200)
  - Mean decrease in heart rate of 13 beats/min at 6 hours after dose
- AV conduction abnormalities (~1:1000, first- or second-degree AV block)
- Macular edema (1:250)
- Increased LFTs (8%)
- Possible decreased pulmonary diffusion capacity
- Possible teratogenicity
- Vascular events (only at higher doses)
- Lymphomas (low numbers, association is uncertain)

AV = atrioventricular; LFTs = liver function tests.
Fingolimod Safety

- The FDA changed the Prescribing Information for Gilenya in April 2012 based on one case of sudden death within 24 hours of Gilenya use and other deaths in Gilenya patients that may have had a cardiac etiology
  - 3 myocardial infarctions
  - 2 sudden unexplained deaths
  - 2 drowning
  - 1 arrhythmia due to hypertensive cardiomyopathy
  - 3 deaths due to advanced MS

Teriflunomide

- **MoA:** mimics DNA building blocks (pyrimidine); interferes with DNA synthesis and inhibits dihydro-orotate dehydrogenase (DHODH)
  => cytostatic to proliferating B & T cells
  => reduces T-cell proliferation, activation, & production of cytokines
  => interferes with the interaction between T-cells & antigen-presenting cells

- Oral medication administered daily
- Side effects/Risks: diarrhea, nausea, hair thinning, transaminitis, teratogenic, neuropathy, etc.
Teriflunomide (cont.)

- TEMSO (Phase III Trial)
  - double blinded, placebo controlled 2 year trial
  - N = 1,088
  - 2 doses: 7 mg and 14 mg (p=0.002, p=0.005)
  - ARR: ↓ 31% in both 7mg and 14 mg groups (p= 0.001)
  - MRI lesion volume: ↓ 39% and 67% (p= 0.032 and p= 0.003)
  - Disability :↑ 24% and 29.8 % (not significant in 7 mg arm)


BG-12
(Dimethyl fumarate)

- MoA: changes balance of Th1 to Th2 & activates Nrf2 transcriptional pathway (oxidative, metabolic & inflammatory stress)

- Oral medication: Licensed BID

- Side effects/Risks: flushing, gastrointestinal distress, transaminitis, leukopenia, proteinuria, etc.
**BG-12 (cont.)**

- **DEFINE (Phase III)**
  - 2 year, double blind; BG-12 vs. placebo
  - N= 1234
  - 2 dosages BG-12: 240 mg BID or 240 mg TID
  - *Met primary and all secondary end points*
    - ~50% reduction in ARR
    - 34-38% reduction in risk of disability progression
    - 74%-85% reduction in new or enlarging T2 lesions
    - 73%-90% reduction in new GD+ lesions
- **CONFIRM (Phase III)**
  - 2 year, double blinded; BG-12 (2 doses), glatiramer acetate, or placebo
  - *Met primary end point; ARR reduced 44% vs. placebo in lower-dose group, 51% in higher-dose group, and 29% in glatiramer acetate group*
  - Disease activity on MRI/relapses were reduced significantly more in the BG-12 groups vs. placebo
  - Disability progression not reduced significantly more for BG-12 vs. placebo

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**Laquinimod**

- **MoA:** quinolone compound, affects Th1/Th2 balance without clear immunosuppressant action, & may decrease antigen presentation

- **Oral medication administered daily**

- **Side effects/Risks:** well-tolerated (94% completed trial), transient transaminitis, abdominal pain, arthralgias, & headache

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Laquinimod (cont.)

- **BRAVO**
  - Randomized, placebo-controlled in RRMS with rater-blinded comparator arm of IFNβ-1a (Avonex)
  - N=1106
  - Missed primary endpoint at year 2; however, baseline characteristics of disease burden were not evenly distributed between the groups (after a preplanned adjustment vs. placebo)
    - ARR reduction: ↓ 21.3%, p=0.026
    - Risk of disability progression: ↓ 33.5%, p=0.044
    - Brain volume loss: ↓ 27.5%, p<0.0001

- **ALLEGRO**
  - Randomized, placebo-controlled study; N=1,106
  - 23% reduction in relapses (p=0.0023)
  - 36% reduction in disability (p=0.0122)
  - 37% reduction in Gd MRI lesions (p<0.0001)
  - 30% reduction in T2 lesions (p=0.0002)


Emerging Treatments for Multiple Sclerosis
Alemtuzumab

- Currently approved for: B-cell chronic lymphocytic leukemia
- Currently approved for relapsing MS in the majority of jurisdictions outside of the US
- Depletes B and T cells (anti-CD52 humanized monoclonal antibody)

Alemtuzumab (cont.)

- CARE-MS I
  - Alemtuzumab vs. high-dose IFNβ-1a (Rebif)
  - N=581; RRMS treatment naïve; Dz duration <5 years and EDSS <3.0
  - 55% reduction in relapse rate for alemtuzumab-treated patients vs. IFNβ-1a (p< 0.0001)
  - Second primary endpoint not met (disability progression); 8% increase in EDSS score in alemtuzumab group vs. 11% in IFNβ-1a group (HR = 0.70, p= 0.22)

- CARE-MS II
  - Alemtuzumab vs. IFNβ in patients who have relapsed on therapy
  - N=840
  - 49% reduction in ARR (p<0.000)
  - 42% reduction in sustained disability measured by EDSS (p=0.008)
Phase 3 Safety*: Alemtuzumab (12 mg/day)

<table>
<thead>
<tr>
<th></th>
<th>CARE-MS I</th>
<th>CARE-MS I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>90% (3% serious; 1 anaphylactoid, 1 angioedema)</td>
<td>90% (3% were serious, no anaphylaxis)</td>
</tr>
<tr>
<td>Infection</td>
<td>HSV (13%, vs. 2% in IFN); VZV zoster (3%, vs 0%); 1 each of: herpes meningitis, PNA, varicella</td>
<td>HSV (10%, vs. 4% in IFN patients) VZV zoster (6% versus 1%)*</td>
</tr>
<tr>
<td>ITP</td>
<td>1% (vs 0%)</td>
<td>1% (vs 0%) with serious</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>18% (vs 6%)</td>
<td>16% (vs 5%)</td>
</tr>
</tbody>
</table>

*No anti-glomerular basement membrane disease (seen in 2 cases from phase 2 trial)

Daclizumab

- **MoA**: Humanized monoclonal antibody against the alpha subunit of the IL-2 receptor (CD25) on T cells
  - => reduces T-cell activation/proliferation
  - => expands CD56 bright cells that inhibit T-cell survival
- Subcutaneous injection monthly
- Side effects/Risks: nasopharyngitis, upper respiratory infection, headaches, & transamanitis
- SELECT trial (Phase 2b)
  - Evaluate safety & efficacy of DAC HYP monotherapy in patients with RRMS.
  - N=600
  - 150 mg or 300 mg of daclizumab or placebo given by subcutaneous injection every 4 weeks for 52 weeks.
Daclizumab (Cont.)

• SELECT trial (cont.)
  – ARR: ↓ 50-54% (150 mg, 300 mg)
  – Relapse free: 80% of daclizumab-treated & 64% of placebo patients
  – Disability progression confirmed at 3 months
    • 57% reduction in the 150-mg group (p= 0.021)
    • 43% reduction in the 300 mg group (p= 0.09)
  – MRI: 79% to 86% reduction in new gadolinium-enhancing lesions at week 52 vs. placebo
  – Reduction in disability progression, was independent of relapses, and is one of the most noteworthy findings from the study

Gold et al., Lancet 2013
Saidha et al., Lancet 2013

Potential Roles of B Cells in MS

Diagram showing potential roles of B cells in MS with cytokines, cells, and pathways involved in inflammation and immune response.
Rituximab in Adults with Relapsing-remitting MS

Hauser SL, NEJM 2008

Ocrelizumab

- MoA: Fully humanized monoclonal antibody targeted against CD20 B cells
  => kills newly maturing B-cells

- Infusion (baseline & at 2 weeks)

- Side effects/Risks: infusion reactions, infections, lymphopenia, etc.

- Currently in Phase 3 trials
Ocrelizumab (cont.)

• Phase II
  – Evaluate efficacy and safety of ocrelizumab in RRMS; 96 weeks
  – N=220
  – randomized 1:1:1:1 (ocrelizumab [2 doses], placebo, or Avonex); wks 24, 48 & 72 all pts were treated with ocrelizumab
  – Results: 78.2%-80.0% relapse-free, 76.4% no disease progression, ARR reduced between wks 24-96 in pts switched from placebo (0.64 to 0.20) & Avonex (0.36 to 0.16), & at wk 96 there were no Gd-enhancing lesions in all groups

COUNSELING

• Optimal utilization goes beyond suppression of relapses & MRI activity alone
• Adherence rooted in DMD counseling
• AE’s as much managed with counseling, as well as symptomatically
Don’t forget other therapies for MS patients

- Symptom management (depression, bladder, pain, spasticity, headaches, fatigue etc)
- Vitamin D
- Bone density (DEXA scan)

Remyelination can occur in MS brain

OPCs, which exist in all of our brains, can be induced to become oligodendrocytes and remyelinate lesions in animals: Several inhibitors of OPC differentiation identified: Notch-Jagged, PSA-NCAM, hyaluronan, LINGO-1 (RENEW & SYNERGY)
Agents of interest for neuroprotection in MS

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium channel blockers</td>
<td>Lamotrigine, amiloride, phenytoin, flecaïnide, carbamazepine</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Nimodipine, nifedipine, ryanodine, CYLA, bepridil</td>
</tr>
<tr>
<td>Glutamate antagonists</td>
<td>Riluzole, NBQX, talampanel, memantine</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Erythropoietin, rhIGF</td>
</tr>
<tr>
<td>NO blockers</td>
<td>Furoxan</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Estriol, testosterone</td>
</tr>
<tr>
<td>Phenols</td>
<td>Resveratrol, epigallocatechin-3-gallate</td>
</tr>
<tr>
<td>Statins</td>
<td>Simvastatin, atorvastatin</td>
</tr>
<tr>
<td>Immunophilin ligands</td>
<td>Cyclosporin A, FK506, rapamycin</td>
</tr>
<tr>
<td>PPARg agonists</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Agents with pleiotropic effects</td>
<td>Ibudilast, minocyclin, co-Q10, galectine-1, vitamin D</td>
</tr>
</tbody>
</table>

Summary

- MS therapeutics is a dynamic field
- Future of MS treatment may be three tiered
- Ongoing need to balance efficacy & safety
- Clinical & MRI remain mainstay methods for assessing success/progression
- Adherence deeply seeded in counseling (not just an issue of oral vs injections)
- AE’s not just managed strategically. Counseling critical for AE’s too
Questions?