Multiple Sclerosis: Current Treatment Strategies

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Demographics of MS

- Prevalence: >400,000 cases in United States\(^1\) and 2.3 million worldwide\(^2\)
  - ~8500-10,000 new cases annually\(^3\)
- Most cases occur between ages 15 and 45\(^3\)
  - Women outnumber men 3:1\(^2\)
- 85% present with relapsing-remitting MS (RRMS)\(^3\)
  - Without treatment, 50% of these patients develop secondary-progressive MS (SPMS), with significant disability within 10 years

MS Worldwide Prevalence

Pathogenesis of MS: Current Paradigm

- Cause is uncertain
- Immune-mediated inflammatory disease of CNS
- May develop in genetically susceptible individuals exposed to undefined “triggers”
- Leukocytes penetrate blood-brain barrier, secrete inflammatory cytokines
- T cells, B cells, and macrophages may orchestrate autoimmune attack against myelin antigens

CNS = central nervous system.
Molecular Mimicry: An Inability to Distinguish Nonself From Self

**Potential Nonself Antigens**
- Viruses: Herpes, Adenovirus, Rubella, Retrovirus
- Bacteria/Toxins: *Borrelia*, Chlamydia, Superantigens

**Potential Self-Antigens**
- Myelin basic protein
- Proteolipid protein
- Myelin oligodendrocyte glycoprotein
- Myelin-associated glycoprotein

Courtesy of C. Markowitz.
Genetics of MS: Identification of MS Genetic Variants

- Evidence of genetic risk ($\lambda_s \approx 40$)
  - Population risk: 0.1%
  - Sibling risk: 2–4%
  - Dizygotic twin risk: 5%
  - Monozygotic twin risk: 30%
- MS genetics dictates lower activation threshold of Th17, B cells, and macrophages
- Majority of causal variants
  - Noncoding
  - Map to immune-cell specific enhancers
- SNP for MS are enriched within immune-related transcription factor binding sites (NFκB, PU1, EBF1, MEF2A, TOF12)

SNP = single nucleotide polymorphism.
Hafler DA. ACTRIMS-ECTRIMS September 2014; Boston, MA [PS1].
Risk Factor: Smoking

- Increased risk of MS in smokers
- Smoking is associated with more rapid disease progression
  - Including EDSS scores
- Increased mortality in smokers vs non-smokers

EDSS = expanded disability scale status.
Risk Factor: Vitamin D

- Prognostic factor for the conversion of the first attack into CDMS
- Investigate correlation with risk of relapses in the short term
- Putative disease-modifying therapy

CDMS = clinically definite multiple sclerosis.
Martinelli et al. ECTRIMS 2012. Abstract P373.
Risk Factor: Epstein-Barr Virus

• Previous exposure to Epstein-Barr associated with higher risk for MS
  – Exposure present in 100% of MS patients in one study
• Exposure in pediatric populations is more variable than adult exposure
  – Impaired suppression of Epstein-Barr virus latency in children with MS

Yeh EA et al. ECTRIMS 2012. Abstract P374.
High Sodium Intake Associated with Increased Disease Activity and Immune Dysregulation

- People consuming moderate-to-high amounts of salt:
  - 4x as likely to have exacerbating MS symptoms
  - 3.5x as likely to have new lesion on MRI

<table>
<thead>
<tr>
<th>Salt (g/day)</th>
<th>New Gd or New/Enlarging T2</th>
<th>P Value</th>
<th>Exacerbation Rate</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>1 (baseline)</td>
<td>-</td>
<td>1 (baseline)</td>
<td>-</td>
</tr>
<tr>
<td>2–4.8</td>
<td>2.68</td>
<td>0.002</td>
<td>2.56</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt; 4.8</td>
<td>3.56</td>
<td>0.001</td>
<td>3.37</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- GWAS have identified 20 salt-induced genes that are enhanced in MS
- High salt was found to both reduce the suppressive capacity of regulatory T cells and induce Th17; all mediated by SGK1

GWAS = genome-wide association studies; SGK1 = serum/glucocorticoid-regulated kinase1.
Disease Type and Disability Progression

- Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity

Preclinical | RRMS | SPMS

Time

Disability

Adapted with permission from JS Wolinsky.
What Is Clinically Isolated Syndrome?

• A first neurologic episode that lasts at least 24 hours
• Caused by inflammation/demyelination in the CNS
• Can be monofocal or multifocal
• Various factors determine risk of developing CDMS

National MS Society.
Available at: http://www.nationalmssociety.org/symptoms-diagnosis/clinically-isolated-syndrome-(CIS).
Clinically Isolated Syndrome

- Initial presentation in 90% of MS patients
  - Spinal cord syndrome in 50%
  - Optic neuritis in 25%
  - Brainstem syndrome in 15%
- Risk of developing MS after CIS
  - 30% to 75% with optic neuritis
  - 47% with brainstem syndrome
  - 39% with spinal cord syndrome
- Risk is greatest in first 5 years, continues for many years
- Progression risk to CDMS is greater with abnormal baseline MRIs

CIS = clinically isolated syndrome; MRIs = magnetic resonance images.
52 patients with CIS were followed for 6 years. Risk of CDMS was determined.

CSF was examined for OCBs using isoelectric focusing.

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>No MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCB -</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>OCB +</td>
<td>32</td>
<td>1</td>
</tr>
</tbody>
</table>

Sensitivity = 91%
Specificity = 94%
Follow-Up MRI After CIS

Patient has no new symptoms

Initial FLAIR after CIS

Follow-up MRI 6 months post FLAIR
Now dissemination in space, dissemination in time

FLAIR = fluid-attenuated inversion recovery.
Images courtesy of Clyde Markowitz, MD.
RIS 5-Year Risk for an Initial Clinical Event From a Multinational Cohort (RISC)

- Retrospective analysis of 22 databases from 5 countries
- >430 patients (largest cohort examined to date)
- 5-year observed conversion rate to first clinical event: 34%
- In multivariate model, several factors are significantly associated with conversion:
  - Age (younger > older)
  - Gender (M > F)
  - Presence of spinal cord lesions

RIS: Management Implications

- Potential for misdiagnosis
- High probability of benign MS
- “Wait and watch” approach may be best
- Future challenges:
  - How to identify high-risk RIS group
  - Standardized MRI
  - Combining MRI with other predictors
  - Population-based prospective study

## 2010 Revised McDonald MS Diagnostic Criteria

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space (DIS) and time (DIT).

<table>
<thead>
<tr>
<th>Clinical (Attacks)</th>
<th>Lesions</th>
<th>Additional Criteria To Make DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS</td>
</tr>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS; OR await further clinical attack implicating a different CNS site</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of ≥2 lesions</td>
<td>DIT; OR await a second clinical attack</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS; OR await clinical attack implicating a different CNS site AND DIT; OR await a second clinical attack</td>
</tr>
<tr>
<td>0 (progression from onset)</td>
<td></td>
<td>One year disease progression (retrospective or prospective) AND at least 2 of: DIS in the brain based on ≥1 T2 lesion in periventricular, juxtacortical, or infratentorial regions; DIS in spinal cord based on ≥2 T2 lesions; or positive CSF</td>
</tr>
</tbody>
</table>

## Diagnostic Criteria for MS: Application of MRI

<table>
<thead>
<tr>
<th>DIS (on either baselines or follow-up MRI)</th>
<th>McDonald 2001(^1)</th>
<th>McDonald 2005(^1)</th>
<th>MAGNIMS 2010 Proposal(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 of:</td>
<td>≥3 of:</td>
<td>≥1 lesion in each of ≥2 characteristic locations</td>
<td></td>
</tr>
<tr>
<td>≥ 9 T2 lesions or ≥1 gadolinium-enhancing lesion</td>
<td>≥9 T2 lesions or ≥1 gadolinium-enhancing lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 periventricular lesions</td>
<td>≥3 periventricular lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 juxtacortical lesion</td>
<td>≥1 juxtacortical lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 posterior fossa lesion</td>
<td>≥1 posterior fossa lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 cord lesion can replace 1 brain lesion</td>
<td>Any number of lesions can be included in lesion count</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Periventricular</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Juxtacortical</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior fossa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All lesions in symptomatic regions excluded in brain stem and spinal cord syndromes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIT</th>
<th>McDonald 2001(^1)</th>
<th>McDonald 2005(^1)</th>
<th>MAGNIMS 2010 Proposal(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) ≥1 gadolinium-enhancing lesion ≥3 months after CIS onset (if not related to CIS)</td>
<td>1) ≥1 gadolinium-enhancing lesion ≥3 months after CIS onset (if not related to CIS)</td>
<td>1) Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time</td>
<td></td>
</tr>
<tr>
<td>2) A new T2 lesion with reference to a prior scan obtained ≥3 months after CIS</td>
<td>2) A new T2 lesion with reference to a prior scan obtained ≥30 days after CIS</td>
<td>2) A new T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of timing of baseline scan</td>
<td></td>
</tr>
</tbody>
</table>

MAGNIMS = magnetic resonance imaging in MS
Patient Meets Criteria for MS Using MAGNIMS 2010 Criteria

- Juxtacortical lesion
- Periventricular lesion
- Posterior fossa lesion
- Asymptomatic gadolinium-enhancing lesion
- Asymptomatic T2 lesion

Images courtesy of Omar Khan, MD.
<table>
<thead>
<tr>
<th>1996 MS Clinical Description Subtypes</th>
<th>2013 MS Disease Modifiers Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive accumulation of disability from onset; with or without temporary plateaus, minor remissions and improvements</td>
<td>Progressive accumulation of disability from onset</td>
</tr>
<tr>
<td>Progressive accumulation of disability after initial relapsing course, with or without occasional relapses and minor remissions</td>
<td>Active* and with progression**</td>
</tr>
<tr>
<td>Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery</td>
<td>Active but without progression</td>
</tr>
<tr>
<td>Not active but with progression</td>
<td></td>
</tr>
<tr>
<td>Not active and without progression (stable disease)</td>
<td>PP</td>
</tr>
</tbody>
</table>

*Activity determined by clinical relapses assessed at least annually and/or MRI activity.
**Progression measured by clinical evaluation, assessed at least annually.
PP = primary progressive; SP = secondary progressive; PR = progressive relapsing.
Natural History of Brain Atrophy in MS

These images were acquired over the course of 7 years from the same untreated patient with MS

Images courtesy of C. Markowitz, MD.
28-Year-Old Patient With RRMS and EDSS 1.0

WM = white matter; WMLL = white matter lesion load.
Images courtesy of C. Markowitz, MD.
Clinical Applications of New MRI Techniques

• Magnetization transfer imaging
• Diffusion-weighted imaging
• Functional MRI
• Magnetic resonance spectroscopy
• High-field strength imaging
Nonconventional MRI Techniques: Higher Pathologic Specificity Than Conventional MRI

- Magnetization transfer imaging (MTI)
- Improved information regarding tissue integrity
- Visualizes water bound to macromolecules (myelin, etc)
  - MTR
  - MTR ↓ due to signal intensity ↓
  - ↓ MTR = worse tissue destruction
  - MTR ↓ in NAWM

NAWM = normal-appearing white matter; MTR = magnetization transfer ratio.
A. NWM
healthy individual

B. Severely hypointense T1

C. Mildly hypointense T1 = changes within MS lesion

D. NWM NAWM

NWM = normal white matter.
Diffusion-Weighted Imaging (DWI)

Image courtesy of AG Filler.
High-Resolution OCT

- Better precision (4-6 μm)
- More reliable
- Can separate retinal layers

OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

Above courtesy of James Fujimoto, PhD.
Natural History of Untreated MS

- 30% to 50% of patients worsen by 1.0 EDSS unit within 2 to 3 years\(^1\)
- Up to 44% of patients need an assistive device for walking within 5 years\(^1\)
- Relapsing MS leads to progressive MS after 10 years in 50% of cases\(^2\)
- 54% to 65% of patients with MS experience cognitive impairment, affecting employment, social life, and daily functioning\(^3\)

Approach to Therapy

• Treatment of acute exacerbations
• Modification of disease progression
• Management of disease signs and symptoms
Approved therapies

Current Disease-Modulating Agents

- **Avonex** - Interferon-1a  
  - Weekly IM, 30 µg
- **Plegridy** – PEG-Interferon-1a  
  - Bimonthly SQ, 125 µg
- **Betaseron/Extavia** - Interferon-1b  
  - SQ, 8 M units QOD
- **Rebif** - Interferon-1a  
  - SQ, 44 µg units TIW
- **Copaxone** - glatiramer acetate  
  - SQ, 20 mg QD,  
  - SQ, 40mg TIW
- **Novantrone** - mitoxantrone  
  - IV q3 months – 12 mg/m²
- **Tysabri** - natalizumab  
  - IV 300mg Monthly
- **Gilenya** - fingolimod  
  - Oral – 0.5 mg Daily
- **Aubagio** - teriflunomide  
  - Oral -7mg/14mg Daily
- **Tecfidera** - dimethyl fumarate  
  - Twice -240mg BID
- **Lemtrada**- Alemtuzumab  
  - IV 12mg x5 yearly x2
Disease-Modifying Therapies: The Benefits

- Reduction in number and severity of relapses, improved recovery
- Reduction in sustained worsening in neurological exam/transition to progressive disease
  - Expanded Disability Status Scale (EDSS)
- Reduction of lesions on MRI
  - Gadolinium-enhancing, T1, and T2
  - Decrease in atrophy
- Improved quality of life

Rationale for Early Treatment

• Time is ticking…
• What is lost by delaying early therapy is not regained by starting later
## Trials of Disease-Modifying Therapy in CIS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Follow-Up Years</th>
<th>Conversion to CDMS (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug</td>
<td>Placebo</td>
</tr>
<tr>
<td>CHAMPS ¹</td>
<td>Interferon beta-1a 30 μg IM qwk</td>
<td>383</td>
<td>3</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>ETOMS ²</td>
<td>Interferon beta-1a 22 μg SC qwk</td>
<td>308</td>
<td>2</td>
<td>34</td>
<td>45</td>
</tr>
<tr>
<td>REFLEX ³</td>
<td>Serum-free formulation interferon beta-1a 44 μg SC qwk</td>
<td>517</td>
<td>2</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td>BENEFIT ⁴</td>
<td>Interferon beta-1b 250 μg SC q48h</td>
<td>468</td>
<td>2</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>PreCISe ⁵</td>
<td>Glatiramer acetate 20 mg/day</td>
<td>481</td>
<td>3</td>
<td>25</td>
<td>45</td>
</tr>
</tbody>
</table>

Early treatment with disease-modifying therapy decreases the conversion to CDMS

IM = intramuscular; SC = subcutaneous.
Pivotal Phase 3 Studies Demonstrating Significant Reduction in Relapse Rates: Traditional DMTs

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN β-1a 44 ug SC (n = 371)</td>
<td>*↓33%</td>
<td></td>
</tr>
<tr>
<td>IFN β-1b 250 ug SC (n = 372)</td>
<td>*↓34%</td>
<td></td>
</tr>
<tr>
<td>IFN β-1a 30 ug IM (n = 301)</td>
<td>**↓32%</td>
<td></td>
</tr>
<tr>
<td>GA 20mg SC (n = 251)</td>
<td>***↓29%</td>
<td></td>
</tr>
</tbody>
</table>

*P ≤ 0.0001; **P = 0.002; ***P = 0.007.

IFN = interferon; GA = glatiramer acetate.
Pivotal Phase 3 Studies Demonstrating Significant Reduction in Relapse Rates: Recently Approved DMTs

Laquinimod is an investigational drug not yet approved for the treatment of MS.

Glatiramer Acetate 40 mg

- GALA study evaluated 40 mg SC GA 3x weekly vs placebo over 1 year
- ARR ↓ 34.4%
- New/enlarging T2 lesions ↓ by 34.4%, contrast lesions ↓ by 44.8%
- Free of disease activity 23.3%
- Now approved and available
- Role of generics?

PEG-IFNβ

- Phase 3 ADVANCE trial
  - 2 years, N = 1516
  - PEG-IFNβ-1a 125 μg given q2 weeks or q4 weeks vs placebo for 1 year; placebo re-randomized for Year 2
- ARR (Year 1) reduced 35.6% ($P<0.001$) and 27.5% ($P<0.02$) (0.256, 0.288 vs 0.397)
- EDSS disability reduced 38% ($P<0.04$)

PEG-IFNβ (cont)

- ↓ in new/enlarging T2 lesions 67% ($P<0.001$) and 28% ($P<0.001$)
- 4-year follow-up in ATTAIN
- 2-week data looks better than 4-week data
- Will this replace IM IFNβ-1a?

Current Agents

- Fingolimod
  - Phase 3 PPMS
- Natalizumab
  - Phase 3 SPMS
- Rituximab
  - Phase 1/2 SPMS

PPMS = primary-progressive multiple sclerosis.
Breakthrough Disease Facts

• Disease activity is expected??
  – Patients should be educated regarding treatment options and realistic expectations of therapy
• “Breakthrough” activity is NOT necessarily a reason for therapy discontinuation (but it can be)
• Tolerance for ongoing disease activity should be defined (both clinically and radiologically)
• Regular evaluation of disease activity
  – Sustained disability, relapses, MRI scans, and cognitive deficit
  – ?NAb levels (IFNβ therapies)

NAb = neutralizing antibody.
Why Ascertain Adherence?

• Precondition for confirming breakthrough
• Risk of unnecessary medication intensification
• Patient safety
• Confidence in the therapeutic alliance

Image courtesy of AG Filler.
Assessing Therapy: Factors to Consider

- Changes on physical exam
- Relapses
- Progression
- MRI
- Side effects
- Other measures: fatigue, cognition, depression, etc
- Therapeutic risks vs benefits assessment
  - 10 available pharmacological therapies
  - At least 6 new therapeutic options in late-stage development
- Patient perceptions and perspectives
Therapeutic Response

- Trials provide group data; clinical concern is individual response
- Patient must be on therapy for a minimum time period (6 months)?
  - Can early MRI predict responder?
- Must exclude:
  - Comorbidity/alternate diagnosis
  - Adverse effects (which may be treatable)
Suboptimal Response: Proposed Criteria

- Attack rate >1 per year
  - No ↓ in attack rate
- Incomplete attack recovery
  - Especially with accumulating disability
- New/recurrent brainstem or spinal cord lesions
- Polyregional disease
- Worsening motor/cognitive impairment with disruption of ADL

ADL = activities of daily living.
Switch Therapy

- Change from IFN to GA or vice-versa
- Consider natalizumab
- Consider an oral immunomodulator
- Oral or IV chemotherapies
- New agents in development (clinical trials and off label use)

GA = glatiramer acetate.
Questions About Natalizumab

- Is the PML risk acceptable to patients and physicians (1:80-1:1000)?
- Which patients should we use it for?
- JC virus antibody assay—if negative, is it first line?
- How long should we keep patients on natalizumab?
- Washout period before and after treatment—prior immunosuppression?
- Drug holiday
- Can we detect cases early enough to prevent irreversible damage?
- What algorithm should be used to treat cases of PML?

JC = John Cunningham; PML = progressive multifocal leukoencephalopathy.
Questions About Oral Immunomodulators

• Should they be first-line therapies?
• What are the short-term safety issues?
• What are the long-term safety concerns?
• What should the washout be for patients on DMT prior to starting an oral agent?
• What type of monitoring should patients have, and how frequently? Who will do the monitoring? PMD? Neurologist?
New Agents in Development

- Novel therapies continue to be developed
- Clinical trials face growing challenges
  - Increasing use of therapy; shrinking untreated population
  - Concerns about placebo
  - Patients with less active disease are being entered
  - Impact on outcomes (harder to show differences)
Oral Agents

- Amiloride
- Epigallocatechin-gallate
- Idebenone
- Ibudilast
- Laquinimod
- Masitinib
- Oxcarbazepine
- Riluzole
- Second-generation S1P receptor modulators
Laquinimod

- Oral quinoline-3 carboxamide
- Decreased inflammation, demyelination, and axonal injury; may boost BDNF
- Phase 3 two-year trial (ALLEGRO)
  - 0.6 mg laquinimod vs placebo (N = 1106)
  - ARR 0.30 vs 0.39 ($P = 0.002$)
  - ↓ EDSS disability 11.1% vs 15.7% ($P = 0.01$)
  - ↓ contrast and T2 lesions

Laquinimod (cont)

• Phase 3 two-year trial (BRAVO)
  – 0.6 mg laquinimod vs placebo and IM IFNβ-1a (N = 1331)
  – ARR NS (0.28 vs 0.26 vs 0.34), EDSS disability NS ($P = 0.063$)
  – Benefits on atrophy

• Phase 3 trial (CONCERTO)
  – Evaluating 0.6 mg and 1.2 mg doses vs placebo
  – Primary outcome: disability

ARR = annual relapse rate.
Second-Generation S1P Receptor Modulators

- Fingolimod binds to S1P-1,3,4,5 receptors
- Might want to spare S1P-2,3 (cardiovascular receptors); maintain S1P-1 (lymphocytes and astrocytes) and possibly S1P-5 (oligos)
- Multiple agents
  - All produce first-dose bradycardia

Second-Generation S1P Receptor Modulators (cont)

- Siponimod (S1P1 = S1P5)$^1$
  - Phase 3 EXPAND trial in SPMS; N = 1530; 2 mg daily vs placebo
  - Shorter half life
- Ponesimod (S1P1 > S1P5 > S1P3)$^2$
  - Positive Phase 2 relapsing MS (especially 20 mg dose)
- ONO-4641 (S1P1 = S1P5 > S1P4)$^2$
  - Positive Phase 2 relapsing MS

Monoclonal Antibodies

- Alemtuzumab (anti-CD52)
- Anti-CD20s
- Daclizumab (anti-CD25)
- Secukinumab
  - Anti-IL17
Alemtuzumab

- Therapeutic class
  - Humanized MAb directed against CD52 antigen
- Molecular MOA
  - Binds to CD52, a cell-surface glycoprotein present on >95% of T cells, B cells, monocytes, and eosinophils
- CD52 function is unknown
- Targeted depletion of CD52-expressing cells within 2 days
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
- Approved for leukemia

MOA = mechanism of action.
Alemtuzumab: Effects on the Immune System (cont)

- Median recovery time to baseline levels
  - CD4+ T cells: 61 months
  - CD8+ T cells: 30 months
  - Monocytes: 3 months
  - B cells: 3 months
- B cells rise to 124% of pretreatment levels after 27 months posttreatment

Alemtuzumab CAMMS223 Trial: 5-Year Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alemtuzumab</th>
<th>IFNβ-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients evaluated at 60-month follow-up</td>
<td>59.9%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Annualized relapse rate (0-60 months)</td>
<td>0.11</td>
<td>0.35*</td>
</tr>
<tr>
<td>Patients experiencing sustained accumulation of disability</td>
<td>13%</td>
<td>38%*</td>
</tr>
<tr>
<td>EDSS change from baseline to 60 months</td>
<td>-0.30</td>
<td>+0.46*</td>
</tr>
</tbody>
</table>

• Key safety considerations:
  – Idiopathic thrombocytopenia purpura (ITP) - 2.8%
  – Thyroid autoimmunity - 30%
  – Goodpasture’s syndrome (n = 1)

*Statistically significant for treatment group comparisons.
## CARE MS-I

<table>
<thead>
<tr>
<th></th>
<th>Alemtuzumab</th>
<th>SC IFNβ-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>0.18 (↓55%)</td>
<td>0.39 (P&lt;0.0001)</td>
</tr>
<tr>
<td>Proportion relapse-free</td>
<td>78%</td>
<td>59% (P&lt;0.001)</td>
</tr>
<tr>
<td>EDSS disability (6 months)</td>
<td>8%</td>
<td>11% (NS)</td>
</tr>
<tr>
<td>Contrast lesions</td>
<td>7%</td>
<td>19% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Median BPF change</td>
<td>-0.87%</td>
<td>-1.49% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Proportion with new/enlarging T2 lesions</td>
<td>48%</td>
<td>58% (P = 0.04)</td>
</tr>
<tr>
<td>Disease activity-free</td>
<td>39%</td>
<td>27% (P&lt;0.006)</td>
</tr>
</tbody>
</table>

BPF = brain parenchymal fraction.
CARE MS-II

- 2-year trial of patients with relapsing MS (N = 840)
  - 12 mg IV for 5 days, then 3 days in Year 2 (N = 426)
  - IFNβ-1a 44 µg 3x weekly (N = 202)
  - Rater-masked design
  - Relapse on therapy required
  - Initially 2:2:1 allocation that included alemtuzumab 24-mg treatment group, which was later discontinued

CARE MS-II (cont)

- ARR 0.26 (↓ 49%) vs 0.52 (P<0.0001)
- Relapse-free 65% vs 47% (P<0.0001)
- Mean EDSS change at 24 months -0.17 vs +0.2 (P<0.0001)
- Contrast lesions at 24 months 9% vs 23% (P<0.0001)
- EDSS disability (6 months) 13% (↓42%) vs 21% (P<0.008)
- New/enlarging T2 lesions 46% vs 68% (P<0.0001)
- Disease activity-free 32% vs 14% (P<0.0001)

CARE MS-I Adverse Events

- Infusion reaction
  - Fever, headache, rash in 90% of patients
  - 3% serious cases
- Infections in 67% (vs 45%)
  - Nasopharyngitis, UTI, herpes (16% vs 2%)
  - Acyclovir given for 1 month post-therapy
- Autoimmune disorders
  - Thyroid disorder (18% vs 6%); thyroid papillary carcinoma (N = 2)
  - Thrombocytopenia (1%)
  - Renal disease (N = 1)
  - Pancytopenia with death (N = 1)

CARE MS-II Adverse Events

- Infusion reaction in 90%-97% of patients
  - 3% serious cases
- Infections in 77%-83% of patients
  - Nasopharyngitis, UTI, URI, herpes (16% vs 4%)
- Autoimmune disorders
  - Thyroid disorder (16%-19% vs 5%)
  - Thrombocytopenia 1%

Alemtuzumab

• Pros
  – Great efficacy
  – Only used for several days over 2 years
  – Appealing induction strategy

• Cons
  – Rejected by FDA 12/13; under resubmission
  – Phase 3 trial data not as impressive as Phase 2
  – Irreversible effect over years
  – Adverse event issues, ongoing monitoring
  – Unclear how long the 2 courses of treatment last
  – MS population for this therapy is shrinking

Anti-CD20s: Role of B Cells

• Antigen-presenting cells
• Immune regulation
  – By expression of accessory molecules, cytokine production
• Antibody secretion
  – Through plasma cells

Novel Anti-CD20 MAbs

• Ocrelizumab (Genentech; Roche; Biogen Idec)
  – Humanized IgG1
  – Enhanced ADCC, reduced CDC
  – Binds to different overlapping epitope

• Ofatumumab (GlaxoSmithKline; Genmab)
  – Human IgG1k; approved for refractory CLL
  – Binds to novel membrane-proximal CD20 epitope
  – Increased CDC

• Ocaratuzumab (Mentrik Biotech)
  – Humanized with 13-to 20-fold higher CD20-binding affinity

Ocrelizumab Phase 2 Trial

- Relapsing MS (N = 220)
  - 1000 mg or 300 mg ocrelizumab Days 0, 15 vs placebo vs IFNβ-1a IM
- Primary outcome
  - Total number of contrast MRI lesions at 12, 16, 20, and 24 weeks
    - 5.5 placebo vs 6.9 (IFNβ-1a IM), 0.6 ocrelizumab 600 mg (↓ 89%), 0.2 ocrelizumab 2000 mg (↓ 96%)
  - ARR 0.64 vs 0.36, 0.13, 0.17
  - IRR ↓ by 2nd infusion; 1 death involved a systemic inflammatory reaction

Ocrelizumab Phase 2 Study: Gd-Enhancing T1 Lesions

Lesions on MRI by Week (ITT)

↓ 89%-96%, $P<0.0001$ for both ocrelizumab doses vs placebo

IFNβ-1a arm was open-label; all efficacy comparisons were exploratory.
Emerging Concepts

• New MS therapies are on the horizon
  – Will add to treatment complexity
• Novel MOAs will raise concern about unknown, rare, or long-term safety issues
  – Risk-benefit ratio analysis
• Personalized medicine
• Cost
• Future focus
  – Optimal drug selection, induction/combination strategies, when/how to switch, CNS repair strategies