Update on Multiple Sclerosis

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McDonald Criteria for MS (2005)

Determining Abnormal MRI

Three out of four of the following:

• 1 Gd+ lesion or 9 T2 hyperintense lesions
• 1 infratentorial lesion
• 1 juxtacortical lesion
• 3 periventricular lesions

(1 spinal cord lesion = 1 brain lesion)

After Barkhof et al and Tintore et al
Dublin Revision 2011

• For DIS: At least one T2 lesion in two of the following locations:
  – Periventricular
  – Juxtacortical
  – Infratentorial
  – Spinal cord

• For DIT: Any new lesion on any follow-up scan after a baseline scan done anytime after onset of CIS
Single Early MRI

- In CIS, a single MRI, even in 1st 3 months, with Gad enhancing lesion(s) and T2H has high specificity for development of CDMS
Radiologically Isolated Syndrome

• Lebrun 2009
  – 70 patients, with mean F/U 5.2 years
  – 23/70 convert to CIS at mean of 2.3 years
  – 91% with dissemination in time by MRI

• Okuda 2009
  – 44 patients; 30 with clinical F/U; 41 MRI F/U
  – 10/30 convert to CIS at median time of 5.4 yrs
  – 59% with MRI progression at median 2.7 yrs
Risk Factors for RIS to Convert to MS

- Okuda (2011): Asymptomatic spinal cord lesions are associated with conversion to MS
- 25/71 RIS patients had cord lesions
- 21 patients (84%) converted to CIS (19) or PPMS (2) in median time of 1.6 years
- Odds ratio 75.3 (CI=16.1—350.0)
Genetics

- HLA-DRB1*1501 remains most important MS risk locus
- Multiple genome wide association studies have identified $\geq 50$ risk loci
  - Each locus has very low odds ratio (1.04-1.33)
  - In total explain $\sim 3\%$ of total variance in MS risk
  - Nearly all are implicated in immunologic function
Vitamin D: What’s New?

- Nurses Health Study: High milk intake or vitamin D intake during pregnancy associated with 38% lower risk of MS in offspring
  - Higher incidence of MS with births in spring
- With each 10 ng/ml increase, 15% decrease in T2H, 32% decrease in Gad + lesions
- Predictive correlation in CIS (ECTRIMS 2012)
- Lower levels associated with more relapses
- CLINICAL BENEFIT OF SUPPLEMENTATION UNCERTAIN
Smoking and MS

• Increased risk of MS (multiple studies)
• Handel (2011) meta-analysis of multiple studies:
  – Increased relative risk of 1.48
  – Increased risk of conversion to SPMS (1.88), just missed statistical significance (p=.06)
  – Dose response for number of cigarettes smoked
• Passive exposure raises risk (ECTRIMS 2011)
• Doubles mortality rate (ECTRIMS 2012)
Update on EBV and MS

• Munger (2011) study of US veterans
  – Largest study to date
  – Increased risk of MS with increased titers of anti-EBNA complex IgG and anti-EBNA-1 IgG
• Very low odds ratio if EBV seronegative
Original Article

Potassium Channel KIR4.1 as an Immune Target in Multiple Sclerosis

Rajneesh Srivastava, M.Sc., Muhammad Aslam, Ph.D., Sudhakar Reddy Kalluri, M.Sc., Lucas Schirmer, M.D., Dorothea Buck, M.D., Björn Tackenberg, M.D., Veit Rothhammer, M.D., Andrew Chan, M.D., Ralf Gold, M.D., Achim Berthele, M.D., Jeffrey L. Bennett, M.D., Thomas Korn, M.D., and Bernhard Hemmer, M.D.

N Engl J Med
Volume 367(2):115-123
July 12, 2012
Validation of KIR4.1 as the Target of the Serum IgG Reactivity in Patients with MS.

High-Titer Serum Reactivity to the KIR4.1 Protein in a Subgroup of Patients with MS.

“I look to the future because that’s where I’m going to spend the rest of my life.”

-George Burns
Predicting the Course of MS

- Clinical features of onset bout
  - Motor worse than sensory
  - Polyregional worse than monosymptomatic
  - Early bladder involvement poor prognosis
- Incomplete recovery from initial attack
- Short interval between attacks
Initial MRI

- T2 lesion numbers
- Median EDSS at 20 years = 6 for ≥10 T2 lesions
- 3 or 4 Barkhof criteria moderate correlation with EDSS at 5 years
“The future ain’t what it used to be.”

Lawrence Peter “Yogi” Berra
### Existing and Emerging MS Therapies

**Injectables**
- IFNB-1a SQ
- IFNB-1b
- IFNB-1a IM
- Mitoxantrone
- Glatiramer acetate
- Natalizumab

**Oral**
- Cladribine
- Fingolimod
- Dalfampridine
- Extavia
- Teriflunomide
- BG-12
- Firategrist
- Laquinimod
- Teriflumonide
- Ofatumumab
- Alemtuzumab
- Daclizumab

**Approval Status:**
- **Approved**
- **In phase III**
- **Phase II**
- **Application Withdrawn**
Biogen Idec Announces Positive Top-Line Results from Phase 3 Study of Peginterferon Beta-1a in Multiple Sclerosis

– Every Two-Week and Every Four-Week Dosing Demonstrate Significant Reductions in Annualized Relapse Rate – [35.6% and 27.5%, respectively]

– Secondary Endpoints on Reduction of Disability Progression [Decreased 38% both doses], Proportion of Patients Who Relapsed and MRI Assessments Also Met

BiogenIdec Press Release, Jan. 24, 2013
GALA: ARR (Primary Endpoint)

ARR = annualized relapse rate.; SEM = standard error of mean
Khan O, et al. Presented at ECTRIMS 2012; October 9–13, 2012; Lyon, France. [Abstract 166]
CombiRx

- Combination of glatiramer acetate plus weekly IM IFNB-1a vs either agent alone
- 3 year study of 1000 patients
- Primary endpoint: No significant difference in annualized relapse between combination and best performing single agent
- GA significantly better than IFNB-1a on ARR
- Combination better on some MRI end points
SAM Inhibition
Implications for Multiple Sclerosis Therapy

Natalizumab

Use in the Post Marketing Setting and PML Risk

*As of October 22, 2012: 298 cases of natalizumab-associated PML have been reported; of these, 62 patients have died (22%)
Natalizumab v Placebo
Affirm Study (1801)

P < 0.0001

Placebo
n = 315

0.81

Natalizumab
n = 627

0.26

Annualized Relapse Rate (95% CI)

Estimated Incidence of Natalizumab-Associated PML Stratified by Risk Factors

**Anti-JCV Antibody Status**

- Negative
  - ≤ 0.11/1000
  - 95% CI: 0-0.59
  - (based on 1 hypothetical Anti-JCV antibody negative PML case)

- Positive
  - Prior IS Use?
    - No
    - Yes

<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>0.35/1000</td>
<td>1.2/1000</td>
</tr>
<tr>
<td>95% CI: 0.19–0.60</td>
<td>95% CI: 0.58–2.2</td>
<td></td>
</tr>
<tr>
<td>25–48 months</td>
<td>2.5/1000</td>
<td>7.8/1000</td>
</tr>
<tr>
<td>95% CI: 1.8–3.4</td>
<td>95% CI: 5.2–11.3</td>
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</table>

FTY720 results in internalisation of the S1P1 receptor.

This blocks lymphocyte egress from lymph nodes while sparing immune surveillance by circulating memory T cells.

Prevents T cell invasion of CNS.

FTY720 traps circulating lymphocytes in peripheral lymph nodes.
MRI: decreased number of new and enlarging T2H and Gad + lesions (p<0.001)
Teriflunomide: a selective dihydro-orotate dehydrogenase inhibitor

- A new oral disease-modifier for relapsing forms of MS (RMS)
- Blocks *de novo* pyrimidine synthesis, reducing T- and B-cell proliferation and function in response to autoantigens
- Preserves replication and function of cells (e.g. haemopoietic cells, memory T-cells) living on the existing pyrimidine pool (salvage pathway)

DHO-DH, dihydro-orotate dehydrogenase;
Teriflunomide for RRMS (Phase III TEMSO Study): Key Clinical Outcomes

**Annualized Relapse Rate**

- Placebo (n=363): 0.539
- 7 mg (n=365): 0.370
- 14 mg (n=358): 0.369

Relative Risk Reduction (RRR):
- Placebo vs 7 mg: 31.2% with a p-value of 0.0002
- Placebo vs 14 mg: 31.5% with a p-value of 0.0005

**EDSS 12 Week Sustained Change**

- Placebo (n=363): 27.3 with a p-value of 0.0835
- 7 mg (n=365): 21.7
- 14 mg (n=358): 20.2

RRR = relative risk reduction

Teriflunomide: Phase III TOWER Study

Primary Endpoint: ARR

- Placebo (n = 388): ARR = 0.501
- Teriflunomide 7 mg (n = 407): ARR = 0.389, RRR: 22.3%, P = 0.0183
- Teriflunomide 14 mg (n = 370): ARR = 0.319, RRR: 36.3%, P = 0.0001

TOWER = Teriflunomide Oral in people With relapsing multiple sclerosis; RRR = relative risk reduction
Dimethyl Fumarate Has Shown Nrf2 Pathway Activation

- Detoxification enzymes
- Antioxidant enzymes
- NADPH generating enzymes
- GSH biosynthesis enzymes
- Chaperones
- Ubiquitination/proteasome

- Detoxification
- Normalization of energy metabolism
- Repair/degradation of damaged proteins

DMF=dimethyl fumarate; MMF=monomethyl fumarate.
<table>
<thead>
<tr>
<th>Endpoint (at 2 years)</th>
<th>Placebo</th>
<th>BG-12 BID</th>
<th>BG-12 TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR Reduction vs placebo</td>
<td>0.371</td>
<td>0.191*</td>
<td>0.191*</td>
</tr>
<tr>
<td>Time to 12-week confirmed disability progression HR vs placebo</td>
<td></td>
<td>0.68*</td>
<td>0.70*</td>
</tr>
<tr>
<td>Time to 24-week confirmed disability progression HR vs placebo</td>
<td></td>
<td>0.71*</td>
<td>0.68*</td>
</tr>
<tr>
<td>Mean number of Gd-enhancing lesions Reduction vs placebo</td>
<td>1.9</td>
<td>0.3*</td>
<td>0.4*</td>
</tr>
<tr>
<td>Mean number of new or enlarging T2 lesions Reduction vs placebo</td>
<td>16.8</td>
<td>3.7*</td>
<td>4.5*</td>
</tr>
<tr>
<td>Mean number of new T1 hypointense lesions Reduction vs placebo</td>
<td>6.3</td>
<td>2.2*</td>
<td>2.3*</td>
</tr>
</tbody>
</table>

*Statistically significant vs placebo.
Proposed Mechanisms: Alemtuzumab

- Humanized mAb directed against CD52 (expressed on leukocyte surface)
- Rapidly and profoundly depletes T cells, B cells, and monocytes through:
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Complement-mediated cytotoxicity (CDC)
- CD4+ cells may take ~5 years to fully recover
- Reconstituted lymphocytes appear to have regulatory properties

CARE-MS I: Annualized Relapse Rates

P < 0.0001

SC IFNβ-1a
Alem 12 mg/day

55% Rate Reduction
P < 0.0001

<table>
<thead>
<tr>
<th>Drug</th>
<th>Natalizumab</th>
<th>Fingolimod</th>
<th>Teriflunomide</th>
<th>Dimethyl fumarate</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ ARR</td>
<td>68%</td>
<td>48-54%</td>
<td>31-36%</td>
<td>44-53%</td>
</tr>
<tr>
<td>Disability Progress</td>
<td>0.58</td>
<td>0.70</td>
<td>0.70</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.83 (NS)</td>
<td>0.68</td>
<td>0.79 (NS)</td>
</tr>
<tr>
<td>MRI</td>
<td>92%</td>
<td>82%</td>
<td>80%</td>
<td>83%</td>
</tr>
<tr>
<td>↓ Gad lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>PML</td>
<td>Cardiac</td>
<td>Hepatotoxicity</td>
<td>Lymphopenia GI</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>Macular edema</td>
<td>GI Alopecia</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Category C</td>
<td>???Infection Category C</td>
<td>Category X</td>
<td>Category C</td>
</tr>
<tr>
<td>Head-to-head</td>
<td>None</td>
<td>Better than IM Weekly IFNB-1a</td>
<td>Equal to SC IFNB-1a 3X/wk</td>
<td>Better than Glatiramer acetate</td>
</tr>
</tbody>
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Choice of Therapy

Aggressive Disease?

Yes

JCV AB Positive?

JCV AB Negative

Safest

Pregnancy?

Non-injection

NTZ?

Fingo

DMF

NTZ

GA

IFN

GA

Teri

DMF

Fingo

?NTZ

INSURANCE
Ocrelizumab* Phase II Study: Gd-Enhancing T1 Lesions

Lesions on MRI by Week (ITT)

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

Mean Number T1 Gd-enhancing Lesions

*Humanized anti-CD20 mAb
IFNβ-1a arm was open-label; all efficacy comparisons were exploratory

Hypothesized Immunomodulatory Effect of Daclizumab Treatment

DAC Treatment Increases CD56^{bright} NK Cell Proliferation and Cytotoxicity via Intermediate-Affinity IL-2 Signaling

TCR activation

Anti-CD25

CD25

CD4

IL-2

NK cells are activated and expanded by IL-2 binding to the intermediate-affinity IL-2R

IL-2 not consumed by T cells

NK cells are activated and expanded by IL-2 binding to the intermediate-affinity IL-2R

TCR=T-cell receptor.
**Daclizumab – SELECT Study**

- **54% Reduction in ARR (P<0.001)**
- **50% Reduction in ARR (P=0.002)**

- **Out of 600 enrolled, 559 patients completed the study period (93%)**

- **Relapse Free (P<0.001)**

- **Risk of 3-month sustained disability progression compared to placebo**

<table>
<thead>
<tr>
<th>150 mg DAC</th>
<th>300 mg DAC</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>80%</td>
<td>81%</td>
<td>64%</td>
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</table>

<table>
<thead>
<tr>
<th>150 mg DAC</th>
<th>300 mg DAC</th>
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<tr>
<td>57% (P=0.02)</td>
<td>43% (P=0.09)</td>
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Trials in Progressive MS

• Secondary Progressive MS
  – ASCEND: Natalizumab v. Placebo
  – Siponimod v. Placebo

• Primary Progressive MS
  – INFORMS: Fingolimod v. Placebo
  – ORATORIO: Ocrelizumab v. Placebo
Doctor...I looked up my symptoms on the internet...and I think I might be dead!

Don't believe everything you read on the net.