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Differentiating Disease and the Role of the Immune System

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Disclosure

- Consulting Fee: Almirall, Biogen, Excemed, Forward Pharma, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi, Teva
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Autoreactive T and B cells
Genetics1,2 Environment1,3

Many genes associated with increased risk for MS are immune-system related

Smoking
Geographic factors

Immune, Genetic, and Environmental Factors Contribute to the Development of RMS

Immune Dysregulation
Activated Autoreactive T and B cells
Entry Into CNS – Development of MS

Environmental risk factors/trigger:
- Virus
- Bacteria
- Vitamin D levels
- Smoking
- Geographic factors
B and T Cells are Drivers of the Neuroinflammatory Process of MS in the Lymph Node and the CNS

T Cell Mechanisms

Role of B Cells in MS

- B cells can contribute to the pathogenesis of MS through:
  - Cytokine production
  - Focused antigen presentation (APC)
  - Formation of autoantibodies
- Antibodies to multiple viruses, ANA, brain antigens, and "nonsense" antibodies can be detected in MS patients.
- High CD80 (B7-1) on the surface of MS B cells allows them to activate antigen-specific T cells.

T and B Cells Contribute to MS Pathophysiology, Independently and by Interacting with Each Other

Interactions Between T and B Cells

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MS is a Result of Imbalanced Immune Regulatory Networks: T and B Cells

Mechanisms of Damage and Recovery in MS: Summary

- Damage
  - Inflammation
  - Demyelination
  - Acute axonal transection
  - Chronic axonal degeneration
- Recovery
  - Remyelination
  - Brain plasticity

Disability Progression in Two Phases

This is one important factor in deciding to manage patients early to help slow progression, irrespective of initial clinical presentation.
**Pathological Differences Between RRMS and Progressive MS (SPMS, PPMS)**

- **RRMS**
  - New waves of inflammation entering the CNS from circulation
  - Focal demyelinating lesions with variable axonal injury and blood-brain barrier injury mainly in the white matter

- **RPMS**

- **SPMS / PPMS**
  - Compartmentalized inflammation in the CNS
  - Slow expansion of pre-existing white matter lesions
  - Diffuse inflammation and axonal injury in NAWM
  - Extensive cortical demyelination

---

**Pathogenetic Mechanisms Underlying Progression**

- Archelos JJ, Hartung HP. *Trends Neurosci.* 2000;23(7):317-27;

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**Meningeal B Cell Follicles**

- Archelos JJ, Hartung HP. *Trends Neurosci.* 2000;23(7):317-27;

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B Lymphocyte Roles in Multiple Sclerosis

Antibody production  Antigen presentation  Cytokine production  Ectopic lymphoid tissue

CIS  Relapsing MS  Progressive MS

Acute Axonal Loss Remains Clinically Silent Until:

- A critical threshold in a given pathway is reached
- The compensatory CNS resources are exhausted

Disease Activity and Disability Progression in MS: Brain Adaptability is Finite and Individual

- A degree of functional reorganisation compensates for initial structural damage; however, this resource is finite

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Changing Perspectives on the Role of the Immune System in Multiple Sclerosis:
Pathology, Differentiation, and Targeted Therapies

“Delaying Treatment in MS:
What is Lost is Not Regained”

Inflammation
Degeneration
Disability
Response to treatment

? Clinical onset Time

EDSS 3

Dissecting the Data on New and Emerging High-efficacy Agents for RRMS and PPMS

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Disclosure

• Scientific Advisory Board: Annexon, Bionure, Molecular Stethoscope, Symbiotix
• Board of Trustees: Neurona

Targeting CD20+ B Cells May Preserve B Cell Reconstitution and Long-term Immune Memory

Ocrelizumab, Ofatumumab, and Ublituximab are monoclonal antibodies that selectively deplete CD20+ B cells

Ocrelizumab in Relapsing MS: Reduction in Annualized Relapse Rate Compared With IFN β-1a

<table>
<thead>
<tr>
<th></th>
<th>IFN β-1a (44 μg) (n=411)</th>
<th>Ocrelizumab (600 mg) (n=410)</th>
<th>Adjusted ARR at 96 Weeks*</th>
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<tbody>
<tr>
<td>OPERA I</td>
<td>0.292</td>
<td>0.156</td>
<td>0.46% ARR reduction vs IFN β-1a, P &lt; .0001</td>
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<tr>
<td>OPERA II</td>
<td>0.290</td>
<td>0.155</td>
<td>0.47% ARR reduction vs IFN β-1a, P &lt; .0001</td>
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Ocrelizumab in Relapsing MS: Reduction in Mean Gadolinium-Enhancing Lesions Compared With IFNβ-1a

<table>
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<th>Week 24</th>
<th>Week 48</th>
<th>Week 96</th>
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<tr>
<td>IFN β-1a 44 μg</td>
<td>0.107</td>
<td>0.097</td>
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<tr>
<td>Ocrelizumab 600 mg</td>
<td>0.099</td>
<td>0.094</td>
<td>0.088</td>
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</tbody>
</table>

OPERA I

- IFN β-1a: 372, 357, 335
- Ocrelizumab: 382, 377, 359

- 95% reduction in number of lesions from baseline: P < 0.0001
- 98% reduction in number of lesions from baseline: P < 0.0001
- 91% reduction in number of lesions from baseline: P < 0.0001
- 92% reduction in number of lesions from baseline: P < 0.0001
- 96% reduction in number of lesions from baseline: P < 0.0001
- 97% reduction in number of lesions from baseline: P < 0.0001

Ocrelizumab in Primary Progressive MS: Reduction in 12-week Confirmed Disability Progression

- 24% reduction in risk of CDP: HR (95% CI): 0.76 (0.59, 0.98); P = 0.0321

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ocrelizumab</th>
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<tr>
<td>Time to 12-week Confirmed Disability Progression</td>
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<tr>
<td>Placebo</td>
<td>244</td>
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<td>IFN β-1a</td>
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<td>7</td>
</tr>
<tr>
<td>46</td>
<td>7</td>
<td>2</td>
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</table>
Daclizumab-HYP Inhibits High Affinity Interleukin-2 Receptor Signaling

- Humanized Mab
- Binds to α-subunit of the interleukin-2 receptor (CD25, IL-2Rα)
- Selective block of IL-2 signaling through the high-affinity IL-2 receptor
- Immunomodulatory effects:
  - Inhibits activated effector T cells
  - Expands CD56bright NK Cells
  - Decreased number of regulatory T (Treg) cells
- DAC-HYP does not have immune depleting or broadly immunosuppressive effects

Daclizumab-HYP in Relapsing MS: Primary Endpoint - Annualized Relapse Rate (ARR)

45% Reduction
(95% CI, 35.5%-53.1%)
\( P < .0001 \)

Daclizumab-HYP in Relapsing MS:
Effect on MRI-defined Lesions at Week 96

New/Newly Enlarging T2 Lesions

54% Reduction
\( P < .001 \)

New Gd+ Lesions

65% Reduction
\( P < .0001 \)

New T1 Hypointense Lesions ‘black holes’

52% Reduction
\( P < .0001 \)

IFN Beta-1a DAC HYP 150 mg

0.395
0.216

Annualized relapse rate

Estimated from a negative binomial regression model adjusted for baseline relapse rate, history of prior IFN use, baseline EDSS (<=2.5 vs > 2.5), days of treatment (n=919). Subjects are censored at the earlier of:
1) start of alternative MS medication, 2) 180 days post treatment discontinuation, or 3) end of treatment period.
Autologous Stem Cell Transplantation

- Multistep Procedure:
  - Hematopoietic stem cells harvested from PBL (or BM)
  - Immune system then ablated (varying intensity of conditioning regimen)
  - Harvested stem cells then re-infused, restoring a “naive” immune system
- Greater risk with more intensive conditioning regimens
- Studies to-date in MS have utilized various regimens, small cohorts, and variable follow-up periods

Imunoablation and Autologous Haemopoietic Stem Cell Transplantation for Aggressive MS: Multi-center Single Group Phase 2 Trial

- Between diagnosis and aHSCT, 24 patients had 167 clinical relapses over 140 patient-years with 188 Gd-enhancing lesions on 48 pre-aHSCT MRI scans
- Primary outcome, multiple sclerosis activity-free survival at 3 years after transplantation was 69.6% (95% CI 46.6–84.2)
  - With up to 13 years of follow-up after aHSCT, no relapses occurred and no Gd enhancing lesions or new T2 lesions were seen on 314 MRI sequential scans
- Rate of brain atrophy decreased to that expected for healthy controls

MS Therapies Have Consistent Effects on B cells

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Modulation</th>
<th>Differentiation</th>
<th>Activation</th>
<th>Migration</th>
<th>Depletion</th>
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<tbody>
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<td>IFN-beta</td>
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<td>3</td>
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<td>1</td>
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<tr>
<td>GA</td>
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<td>1</td>
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<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<td>DMF</td>
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<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Ter</td>
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<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>MTX</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Natalizumab</td>
<td>6</td>
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<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Alemtuzumab</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*In humans and experimental models
Best Practices When Using Selective High-efficacy Agents

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Director, Multiple Sclerosis Centre of Catalonia
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Barcelona, Spain
Disclosures

- Consulting Fee: Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi-Genzyme, Teva

Key Aspects in the Management of MS

- Early and Accurate Diagnosis
- Early Treatment if Indicated
- Early Identification of Non-responders

In November 2016 in Philadelphia, US, the International Panel on Diagnosis of MS will meet for a forth time to….

New revision in Nov 2016
Do We Have Fundamental Treatment in Relapsing MS?

**CIS/MS**
- Interferon beta 1a SC
- Interferon beta 1a pegylated
- Interferon beta 1b SC
- Interferon beta 1a IM
- Glatiramer acetate 40 TIW
- Mitoxantrone
- Natalizumab
- Fingolimod
- Teriflunomide
- DMF
- Alemtuzumab
- Daclizumab
- Ocrelizumab

**RELAPSING-REMITTING**
- YES

**SECONDARY PROGRESSIVE**
- NO

Do We Have Fundamental Treatment in Progressive MS?

**SECONDARY PROGRESSIVE**
- NO

**PRIMARY PROGRESSIVE**
- YES

Treatment Decision in MS?

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Changing Perspectives on the Role of the Immune System in Multiple Sclerosis: Pathology, Differentiation, and Targeted Therapies

Disease MR predictors
- High T2 lesion burden
- ≥2 Gd+ / new T2 lesions
- Presence of T1 “black holes”
- Early discernable atrophy
- Infratentorial lesions
- Spinal cord lesions

Disease clinical predictors
- High number of relapses
- Incomplete recovery from relapses
- Early progression of disability
- Cerebellar, cognitive involvement

Demographics
- Male
- Older than 40 years
- Smoker
- Non-caucasian

Biological predictors
- Presence of IgG and IgM oligoclonal bands
- High levels of NFL
- High levels of Chitinase
- Low levels of Vit D

Treatment Decision Making Process

PROGNOSIS
Comorbidities:
- Diabetes
- Chronic lung disorders
- Hypertension
- Cardiac problems
- Chronic active infections (hepatitis, TB)
- Concomitant drugs
- Other concomitant autoimmune disorders (psoriasis, RA, others)
- Severe depression
- JCV status

Pregnancy
- Patient preferences

Other factors:
- Fatigue
- Profession
- Distance from hospitals
- Travels needs
- Needle phobia
- Adherence expectations

Assessing Treatment Failure: The Rio Score

The Rio Score
- Relapse: ≥1 in first 12 months
- EDSS: increase of 1 point confirmed 6 months
- MRI: ≥3 active lesions (T2 or Gd+)

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Changing Perspectives on the Role of the Immune System in Multiple Sclerosis: Pathology, Differentiation, and Targeted Therapies

**Predictors of Long-Term Disability**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NewT2 &gt;0</td>
<td>2.1 (1.1 - 4.2)</td>
</tr>
<tr>
<td>NewT2 &gt;1</td>
<td>2.3 (1.7 - 3.0)</td>
</tr>
<tr>
<td>NewT2 &gt;2</td>
<td>3.5 (2.4 - 5.0)</td>
</tr>
<tr>
<td>Gad 1</td>
<td>1.2 (0.7 - 2.0)</td>
</tr>
<tr>
<td>Gad 1+2</td>
<td>1.2 (0.7 - 2.0)</td>
</tr>
<tr>
<td>Relapses</td>
<td>1.8 (0.9 - 3.2)</td>
</tr>
<tr>
<td>Δ 1 EDSS</td>
<td>3.1 (1.7 - 5.6)</td>
</tr>
<tr>
<td>MRI</td>
<td>1.6 (0.7 - 3.4)</td>
</tr>
</tbody>
</table>

**Treatment Algorithms in Patients with Ongoing Disease Activity**

- Interferon beta 1b
- Interferon beta 1a SC
- Interferon beta 1a IM
- Glatiramer Acetate
- Teriflunomide
- DMF
- Fingolimod
- Natalizumab
- Alemtuzumab
- Rituximab/Ocrelizumab
- Others

**Shared Decision Making**

Shared decision making combines the measurement of patient preferences with evidence-based practice.

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