Multiple Sclerosis 2012

February 15, 2012

Stephen L. Hauser, MD
Department of Neurology, University of California, San Francisco
Conflicts of Interest: BioMarin, Receptos

The Origins of Multiple Sclerosis

Sir Augustus d’Este (1794-1848)
Victoria and Albert Museum, London

Two Populations of MS Patients

Relapsing and Progressive

Harrison’s Principles of Internal Medicine 3rd Ed, 1958

The most that can be done is to reassure and encourage the patient through moderate exercise and supportive measures... during an acute episode it is surely preferable to assure the patient that he will recover and to preserve silence on the subject of relapse.

John N. Walton
The Therapeutic Landscape in MS (2011)

The Therapeutic Landscape in MS

Vesicular Demyelination in MS
A Pattern of Humoral Immune Pathology

Rituximab in Relapsing Remitting MS
Gadolinium-Enhancing Lesions from Baseline to Week 48

Rituximab in Primary Progressive MS
Time to Confirmed Disease Progression


**Rituximab in Primary Progressive MS**

*Time to Confirmed Disease Progression Subgroup Analysis*

- **Age <51**
  - Gd (-) at Baseline
  - n=143
  - HR: 0.33 (95% CI: 0.14-0.79) p=0.0088

- **HR: 0.63 (95% CI: 0.34-1.18) p=0.1427**

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**The Development of Anti-CD20 Therapy**

*Rituximab and Ocrelizumab*

- **1986** Synthesis
- **1995** Co-development
- **2003** Merger
- **2009** Merger

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**Technological change moves faster than the pace of clinical experiments**

**Ocrelizumab**

- Overlapping epitope
- Chimeric vs humanised VH- VL
- 2 mutations in RTX reduce affinity for NK cells

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**Study Design for Ocrelizumab Phase II Trial**

- **Design** Randomized, double-blind, placebo-controlled ocrelizumab; blinded rater Avonex™; 1:1:1:1 randomization stratified by geographical region
- **Sample Size/No. sites** N = 200 planned (220 actual); ~100 sites European Union, United States, & Rest of World
- **Population** RRMS, Expanded Disability Status Scale (EDSS) of 1.0-6.0, inclusive. At least two documented relapses within last 3 years, at least one of which occurred within last year prior to screening, MRI evidence of disease burden
- **Schedule and dose** Placebo × 2 for Cycle 1 only ➔ 600 mg open-label ocrelizumab 300 mg × 2 ➔ by 600 mg q24 wks 1000 mg × 2 ➔ 1000 mg q24 and q48 wks ➔ 600 mg q24 wks Avonex™ 30 µg IM qwk × 24 wks ➔ 600 mg open-label ocrelizumab
- **1° Endpoint** Total number of Gd-enhancing lesions at Wks 12, 16, 20, and 24
- **2° Endpoint** Annual relapse rate (ARR) by Wk 24; Proportion of patients relapse-free by Wk 24; total # new gadolinium (Gd) enhancing lesions; change in total volume T2 lesions
- **Study duration** 244 wks total = 96-week treatment period + 48 wks for follow-up

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**Ocrelizumab**

- **AUP**
- **N-terminal**
- **C-terminal**
- **Fc**
- **Constant region**
- **Variable domains**
- **X = mutation**

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**NK:** natural killer cell
### Ocrelizumab in Relapsing Remitting MS

**Primary Endpoint: Mean Gad+ Lesions Week 12 to Week 24**

- **Placebo (N=54)**
- **Ocrelizumab 600mg (N=51)**
- **Ocrelizumab 2000mg (N=52)**
- **IFN beta-1a (N=52)**

*IFN beta-1a arm was open label, all efficacy comparisons were exploratory*

**Primary Endpoint**

- **P<0.0001** for both Ocrelizumab doses vs placebo

**Lesions on MRI by week (ITT): average imputation**


### A Fatality in the Ocrelizumab RRMS Trial!

- 41 year old woman, disease duration 10 years, prior Rx IFN beta
- Randomized to OCR 2000 mg group
- At week 12, on day of routine blood and MRI follow-up studies (all unremarkable), developed delirium, thrombocytopenia and status epilepticus, then fever, and over the next 48 hrs a Systemic Inflammatory Response Syndrome (SIRS) with multiorgan dysfunction, brain edema
- Had sustained a bee sting on face 5 days earlier
- Multiple blood, CSF cultures (including viral PCR) negative for infection
- Treatment with platelets, IVIg, antibiotics to no avail; death on day 15
- Pathology: severe cerebral ischemia with herniation; several perivascular CNS hemorrhages; several septic emboli; multi-organ dysfunction; no evidence for TTP, DIC, or primary infection in brain or hepatic tissue

### Ocrelizumab (OCR) Phase II Updated Results

**96-Week ARR**

- There were 7 serious AEs in phase 2 RRMS trial: 1 in placebo; 1 in 600 mg; 3 in 2000 mg; 2 in IFNbeta1a; no imbalance or increase over time
- Two serious AEs were thought to be infection-related: 1 in placebo; 1 in 2000 mg OCR
- No opportunistic infections were noted; no dropouts due to adverse events; no imbalance in infection rate during weeks 48-96
- Infusion-related reactions occurred after initial infusion (30-44%) and decreased on subsequent infusions; led to withdrawal in only 3 pts
- Through 96 weeks, with open-label Ocrelizumab 600 mg treatment:
  - No loss of efficacy; most patients had no clinical disease activity
  - No patient experienced a new or enlarging T2 lesion from Week 24 to Week 96
  - At the Week 96 MRI scan, no patient on Ocrelizumab experienced a Gd enhancing TI lesion
Ocrelizumab: The Path Forward

- Rheumatoid Arthritis (RA) phase 3 OCR program halted in May 2010 due to cases of serious/fatal opportunistic infections; dose, chronic GC use, co-morbid illness, Asian ancestry implicated as risk factors
- RA phase 3 trials: no increase in risk of opportunistic infections at 200 mg x2 dosing of OCR (>1500 pt/hrs)
- No cases of PML with OCR; with Rituxan (2 million Rx), PML noted in 6 RA (118,000 pts treated); 8 SLE; 6 other AID; 137 oncology; 0 MS cases
- Phase 3 OCR trials in MS launched in 2011: 2 in RRMS; 1 in PPMS
BLyS and APRIL are B cell maturation & survival factors

Bone-marrow environment

Malignant B cell survival

Tumour environment

Class switch to IgA or IgG

B cell survival

Activated B cell

Resting B cell

Antibody-producing plasma cell

T cell division

B cell division


BLyS and APRIL bind to B cell-expressed receptors

Ligands

Receptors

B cell

Proteoglycans

ATAMS: Atacicept in MS

- Atacicept: Recombinant fusion protein with immunomodulatory effects on B cells
- ATAMS: 36-week phase II RCT of atacicept 25, 75, 150 mg vs placebo (PBO) in relapsing MS
- Mean ARRrs were greater in atacicept vs PBO arms (Figure)
- Significantly more T1 Gd+ lesions were observed in atacicept 75 mg (2.64) vs PBO (1.14; P = 0.017)
- Effects reversed after atacicept cessation in safety follow-up
- Conclusion: Atacicept was associated with worse outcomes
- Study stopped

Lessons From the B-Cell Experience in MS

- The anti-CD20 trials have revealed that B-cells are central players in the pathogenesis of focal lesions in MS
- The MOA is likely to involve interference with activation of pathogenic T-cells promoted by B-cells via APC or cytokine functions, but many questions remain
- The attractiveness of B cell therapies for MS will likely be determined by their safety profile in phase 3 trials and beyond
- These trials also set the stage for testing more selective therapies that target subsets of B-cells, B-cell growth/survival factors, or germinal center interactions
- More than 15 years will have passed from the initial proposal to employ anti-CD20 therapy in MS to completion of the pivotal phase 3 trials!
Will the Clinical Landscape of MS Look Different in 2016?

- Many available therapies for RRMS
- Aggressive early treatment is the norm
- Still no antigen-specific therapy on the horizon
- Strategies for primary prevention available
- Exquisite imaging capabilities of the entire neuraxis
- Biomarkers stratify patients for prognosis and treatment
- Fewer patients with progressive MS
- Promising prospects for remyelination (anti-LINGO; Wnt pathway; retinoid X receptor [RXR-γ] signaling)
- Treatment for the neurodegenerative component of MS remains a challenge

Gene Discovery in MS

<table>
<thead>
<tr>
<th>Year</th>
<th>First reported association between MS and HLA</th>
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<tbody>
<tr>
<td>1972</td>
<td>Separation from common ancestry</td>
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<tr>
<td>1996</td>
<td>First generation genome-wide linkage study</td>
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<tr>
<td>2005</td>
<td>Meta-analysis of GWAS</td>
</tr>
<tr>
<td>2007</td>
<td>First generation genome-wide linkage study</td>
</tr>
<tr>
<td>2009</td>
<td>First generation genome-wide linkage study</td>
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<td>2009</td>
<td>Whole genome sequencing of MS twins</td>
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MS Susceptibility Genes in T Cell Activation Pathways

Functional Studies of MS Variants

<table>
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<tr>
<th>Gene</th>
<th>Variant</th>
<th>Putative Mechanism</th>
<th>Reference</th>
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<tbody>
<tr>
<td>IL7R</td>
<td>Susceptibility (exon 6) rs6897932c OR = 1.2</td>
<td>Low level skipping of exon 6, changes in the soluble / membrane bound ratio with higher sIL7R</td>
<td>Gregory et al. Nat Genet (2007)</td>
</tr>
<tr>
<td>IL2RA</td>
<td>Susceptibility (intrinsic) rs2194286 OR = 1.15*</td>
<td>Changes in the soluble / membrane bound ratio with higher sIL2RA</td>
<td>Maier et al. PLOS Genet (2009)</td>
</tr>
<tr>
<td>TNFRSF1A</td>
<td>Susceptibility (intrinsic) rs1800993 OR = 1.6</td>
<td>Alternative splicing, deletion of exon 6</td>
<td>De Jager et al. PNAS (2009)</td>
</tr>
<tr>
<td>CD58</td>
<td>Protective (intrinsic) rs2000747 OR = 0.85</td>
<td>Higher membrane expression of CD58 and correction of CD4+ regulatory cell function</td>
<td>De Jager et al. PNAS (2009)</td>
</tr>
<tr>
<td>IRF8</td>
<td>Protective (intrinsic) rs17445836 OR = 0.83</td>
<td>Widespread effect on the type I interferon transcriptional responses</td>
<td>De Jager et al. PNAS (2009)</td>
</tr>
<tr>
<td>TYK2</td>
<td>Protective (intrinsic) rs34536443 OR = 0.63</td>
<td>Decreased TYK2 kinase activity and cytokine shifting towards Th2</td>
<td>Couturier et al. Brain (2011)</td>
</tr>
</tbody>
</table>

* Risk alleles represent <1% of genetic susceptibility to MS but explain 18% of the variance in sIL2RA level
A Disease-Focused Neuroscience Center at Mission Bay

Thank you!