Monoclonal Antibodies In the Treatment of Multiple Sclerosis

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Disclosures

• John Rose, MD
  Grants/research support: NMSS, NIH, Teva Neuroscience, Biogen, VA
  Advisory Board Member: DECIDE trial Biogen/Abbott
  Honoraria from Industry: None

• CME Support: Unrestricted Education Grants from Biogen and Teva Neuroscience

• Monoclonal Antibodies except for Natalizumab are investigational therapies for MS and the subject of ongoing clinical trials (Clinical Trials.gov)

• CME Staff Disclosures
  Professional Education Services Group staff have no financial interest or relationships to disclose.
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Commercial Support was not received for this activity.
Learning Objectives

At the conclusion of this activity, the participant will:

• A. Describe the benefits and risks of FDA approved therapy for MS, Natalizumab.

• B. Recognize the pharmacologic and clinical features of emerging monoclonal antibody therapies for MS

• C. Discuss the relative merits of contemporary treatment and emerging monoclonal antibody therapies
Nobel Prizes: Immunology

- 1977 Radioimmunoassay Yalow
- 1980 MHC Snell, Dausset, Benacerraf
- 1984 MAbs Kohler & Milstein
- 1984 Immune Networks Jerne
- 1987 Ab Gene Rearrangement Tonegawa
- 1991 Transplantation Immunology Thomas & Murray
- 1996 Cell Mediated Immunity Doherty & Zinkernagel
<table>
<thead>
<tr>
<th>MAb Specificity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD11</td>
<td>Augments EAE</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Augments EAE</td>
</tr>
<tr>
<td>CD4</td>
<td>Blocks EAE</td>
</tr>
<tr>
<td>α4</td>
<td>Inhibits EAE</td>
</tr>
<tr>
<td>IL-2R</td>
<td>Inhibits EAE</td>
</tr>
<tr>
<td>Lingo-1</td>
<td>Increases Remyelination</td>
</tr>
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Humanized Monoclonal Antibody

FIG. 1. Topology and functional architecture of the IgG molecule. (From Wasserman and Capra, ref. 1, with permission.)
Monoclonal Antibodies

ixmab  zumab  umab
## Monoclonal Antibody Rx for MS

<table>
<thead>
<tr>
<th>Mab</th>
<th>Specificity</th>
<th>Target</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>α4 integrin</td>
<td>Adhesion</td>
<td>+</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td>T Cells</td>
<td>+</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>B Cells</td>
<td>+</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>B cells</td>
<td>+</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>CD20</td>
<td>B cells</td>
<td>+</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>CD20</td>
<td>B cells</td>
<td>?</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>IL-2Rα</td>
<td>Activated</td>
<td>+</td>
</tr>
<tr>
<td>Li81/BIIB033</td>
<td>Lingo</td>
<td>OPCs</td>
<td>?</td>
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</tbody>
</table>
Natalizumab

- FDA Approved for Relapsing MS
- Mechanism of Action: Binds Integrin and Blocks Entrance of Inflammatory Cells into the CNS
- Side Effects: PML, Respiratory Tract and Bladder Infections
- Cost: High
- Utilization: Refractory or Aggressive RRMS
- Efficacy: Highly Effective Immunosuppressive Therapy; Improved Quality of Life
- Importance of JC titer and Previous Immunosuppressive Rx & Anti-JC Virus Ab
H. Waldmann developed the Campath-1 (Cambridge Pathology) series of antibodies

- IgG1κ with human variable and constant regions and murine CDR
  - “Humanised” by Winter that reduces the chances of mounting an immune response

- Targets CD52 antigen: Found on thymocytes, NK cells, B cells but not plasma cells, monocytes and granulocytes
Side Effects of Alemtuzumab

- Hyperthyroidism (16%)
- Immune Thrombocytopenic Purpura (3%)
- Goodpasture’s Disease (infrequent)
- Serious Infections (7%)
- Recapitulation of Previous Symptoms
- Long-Term Immunosuppression
Alemtuzumab vs IFN Beta 1a

Alemtuzumab decreases risk of relapse
Alemtuzumab decreases risk of progression
Alemtuzumab vs IFN 5 year follow-up

Alemtuzumab Open label study for refractory MS
Rituximab

- Targets and selectively depletes CD20 positive B cells
- FDA approved for relapsed or refractory, low-grade or follicular, CD 20+, B cell non-Hodgkins lymphoma, diffuse large B-cell lymphoma in combination with CHOP, refractory rheumatoid arthritis
Rituximab

- Chimeric murine/human mAb
- Contains a human IgG1 immunoglobulin region and a murine variable region specific for CD20
CD 20

- Integral transmembrane nonglycosylated hydrophobic phosphoprotein
- Present on surface of normal pre-B cells and mature B cells
- Not on plasma cells
- Precise function is unknown
Rituximab: mechanisms of action

- Antibody dependent-cell mediated cytotoxicity
- Complement-dependent cytotoxicity
- Induction of apoptosis
- B-cell depletion from 6-9 months or longer (variable)
Side Effects of Rituximab

- Infusion related reactions
  - Rigors, chills
  - Fevers, headache
  - Rash
  - bronchospasm

- Infectious
  - URI
  - Herpes Zoster
  - PML

- Hematologic
  - Neutropenia
  - Thrombocytopenia
  - Human anti-chimeric antibodies?
Rituximab In MS

- Phase I Open Label in RRMS
- Phase II Multi-Center Randomized Trial in RRMS
- Open Label Treatment in NMO
- Retrospective of Treatment for NMO
- Current Use Similar to Phase II Trial
Anti-CD20 Mabs In Clinical Trials

- Ofatuzumab Dose Study in RRMS: Phase 2
- Ocrelizumab + Placebo (IFN) vs Placebo (Ocrelizumab) + IFN = 2 Trials: Phase 3
- Ocrelizumab vs IFN in PPMS: Phase 3

- Clinical Trials.gov
DACLIZUMAB: Anti IL-2Raα
IL-2 Receptor

- Intermediate affinity: NK cells, Resting T cells
- High affinity: Activated T cells, B cells
- Low affinity: IL-2
Daclizumab: Mechanism of Action
Daclizumab Mechanism of Action

- Blocks IL-2 Binding to Receptor
- Inhibits Immune Response to Antigenic challenge
- Recall Responses Generally Preserved
- Inhibits Allograft Rejection
- Increases NK Cell Activity
- Interferes with Transpresentation of IL2
- Reduces CSF IgG Index and CXCL13
Autoreactive T Cells In MS
Daclizumab Pharmacology

- Humanized IgG1 MAb
- MW = 144KD
- 90% Human/10% Mouse
- Targets Activated Lymphocytes
- 1/2 Life = 20 days (range 11-30)
- Rare Hypersensitivity Reactions
- Anti-Id Abs: 8.4% low titer
- Side Effects: Rash, Lymphadenopathy, Respiratory Infections
Daclizumab Therapy

- Renal Allograft: FDA Approved
- Uveitis: NEI
- MS: NIB & UofU
- Ulcerative Colitis: Multiple Centers
- Asthma: Multiple Centers
- Tumor Vaccination Rx: Phase II Studies
MS Treatment With Daclizumab: A Case Series

- Off Label Rx
- Failure of other Therapies
- EDSS at Baseline
- Duration of Treatment
- Dosage
- $\Delta$EDSS -1.0 to -4.5 responders
- $\Delta$EDSS -0.5 to 0 stable
- Early Discontinuation of Rx
- Side Effects:

21 Ambulatory Patients
19/21 Patients
2.5-6.5
5-25 months (ave 13.6 mos)
0.8-1.9 mg/kg q 28 days IV
10 Patients (5 RR & 5 2P)
9 Patients (1RR & 8 2P)
2 Patients
paraesthesias, mild rash, GI, anemia, URI
Daclizumab: MRI Effects
Daclizumab/Zenapax Study Design for RRMS

With Concurrent IFN-beta
Including the Extension With IFN-beta Withdrawal (NIB/NIH*)

3 months 5.5 months 10 months follow-up (12 months)

Daclizumab start IFN-beta off End of study period

Baseline 3 months 4 MRIs
Daclizumab Monotherapy
+ IFN-b
5.5 months
7 infusions

Continuation of Daclizumab (12 months)

Inclusion Criteria: Relapse in past 12M and 2 or more CEL on Baseline MRIs on IFN

The Cumming Foundation provided funding for the clinical trial. Protein Design Laboratories supplied the Daclizumab. *Dr. Roland Martin
Daclizumab Rx: Primary Outcome Measure

ANOVA: Tukey-Kramer Multiple Comparisons Test
DAC Phase II Secondary Outcomes

A. Relapses (Average)

B. Timed Ambulation

C. EDSS (Average)

D. NRS
CHOICE Trial Cumulative CELs

- **Placebo**
- **DAC 1 mg/kg**
- **DAC 2 mg/kg**

**Mean cumulative number of Gd+ lesions ± SEM**

**Study week:**
- 0
- 4
- 8
- 12
- 16
- 20
- 24

* indicates significant difference from placebo.
New and Enlarged Gd+ Lesions by Quartile of CD56\textsuperscript{bright} NK cell Counts when Measured at the Last DAC Dose (week 20)

*Mean number of new/enlarged Gd+ lesions between weeks 8–24 adjusted for number of Gd+lesions on baseline MRI. †Test for linear trend by quartile, p=0.006. ‡Number of subjects (n) for quartiles ranking by CD56\textsuperscript{bright} NK cell count and the number of subjects in the DAC low/IFNβ verses DAC high/IFNβ treatment (x:y).
Daclizumab Trials

- SELECT Trial: Completed Multicenter Phase II trial demonstrated 55% reduction in relapses with SC administration.
- DECIDE Trial: Ongoing International Multicenter Phase III Trial of DAC HYP (SC) versus IFNB-1a (2013 completion)
Anti-Lingo 1

- Safety and Tolerability in Healthy Volunteers: Completed Study
- Safety, Tolerability and PK Profile in MS Patients: Study Completed
- Phase II Trial In Development: Expected to start soon
- First MAb to Promote Remyelination
Monoclonal Antibody Rx for MS: Limitations

- Side Effects: Allergy, Fever, Rash, Infection, Autoimmune Disease, Recurrence of Sx, lymphadenopathy
- Unknown Long Term Effects
- Cost Effectiveness
- Routes of Administration
- Duration of Therapy & Proper Follow-up
Monoclonal Antibodies In MS Rx: A Bright & Stormy Future
Future Directions MS RX

• Antibodies to New Determinants: CDs, Cytokine and Chemokine Receptors, Adhesion Molecules, Cell Differentiation Factors

• Combination and Sequential Therapies: Anti-inflammatory, Neuroprotective & Regenerative Agents
Mitoxantrone 2012

- FDA Approved for Rx MS
- Mechanism of Action: Chemotherapeutic Immunosuppressive Agent
- Side Effects: Cardiotoxicity (20%/6%), Post Therapy Leukemia (0.1 to 1.0%), Infection
- Dosing Q3 Months: 5-12 mg/m²: Switzerland
- Relative Cost: Low to Moderate
- Utilization: Treatment of Refractory or Aggressive MS, Induction Prior to Other Rx (IFN or GA)
- Efficacy: Effective Immunosuppressive Rx in Multiple Studies: France, Germany, Italy, Ireland
Judging Efficacy of Treatment

- Number of Relapses/Year
- Severity of Relapses and Degree of Recovery
- Progression
- MRI Activity
- Biomarkers: Immunologic, Markers of Neurodegeneration, Advanced MRI Measures, OCT
MS Rx: Complex Decision

- Stratification Of Rx: Efficacy; Safety & Cost
- Individualized Rx Choice: Clinical Course, Coexisting Medical Conditions, Previous Rx, Evidence of Ineffective Rx
- Disease Severity
- Expected Duration of Rx
- Neuroprotective Rx and Immunologic Rx
- Monitoring Immunotherapies: Immunologic Measures- Lymphocytes & Phenotypes
Collaborators

- Noel Carlson, Ph.D.
- Kenneth Hill, B.S.
- Monica Rojas, M.D.
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- Julia Klein, APRN
- Connie Kawai R.N.
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- Jane Bjorklund
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- Ikuo Tsunoda
- William Stroop
- Mark Leppert
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