Monoclonal Antibodies In The Treatment of Multiple Sclerosis: Focus On Daclizumab

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Disclosures

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Dr. Rose is a member of the Utah/Southern Idaho Chapter Board of the National Multiple Sclerosis Society
Neuroimmunology & Neurovirology (NINV) Division: Translational Research

Pathogenesis

MRI Correlates

Epidemiology, Genes & Environment

Innovative Rx

n=490
Diagnosis

- History
- Neurologic Examination
- MRI: Brain, Spinal Cord, Optic Nerves
- Cerebrospinal Fluid
- Evoked Potentials
- Bladder Testing
- Neuropsychological Testing
Clinical Features of Multiple Sclerosis

**Classification**

1. BENIGN MULTIPLE SCLEROSIS
2. RELAPSING REMITTING MULTIPLE SCLEROSIS
3. SECONDARY CHRONIC PROGRESSIVE
4. PRIMARY PROGRESSIVE (10-20% OF PATIENTS)

**Oligoclonal Bands in CSF**

- Normal
- Abnormal

**Visual Evoked Potentials**

- Normal Latency: 107 msec
- Abnormal Latency: 134 msec
MS Differential Dx

- Autoimmune Diseases: Neuromyelitic Optica (NMO & NMOSD), Anti-MOG, SLE, Sjogren’s, Neurosarcoidosis
- Infectious/Post Infectious: Lyme, Neurosyphilis, Encephalitis, Viral Transverse Myelitis, ADEM (Acute Disseminated Encephalomyelitis)
- Vascular: Cerebrovasculitis-Idiopathic or Drug induced (Amphetamines and Cocaine), Migraine
- Metabolic: B12 Deficiency,
- Microvascular Disease: Age, DM, Migraine, Head Injuries/Concussion, Leukoariosis
- Diagnostic Testing: ANA, ACE, Lyme, FTA-ABS, B12, AQP-4 Ab, Anti-MOG Ab
Diagnostic criteria

- Relapsing remitting presentation
- MRI lesions, T2/FLAIR callosal, pericallosal, subcortical, brainstem, cord
- MRI Contrast Enhancing Lesions
- CSF: OCBs, Increased IgG Index and IgG synthesis rate, sometimes few WBCs, lymphs
- Increased conduction VEPs, can be abnormal BAEPs
- Abnormal OCT
McDonald 2017 Criteria
C spine Gad, C and T Spine T2 MRI
Spectralis SD-OCT (Heidelberg Engineering)
Retinal Nerve Fiber Layer

Temporal Nerve Fiber Layer

Blood Vessels

Choroid

External Limiting Membrane
Inner Photoreceptor Seg.
Inner / Outer Photoreceptor Seg. Junction
Outer Photoreceptor Seg.
RPE Interdigitation
RPE / Bruch’s Membrane Complex

Nerve Fiber Layer
Ganglion Cell Layer
Inner Plexiform Layer
Inner Nuclear Layer
Outer Plexiform Layer
Outer Nuclear Layer
**Purpose**: examine mean RNFL and RNFL quadrants and sectors, and TMV in RR-MS pt’s with and w/out prior ON and compare to controls.

**Hypotheses**: 1) RNFL quadrants and sectors may be selectively compromised in RR-MS vs. controls, 2) RNFL lower in RR-MS ON lower vs. RR-MS no ON. 3) TMV lower in RR-MS vs. controls.
Optical Coherence Tomography (OCT) Demonstrates Neurodegeneration and Need for Neuroprotection

Fjeldstad, Carlson and Rose 2012
OCT Following Optic Neuritis

Warning: Classification results valid for Caucasian eyes only.
Dx Criteria and Clinical Scales

- Adult McDonald Criteria
- Pediatric McDonald Criteria
- Ambulatory Index
- Kurtzke Scale/EDSS
- Scripps Neurologic Rating Scale
- Snellen & Low Contrast Visual Acuity

- NMSS.ORG
Goal Of Immunotherapy

- NEDA: No evidence of disease Activity
- Essentially the long-term goal
- Patient stable or improved
- No Relapses or Disease Progression
- Neurologic exam stable or improved
- No new or active MRI lesions
- No progression of MRI measures of atrophy
## Immunotherapies that Augment MS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism(s) of Action</th>
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<tbody>
<tr>
<td>Interferon $\gamma$</td>
<td>Augments Th1 Response</td>
</tr>
<tr>
<td>G CSF</td>
<td>Stimulates Autoreactive Lymphocytes</td>
</tr>
<tr>
<td>Anti-TNF$\alpha$</td>
<td>Blocks Beneficial Effects of TNF$\alpha$ (*) immunomodulatory, neuroprotection</td>
</tr>
<tr>
<td>Year</td>
<td>Treatment</td>
</tr>
<tr>
<td>------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>1970</td>
<td>Prednisone, ACTH, AZA</td>
</tr>
<tr>
<td>1970</td>
<td>Copolymer 1, IT IFN, Poly ICLC, CTX, PLEX, CSA</td>
</tr>
<tr>
<td>1980</td>
<td>Copolymer 1, IT IFN, Poly ICLC, CTX, PLEX, CSA</td>
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<tr>
<td>1993</td>
<td>Interferon Beta 1b SC</td>
</tr>
<tr>
<td>1995</td>
<td>Glatiramer Acetate SC</td>
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<tr>
<td>1996</td>
<td>Interferon Beta 1a IM</td>
</tr>
<tr>
<td>2000</td>
<td>Mitoxantrone IV</td>
</tr>
<tr>
<td>2002</td>
<td>Interferon Beta 1a SC</td>
</tr>
<tr>
<td>2006</td>
<td>Natalizumab IV</td>
</tr>
<tr>
<td>2009</td>
<td>Interferon Beta 1b SC</td>
</tr>
<tr>
<td>2010</td>
<td>FTY 720 (Fingolimod)</td>
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<tr>
<td>2012</td>
<td>Teriflunimide</td>
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<tr>
<td>2012</td>
<td>Dimethyl Fumarate</td>
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<tr>
<td>2014</td>
<td>Glatiramer Acetate SC (40mg)</td>
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<tr>
<td>2014</td>
<td>Pegylated Interferon</td>
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<tr>
<td>2014</td>
<td>Campath Alemtuzumab</td>
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<tr>
<td>2016</td>
<td>Daclizumab</td>
</tr>
<tr>
<td>2017</td>
<td>Ocrelizumab</td>
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</tbody>
</table>
MS Immunotherapy

- Glatiramer Acetate SC (Immunomodulation)
- Interferon Beta 1a and Beta 1b SC & IM (Immunomodulation)
- Oral Immunosuppressants:
  - Dimethyl Fumarate
  - Fingolimod
  - Teriflunimide
- Mitoxantrone: Chemotherapy
- Monoclonal Antibodies:
  - Anti-alpha 4 Integrin (Natalizumab)
  - Anti-CD20 (Rituximab and Ocrelizumab)
  - Anti-CD 52 (Alemtuzumab)
- Future Therapies: HSCT, Remyelination Rx
Glatiramer Acetate

- Safest DMT
- Not Immunosuppressive
- ARR Decrease 33%
- Potential Long Term Rx
- Daily or 3X/week Injections
- Transient Reactions
- Injection Site Reactions
- Lipoatrophy
- Rarely Urticaria
Interferon Beta 1a & 1b

- Relatively Safe
- Not Immunosuppressive
- Injections; SC or IM
- Blood Monitoring Q6M
- Contraindications: SZ, Depression
- Spontaneous Abortion Potential
- ARR Decrease 33%
- Long Term Rx Potential

Neutralizing Antibodies

- Avonex 5%
- Rebif 25%
- Betaseron 25%
Oral DMTs

- Therapeutic considerations:
- Lymphopenia with DMF and Fingolimod: a significant concern;
- Teriflunimide is used infrequently due to several factors, 1) category X for pregnancy, 2) lesser efficacy and 3) hepatotoxicity
- Immunosuppressive Treatments
- ARR Reduction DMF and Gilenya 50%
- ARR Reduction Teriflunimide 25%
Purification of MBP
Immunotherapy In EAE

IL2 Toxin Blocks Disease and Prevents Relapses

Rose et al JNI 1991, Baldassri & Rose Neurotherapeutics 2018
Nobel Prizes: Immunology

- 1977 Radioimmunoassay  Yalow
- 1980 MHC  Snell, Dausset, Benacereff
- 1984 MAbs  Kohler & Milstein
- 1984 Immune Networks  Jerne
- 1987 Ab Gene Rearrangement  Tonegawa
- 1991 Transplantation Immunology  Thomas & Murray
- 1996 Cell Mediated Immunity  Doherty & Zinkernagel
- etc
<table>
<thead>
<tr>
<th>MAb Specificity</th>
<th>Effect</th>
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<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>EAE Increases Remyelination</td>
</tr>
</tbody>
</table>
THERAPEUTIC MONOCLONAL ANTIBODIES

Chimeric=ixmab, Humanized=zumab, Human=umab

Rose, Foley and Carlson
Humanized Monoclonal Antibody

Importance of Antibody Fc Structure & Functions
Daclizumab Phase I/II Trial in Relapsing and Remitting MS: MRI and Clinical Results

John W. Rose, James B. Burns, Jane Bjorklund, Julia Klein, Hilary Watt and Noel G. Carlson

Humanized MAb, anti-IL2Rα

Interleukin 2 Receptor
Daclizumab: MRI Effects

Pt. 1

Pre

A

B

C

Post

D

E

F
Natalizumab

- Humanized Monoclonal: Highly Effective for RRMS
- Targets Adhesion Molecule: Alpha4 Integrin
- Blocks Migration of Lymphocytes Through BBB
- Reduction of ARR 75%
- Marked Reduction of Active Lesion Formation
- Progressive Multifocal Leukoencephalopathy Risk
- Administered via TOUCH Program
- PML Risk Assessed with Detection of JC Virus Antibody in Serum & Periodic Brain MRI
- With Conversion to Sero-Positive Status Rx is Changed
- If PML Suspected: PCR for JC Virus Performed on CSF
Anti-CD20 MAbs

- First Generation: Rituximab
- Second Generation: Ocrelizumab, Veltuzumab & Ofatumumab
- Third Generation: Obinutuzumab, Pro131921 & Ocaratuzumab
CD 20 is a non-glycosylated cell tetratransmembrane phosphoprotein that acts as a calcium ion channel and binds to tyrosine kinases; it is exclusively expressed on B cells during most stages of B cell development.
Rituximab Mechanisms of Action

- CDC: Complement
- ADCC: Cells + Mab
- B Cell Death: MAb Mediated Apoptosis
- ROS: MAb Induces NADPH
- RRMS: Phase II Trial In RRMS*
- FDA Approved: Lymphoma, RA
Ocrelizumab

- Increased CDC and ADCC
- Similar to Rituximab in CDR
- Improved Binding to Variants of FcgRIIIa
- Phase III Trials RRMS: OPERA I & II
- Phase III Trial in PPMS: ORATORIO
- Status: FDA Approved for Indication in RRMS and PPMS
Ofatumumab

- Human IgG1 MAb
- Increased CDC and ADCC
- Binding to CD 20 Small Loop
- Dosing and Phase II Trials
- Active Comparator Trial Ofatumumab SC Versus Oral Teriflunimide
Alemtuzumab

- Campath 1h
- Anti-CD 52 Mab
- Humanized
- ARR Reduction 50-60%
- Long Duration of Action
Alemtuzumab Side Effects

- Autoimmune Thyroid Disease 30%
- Glomerulonephritis 1%
- ITP 3%
- Infections
- Long Duration Immunosuppression
MAb Dosing

- **Rituximab**: Cycle of 1000 mg IV Repeated after 15 Day Interval every 6 to 12 months. Concommittant administration of Solumedrol.

- **Alemtuzumab**: mg IV/Day X5; Concommittant administration of Solumedrol; 6-12 months later second infusion mg IV/Day X3; Concommittant administration of Solumedrol

- **Natalizumab**: 300 mg IV Each Month
Summary: MAb SAEs

- **Rituximab/OCRELIZUMAB**: Infusion Reactions, HBV, PML, Mucocutaneous Reactions Including Stevens-Johnson

- **Alemtuzumab**: Infusions Reaction, Cytopenias, Autoimmune ITP, Thyroid Disease, Infections

- **Natalizumab**: PML, Increased Infections
Further Development of Immunotherapeutic MAbs

- Duration of Treatment
- Degrees of Immunosuppression
- Effects of Cumulative Treatments
- Combination Therapies
- Safety and Cessation of Treatment
- Comparison to Other Therapies
- More Advanced Formulations
Monoclonal Antibodies In The Therapeutic Arsenal

- Substantial Efficacy
- Effective In Patients With Sub Optimal Response To Other DMTs
- Anti-CD 20 MAbs: Ocrelizumab FDA Approved specifically For MS
- Increasing Studies of MAbs In Neurologic Disease
ImmunoRx Ped MS

Wide Range of Therapies Utilized
  Interferons
  Glatiramer Acetate
  Daclizumab IV
  Natalizumab
  IVIG

Now Expanding to Oral Immunotherapies

Waldman et al & Gorman et al; USNPMSC submitted
PARADIGMS
Fingolimod vs Interferon Beta 1a IM
Marked Reduction of Relapses
High Efficacy by MRI Parameters
SAE: Fingolimod 19% & IFN 9%
AE: Fingolimod < IFN
Fingolimod Under Expedited FDA Review

Chitnis ECTRIMS 2017 Presentation
PharmacoEconomics

- Glatiramer Acetate 50-90k/yr*
- Interferons 60k/yr*
- Oral DMTs 60-90k/yr**
- MAbs 25-100k/yr

*Generic Available; **Generic In Future
TREAT-MS Trial

- Multi-Center
- PCORI/NIH Trial
- Ellen Mowry JHU PI
- Univ of Utah Site PI John Rose
The TReditional versus Early Aggressive Therapy for Multiple Sclerosis (TREAT-MS) trial is a pragmatic, randomized controlled trial that has two primary aims:

1) to evaluate, jointly and independently among patients with multiple sclerosis (MS) deemed at higher risk vs. lower risk for disability accumulation, whether an “early aggressive” therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability.

2) to evaluate if, among MS patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability.
TREAT-MS Study Population & Parameters

- Male or Female
- 18 to 60 years, inclusive, with a RRMS by the 2017 McDonald criteria
- 900 patients will be enrolled in the study
- 22 patients per site projected
- 1st Line DMTs: GA, IFN, FIN, TEC, TERI
- 2nd Line DMTs: MAbs
TREAT-MS Primary Endpoint

- Time to sustained disability progression
- Determined by Expanded Disability Status Scale plus (EDSS+)
TREAT-MS Secondary Endpoints

- Patient-Determined Disease Steps (PDDS)
- MSFC
- Relapse recovery
- Cognition using Symbol Digit Modality Test (SDMT)
- Quality of Life in Neurological Disorders (Neuro-QoL)
- Social status
- Serious Adverse Events (SAEs)
TREAT-MS Tertiary Endpoints

- Brain MRI evidence of neurodegeneration
- Relapses
- New brain lesions
- Optical coherence tomography (OCT): Evidence of Neurodegeneration
- Number of new medications, escalated dosage of medications, and non-pharmacologic interventions for MS-related symptoms
### Monoclonal Antibody Rx for MS

<table>
<thead>
<tr>
<th>Mab</th>
<th>Specificity</th>
<th>Target</th>
<th>Efficacy</th>
</tr>
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<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>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>Ustekinumab</td>
<td>IL-12/IL-23p40</td>
<td>Cytokines</td>
<td>-</td>
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<tr>
<td>BIIB033</td>
<td>Lingo</td>
<td>OPC Diff.</td>
<td>?</td>
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<tr>
<td>Daclizumab</td>
<td>IL-2Rα</td>
<td>Activated</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>CD25</td>
<td>T&amp;B Cells</td>
<td></td>
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</tbody>
</table>
Potential For Remyelination In MS

Multiple Lesion Types By MRI and Pathology: Myelin and Axons

Zollinger, Jeong and Rose et al J Magnetic Resonance 2010; Rose, Wood and Carlson et al in prep.
Hematogenous Stem Cell Transplant (HSCT) For RRMS

- MIST Trial: HSCT vs STD Rx
- Multi Center: Randomized with Cross Over to non myeloabaltive HSCT
- NW, England, Brazil and Sweden
- Other Studies: Israel, Canada, Univ. WA
- Experience = Safety
- Critical Period: 2-3 weeks post Transplant
### Initial Treatment In MS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>CIS, RRMS</td>
<td>Immune Rx</td>
</tr>
<tr>
<td>Benign</td>
<td>Observation</td>
</tr>
<tr>
<td>ProgMS</td>
<td>Immune Rx</td>
</tr>
<tr>
<td>Aggressive MS</td>
<td>Advanced Rx</td>
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</tbody>
</table>
Considerations For Choice Of ImmunoRx

- Premorbid Conditions
- Gender
- Previous Immunotherapy
- Viral Exposures
- Concomitant Medication
- Severity
- Efficacy Varies Widely Across Individuals
- Pharmacokinetics & Pharmacodynamics
Judging Efficacy of Treatment

- Number of Relapses/Year
- Severity of Relapses and Degree of Recovery
- Progression
Judging Efficacy of Treatment

- Clinical Indicators: Neurologic exam and rating scales (EDSS, SNRS, AI, etc), Cognitive Measurements: Neuropsychological Testing
- MRI Outcomes: Gd+ lesions, new T2, new T1, Lesion Volume and Atrophy
- Goal NEDA
# Targets Of MS therapies

## Immunologic Mechanisms of Action for MS Therapies
Reveal Important Components of Pathogenesis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism(s) of Action</th>
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<tbody>
<tr>
<td>GA</td>
<td>Block Antigen Presentation</td>
</tr>
<tr>
<td></td>
<td>Bystander Suppression</td>
</tr>
<tr>
<td></td>
<td>Regulation of Immune Response by CD8 T cells</td>
</tr>
<tr>
<td>IFN</td>
<td>Induces anti-inflammatory cytokines</td>
</tr>
<tr>
<td></td>
<td>Inhibits synthesis of MMPs (Matrix metallo proteinases)</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Traps autoreactive T cells in Lymph Nodes</td>
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<tr>
<td>Estriol</td>
<td>Shifts immune response to Th2</td>
</tr>
<tr>
<td>Plasma Exchange</td>
<td>Reduces circulating Immunoglobulins &amp; Complement</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Blocks CNS infiltration</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Increases NK cell function (? Blocks T cell activation)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Sustained reduction of T cells</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Sustained reduction of B cells</td>
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</table>
Collaborators & Support

- Noel Carlson, Ph.D
- Monica Rojas, M.D.
- James Burns, M.D.
- Jane Bjorklund CCRC
- Andrea White, Ph.D
- Hilary Watt, B.S.
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- Dana DeWitt M.D.
- Dee Husebye, CCRC
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- Protein Design Lab
- Cumming Foundation
- AbbVie Biotherapeutics
- Biogen