Evolving Treatment Options and Strategies in Multiple Sclerosis

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Cleveland Clinic
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Case presentation
Case History

- 31 year old right-handed woman with the recent diagnosis of MS seeking recommendations for treatment
- 2013: optic neuritis OS treated with IVMP with good recovery. MRI brain reportedly showed lesions. She did not return for followup.
- 2014: numbness from the chest down and heaviness of both legs. Did not seek medical attention and symptoms resolved after 1 month.
- Two weeks ago: numbness and clumsiness of the right arm and leg.
MRI Cervical Spine

Questions

• Should she initiate disease therapy for MS?
• With what medication?
• What is the goal of therapy?
• How should she be monitored after starting treatment?
Overview of MS management

MS is UNPREDICTABLE
Overview of MS Management

• Address symptoms/disease sequelae

• Shorten relapses and improve recovery

• Disease Therapy
  – Reduce the number and severity of relapses
  – Prevent the accumulation of disability
  – Reverse disability

• Wellness and comorbidities

RRMS Therapeutic Landscape

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunomodulation</td>
<td>Interferon-beta, glatiramer acetate, dimethyl fumarate, daclizumab</td>
</tr>
<tr>
<td>Inhibition of cell replication</td>
<td>mitoxantrone, teriflunomide</td>
</tr>
<tr>
<td>Cell depletion</td>
<td>alemtuzumab, ocrelizumab</td>
</tr>
<tr>
<td>Altered cell trafficking</td>
<td>natalizumab, fingolimod</td>
</tr>
</tbody>
</table>

The available medications represent a range of mechanisms of action.

Effective therapy for progressive MS is a major unmet need.
Guiding principles in MS disease therapy

Prototypic Course of Relapsing MS

- Relapses and Impairment
- MRI Activity
- MRI Burden of Disease

Disease Duration (Years)

0 5-10 15-20+

Preclinical RR-MS SP-MS
New MS Phenotype Definitions

<table>
<thead>
<tr>
<th>Active disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical: relapses, acute or subacute episodes of new or increasing neurologic</td>
</tr>
<tr>
<td>dysfunction followed by full or partial recovery, in the absence of fever or</td>
</tr>
<tr>
<td>infection</td>
</tr>
<tr>
<td>and/or</td>
</tr>
<tr>
<td>Imaging (MRI): occurrence of contrast-enhancing T1 hyperintense or new or</td>
</tr>
<tr>
<td>unequivocally enlarging T2 hyperintense lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical: steadily increasing objectively documented neurologic dysfunction/</td>
</tr>
<tr>
<td>disability without unequivocal recovery (fluctuations and phases of stability</td>
</tr>
<tr>
<td>may occur)</td>
</tr>
<tr>
<td>Imaging (MRI): imaging measures of progression are not established or</td>
</tr>
<tr>
<td>standardized and not (yet) useful as phenotype descriptors for individual</td>
</tr>
<tr>
<td>patients. Under consideration are</td>
</tr>
<tr>
<td>increasing number and volume of T1-hypointense lesions, brain volume loss,</td>
</tr>
<tr>
<td>and changes in magnetic transfer imaging and diffusion tensor imaging</td>
</tr>
</tbody>
</table>


The therapeutic landscape in RRMS

- We are well-equipped to treat and monitor the inflammatory component of RRMS
  - 14 approved therapies
  - Widespread availability of MRI for monitoring
- DMTs are variably effective in individuals
- No biomarker to prospectively predict efficacy of specific treatments in individual patients
- Monitoring on therapy (clinically and with MRI) is common, though there are no standards or defined targets in the clinic
The Current Cleveland Clinic General Approach:

Rationale For Early Treatment of Multiple Sclerosis

- Most patients ultimately evolve into a secondary progressive course with some degree of permanent disability.
- Although “benign” MS exists, it is rare.
- The ability to predict prognosis in individual patients is limited, particularly benign MS.
- Clinical features correlate poorly with the ongoing inflammation and resultant irreversible tissue destruction in early RRMS.
- Standard MRI is difficult to quantify in clinical practice and captures MS pathology incompletely.
- The available treatments are effective in RRMS but not progressive disease and do not restore damaged tissue.
“Treat to Target” in MS

• Concept borrowed from rheumatoid arthritis
• Shared, explicit goal of therapy:
  – To maximize longterm outcomes (neurologic function and health-related quality of life) through effective prevention of MS-related CNS tissue damage
• Selection and/or adjustment of therapy based on ongoing measurement of disease activity and severity to optimize treatment
• Suggests need for formal treatment algorithms

“No Evidence of Disease Activity” (NEDA) as a treatment target in MS

• Increasingly reported in clinical trials and utilized in practice
• Complete absence of detectable disease activity while on a disease therapy
• Criteria
  – MRI lesion activity (Gd-enhancing lesions, new/enlarged T2 lesions)
  – Clinical relapses
  – Disability worsening
Personalization in its Infancy: Features Suggesting a Poor Prognosis and Need for Early Definitive Therapy

- Frequent relapses, particularly if severe, with incomplete recovery, and with resultant increasing impairment
- Substantial MRI lesion burden
- Repeatedly active MRI scans with increasing lesion burden
- Continued activity despite treatment with a standard agent
- Note: prognosis and responsiveness to treatment are not synonymous

Uncertainties in MS Disease Therapy

- The available options and how they are used are continually evolving
- Roles of emerging therapies: peg-interferon, alemtuzumab, daclizumab, anti-CD20 agents
- Utility of “induction” therapy
- Utility of combination therapy
- Restrictions imposed by insurance coverage, including impact of generics
- How to treat progressive MS
Interferon-Beta and Glatiramer Acetate

Interferon-beta Mechanism of Action

- Induction of a large number of genes in a sizable number of cells, including immune cells:
  - Inhibition of lymphocyte proliferation
  - Immunomodulatory effects, including Th1 to Th2 shift, altered cytokine production, decreased MHC expression
  - Decreased inflammatory cell migration across the blood-brain barrier
Early MRI activity on IFN predicts poor long-term outcome

ASSURANCE Study (15-year f/u of IM IFN beta1a): Results:

MRI activity and relapses predicted future disability in patients treated with IFNβ

Bermel RA et al, Ann Neurol 2013

Interferon Beta Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1b: 8 MIU SC QOD</td>
<td>Injection site reactions</td>
<td>CBC, ALT, AST prior to therapy, at months 1, 3, 6, then every 6-12 months</td>
<td>C</td>
</tr>
<tr>
<td>IFNβ-1a: 30 μg IM qwk</td>
<td>Flu-like symptoms</td>
<td>Pregnancy test prior to therapy and for suspected pregnancy</td>
<td></td>
</tr>
<tr>
<td>IFNβ-1a: 22-44 μg SC 3/wk</td>
<td>Lymphopenia or increased LFTs</td>
<td>NAbs after 1-2 years of therapy, particularly with ongoing activity</td>
<td></td>
</tr>
<tr>
<td>pegIFNβ-1a: 125 μg SC q14d</td>
<td>Accentuation of spasticity, headache, depression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Glatiramer Acetate Putative MOA

- Competitive binding to MHC on antigen presenting cells in preference to myelin protein antigens
- Antigen-specific interaction of GA-MHC with antigen receptors on GA-specific T-cells induces:
  - Tolerance
  - GA-specific Th2 cells with bystander suppression in both the periphery and CNS
- Expression of neurotrophic factors by GA-specific T-cells

Glatiramer Acetate Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg SC daily</td>
<td>Injection site reactions IPIRs Lipoatrophy</td>
<td>Pregnancy test prior to therapy and for suspected pregnancy No laboratory monitoring required on therapy</td>
<td>B</td>
</tr>
<tr>
<td>40 mg SC 3/wk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Switching from brand name to generic glatiramer acetate is treated as a change in therapy in our practice.
General Comments About ABCR Drugs

• Good safety and extensive track record
• Some patients do well
• Modest efficacy, many patients “break through” treatment
  – MRI lesion activity at 6-12 months after starting IFNβ predicts an inadequate treatment response long term
  – Selected patients benefit from switching between classes but we don’t favor switching among IFNβs
  – In most cases, consider moving to a more potent agent
• Patients dislike the frequent injections and bothersome side effects

ABCR Drugs vs. Newer Agents

• We do not routinely advise RRMS patients with effective disease control on IFNβ or GA and good tolerability to change therapy
• We still sometimes use IFNβ or GA as initial therapy for RRMS patients
• However, with post-marketing studies and use in clinical experience generally supporting better efficacy and good safety, routine use of newer agents is increasing
Fingolimod MOA: Stimulation then down-modulation of S1P₁

Fingolimod MOA: Interruption of Lymphocyte Recirculation and Potential Direct CNS Effects

Efficacy of Fingolimod 0.5 mg in Phase 3 Trials

- **FREEDOMS**
  - 54% reduction in ARR vs. placebo
  - HR 0.70 for 3-month confirmed EDSS worsening
  - Significant benefit on MRI lesion activity and atrophy

- **FREEDOMS II**
  - Confirmed results on ARR and MRI lesion activity vs placebo

- **TRANSFORMS**
  - Significant benefit on ARR, MRI lesion activity, and atrophy vs IM IFNβ-1

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*a* Kappos L. *NEJM* 2010;362:387-401

*b* Cohen J. *NEJM* 2010;362:402-15

*c* Calabresi P. *Lancet Neurol* 2014;13:545-56
Fingolimod Peripheral Effects Relate to Biological Processes Regulated by S1P Signaling

Acute and Chronic Heart Rate Effects
# Fingolimod Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg PO daily</td>
<td>Headache, Back pain, 1st dose cardiac, Macular edema, Infection (VZV, PML), Hypertension, Abnormal LFTs, SOB, cough</td>
<td>CBC, ALT, AST prior to initiation, month 3 and 6, every 6 months, Pregnancy test prior to initiation and for suspected pregnancy, VZV titer prior to initiation in the absence of a history of chicken pox or shingles, VZV vaccine, EKG prior to treatment, Eye exam or OCT prior to treatment, at month 3, Pulmonary referral and/or PFTs for pulmonary symptoms</td>
<td>C</td>
</tr>
</tbody>
</table>
Dimethyl Fumarate (Tecfidera)

- Delayed release form of dimethyl fumarate
- Developed from Fumaderm (a mixture of mono- and dimethyl fumarate used to treat psoriasis)
- Activates nuclear-factor E2-related factor-2 (Nrf2) transcription pathway and inhibits NFκB transcription pathway
- Immunomodulatory effects and cytoprotective effects

DMF Phase 3 Trial Efficacy Results

- DEFINE Phase 3 trial
  - 50% reduction in proportion of relapsing patients
  - 34-38% reduction in confirmed EDSS worsening
  - Benefits on GdE lesions, N/E T2 lesions, new T1 lesions
  - Reduced brain volume loss M6-M24

- Results of the CONFIRM Phase 3 trial supported those of DEFINE on ARR and MRI lesion activity but not brain atrophy

\[ ^a \text{Gold R et al. NEJM 2012;267:1098-107.} \]
\[ ^b \text{Fox RJ et al. NEJM 2012;367:1087-97.} \]
## Dimethyl Fumarate Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
</table>
| 120 mg PO BID for 7 days 240 mg PO BID | Skin flushing  
GI: dyspepsia, nausea, vomiting, abdominal pain, cramps, diarrhea  
Leukopenia  
PML | CBC prior to initiation then every 6 months  
Pregnancy test prior to therapy and for suspected pregnancy  
Monitor for serious infection | C                  |
Teriflunomide

- Active metabolite of leflunomide used to treat rheumatoid arthritis
- Blocks dihydro-orotate dehydrogenase
  - Inhibits de novo pyrimidine synthesis
  - Inhibits T-cell and B-cell proliferation

Teriflunomide Efficacy in Phase 3 Clinical Trials

- TEMSO (RRMS)\(^a\)
  - \(\sim 30\%\) reduction in ARR with 7 and 14 mg
  - \(\sim 30\%\) reduction in confirmed disability progression with 14 mg
  - Benefit on GdE lesions, N/E T2 lesions, T2 lesion volume with dose effect
- TOWER (RRMS)\(^b\)
  - Largely confirmed the TEMSO results
- TENERE (RRMS)\(^c\)
  - No difference in rate of treatment failure or relapse rate vs. SC IFNβ-1a
- TOPIC (CIS)\(^d\)
  - Both doses reduced risk of conversion to CDMS 7 mg (37%), 14 mg (43%)

Teriflunomide Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 and 14 mg PO daily</td>
<td>Nausea, diarrhea, Alopecia, Hepatotoxicity, Bone marrow suppression, Immune suppression, Peripheral neuropathy</td>
<td>LFTs prior to initiation and monthly for 6 months, CBC prior to initiation and monitor for infection, Pregnancy test prior to therapy and for suspected pregnancy, Screen for TB, Check BP prior to initiation and monitor on therapy, Monitor for signs/symptoms of peripheral neuropathy</td>
<td>X</td>
</tr>
</tbody>
</table>

Teriflunomide Metabolism and Pharmacokinetics

- Slow elimination is an issue e.g. with unplanned pregnancy
- Elimination T½ averages 18-19 days
  - Average 8 months to reach plasma conc <0.02 mg/L (up to 2 years in some individuals)
  - Eliminated primarily through biliary excretion of unchanged drug into feces; some elimination of metabolites in urine
  - Elimination can be accelerated by administration of cholestyramine (8 g q8h) or activated charcoal (50 g q12h) for 11 days
Natalizumab

MOA of Natalizumab in MS

Ransohoff. NEJM 356:2622, 2007
Natalizumab Effect On Relapse Rate Compared to Standard Therapies

Rate ratio (treated/placebo) and 95% CI for relapse rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC IFNβ-1a</td>
<td>0.7</td>
<td>0.5-0.9</td>
</tr>
<tr>
<td>IM IFNβ-1a</td>
<td>0.8</td>
<td>0.6-1.0</td>
</tr>
<tr>
<td>IFNβ-1b</td>
<td>0.9</td>
<td>0.7-1.1</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>1.0</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>1.2</td>
<td>1.0-1.4</td>
</tr>
</tbody>
</table>

Natalizumab and PML Current Status

- 146,200 patients treated as of 31 OCT 2015
  - Overall risk 4.11 /1000
- Factors that increase risk
  - Presence of JCV antibodies
  - Rx duration >24 months. Very low risk for year 1.
  - Prior immune suppression
  - Possibly decreased body weight

Medical Information Services, Biogen, Dec 2015
Risk Stratifying for PML

<table>
<thead>
<tr>
<th>JCV Ab Status</th>
<th>Prior immunosuppressant therapy</th>
<th>Risk up to 24 mos of therapy</th>
<th>Risk after 24 mos therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>No</td>
<td>~1:45,798</td>
<td>~1:5022</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>~1:16,151</td>
<td>~1:1171</td>
</tr>
<tr>
<td>Positive</td>
<td>No</td>
<td>~1:1145</td>
<td>~1:126</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>~1:404</td>
<td>~1:44</td>
</tr>
</tbody>
</table>


Natalizumab to Treat MS
Current Trends

- Test for JCV antibodies prior to and during use
  - JCV(-) → liberalize use
  - JCV(+) → use in some circumstances, if no history of immunosuppression, restrict use to 1-2 years
- “Rebound” after discontinuation of natalizumab
Natalizumab Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg IV monthly</td>
<td>Headache, Allergic reaction, Hepatotoxicity, PML, HSE</td>
<td>ALT, AST prior to initiation, at months 3 and 6, then every 6 months&lt;br&gt;Pregnancy test prior to therapy and for suspected pregnancy&lt;br&gt;NAbs at month 6&lt;br&gt;JCV serology prior to initiation then every 3 months&lt;br&gt;MRI prior to therapy then every 6 months</td>
<td>C</td>
</tr>
</tbody>
</table>

Alemtuzumab
Alemtuzumab (Lemtrada, Campath-1h)

- Humanized MAb that targets the CD52 Ag, an anonymous surface protein expressed by T-cells, B-cells, monocytes, and eosinophils
- Produces rapid, profound, and prolonged lymphocyte depletion
- Gradual reconstitution with altered cell profile and function
- Previously approved for CLL
- Approved for MS in 2014

General Comments About Alemtuzumab

- Advantages
  - Potent efficacy
  - Convenience of annual administration
- Disadvantages
  - Safety concerns
  - Complicated start-up process
  - Required monitoring
- Principal indication: patients with active relapsing MS who have failed (several) other therapies
## Alemtuzumab Use in Practice

<table>
<thead>
<tr>
<th>Dose</th>
<th>Main Adverse Effects</th>
<th>Laboratory Monitoring</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mg IV daily for 5 days 3 days at M12</td>
<td>Infusion reactions Antibody-mediated autoimmunity Infection Malignancy Pneumonitis</td>
<td>Pretreatment: CBC, Cr, LFTs, TSH, hepatitis panel, VZV IgG, HIV, bHCG, UA, skin exam, gynecologic exam, (PPD or Quantiferon), brain MRI Posttreatment: CBC, UA monthly for 4y TSH q3M for 4y, annual skin and gynecological exams Monitor for serious infection</td>
<td>C Auto-Ab can transfer trans-placentally</td>
</tr>
</tbody>
</table>

### Alemtuzumab Infusion

- **Premedication**
  - Cetirizine 10 mg PO for 14 days
  - Ranitidine 150 mg for 14 days
  - Acyclovir 200 mg BID for 2 years
  - IVMP 1000 mg
  - Acetaminophen 1000 mg PO and q4h PRN
  - Diphenhydramine 50 mg PO then 25-50 mg PO or IV q4h PRN

- **Alemtuzumab 12 mg IV over 4-8 hours for 5 days at M0 and 3 days at M12**

- **2-hour monitoring period post-infusion**
Daclizumab

- Humanized MAb vs. IL-2Rα (CD25, Tac)
  - Mouse (~10%) CDR
  - Human (~90%) IgG1 constant and variable regions
- Biological activity
  - Binds to IL-2R α-chain, blocking IL-2 binding and signaling
  - Inhibits T-cell and B-cell activation by IL-2
  - Expansion of CD56bright regulatory NK cells
- Approved for prevention of renal allograft rejection by FDA (1997) and EMA (1999)
  - 3rd MAb, 1st humanized, 1st vs. a cytokine receptor
- Approved to treat relapsing forms of MS in 2016

Waldmann. JCI 27:1, 2007
Daclizumab Efficacy in RRMS Phase 3 Trials

- **SELECT**
  - Daclizumab 150 mg (n=208), 300 mg (n=209) or placebo (n=204) SC every 4 weeks for 52 weeks
  - Significant ↓ ARR with 150 mg (54%) and 300 mg (50%) vs placebo
  - Significant ↑ relapse-free with 150 mg (81%) and 300 mg (80%) vs placebo (64%)
  - Reduced ↓ 3-month disability worsening with 150 mg (57%, p=0.021) and 300 mg (43%, p=0.091) vs placebo
  - Both doses reduced MRI lesion activity

*Gold R et al. Lancet 2013;381:2167-75*

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Daclizumab Efficacy in RRMS Phase 3 Trials

- **DECIDE**
  - Daclizumab 150 mg SC every 4 weeks (n=919) or IFNβ-1a 30 µg IM weekly (n=922) for 144 weeks
  - 45% ↓ ARR with daclizumab vs IFNβ-1a
  - 12-week confirmed disability progression daclizumab (16%) vs placebo (20%) (p=0.16)
  - Daclizumab reduced MRI lesion activity vs IFNβ-1a

*Kappos L et al. NEJM 2015;373:1418-28*
Daclizumab Safety and Tolerability in Phase 3 Trials

- Cutaneous events—pruritis, rash, dermatitis (eczema, atopic, allergic, seborrheic, exfoliative), acne, erythema nodosum, angioedema
- Increased infections
- Increased LFTs (usually mild)

These factors currently limit the clinical use of daclizumab
Ocrelizumab Mechanism of Action

• Anti-CD20 MAb that selectively depletes B-cells via:
  – Antibody-dependent cellular cytotoxicity (ADCC)
  – Complement-dependent cytotoxicity (CDC)
  – Apoptosis

• Note: CD20 is not expressed by pre-B or plasma cells

• Similar to rituximab but:
  – Humanized vs chimeric
  – Different though overlapping Ag site
  – More potent ADCC and apoptosis, and less potent CDC

Rituximab volumes at Mellen

Mellen Center rituximab use

Month

Number of infusions administered per month

14
12
10
8
6
4
2
0
Mar 13 May 13 Jul 13 Sep 13 Nov 13 Jan 14 Mar 14 May 14 Jul 14 Sep 14 Nov 14 Jan 15 Mar 15 May 15 Jul 15 Sep 15 Nov 15 Jan 16
OPERA I and OPERA II

- Compared with IFNβ-1a, ocrelizumab reduced:
  - ARR
  - 12- and 24-week CDP (by 40%)
  - T1 Gd+ lesions (by 94–95%)
  - New and/or enlarging T2 lesions (by 77–83%)

- Safety profile ocrelizumab:
  - Similar to IFNβ-1a
  - Most common: IRR (at first dose)


Ocrelizumab in Clinical Practice: PPMS

- Some efficacy in ORATORIO Phase 3 trial in PPMS
  - Driven by “inflammatory” 25% subset

- “Good” safety profile as in RRMS
  - No new safety issues in older, more disabled population

- What will FDA do regarding PPMS label?
  - Trial was different than other progressive MS studies: younger, more inflammatory
  - Restrictions possible e.g. age, disease duration
How are we doing?
Summary and
Future Directions

NEDA in Clinical Studies

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Study Duration, y</th>
<th>Patients With NEDA Status, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>1</td>
<td>Placebo, 15%; pegylated interferon beta-1a every 2 weeks, 34%</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>1</td>
<td>Placebo, 15%; natalizumab, 47%</td>
</tr>
<tr>
<td>SELECT</td>
<td>1</td>
<td>Placebo, 11%; daclizumab, 39%</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>2</td>
<td>Placebo, 7%; natalizumab, 37%</td>
</tr>
<tr>
<td>CARE-MS I</td>
<td>2</td>
<td>SC interferon beta-1a, 27%; alemtuzumab, 39%</td>
</tr>
<tr>
<td>CARE-MS II</td>
<td>2</td>
<td>SC interferon beta-1a, 13%; alemtuzumab, 32%</td>
</tr>
<tr>
<td>CLARITY</td>
<td>2</td>
<td>Placebo, 16%; cladribine, 46%</td>
</tr>
<tr>
<td>CLIMB</td>
<td>2</td>
<td>Early MS, 24%; established MS, 31%</td>
</tr>
<tr>
<td>FREEDOMS</td>
<td>2</td>
<td>Placebo, 13%; fingolimod, 33%</td>
</tr>
<tr>
<td>DEFINE</td>
<td>2</td>
<td>Placebo, 15%; dimethyl fumarate, 28%</td>
</tr>
<tr>
<td>CombiRx</td>
<td>3</td>
<td>IM interferon beta-1a alone, 21%; glatiramer acetate alone, 19%; glatiramer acetate and IM interferon beta-1a, 33%</td>
</tr>
<tr>
<td>CLIMB</td>
<td>7</td>
<td>Early MS, 6%; established MS, 10%</td>
</tr>
</tbody>
</table>

## Comparison of RRMS Treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
<th>Safety</th>
<th>Tolerability</th>
<th>Ease</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ’s</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>GA</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>DMF</td>
<td>++</td>
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</tr>
<tr>
<td>Mitoxantrone</td>
<td>++</td>
<td>+</td>
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</tr>
<tr>
<td>Natalizumab</td>
<td>+++</td>
<td>+ or +++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>+++</td>
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<td>+++</td>
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<tr>
<td>Daclizumab</td>
<td>++</td>
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<td>++</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>+++</td>
<td>++</td>
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</tr>
</tbody>
</table>

Subjective ratings: + = low (worst), ++ = moderate, +++ = high (best)

## General Comments About The Current MS Therapies

- **Interferon-β, glatiramer acetate:**
  - Safe but common non-life-threatening AEs and administered by frequent injection
  - Modest potency
- **MAbs, oral agents:**
  - Convenient and generally well tolerated
  - More potent efficacy
  - Rare but potentially severe AE
- **Lack of biomarker to monitor or predict efficacy is a major issue**
- **All are expensive**
Future Prospects

• New medications for RRMS
  – Other anti-CD20 MAbs
  – Selective S1P receptor modulators
  – Small molecule $\alpha_4\beta_1$-integrin antagonists
  – Generics

• Treatments for progressive MS
  – Comorbidities
  – High dose Biotin
  – Ocrelizumab
  – Repair and neuroprotective strategies

MS IS UNPREDICTABLE
But we are learning how to use our tools to control it.