How do the Current DMT’s Affect the Altered Immune Response in MS

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**MS Subtypes**

- Clinically isolated syndrome (CIS)
- Relapsing-remitting
- Secondary progressive
- Primary progressive
- Progressive relapsing

**Natural History of MS: Summary**

- Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity
- Axonal loss

Adapted from Goodkin DE. UCSF MS Curriculum. 1999.
Strategies to block the Immune system’s attack

Broad-spectrum Immunosuppression

Antigen-specific

Non-selective

Selective

Toxicity

Antigens unknown or multiple ones!
Expanding Landscape of MS Therapeutics

Currently Approved MS Disease-modifying Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approval Year</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>1993</td>
<td>Subcutaneous injection every other day</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>1996</td>
<td>Intramuscular injection every week</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>1996</td>
<td>Subcutaneous injection daily</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>2000</td>
<td>Intravenous every 3 months</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif)</td>
<td>2002</td>
<td>Subcutaneous 3 times per week</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>2004</td>
<td>Intravenous monthly</td>
</tr>
<tr>
<td>IFNβ-1b (Extavia)</td>
<td>2009</td>
<td>Subcutaneous every other day</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>2010</td>
<td>Oral daily</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>2012</td>
<td>Oral daily</td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>2013</td>
<td>Oral twice a day</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>2014</td>
<td>Subcutaneous 3 times per week</td>
</tr>
</tbody>
</table>
Injectable Disease-modifying Therapies

Interferon β

- **Early findings MoA:** reduce T-cell activation/proliferation, reduce T-cell secretion of matrix metalloproteinases, inhibit interferon gamma release, limit T-cell migration across blood brain barrier, & reduce expression of HLA

- **Recent findings MoA:** interfere with antigen processing, reduce antigen presentation to T-cells, & Th1/Th2 expression

Glatiramer acetate

• **Early findings MoA**: Th1 to Th2 shift & blocking MHC peptide antigen

• **Recent findings MoA**: CNS migration of Th2 cells, modify antibody production by plasma cells, regulates B-cell properties, cytokine modulation, inhibits antigen presentation to T-cells, & oligodendrocyte precursor cells (myelin repair)

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**Injectable Disease-modifying therapy efficacy**

<table>
<thead>
<tr>
<th>Initial Placebo controlled Pivotal Clinical Trials</th>
<th>Agent</th>
<th>Relapses</th>
<th>MRI activity</th>
<th>12 week Disability Progression- EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis Collaborative Research Group</td>
<td>IFNβ-1a (low dose)</td>
<td>ARR: ↓ 18%</td>
<td>Gd+ lesions: ↓50% T2 lesions: no effect</td>
<td>↓ 37%</td>
</tr>
<tr>
<td>PRISMS. Lancet 1998; 352: 1498–504.</td>
<td>IFNβ-1a (high dose)</td>
<td>ARR: ↓ 33%</td>
<td>Gd+ lesions: ↓84% T2 lesions: ↓78%</td>
<td>↓ 30%</td>
</tr>
<tr>
<td>IFNB Multiple Sclerosis Study Group. Neurology. 1993 Apr;43(4):655-61.</td>
<td>IFNβ-1b</td>
<td>ARR: ↓ 34%</td>
<td>Gd+ lesions: ↓83% T2 lesions: ↓75%</td>
<td>Barely significant</td>
</tr>
<tr>
<td>Copolymer 1 Multiple Sclerosis Study Group. NEUROLOGY 1995;45: 1268-1276.</td>
<td>Glatiramer acetate</td>
<td>ARR: ↓ 29%</td>
<td>Not adequately assessed</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Lalive Ph, et al. CNS Drugs. 2011 May;25(3):140-144.
Oral Disease-modifying Therapies

Fingolimod

- Sphingosine 1-phosphate receptor (S1PR) modulator; S1P1, S1P3, S1P4, S1P5 receptors

- **MoA**: Functionally antagonizes S1PR blocking lymphocyte egress from secondary lymphoid organs to the peripheral blood circulation

- Oral medication given daily
**Teriflunomide**

- Active metabolite of Leflunomide

- **MoA:** mimics DNA building blocks (pyrimidine); interferes with DNA synthesis and inhibits dihydro-orotate dehydrogenase
  - => cytostatic to proliferating B & T cells
  - => reduces T-cell proliferation, activation, & production of cytokines
  - => interferes with the interaction between T-cells & antigen-presenting cells

- Oral medication administered daily (7mg or 14mg)

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**Dimethyl fumarate**

- **MoA:** changes balance of Th1 to Th2 & activates Nrf2 transcriptional pathway (oxidative, metabolic & inflammatory stress)

- Oral medication given twice a day
### Oral Disease-modifying therapy efficacy

<table>
<thead>
<tr>
<th>Initial Placebo controlled Pivotal Clinical Trials</th>
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<th>Relapses</th>
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</thead>
</table>

### Intravenous Disease-modifying therapies

- Intravenous Disease-modifying therapies

  - Fingolimod
    - ARR: ↓ 54%
    - Gd+ lesions: ↓82%
    - T2 lesions: ↓74%
    - ↓ 32%

  - Teriflunomide (14mg)
    - ARR: ↓32%
    - Gd+ lesions: ↓80%
    - Lesion volume: ↓67%
    - ↓ 30%

  - Dimethyl fumarate
    - ARR: ↓53%
    - Gd+ lesions: ↓90%
    - T2 lesions: ↓85%
    - ↓ 38%
Mitoxantrone

- Mainly used to treat leukemia and prostate cancer
- **MoA**: DNA topoisomerase II inhibitor; suppresses proliferation of T cells, B cells, and macrophages
- Lifetime dose of 140mg/m²

Natalizumab

- First drug developed in the class of selective adhesion molecule inhibitors
- **MoA**: Humanized monoclonal antibody against alpha-4 (α4) integrin
- α4-integrin is required for WBC to move into organs
### Intravenous Disease-modifying therapy efficacy

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<thead>
<tr>
<th>Initial Placebo controlled Pivotal Clinical Trials</th>
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<th>Relapses</th>
<th>MRI activity</th>
<th>12 week Disability Progression-EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIMS trial. Lancet 2002; 360: 2018–25.</td>
<td>Mitoxantrone (12 mg/m2)</td>
<td>ARR: ↓ 68%</td>
<td>Gd+ lesions: + trend T2 lesions: ↓85%</td>
<td>↓43%</td>
</tr>
</tbody>
</table>

### Injectable Disease-modifying therapy side effects/monitoring

<table>
<thead>
<tr>
<th>Agent</th>
<th>Minor side effects</th>
<th>Major side effects</th>
<th>Pregnancy category</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a (low dose)</td>
<td>Flu-like symptoms, headache, transaminitis, depression</td>
<td>Suicidal ideation, anaphylaxis, hepatic injury, blood dyscrasias, seizures, autoimmune hepatitis</td>
<td>C</td>
<td>CBC with differential, LFTs, TFTs, interferon neutralizing antibodies (if clinically warranted)</td>
</tr>
<tr>
<td>IFNβ-1a (high dose)</td>
<td>Same as above and injection-site reactions</td>
<td>Same as above and skin necrosis</td>
<td>C</td>
<td>Same as above</td>
</tr>
<tr>
<td>IFNβ-1b</td>
<td>Same as above</td>
<td>Same as above</td>
<td>C</td>
<td>Same as above</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Injection-site reactions and post-injection vasodilatory reaction</td>
<td>Lipoatrophy, skin necrosis, anaphylaxis</td>
<td>B</td>
<td>None required</td>
</tr>
</tbody>
</table>

### Oral Disease-modifying therapy side effects/monitoring

<table>
<thead>
<tr>
<th>Agent</th>
<th>Minor side effects</th>
<th>Major side effects</th>
<th>Pregnancy category</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod</td>
<td>Lymphopenia (absolute lymphocyte count &gt;200), transaminitis</td>
<td>Bradycardia, heart block, hypertension, risk of infections (herpetic), lymphopenia (absolute lymphocyte count &lt;200), transaminitis, macular edema, skin cancer, reactive airway, PRES</td>
<td>C</td>
<td>1st dose cardiac monitoring, eye and skin exams, CBC with differential, LFTs, VZV IgG prior to starting medication, PFTs (if clinically indicated)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Diarrhea, nausea, hair thinning</td>
<td>Transaminitis, lymphopenia, teratogenic (men &amp; women), latent tuberculosis, neuropathy, hypertension</td>
<td>X</td>
<td>CBC with differential, LFTs (monthly for first 6 months), PPD prior to starting, wash out (if needed)</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Flushing, gastrointestinal distress</td>
<td>Transaminitis, leukopenia</td>
<td>C</td>
<td>CBC with differential, LFTs</td>
</tr>
</tbody>
</table>
## Intravenous Disease-modifying therapy side effects/monitoring

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<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>Headaches, joint pain, fatigue, wearing off phenomenon</td>
<td>Progressive multifocal leukoencephalopathy, infusion reaction, Herpes Zoster, other infections</td>
<td>C</td>
<td>CBC with differential, LFT’s, serum JCV antibody (Q6 months), MRI, Tysabri antibodies (if clinically warranted)</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Nausea, vomiting, hair thinning, menstrual irregularities</td>
<td>Cardiac toxicity, acute myelogenous leukemia, infections, infertility, liver dysfunction</td>
<td>D</td>
<td>CBC with differential, LFT’s, ECG, Echo/MUGA scan (even after therapy completed), lifetime dose 140 mg/m2</td>
</tr>
</tbody>
</table>

## Many faces of side effects

![Image of side effects](image)
# Emerging Therapies for Multiple Sclerosis

## Late Stage Clinical Development of Emerging Disease-modifying Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism(s) of Action</th>
<th>Side effects</th>
<th>Route</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (anti-CD52, pan leukocyte marker)</td>
<td>Targets against CD52+ cells (present on mature lymphocytes); depletes B and T cells</td>
<td>Infusion reactions, autoimmune thyroid disease, ITP, Goodpastures, infections (HSV, VZV)</td>
<td>Infusion yearly</td>
<td>Monthly CBC with differential, LFTs, TFTs</td>
</tr>
<tr>
<td>Daclizumab (anti-CD25, IL-2 receptor alpha)</td>
<td>Targets against the alpha subunit of the IL-2 receptor on T cells; reduces T-cell activation/proliferation and expands CD56 bright cells that inhibit T-cell survival</td>
<td>Transaminitis, autoimmune hepatitis, lymphadenopathy, rash, alopecia universalis</td>
<td>Subcutaneous injection monthly</td>
<td>Exact monitoring to be determined; LFTs, CBC with differential</td>
</tr>
<tr>
<td>Ocrelizumab (anti-CD20, B cells)</td>
<td>Fully humanized monoclonal antibody targeted against CD20 B cells</td>
<td>Infusion reactions, lymphopenia, infections</td>
<td>Infusion every 6 months</td>
<td>CD19/CD20 B cell counts</td>
</tr>
<tr>
<td>PEG-INF (Interferon beta-1a with polyethylene glycol)</td>
<td>Same as other interferon products</td>
<td>Injection-site reactions, flu-like side effects</td>
<td>Subcutaneous injection twice a month</td>
<td>Similar to other interferon products</td>
</tr>
</tbody>
</table>
Emerging Therapies: 
Increased Efficacy, Increased Risks

Existing Drugs with proven efficacy and variable safety and new drugs additional concerns:

Serious Safety Concerns*
- Immune surveillance
- Infections
- Malignancies
- Long-lasting and irreversible effects
- Autoimmunity
- Teratogenicity
- Rare but serious infusion reactions
- The unknown

Manageable Safety Concerns*
- Bradycardia
- Blood pressure elevations
- Reactive airway disease
- Liver function abnormalities
- Flushing
- GI discomfort
- Arthralgias
- Back/limb pain

Care-MS. http://care-ms.com/carems-program.aspx;
Comi G, et al. AAN April 2011; P05.288;
Miller A, et al. AAN April 2011; S41.002;
Wolinsky J, et al. AAN April 2011; S41.003.
*This information represents expert faculty opinion.

Additional References