Treatment of Relapsing-Remitting Multiple Sclerosis
A Focus on Disease Modifying Therapy

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Disclosure

• No commercial or financial interests

Objectives

• Describe the pathophysiology of multiple sclerosis.
• Explain the mechanism of action of disease modifying therapies for RRMS.
• Compare current options for disease modifying therapy in RRMS.
• Formulate a monitoring plan for a patient taking a disease modifying therapy.
• Recognize disease modifying therapies in the pharmaceutical pipeline.
Pathophysiology


Disease Modifying Therapy (DMT)

- Interferons
- Glatiramer
- Natalizumab
- Fingolimod
- Mitoxantrone

Evidence Summary for Treatment in Relapsing-Remitting MS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annualized relapse rate (RR)</th>
<th>Patients progressing, % (RR)</th>
<th>Relapse free, % (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferons (Avonex, Rebif, Extavia)</td>
<td>0.66-0.70</td>
<td>0.63-0.76</td>
<td>1.46-2</td>
</tr>
<tr>
<td>Glatiramer (Copaxone)</td>
<td>0.70</td>
<td>0.79</td>
<td>1.24</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>0.32</td>
<td>0.59</td>
<td>1.5</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>0.45</td>
<td>0.73</td>
<td>1.08</td>
</tr>
</tbody>
</table>

RR = Relative Risk vs placebo

Disease Modifying Therapy (DMT)

- Interferons
- Glatiramer
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- Mitoxantrone

Interferon

Proposed immunologic effects
- Blocking T-cell activation
- Apoptosis of autoreactive T-cells
- INFγ antagonism
- Restoration of T-regulatory cell activity
- Neurotrophic factor expression
- Cytokine shifts
- Blood-brain barrier effects
- Antiviral effects


Interferon

FDA-approved for patients with RRMS:

<table>
<thead>
<tr>
<th></th>
<th>Avonex®</th>
<th>Betaseron®</th>
<th>Rebif®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease clinical exacerbations</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Slow accumulation of physical disability</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Avonex® Prescribing Information
Betaseron® Prescribing Information
Rebif® Prescribing Information
Interferon

Betaseron® = Extavia®

Drug Name Availability Storage

Interferon-beta 1b
Betaseron®
Extavia®
Lyophilized powder* Room temp

Interferon-beta 1a
Avonex®
Lyophilized powder
Prefilled syringe
Prefilled autoinjector Refrigeration
Rebif®
Prefilled syringe* Refrigeration

*Autoinjector device available

Interferon

Drug Name Titration Dose Maintenance Dose

Interferon-beta 1b
Betaseron®
Week 1-2: 25% dose
Week 3-4: 50% dose
Week 5-6: 75% dose
Week 7: full dose
250 µg SQ every other day

Interferon-beta 1a
Avonex®
Week 1: ¼ dose
Week 2: ½ dose
Week 3: ½ dose
Week 4: full dose
30 µg IM weekly

Rebif®
Week 1-2: 20% dose
Week 3-4: 50% dose
Week 5: full dose
22-44 µg SQ thrice weekly
Interferon

- Common adverse events
  - Influenza-like symptoms
  - Injection site reactions
- Serious adverse events
  - Hepatotoxicity
  - Myelosupression
  - Depression
- 5-30% develop neutralizing antibodies


Disease Modifying Therapy (DMT)

- Interferons
  - Glatiramer
- Natalizumab
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Monitoring recommendations:

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC w/ differential</td>
<td>1, 3, and 6 months after initiation, then periodically</td>
</tr>
<tr>
<td>LFTs</td>
<td>1, 3, and 6 months after initiation, then periodically</td>
</tr>
</tbody>
</table>

- signs/symptoms of depression
Glatiramer acetate (Copaxone®)

Proposed immunologic effects

Racke MK. Neurology 2010;74:S25-30

Glatiramer acetate

• FDA approved for patients with RRMS to reduce the frequency of relapses

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Availability</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg SQ daily</td>
<td>Prefilled syringe</td>
<td>Refrigeration</td>
</tr>
<tr>
<td></td>
<td>Autoinjector available</td>
<td></td>
</tr>
</tbody>
</table>

Copaxone® prescribing information.

Glatiramer acetate

Adverse events

• Injection site reactions most common
• ~10-15% develop post-injection reaction
• No routine lab monitoring

Copaxone® prescribing information.
Disease Modifying Therapy (DMT)

- Interferons
- Glatiramer
- **Natalizumab**
- Fingolimod
- Mitoxantrone

Natalizumab (Tysabri®)

- Monotherapy for treatment of RRMS to:
  - Delay accumulation of physical disability
  - Reduce frequency of clinical exacerbation
- Generally recommended as second-line therapy
- Dosing: 300 mg IV q4 weeks

Natalizumab (Tysabri®)

History
- Approved in US in 2004
- Withdrawn from market in 2005
- Reintroduced in 2006 with REMS program
Natalizumab (Tysabri®)
Proposed immunologic effects


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Natalizumab (Tysabri®)

- Infusion-related reactions
  - Pre-treatment: loratadine, acetaminophen
  - Slow infusion rate
- Hypersensitivity reactions
  - Stop natalizumab, do not rechallenge


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Progressive Multifocal Leukoencephalopathy (PML)

- Caused by JC virus
  - ~50% of population carry benign form of JCV
- Most common in patients with HIV
- Possible sites of JCV persistence
  - Kidney
  - Bone marrow
  - Lymphoreticular system

PML Pathophysiology


PML Survival

• Mortality rate ~20% w/ NTZ-associated PML
• 47 survivors w/ 6 month follow-up:
  – 13% mild disability
  – 47% moderate disability
  – 40% severe disability
• Predictors of survival
  – Younger age at diagnosis
  – Less disability before diagnosis
  – Shorter time between symptom onset and PML disease


PML Risk Factors

• Three factors that increase risk:
  – Longer duration of treatment
  – Prior treatment with an immunosuppressant
  – Presence of anti-JCV antibodies

PML Estimated Risk


PML Clinical Features

MS relapse  
Onset  
Acute onset  
Subacute onset

PML  
Onset  
Subacute onset

Presentation  
Several hours-days, usually stabilizes then resolves  
Several weeks, progressive

Clinical features  
• diplopia  
• optic neuritis  
• myelopathy  
• aphasia  
• behavioral/neuropsych disturbance  
• visual deficits  
• hemiparesis  
• seizures


PML Clinical Management

• Immune reconstitution via:  
  – plasma exchange  
  – immunoadsorption

• Immune reconstitution inflammatory syndrome (IRIS)  
  – high-dose steroids

Disease Modifying Therapy (DMT)

- Interferons
- Glatiramer
- Natalizumab
- **Fingolimod**
- Mitoxantrone

Fingolimod (Gilenya®)

- FDA approved for treatment of patients with RRMS to:
  - reduce frequency of clinical exacerbation
  - delay accumulation of physical disability
- Dosing: 0.5 mg PO daily

Gilenya® prescribing information

Fingolimod (Gilenya®)

Proposed immunologic effects

Aktas O. Nat Rev Neurol 2010;6:373-82.
**Fingolimod (Gilenya®)**

**Proposed immunologic effects**

Fingolimod (Gilenya®)

FREEDOMS Trial

<table>
<thead>
<tr>
<th>Outcome (2 years)</th>
<th>Fingolimod 0.5 mg</th>
<th>Placebo</th>
<th>ARR [95% CI]</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.18</td>
<td>0.4</td>
<td>0.22</td>
<td>NA</td>
</tr>
<tr>
<td>% relapse free</td>
<td>70.4%</td>
<td>45.6%</td>
<td>25%</td>
<td>4 [3-5]</td>
</tr>
<tr>
<td>% disability progression free</td>
<td>87.5%</td>
<td>81%</td>
<td>6%</td>
<td>16 [9-65]</td>
</tr>
</tbody>
</table>


TRANSFORMS Trial

<table>
<thead>
<tr>
<th>Outcome (1 year)</th>
<th>Fingolimod 0.5 mg</th>
<th>Avonex</th>
<th>ARR [95% CI]</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.16</td>
<td>0.33</td>
<td>0.17</td>
<td>NA</td>
</tr>
<tr>
<td>% relapse free</td>
<td>82.6%</td>
<td>69.3%</td>
<td>13%</td>
<td>7 [5-13]</td>
</tr>
<tr>
<td>% disability progression free</td>
<td>94.1%</td>
<td>92.1%</td>
<td>2%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Contraindications

- MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure within the last 6 months
- Mobitz Type-II second-degree or third-degree AV block or sick sinus syndrome, unless the patient has a functioning pacemaker
- Baseline QTc ≥500 ms
- Treatment with Class Ia or Class III anti-arrhythmics

Avoid live-attenuated vaccines during and within 2 months of treatment

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Serious Adverse Effects

Bradyarrhythmia

- Symptomatic 0.5% fingolimod vs 0% placebo
- Maximal HR decline usually within 6 hours
- HR returns to baseline within 1 month

AV block

- 1st-degree: 0.1% fingolimod vs 0% placebo
- 2nd-degree: 0.1% fingolimod vs 0% placebo

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Serious Adverse Effects

Macular edema

- 0.4% fingolimod vs 0.1% placebo
- Risk higher in patients with uveitis or diabetes
- Occurred within 3-4 months of initiation

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Serious Adverse Effects

Other
• Respiratory effects
• Hepatic effects
• Infections
• Lymphoma

Pre-initiation Clinical Assessment
• Labs:
  – LFTs
  – CBC
• Ocular coherence tomography (OCT) or dilated eye exam
• Effective contraception for female patients
  • Pulmonary function tests
  • Varicella zoster titer

First-Dose Monitoring
• Hourly HR & BP measurement for 6 hours
• ECG prior to dosing and after 6 hour observation
• Additional observation recommended if:
  – HR 6 hours post-dose <45 bpm
  – HR 6 hours post-dose has not reached a nadir
  – ECG 6 hours post-dose shows new onset second degree or higher AV block
First-Dose Monitoring, cont.
• Overnight continuous ECG monitoring recommended if patient has:
  – Symptomatic bradycardia after 1st dose requiring pharmacologic intervention
  – Pre-existing CV condition
  – QT interval prolongation or risk factors
  – Concurrent therapy that slows the heart rate

First-Dose Monitoring, cont.
• Within first 2 weeks of initiation:
  – Repeat monitoring if interruption for ≥1 day
• Within weeks 3-4 of initiation:
  – Repeat monitoring if interruption for >7 days
• After 1 month of initiation:
  – Repeat monitoring if interruption of >14 days

Ongoing Clinical Assessment
• OCT or dilated eye exam 3-4 months after initiation
• Signs/symptoms of infection
  • LFTs
  • Pulmonary function tests

as indicated
Disease Modifying Therapy (DMT)

- Interferons
- Glatiramer
- Natalizumab
- Fingolimod
- **Mitoxantrone**

Mitoxantrone

- FDA approved for reducing disability and frequency of clinical relapses in MS:
  - Worsening RRMS
  - Secondary progressive

- Dosing
  - 12 mg/m$^2$ IV q3 months
  - Cumulative lifetime dose ≥140 mg/m$^2$

Mitoxantrone prescribing information.

Mitoxantrone

Proposed immunologic effects:
- Generalized immunosupression
- Inhibits migration of monocytes and lymphocytes
- Induces apoptosis of dendritic cells
- Decrease TNF, IL-2
- Inhibits B cells
- Inhibits myelin degradation by macrophages
- Increased T-cell suppressor function


Mitoxantrone

Toxicities:
- Immunosupression
- Myelosupression
- Cardiac toxicity
- Leukemia
- Infertility


Mitoxantrone

Recommended monitoring with each dose:
- LVEF by ECG or MUGA
- CBC
- LFTs
- Pregnancy test in women

Mitoxantrone prescribing information.
Dalfampridine (Amypra®)

- Indication: improve walking in patients with MS
- Not a disease modifying therapy
- Only available through specialty pharmacies
- Dosing: 10 mg PO twice daily

Dalfampridine (Amypra®)

Proposed mechanism of action


Dalfampridine (Amypra®)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Dalfampridine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timed Walk Responders (%)</td>
<td>8.3%</td>
<td>34.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>9.3%</td>
<td>42.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in walking speed (ft/sec)</td>
<td>0.05</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td>0.21</td>
<td>0.07</td>
</tr>
<tr>
<td>Difference in time (sec)</td>
<td>0.27</td>
<td>1.05</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.02</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Outcomes based on timed 25-ft walk, responder defined as faster walking speed on timed 25-ft walk for ≥3 of 4 on-drug assessments compared to any of the 5 off-drug visits

FDA Review Documents.
Dalfampridine (Amypra®)

Contraindications

• History of seizures
• Moderate to severe renal impairment (CrCl<50 mL/min)
  – Creatinine clearance should be calculated prior to initiation of dalfampridine
  – In mild renal impairment (CrCl 51-80 mL/min), total body clearance is reduced by 45% and risk of seizure may be increased

Ampyra® prescribing information.

Treatments on the Horizon

Alemtuzumab

• Route of administration: annual IV
• Proposed MOA: anti-CD25 glycoprotein that is present on lymphocytes & monocytes
• Phase II trial demonstrated significantly reduced rate of disability, ARR, T2 lesion burden vs IFN-β-1a
• Phase III trials ongoing
• Safety concerns: thyroid disorder, ITP, infections


Treatments on the Horizon

BG-12 (dimethyl fumarate)

• Route of administration: oral bid-tid
• Proposed MOA: decrease leukocyte passage through blood-brain barrier, activate antioxidative pathways
• Phase III trial demonstrated reduced ARR, disability progression at 2 years vs placebo
• Safety concerns: AE leading to discontinuation included flushing, elevated LFTs, nausea, diarrhea, vomiting

**Treatments on the Horizon**

**Daclizumab**
- Route of administration: IV q2-4 weeks
- Proposed MOA: Binds to IL-2 receptor, decreasing T cell activation
- Phase II trial demonstrated reduction in ARR vs placebo
- Phase III trials ongoing
- Safety concerns: cutaneous adverse events, infection


**Laquinimod**
- Route of administration: oral daily
- Proposed MOA: promote anti-inflammatory cytokine profiles in blood mononuclear cells
- Phase III trial demonstrated reduced ARR, disability progression at 2 years vs placebo
- Safety concerns: herpesvirus infection, elevation in LFTs


**Teriflunomide**
- Route of administration: oral daily
- Proposed MOA: reversible inhibitor of dihydroorotate dehydrogenase
- Phase III trial demonstrated reduced ARR, disability progression vs placebo
- Evaluation as combination therapy
- Safety concerns: elevation in LFTs, neutropenia, rhabdomyolysis

Self-Assessment Questions

- T/F Multiple sclerosis is thought to be an autoimmune demyelinating disease of the central nervous system.
- Which of the following is not a disease modifying therapy? a) fingolimod b) glatiramer c) dalfampridine d) natalizumab
- Which of the following medications is an alpha-4 integrin antagonist? a) fingolimod b) glatiramer c) interferon beta 1-b d) natalizumab
- Upon treatment initiation with fingolimod, the patient should be observed in a clinical setting for 6 hours after the first dose due to: a) macular edema b) bradycardia c) infection d) reduced respiratory function
- T/F A laboratory test to detect JCV DNA in the blood may be used to predict the risk of progressive multifocal leukoencephalopathy (PML).

Detailed References

Detailed References