Multiple Sclerosis, Remyelination and Axonal Degeneration

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Disclosures

• I have research grants from the National MS Society.

• In the past three years I have consulted with Teva Neurosciences, Genentech, and Biogen Idec
Saint Lydwina of Schiedam
(1380-1433)
Robert Carswell (1793-1857)
1st Description of MS Pathology 1838
Jean-Martin Charcot (1825-1883)
1st Description of Clinical Features
Joseph Babinski (1857-1932)
MS is a Demyelinating Disease
MS and Axonal Injury

“Dying Back Axonopathy” in MS

Trapp and Stys, Lancet Neuro 8: 280–91, 2009
MS Involves Inflammation and Neurodegeneration

Inflammation

Neurodegeneration

Relapsing MS

Progressive MS
Acute Demyelination

Chronic Demyelination

Waxman, Nat Rev Neurosci 2006; 7:932-941
Acute inflammatory attack

- T cells release cytokines following antigen encounter

Axonal mitochondria

- ATP production
  - Energy deficit
  - Loss of cell homeostasis
  - Impaired axonal transport

- ATP synthase
  - ADP + Pi → ATP

- ETC
  - I
  - II
  - III
  - IV

- NO
  - NO + O₂⁻ → ONOO⁻

- Uniporter
  - ↑Ca²⁺

- CypD
- PTP

- CytC

Progressive/chronic demyelination

- ↑ voltage-gated Na⁺ channel expression along axon
- ↑ metabolic demand
- Reversal of axonal membrane Na⁺/Ca²⁺ transporter

PTP opening

- Solute influx
- Mitochondrial membrane potential dissipation
- Mitochondrial swelling and rupture
- Cytochrome C release

Acute axotomy and axonal degeneration

Microglia

- TNF-β
- IFN-γ

↑NO

↑iNOS

↑glutamate

↑Ca²⁺

↓ ATP production
Consequences of Chronic Demyelination

• Heat sensitivity and nerve fiber fatigue
• Chronic conduction block
• Promotes axonal degeneration
  – Increased axoplasmic Ca$^{2+}$
  – ATP depletion and mitochondrial dysfunction
  – Loss of trophic factors
  – Increased sensitivity to reactive oxygen species
Charcot-Marie-Tooth Disease
Type 1

- Genetic disorder of peripheral myelin
- Chronic demyelination
- Eventually results in axonal degeneration
MS and Shadow Plaques
Spontaneous Remyelination Occurs in MS

- Part of natural repair process
- “Shadow plaques”
- Why does remyelination fail?
Remyelinating Oligodendrocytes in MS Chronic Lesions

OPC in Chronic MS Lesions

Approaches to Promoting Remyelination

• Injection of OPC into brain
• Blocking inhibitors
  – Anti-LINGO antibody
  – Enzymes that inhibit HA production
• Stimulating OPC
  – IgM antibody
  – Thyromimetic drugs
OPC Injections

Windman MS et al, Nat Med 2004; 10:93-97
Anti-LINGO Promotes Remyelination in EON

Mi et al, Ann Neurol 2009; 65:304-315
Human Monoclonal IgM Promotes Remyelination

+ IgM

+ IgM

+ Vehicle

Thyroxine (T4) and Triiodothyronine (T3)
T3 Alters Expression of Multiple Genes
Thyroid Hormone and Myelination

- Thyroid hormone induces myelination during development and promotes differentiation of OPC into T3.
Drug Mimetic of Thyroid Hormone

- Sobetirome has preferential bind of TRβ
- Has minimal effects on heart and bone metabolism
- Phase 1 trial in humans for lowering cholesterol

[Chemical structures of T3 and Sobetirome]
Sobetirome differentiates OPCs
Klf9 induction in OPCs and whole brain

* $p < 0.05$
Lysolecithin Model

• Lysolecithin induces focal demyelination when injected into brain and spinal cord
• Spontaneous remyelination occurs via differentiation of OPC into oligodendrocytes
• Treatments can be assessed for ability to accelerate remyelination
Injection coordinates for corpus callosum
Lysolecithin Lesion
EM Images of Lesions

Day 10 Lesion  Day 15 Lesion  Control
BlackGold Staining for Lesion Size
Experimental Design

- Inject Lysolecithin in brain
- Start T3/sobetiro me/vehicle injections
- Euthanize

<table>
<thead>
<tr>
<th>Time Course (Days)</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>15</td>
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</table>
Lesion Volume Summary

![Graph showing lesion volume changes over time for different treatments.

- **Lesion volumes (mm$^3$)** range from 0.00 to 0.10 on the y-axis.
- **Time course (Days)** range from 5 to 15 on the x-axis.

- **Vehicle** (solid square line)
- **T3** (solid triangle line)
- **Sobetirome** (dashed square line)

The graph illustrates the increase in lesion volume from day 5 to day 12 for all treatments, followed by a significant decrease from day 12 to day 15, with Sobetirome showing the most rapid decline.
Scatter Plots of Lesion Volumes
11.75 T MTR and Histologic Lesions
MTR of Lesion

NAWM  lysolecithin-induced lesion  NAWM

MTR

Distance (mm)
MTR in lesion at Day 5 and 12

Day 5

Day 12

Distance (mm)
Experimental Autoimmune Encephalomyelitis
EAE Histologic Effects

Vehicle

Sobetirome
Summary

- Promoting remyelination in MS may be critical to preventing progressive axonal loss.
- Stimulating OPC differentiation may be an effective way of inducing remyelination.
- A thyromimetic drugs are a promising agents for promoting remyelination in MS.
The cost of multiple sclerosis drugs in the US and the pharmaceutical industry

Too big to fail?

ABSTRACT

**Objective:** To examine the pricing trajectories in the United States of disease-modifying therapies (DMT) for multiple sclerosis (MS) over the last 20 years and assess the influences on rising prices.

**Methods:** We estimated the trend in annual drug costs for 9 DMTs using published drug pricing data from 1993 to 2013. We compared changes in DMT costs to general and prescription drug inflation during the same period. We also compared the cost trajectories for first-generation MS DMTs interferon (IFN)-β-1b, IFN-β-1a IM, and glatiramer acetate with contemporaneously approved biologic tumor necrosis factor (TNF) inhibitors.

**Results:** First-generation DMTs, originally costing $8,000 to $11,000, now cost about $60,000 per year. Costs for these agents have increased annually at rates 5 to 7 times higher than prescription drug inflation. Newer DMTs commonly entered the market with a cost 25%-60% higher than existing DMTs. Significant increases in the cost trajectory of the first-generation DMTs occurred following the Food and Drug Administration approvals of IFN-β-1a SC (2002) and natalizumab (reintroduced 2006) and remained high following introduction of fingolimod (2010). Similar changes did not occur with TNF inhibitor biologics during these time intervals. DMT costs in the United States currently are 2 to 3 times higher than in other comparable countries.

**Conclusions:** MS DMT costs have accelerated at rates well beyond inflation and substantially above rates observed for drugs in a similar biologic class. There is an urgent need for clinicians, payers, and manufacturers in the United States to confront the soaring costs of DMTs. Neurology® 2015;84:2185-2192
MS Disease Modifying Therapies 1870-1992

• ACTH approved in 1970 for treating MS relapses

• Trial of cyclosporin A in “chronic progressive MS” in late 1980s not approved by FDA despite positive results

• “Best way to ruin an academic career is to do a MS clinical trial”
FDA-Approved Disease Modifying Therapies (DMTs) for Relapsing MS

- 1993 Interferon beta-1b (Betaseron)
- 1996 Interferon beta-1a (Avonex)
- 1997 Glatiramer acetate (Copaxone)
- 2000 Mitoxantrone (Novantrone)*
- 2002 Interferon beta-1a (Rebif)
- 2006 Natalizumab (Tysabri)
- 2009 Interferon beta-1b (Extavia, identical to Betaseron)
- 2010 Fingolimod (Gilenya)
- 2012 Teriflunomide (Aubagio)
- 2013 Dimethyl Fumarate (Tecfidera)
- 2015 Alemtuzumab (Lemtrada)
Treatment Goals for Relapsing MS 2015

• Patient centered care
• Initiate treatment early
• Aim for “Disease activity free”
  – No clinical relapses
  – No worsening of disability
  – No evidence of MS disease activity on MRI
Annual Average Wholesale Price of MS Biologics
December 2013

- Betaseron/Extavia: $61,529/$51,427
- Avonex: $62,394
- Rebif: $66,394
- Copaxone: $59,158
- Tysabri: $64,233
- Gilenya: $63,806
- Aubagio: $57,553
- Tecfidera: $63,315
## Cumulative Changes

<table>
<thead>
<tr>
<th></th>
<th>US Approval Date</th>
<th>Approval Date Annual Cost</th>
<th>2013 Annual Cost*</th>
<th>Cumulative % Increase</th>
<th>Annualized Increase</th>
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<tbody>
<tr>
<td>Betaseron</td>
<td>07/23/1993</td>
<td>$10,036</td>
<td>$58,511</td>
<td>483%</td>
<td>24.2%</td>
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<tr>
<td>Avonex</td>
<td>05/17/1996</td>
<td>$8,052</td>
<td>$53,324</td>
<td>562%</td>
<td>32.8%</td>
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<tr>
<td>Copaxone</td>
<td>12/20/1996</td>
<td>$8,178</td>
<td>$58,348</td>
<td>613%</td>
<td>37.1%</td>
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<tr>
<td>Rebif</td>
<td>3/7/2002</td>
<td>$14,088</td>
<td>$54,026</td>
<td>283%</td>
<td>25.0%</td>
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<tr>
<td>Tysabri</td>
<td>11/23/2004</td>
<td>$23,861</td>
<td>$55,934</td>
<td>134%</td>
<td>15.6%</td>
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<tr>
<td>Extavia</td>
<td>08/14/2009</td>
<td>$32,466</td>
<td>$48,437</td>
<td>49%</td>
<td>12.7%</td>
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<td>Gilenya</td>
<td>09/21/2010</td>
<td>$50,080</td>
<td>$62,932</td>
<td>26%</td>
<td>9.2%</td>
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<tr>
<td>Aubagio</td>
<td>09/12/2012</td>
<td>$46,998</td>
<td>$51,651</td>
<td>10%</td>
<td>12.4%</td>
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<tr>
<td>Tecfidera</td>
<td>03/27/2013</td>
<td>$57,024</td>
<td>$57,024</td>
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*July 2013
Quarterly Cost (AWP)

| Product      | Pre-Post Difference
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<tr>
<td>AVONEX</td>
<td>3.1%*</td>
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<tr>
<td>BETASERON</td>
<td>3.3%*</td>
</tr>
<tr>
<td>COPAXONE</td>
<td>3.1%*</td>
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<tr>
<td>ENBREL</td>
<td>No sig. increase</td>
</tr>
<tr>
<td>REMICADE</td>
<td>0.76%*</td>
</tr>
<tr>
<td>HUMIRA</td>
<td>2.0%*</td>
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* p<0.05

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**Legend:**
- AVONEX
- BETASERON
- COPAXONE
- ENBREL
- REMICADE
- HUMIRA

**Timeline Events:**
- REBIF launch (Q1 2002)
- TYSABRI launch (Q2 2006)
- GILENYA launch (Q3 2010)

**Graph:**
- Median Monthly AWP
- Quarter (Year)
<table>
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<tr>
<th>DMT</th>
<th>Medicaid</th>
<th>US VA</th>
<th>Canada</th>
<th>Australia</th>
<th>UK</th>
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<td>$36,500</td>
<td>$33,700</td>
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<td>$22,500</td>
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<tr>
<td>Tecfidera</td>
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<td>$40,700</td>
<td>$21,500</td>
<td>$22,600</td>
<td>$29,700</td>
</tr>
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What does Pharmaceutical Industry Say?

- No one pays average whole sale price
- Co-pay programs protect patients
- “We give away lots of drugs for free”
- High cost of development of new therapies
- Restricting prices will stifle innovation
Why Should We Care?

- Co-pay costs to our patients
- Restricted access to therapies by insurance companies and other insurance actions is response to high cost of drugs
- *Primum non nocere*
What Can Be Done?

- Start advocating for lower prices and end to shadow pricing
- Allow Medicare to negotiate prices of drugs
- Develop treatment guidelines that take into account cost-benefits of drugs
- Allow FDA to recommend pricing based on magnitude of effect
- Allow Patient-Centered Outcomes Research Institute to fund cost-benefit studies
- Ask AAN, ACTRIMS, CMSC and NMSS to advocate for lower costs as well as open access
Questions?