Current Advances In Multiple Sclerosis

Dr. Michael Namaka BSc Pharm; MSc Pharm; Ph D; EPP
Professor; Neuro-immunologist
College of Pharmacy and Medicine (Anesthesia & Rehab Medicine)
University of Manitoba
Educational Objectives

At the end of this section, you will be able to:

- Describe the pathophysiology involved in Multiple Sclerosis (MS).
- Understand the contributing factors associated with MS.
- Understand the diagnostic tests used in the diagnosis of MS.
- Describe the hallmark clinical presentation of MS.
- Identify the classification of the various types of MS.
- Understand the immuno-modulatory treatment of MS.
- Addressing non-conventional treatment approaches to MS.
- Recognizing the realistic treatment outcomes.
Canadian Statistics of Multiple Sclerosis

- 1:500 to 1:1000 (2-3 patients diagnosed every day)
- Canadian population: ~31 Million
- 30,000 to 60,000 MS new patients/year
- Costs: 1.6 million per patient
- 2000-2001: 1 Billion per year Canadian
Contributing Factors

- Race (Caucasian)
- Age (25 and 38)
- Sex: male vs female
- Infection (Epstein-Barr, HHV6, Chlamydia pneumoniae etc)
- Injury
- Genetics
- Geography (less 15 yrs of age acquires susceptibility of the new region but >15 will not affect susceptibility)
- Diet/Sunshine
Susceptibility to MS
Sex, Age and Ethnicity

Sex
Sex ratio: 3F/1M

Age of onset
30-40yrs

Ethnicity
High Risk
Northern Europeans, US Caucasians, Canadians

Low Risk
Australians, South African whites, Southern Europeans
African blacks, Orientals

Genetic factors

- In a first degree family relative of patient with MS, absolute risk of MS is: < 5% which equates to 20 to 40 times increased risk compared to the general population.

- In monozygotic twins: concordance rate for MS is higher (31%) than in dizygotic twins (5%). As such since not 100% concordance rates in identical twins, this is proof that genetics alone is not solely responsible for this disease.

- Presence of HLA-DR2 allele increases the risk of MS.

- MS is not a hereditary disease BUT patients may have a genetic predisposition for the disease.

Theories of MS

- Infectious Theory
  (Measles, Mumps, Rubella, EBV, HHV-6)
- Molecular Mimicry
- Autoimmune Disease
Autoimmune Disease

T Cell

T Cell Receptor

Antigen

Class II MHC

Antigen Presenting Cells: Macrophage/Monocyte/Dendritic Cells

CD28

CD80 = B7.1
Imbalance of the Immune System

Th 0

Th 1

Th 2

Pro-Inflammatory

Anti-Inflammatory
T-CELL BALANCE

**Th1**
(Inflammatory)
- IL-12
- IL-2
- IL-6
- IFN-γ
- TNF-α

**Th2 (Th3)**
(Protective)
- IL-4
- IL-10
- TGF-β

**IMMUNE DEVIATION**
A Model of MS Immunology

1. Activation
   - Th1

2. Adhesion

3. Invasion

4. Reactivation
   - BBB
   - tissue damage
   - CNS

Periphery
Re-Activation of Immune System

Antigen presenting cells (macrophages, monocytes, dendritic cells)

CD4+ T lymphocyte

B lymphocyte

Neutrophil

Large granular lymphocyte

Cytotoxic T cell

Macrophage

Antigen

Cytokines

Cytokines

RE-ACTIVATION

Immune Cells Orchestrates Myelin Damage (White Matter Disease)

- Nerve Impulses
- Damaged Myelin
Exposed De-myelinated Axon
Physical Disability

- Median time to requiring cane/crutch: 15 years\(^1,2\)

- Median time to wheelchair confinement: 25 years\(^3\)

---

What Are the Current Opinions Regarding Treatment Effects?
A Theoretical Model

Clinical Diagnostic Tools
Examination of the Cerebro-spinal Fluid

- Oligoclonal IgG bands
  [in > 95% patients with Clinically Definite MS (CDMS)]
- Severe Headaches post-CSF Sample

Mc Donald I. Diagnostic methods and investigation in Multiple Sclerosis in Mc Alpine’s Multiple Sclerosis. 3rd ed London: Churchill Livingstone 1998.
MRI
T2 Weighted Imaging
<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clinically Isolated Syndrome</td>
</tr>
<tr>
<td>1</td>
<td>First Clinical Attack</td>
</tr>
<tr>
<td>2</td>
<td>Relapsing Remitting</td>
</tr>
<tr>
<td>3</td>
<td>Secondary Progressive</td>
</tr>
<tr>
<td>4</td>
<td>Demyelination</td>
</tr>
<tr>
<td>5</td>
<td>Axonal Loss</td>
</tr>
<tr>
<td>6</td>
<td>Clinical Threshold</td>
</tr>
</tbody>
</table>

**Legend:**
- MS: Multiple Sclerosis
- CL: Clinical
- P: Pathological

**Figures:**
- [Graph] showing the progression of MS with respect to time and clinical symptoms.
MS-Induced Symptoms

Fatigue and weakness
bladder control
neuropathic pain
cognitive defects
optic neuritis
sexual dysfunction
ataxia
depression

PERCENTAGE OF ALL PATIENTS

O'Connor, P (2002) Toronto: Key Porter N/A:N/A
Various Clinical Types of MS

Relapsing-remitting MS

80-85 %

Secondary progressive MS

80 % of RRMS

Primary progressive MS

10 %

Progressive relapsing MS

< 5 %

## Clinical Types of MS

<table>
<thead>
<tr>
<th>Type of MS(^a)</th>
<th>Incidence</th>
<th>Characteristics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-remitting (RRMS)</td>
<td>85-90% of cases at onset</td>
<td>Relapses with stable neurological disability between episodes</td>
<td>DMT should be initiated upon diagnosis</td>
</tr>
<tr>
<td>Primary progressive (PPMS)</td>
<td>10-15% of cases at onset</td>
<td>Steadily increasing objectively documented neurologic disability independent on relapses from disease onset</td>
<td>DMT has no effect, except if relapses occur</td>
</tr>
<tr>
<td>Secondary progressive (SPMS)</td>
<td>65% of patients with RRMS after 15-20 yrs(^{19})</td>
<td>Progressive course following an initial relapsing-remitting course</td>
<td>DMT has no effect, except if relapses occur</td>
</tr>
</tbody>
</table>
Clinical Investigations

Investigations are guided by clinical presentation and may be more extensive or limited depending on how clearly the history, physical examination and MRI indicate MS.

- Complete blood count (CBC) with differential
- Liver function tests (ALT, AST)
- Antinuclear antibody (ANA), rheumatoid factor (RF) and C-reactive protein (CRP)
- Thyroid-stimulating hormone (TSH)
- Vitamin D levels
- Vitamin B12 (deficiency can mimic MS symptoms)
- MRI ± gadolinium to identify and quantify lesions in brain and/or spinal cord
- Cerebrospinal fluid exam for oligoclonal banding and visual evoked potential, to support the diagnosis
- Complete neurologic exam
McDonald Clinical Criteria: RRMS-Definitive Diagnosis

- Clinical attack(s) +/- MRI must show dissemination in time and space.

- 2 clinical attacks where each attack lasted greater than 24 hours. Dissemination in time (at least 30 days apart).

- Does not require a + MRI
MRI Criteria: RRMS
Definitive Diagnosis

✓ ≥1 Gad+ or 9 Peri-ventricular lesions
✓ ≥1 Infratentorial (contains cerebellum that controls motor function) lesion
✓ ≥1 Juxtacortical (spans between grey and white matter) lesion
✓ ≥1 Spinal Cord lesion

Pt must have 3 out of 4 criteria for MRI to fulfill dissemination in space criteria

OR

MRI criteria depicting dissemination in time + 1 clinical attack.
 Clinically Isolated Syndrome (CIS)

✓ 1 attack that lasted greater than 24 hours EVEN with a +/- ve MRI that doesn’t fulfill McDonald criteria in regard to dissemination in time and/or space

✓ NO Definitive Diagnosis of MS
2 attacks where each attack lasts greater than 24 hours and is separated in space by at least 30 days with a positive MRI that meets McDonald criteria within the past 2 years.
SECTION II:
Immunomodulatory Treatment of RRMS
Immunomodulatory (IMA) Therapy for RRMS (20K/YR)

- Interferon beta 1a 30 µg IM once weekly
- Interferon beta 1b 8 M.U. sc EOD
- Interferon beta 1a 44µg sc tiw
- Glatiramer acetate 20 mg sc qd
T-CELL BALANCE SHIFT

**Th1**
(Inflammatory)
- IL-12
- IL-2
- IL-6
- IFN-γ
- TNF-β

**Th2 (Th3)**
(Protective)
- IL-4
- IL-10
- TGF-β

IMMUNOMODULATORY AGENTS SUPPRESS THE IMMUNE SYSTEM INFLAMMATORY RESPONSE
TREATMENT SELECTION
Interferon beta 1a

✓ 30mcg intramuscular (IM) once weekly
✓ No dosage titration
✓ Flu-like symptoms (muscle aches, headache, malaise, fever and chills)
✓ LFT’s (ALT,AST >3 x ULN)
✓ Injection site reactions
✓ Lowest incidence of neutralizing antibodies (NABs) .....2 - 5%
✓ ~30% reduction in annualized relapse rate (ARR)-Biogen
Plegridy™: Long Acting Avonex

✓ Peginterferon beta-1a derived from interferon beta-1a (125mcg/0.5 ml)

✓ Dosed once every 2 weeks via subcutaneous injection for RRMS

✓ Pegylation process is designed to extend the protein’s half-life and prolong its exposure in the body

✓ Results of Phase 3 trial announced March 21st, 2013 – ARR 36% -- Approval in EU (July 2014) and USA (Aug 2014) – Biogen

✓ AE’s: Joint pain; muscle pain; injection site itching; injection site pain
Interferon beta 1a

- 44mcg SC TIW
- Dosage titration over 3-6 weeks
- Flu-like symptoms
- Depression
- LFT’s (ALT, AST >3 x ULN)
- Injection site reactions
- Alopecia
- NAB’s ~20-30%
- ~30% reduction in relapse rate - Serono
Interferon beta 1b

✓ 8 MIU SC EOD
✓ dosage titration over 2-3 weeks
✓ Flu-like symptoms
✓ Depression
✓ LFT’s (ALT, AST > 3 x ULN)
✓ Injection site reactions
✓ Indicated for RRMS and SPMS still experiencing relapses
✓ NAB’s ~20-30 %
✓ ~30% reduction in ARR - Bayer Schering & Novartis
Glatiramer Acetate

- synthetic polypeptides containing 4 naturally occurring amino acids: L-glutamic acid; L-alanine; L-tyrosine; L-Lysine
- 20 mg SC OD
- No dosage titration required
- Injection site reactions
- ~10% of patients experience a reversible pseudo-heart attack (chest tightness, SOB, palpitations, sweating)
- <30% ARR – slightly less ARR than interferon products
- NAB’s not present
Current Unmet Need for Efficacy

Percent Reduction in Annualized Relapse Rate

Avonex
Rebif
Betaseron
Copaxone

Data is from Canadian Product Monographs and is not based on a head to head trial

Avonex is a registered trademark of Biogen Idec MA. Inc.
Betaseron is a registered trademark of Berlex Canada Inc.
Rebif is a registered trademark of Serono Canada Inc.
Copaxone is a registered trademark of Teva Neuroscience
Treatments are not a cure
At best, they slow progression of disease (~30% ARR)
Decrease the number, severity and duration of relapses
Increase quality of life
NAB’s vs Clinical Efficacy
New Advances in Immunomodulatory Therapy
30-40 K/YR
Next Generation Treatments: Natalizumab

Natalizumab is a recombinant humanized monoclonal antibody selective for the α4β1 subunit of human integrin, blocking its ability to interact with its receptor, Vascular Cell Adhesion Molecule (VCAM-1).

It is administered by IV infusion, 300 mg once every 4 weeks. In the phase I and II trials, natalizumab was dosed by weight, then moved to a fixed dose of 300mg in the Phase III trials. - Biogen
Proposed Mechanism of Action

1. Leukocyte migration from blood to tissue

2. Leukocyte priming and activation

VCAM-1 = vascular cell adhesion molecule-1.
Indications

• *Natalizumab is indicated as monotherapy* (i.e. single disease-modifying agent) for the treatment of patients with RRMS:
  – to reduce the frequency of clinical exacerbations,
  – to decrease the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans and
  – to delay the progression of physical disability.

• Generally *recommended as 2\textsuperscript{nd}, 3\textsuperscript{rd} or 4\textsuperscript{th} line treatment* for RRMS patients who have had an inadequate response to, or are unable to tolerate, other therapies.
Natalizumab: Clinical Trials Summary

- TYSABRI exposure in clinical trial programs
  - 4,611 patient-years in MS and Crohn’s disease trials
  - 2,910 patient-years in MS trials

- Three Key RRMS clinical trials
  - 942 patients enrolled in the AFFIRM monotherapy trial
  - 1,171 patients enrolled in the SENTINEL add-on therapy trial (TYSABRI + AVONEX)
  - TYSABRI 300 mg or placebo intravenously (IV) every 4 weeks
  - Duration of both phase 3 studies was 116 weeks
**AFFIRM: Summary of Clinical Efficacy**

- Natalizumab has significant effects on clinical end points
  - Impact on relapses
    - **68% relative reduction in annualized relapse rate (ARR)**
    - Impact seen early and maintained over time
  - Impact on disability progression
    - **42% reduction in risk of sustained change in EDSS (12 weeks)**
    - **54% reduction in risk of sustained change in EDSS (24 weeks)**
  - Significant **slowing of brain atrophy** in the second year
  - Significant **improvement in cognitive function (PASAT-3)**

Summary of Efficacy on MRI Measures

- Natalizumab significantly reduces inflammation and lesion load
  - Significant reductions in number of:
    - Gd+ lesions: 92% ↓
    - T2-hyperintense lesions: 83% ↓
    - T1-hypointense lesions: 76% ↓
  - Significant reduction in burden of disease as measured by T2 and T1 lesion volume
  - Significantly fewer lesions in the TYSABRI group compared to the placebo group

Immunogenicity

• In the monotherapy trial, **6% of patients** developed persistent neutralizing antibodies (NABs) to Natalizumab
  – This occurred within the first 6 months in the majority of patients
  – Usually occurred in the presence of infusion reactions

• Persistent neutralizing antibody positivity was associated with:
  – Reduced efficacy
  – Increased incidence of infusion-related reactions and hypersensitivity reactions

Pre-Market Safety Surveillance
## Common AEs 
**≥5% in Placebo or Natalizumab Groups**

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Placebo (n=312)</th>
<th>Natalizumab (n=627)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Any Event</td>
<td>298 (95.5)</td>
<td>583 (93.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>89 (28.5)</td>
<td>201 (32.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>97 (31.1)</td>
<td>182 (29.0)</td>
</tr>
<tr>
<td>MS Relapse</td>
<td>162 (51.9)</td>
<td>173 (27.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55 (17.6)</td>
<td>147 (23.4)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>55 (17.6)</td>
<td>107 (17.1)</td>
</tr>
<tr>
<td>Influenza</td>
<td>49 (15.7)</td>
<td>99 (15.8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>34 (10.9)</td>
<td>97 (15.5)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>39 (12.5)</td>
<td>84 (13.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>38 (12.2)</td>
<td>83 (13.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (12.2)</td>
<td>81 (12.9)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>42 (13.5)</td>
<td>78 (12.4)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>33 (10.6)</td>
<td>76 (12.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>32 (10.3)</td>
<td>75 (12.0)</td>
</tr>
</tbody>
</table>

*Indicates ≥2.0% higher in natalizumab group.*
Special Safety Considerations
Post-Market Surveillance

- Progressive Multifocal Leukoencephalopathy (PML)
- Sentinel Study (Avonex + Tysabri) D/C
PML cont’d

✓ Attacks oligodendrocytes of CNS white matter, leading to myelin loss in cerebral hemispheres, cerebellum (motor), or brain stem (breathing), causing severe disability or death

✓ 3 cases identified (MS n=2 or Crohn’s n=1)

✓ MS cases Avonex + Tysabri

✓ **Voluntary withdrawal Feb 2005**

✓ **Reintroduced to Market Jan/Feb 2007**
Overview of PML

- PML is an acquired demyelinating disease of the central nervous system (CNS)
- **Present Estimated Risk 5.05:1000** as of Feb 2013 (*JAMA Neurology Aug 5th, 2013*)
- Caused by JC virus, a human polyomavirus
  - Lytic infection of oligodendrocytes
- Primarily affects immunocompromised individuals

Natalizumab Coverage in MB

- Confirmed diagnosis of RRMS. Not indicated for SPMS or PPMS
- >18 years of age
- EDSS < or = 5
- Failed treatment with adequate trial (6 months or longer) of both classes of IMA’s (interferon beta and glatiramir acetate) or contraindications/intolerance to their treatment
Fingolimod is a sphingosine-1-phosphate receptor agonist that blocks the egress of activated, presumably autoimmune lymphocytes into the circulating bloodstream from lymphoid tissues. Novartis
Fingolimod: Dosage and Administration

- One 0.5 mg capsule taken orally once daily, with or without food
- No dose adjustments necessary based on gender or ethnicity or in patients with mild to moderate hepatic impairment
- Should be used with caution in patients with:
  - Severe renal impairment
  - Mild to moderate hepatic impairment
  - Age ≥65 years
  - Diabetes

FREEDOMS
FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

Ludwig Kappos, M.D., Ernst-Wilhelm Radue, M.D., Paul O’Connor, M.D., Chris Polman, M.D., Reinhard Hohlfeld, M.D., Peter Calabresi, M.D., Krzysztof Selmaj, M.D., Catherine Agoropoulou, Ph.D., Malgorzata Leyk, Ph.D., Lixin Zhang-Auberson, M.D., Ph.D., and Pascale Burtin, M.D., Ph.D., for the FREEDOMS Study Group*
TRANSFORMS – Primary Endpoint: ARR~ 50% overall reduction

ARR ratio 0.5 mg vs. IFN β-1a IM = 0.48, p<0.001

Modified ITT population: all patients who underwent randomization and received one dose of a study drug
Negative binomial regression model adjusted for treatment group, country, baseline number of relapses in previous 2 years and baseline disability score; bars represent the 95% CI
TRANSFORMS – Percentage of Relapse-Free Patients and Time to First Relapse

**Graph Description:**
- The graph illustrates the proportion of relapse-free patients over time for two treatment groups: Fingolimod 0.5 mg (n=429) and IFNβ-1a IM (n=431).
- The KM (Kaplan-Meier) estimate for Fingolimod is 83%, while for IFNβ-1a IM it is 69%.
- The p-value indicates a significant difference between the two treatments, with p<0.001 vs. IFNβ-1a.

**Legend:**
- Fingolimod 0.5 mg (n=429)
- IFNβ-1a IM (n=431)

**Modified ITT population:** all patients who underwent randomization and received one dose of a study drug.
TRANSFORMS – MRI Lesion Activity

Number of new and enlarged T2 lesions over 12 months*

- IFNβ-1a IM (n=361) mean lesion number: 2.6 (0 to 63)
- Fingolimod 0.5 mg (n=372) mean lesion number: 1.7 (0 to 38)

Comparison:
- p=0.004* vs IFN β-1a
- 35% reduction

Number of Gd+ T1 lesions at 12 months**

- IFNβ-1a IM (n=354) mean lesion number: 0.51 (0 to 24)
- Fingolimod 0.5 mg (n=374) mean lesion number: 0.23 (0 to 11)

Comparison:
- p<0.001† vs IFN β-1a
- 55% reduction

*Analysis performed using a negative binomial regression model adjusted for treatment group, country, baseline number of relapses and baseline EDSS;
**analysis performed using rank ANCOVA adjusted for treatment group, country and number of lesions at baseline; ITT population with available MRI scans
Fingolimod AE Experience

<table>
<thead>
<tr>
<th>Event, N (%)</th>
<th>Phase III placebo-controlled</th>
<th>All studies*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Fingolimod 0.5 mg</td>
</tr>
<tr>
<td>Number of patients</td>
<td>418</td>
<td>425</td>
</tr>
<tr>
<td>Exposure (pt-years)</td>
<td>703.2</td>
<td>750.2</td>
</tr>
<tr>
<td>At least 1 AE</td>
<td>387 (92.6)</td>
<td>414 (94.4)</td>
</tr>
<tr>
<td>AE leading to study drug discontinuation*</td>
<td>32 (7.7)</td>
<td>32 (7.5)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>56 (13.4)</td>
<td>43 (10.1)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event

*Includes all available data from Phase II and Phase III core and extension studies (2201, 2201E1, 2301, 2301E1, 2302 and 2302E1) with treatment durations varying between 1 to 6 years – data cut-off from 120-day safety update; *includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings)
Precautions Related to Hepatic Effects of Fingolimod

- Fingolimod may increase liver transaminases

- Obtain transaminase and bilirubin levels prior to initiating treatment, then **once per month x 3 months** then **every 3 months during the first year of treatment** and **annual or bi-annually** thereafter in the absence of symptoms or when symptoms suggestive of hepatic injury develop

Precautions Related to Pregnancy/Reproduction

- Based on animal data, fingolimod is potentially teratogenic

- Women of childbearing potential should be counselled on the potential for serious risk to the fetus and the need for effective contraception during, and for 2 months after treatment with fingolimod

- Available data do not suggest that fingolimod would be associated with an increased risk of male-mediated fetal toxicity or reduced fertility
Safety Conclusions

• Extensively studied: >9600 patient-years in >2600 MS patients with comprehensive multi-organ safety assessments in all studies

• Fingolimod 0.5 mg selected as the proposed dose
  – Better overall safety/tolerability than 1.25 mg dose with no differences in efficacy
  – Overall incidence of serious AEs and AEs leading to drug discontinuation similar between 0.5 mg dose and comparator (placebo and IFNβ-1a IM)

• Dose-dependent effects include transient heart rate reduction on treatment initiation, small increase in blood pressure, liver enzyme elevations, pneumonia, macular edema (fluid and protein deposits in retina of the eye)

• Data in pregnancy are limited – contraception recommended in females of child-bearing potential

• Comprehensive risk management strategy proposed to continue to further understand and manage safety profile
Risk/Benefit for Every 1000 MS Patients Treated with 0.5 mg Fingolimod Compared to Placebo over 2 Years

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefit</strong></td>
<td></td>
</tr>
<tr>
<td>Relapses avoided (44%)</td>
<td>440</td>
</tr>
<tr>
<td>Increase in patients free of relapse</td>
<td>233</td>
</tr>
<tr>
<td>Increase in patients without disability progression</td>
<td>56</td>
</tr>
<tr>
<td>Macular edema</td>
<td>3*</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
</tr>
<tr>
<td>5-fold elevation of hepatic transaminases</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
</tr>
</tbody>
</table>

*No cases in Phase III (FREEDOMS) placebo-controlled study, data from overall program
Summary

- Fingolimod 0.5 mg is highly effective in RRMS
  - In a comparative 1-year study vs. a standard of care (IFN beta-1a IM), significant reductions in relapse rate (44-52%) and new MRI lesions (55%) were observed
  - In a placebo-controlled 2-year study, significant reductions in relapse rate, disability progression and new MRI lesions were observed
- There is over 9600 patient-years’ experience with fingolimod
- Fingolimod was generally well tolerated over short and long term
  - Most frequent AEs are headache and influenza viral infection
- Known pharmacodynamic effects include:
  - Asymptomatic heart rate reduction upon initiation
  - Reversible redistribution of lymphocytes
- As with other DMTs, careful initial selection of patients and monitoring following treatment is required: Medication Adherence is Key
- However: 49 year old male patient with RRMS treated for 4 years with 0.5mg per day developed PML Feb 17th, 2015 and tested positive for the JC virus. Detected by routine MRI. Pt did not die.

DMT = disease-modifying treatment
Laquinimod: Phase 3 Trials

- Quinolone-3-Carboxamide
- **Oral agent** induces brain derived neurotrophic factor (BDNF) [0.6mg and 1.2 mg doses being evaluated]
- Induces anti-inflammatory antigen presenting cells that down regulate inflammatory Th1 and Th17 immune cells
- Down regulates nitric oxide production in astrocytes.
- Transient Transaminase Elevation (LF) monitoring required.
- Failed to get EU approval Jan 2014 due to inability to show significant decrease in ARR (23% compared to placebo) - NERVENTRA® (laquinimod) - Teva
Teriflunomide: AUBAGIO®

- Inhibits mitochondrial dihydroorotate dehydrogenase and enzyme used for the de novo synthesis of pyrimidine nucleotides in proliferating cells (T cell proliferation inhibitor)
- Oral: Approved Nov 20th, 2013 in Canada for RRMS [7 mg or 14 mg once daily]
- 35% ARR compared to placebo on 14mg/day + 59% Reduction in Gd enhancing T1 lesions
- Alopecia, diarrhea, increased LFTs, headache
- Approved in US, EU, Argentina, Chile, South Korea and Mexico
- Risk of Tuberculosis – pre-test before starting with purified protein derivative
- 10 day extended half-life----Genzyme
- Leflunomide RA /Psoriasis drug absolute contraindication
Tecfidera®
Dimethyl Fumarate (BG12)

- **Oral:** Approved in Canada April 9th, 2013 (Phase 3-DEFINE and CONFIRM studies). Also approved in EU, Australia

- **Inhibits immune cells** and molecules with anti-oxidant properties – inhibits Nrf2 pathway (neuroprotective)

- **2x120mg capsules twice daily** with or without food.

- Flushing, diarrhea, nausea and upper abdominal pain

- Used in RRMS patients with a contraindication to, or who have failed to respond adequately to at least one interferon formulation and glatiramer acetate

- **53% ARR; 90% decrease in Gd+ lesions, 38% reduction in EDSS**

- Alternative for those who can’t take Fingolimod, Teriflunomide or Injections - Biogen
Alemtuzumab - Lemtrada®/Campath®

- Monoclonal Antibody binds to CD52 on lymphocytes targeting them for destruction
- Indicated for RRMS patients who have an inadequate response to interferons or other disease modifying therapies.
- Lemtrada 12 mg has a dosing and administration schedule of two annual treatment courses. The first treatment course of Lemtrada is administered via intravenous infusion on five consecutive days, and the second course is administered on three consecutive days, 12 months later. Lemtrada patients require monitoring at regular intervals between treatment courses and for 48 months following the final infusion. Potential Cure as no further treatments needed
- Approved in Canada, EU, Australia but FDA declined Dec. 2013
- AAR 49.4%
- Used to treat chronic lymphocytic leukemia (CLL); cutaneous T cell lymphoma (CTCL); T cell lymphoma
- Main pre-caution: Risk of opportunistic infections (cytomegalovirus) - Genzyme
Management of RRMS

Relapsing remitting MS or Clinically isolated syndrome and abnormal brain MRI

- Disease-modifying therapy not desired/feasible, or female patient is breastfeeding or wishes to become pregnant

  - Yes
  - Monitor clinically and radiologically; treat if/when desired and feasible
  - No
  - Interferon beta or glatiramer

- Satisfactory response and well tolerated

  - No
  - Switch to the other first-line agent (if on interferon beta, try glatiramer and vice versa)

- Satisfactory response and well tolerated

  - No
  - Consider alemtuzumab, cladribine, dimethyl fumarate, fingolimod, mitoxantrone, natalizumab or teriflunomide
  - Yes
  - Continue
Dacetuzumab – Ongoing Investigation

- Targets CD40
- Expressed on Antigen presenting cells
- The binding of CD154 (CD40L) on Th cells to CD40 activates antigen presenting cells and induces a variety of downstream effects (Blocks Th1 activation via APC CD40 blockade)
- Because dacetuzumab is still under study, no optimal (IV) dosages have been established yet. Clinical trials have tested different dosages.
DAKLIZUMAB (Zinbryta)

- Anti-CD25 monoclonal antibody for the treatment of RRMS approved in December 2016
- Voluntary withdrawal March 2nd, 2018 by Biogen and AbbVie
Rituximab – Ongoing Investigation

- Monoclonal antibody
- Targets against the protein CD20, which is primarily found on the surface of immune system B cells. Rituximab destroys B cells and is therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells.
- PML Risk with this IV drug infusion
Hormonal Therapy

- Clinical trial
  - 12 female patients (6 RRMS, 6 SPMS)
  - Estriol 8 mg/day x 6 months
  - RRMS: improved MRI
  - SPMS: no changes
- Side effects:
  - Menstrual cycle irregularities
  - Risk of breast cancer, heart attack, and stroke
Stem Cell Transplants

- Intensive (“extreme”) immunosuppression
- “Reboot” a damaged system
  - Reconstitution with healthy stem cells will avoid redevelopment of immune response
  - Ablation of bone marrow may limit damage; stem cells may improve repair (can differentiate into new support cells)
Stem Cell Transplants

- Collect stem cells from patient from blood or bone marrow. Then use chemo and radiation used to destroy diseased cells in bone marrow. Your stored stem cells collected prior to chemo/radiation go back into your body to reboot. Whether stem cells come from your own blood or bone marrow it is called an autologous transplant.

- Phase II, 3-year trial
  - Ottawa, Toronto, Montreal
  - 24 transplants, 8 controls
  - Severe active MS:
    - > 5 relapses in 2 – 3 years
    - Failure of interferons, copaxone, mitoxantrone
  - Mortality rate of 3 – 8%
Vitamin D

- 2000 IU /day
Chronic Cerebrospinal Venous Insufficiency

- 65 MS patient (35 RRMS; 20 SPMS; 10 PPMS)
- Cause or Effect
Conclusions

✓ MS is an autoimmune disease
✓ RRMS is the most prevalent form of the disease
✓ No cure for the disease
✓ Clinical efficacy is ~30% for interferons and ~70% for Tysabri (Caution PML)
✓ NAB’s compromise clinical efficacy
✓ New Oral Medications ~65% reduction in MRI and ~50% ARR reduction
✓ Increase quality of life
Questions ?