Benefit/Risk Strategies in Selecting Therapeutic Solutions for MS: HCP and Patient Viewpoints
Learning Objectives

• Review the benefit/risk strategies in selecting therapy for MS patients while assessing treatment regimens that carry acceptable or diminished risk of disease progression

• Explore emergent concepts in the management of MS, focusing on targeting T- and B-cells including:
  – Risks associated with continuous immunosuppression
  – Action on the inflammatory activity in the CNS compartment

• Identify strategies that simplify patient dosing and side effects to:
  – Increase treatment compliance
  – Improve patients’ quality of life
  – Slow disease progression
As Disability of MS Advances, Work Capacity Decreases

The proportion of MSers employed or on long-term sick leave is calculated as a percentage of MSers aged 65 or younger.

The Traditional Approach to MS Treatment

• Heterogeneity of disease course across different MSers and over time can affect treatment response\textsuperscript{1-3}

• Depending on the definition used, up to 49% of MSers treated with a first-line injectable therapy (IFNB) still have clinical disease activity\textsuperscript{1}

Treating Beyond Symptoms with a View to Improving Outcomes in Inflammatory Bowel Diseases

“FLIPPING THE PYRAMID”

T2T-NEDA ALGORITHM

T2T = treating-to-target; NEDA = no evident disease activity

Define the individual’s MS

Choose a therapeutic strategy

Choose therapy

Maintenance-escalation

Initiate or Switch or Escalate Rx

Choose therapy

Rebaseline

Monitoring

Treatment failure?

Yes

Monitoring

Rebaseline

No

Breakthrough disease

Complete course / Re-treat

Rebaseline

Monitoring

Induction

Choose therapy

X

Y

Z

No

Yes

MS prognosis based on clinical and MRI indices
Life style and goals
Shared goals for therapy

Patient’s preferences?
Your choice?

Patient’s preferences?
Your choice?

Only one licensed induction therapy at present

Rebaselining:
- ifn-β, natalizumab, fingolimod, teriflunomide, dimethyl-fumarate=3-6 months
- glatiramer acetate=9 months
- alemtuzumab=24 months

Individual measures:
- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers, e.g. NABs?

Initiate or Switch or Escalate Rx

Maintenance-escalation

Choose therapy

Rebaseline

Monitoring

No

Yes

T2T-NEDA ALGORITHM

Ifn-β = interferon-beta; NABs = neutralizing antibodies; Rx = treatment.
Interferon-beta Reduced Mortality by 46.8% vs Placebo Over 20 Years

Early treatment with IFNB1b: associated with 46.8% reduction in the hazard rate for mortality-NNT 8

HR=0.532 (95% CI: 0.314–0.902)
46.8% reduction in hazard ratio
Log rank, $P=0.0173$

At risk:
- IFNB-1b 250 µg: 124, 124, 121, 118, 104
- Placebo: 123, 120, 117, 109, 88

Inflammation Drives Acute Axonal Loss and Primes Surviving Axons for Degeneration Later

Table 2. Distribution and Number of Transected Axons in Multiple-Sclerosis Lesions.

<table>
<thead>
<tr>
<th>Tissue (no. of patients)</th>
<th>No. of Lesions Analyzed</th>
<th>No. of Transected Axons/mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active lesions (3)</td>
<td>5</td>
<td>11,236 ± 2,775</td>
</tr>
<tr>
<td>Chronic active lesions (4)</td>
<td>13</td>
<td>3,138 ± 688</td>
</tr>
<tr>
<td>Edge</td>
<td></td>
<td>875 ± 246</td>
</tr>
<tr>
<td>Core</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlesion white matter (5)</td>
<td>11</td>
<td>17 ± 2.8</td>
</tr>
<tr>
<td>Control white matter (4)</td>
<td>5</td>
<td>0.7 ± 0.7</td>
</tr>
</tbody>
</table>

11,000 to 1

Treatment Effect on Disability Predicted by Effect on T2-lesion Load and Brain Atrophy

Meta-analysis of treatment effect on EDSS worsening (y) vs effects on MRI lesions and brain atrophy, individually or combined, in 13 placebo-controlled RRMS trials (13,500 patients)

No Evident Disease Activity: NEDA

**Treat-2-target**

**What is NEDA?**

- No relapses
- No sustained disability progression (EDSS)
- No MRI activity
  - No new or enlarging T2 lesions
  - No Gd-enhancing lesions

Gd, gadolinium.
MS Pyramid

- Relapses
- Unreported relapses
- Clinical disease progression
- Subclinical relapses: focal MRI activity
- Focal gray and white matter lesions not detected by MRI
- Brain atrophy
- Spinal fluid neurofilament levels

Microscopic or biochemical pathology
Risk vs Benefit
Theoretical Model: Treat Early and Effectively

Time is brain

Later treatment

Natural course of disease

Later intervention

Intervention at diagnosis

Treatment at diagnosis

Disease Onset

Disability

Time
EDSS = 3.5: unable to run, play tennis or walk down stairs quickly without the use of a handrail

EDSS = 0.0: fully functional
Cost of Delayed Access to Highly Active Treatment
Large Disparities Exist Among Countries in Access to Disease-Modifying Therapies

DMT, disease-modifying therapy.


Newer DMT
Established DMT
No DMT

All data are from 2013

Established DMTs
DMTs approved for relapsing forms of MS during the 1990s and reformulations or generic versions of these substances

Newer DMTs
DMTs approved for relapsing forms of MS that have a different mechanism of action from established DMTs

Differences in access to DMTs among countries.
Multiple Sclerosis: Unmet Medical Needs

• Disease-modifying drugs (DMDs) are not completely effective in all patients.

• 7 to 49% of relapsing–remitting MS (RRMS) patients do not adequately respond to DMDs

• Current Options Injection/Infusion
  – Needle phobia (25% of population)
  – Clinic infusion visit required

The Goal of Treating MS Should Be to Maximize Lifelong Brain Health

Goal: maximize lifelong brain health

- Early referral and diagnosis
- Early treatment
- Monitoring
- Swift action on evidence of disease activity
- Access to DMTs
- Comprehensive economic approach
- Shared decision-making

Generate Consult

Real-world evidence

Recommendation
Therapeutic strategy
Leads to
Be an early adopter

Pledge your support of the report’s recommendations at www.msbrainhealth.org
Therapeutic Hierarchy

Therapeutic pyramid

Brain Health Initiative

- Smoking
- Exercise
- Diet
- Sleep
- Co-morbidities
- Infections
- Concomitant medications
Strategies to Reduce Time Spent with the Clinician and Enhance Adherence

- Dosing Schedule – 10 days annually for 2 years
- Oral administration – More appealing than needles
- Low Discontinuation Rate – Less anxiety for the patient and demand for HCP time
- Less Monitoring – Depends on the progression of MS and patient specific needs
Evolution In Disease Modifying Drugs For Relapsing Remitting Multiple Sclerosis

- Interferon-beta (1b and 1a)
- Glatiramer acetate
- Mitoxantrone
- Natalizumab
- Fingolimod
- Teriflunomide
- Alemtuzumab
- Dimethyl fumarate
Disease modifying drugs: Benefit/risk evaluation

Established Inconveniences and Risks
- Convenience
- Monitoring
- Tolerability
- Safety

Established Benefits
- Treatment efficacy

Risk Minimization
Established Inconveniences and Possible Risks

- Injectable
  - Frequent s.c. or i.m. injections
- Trivial side effects
  - Flu-like symptoms (IFNβ)
  - Injection site reactions
- Neutralizing Antibodies (Nabs)

Established Benefits

- Moderate effect on disease activity
  (on average 30% reduction in relapse rate)
- Less effect on disability progression
- Excellent response in approximately 30% of patients
- No long-term safety concerns
Glatiramer Acetate: Benefit/Risk Evaluation

Established Inconveniences and Possible Risks

- Injectable
  - Daily injections may decrease adherence

- Trivial side effects
  - Injection site reactions
  - Systemic reactions

Established Benefits

- On average a moderate effect on disease activity (30% reduction in relapse rate)
- Less effect on disability progression
- Excellent response in approximately 30% of patients
- No long-term safety concerns
Established Inconveniences and Possible Risks

- Adverse effects
  - Diarrhea and nausea
  - Hair thinning
  - ALT increase
- Potentially immunosuppressive properties

Established Benefits

- Moderate effect on disease activity
- Moderate effect on disability progression
- Equal to IFN-β 1a SC
- One tablet daily
Established Inconveniences and Possible Risks
- Adverse effects
  - Flushing
  - Abdominal pain
- Administered as two tablets daily
- Low risk of PML

Established Benefits
- Robust effect on disease activity
- Moderate effect on disability progression
- Numerically but not statistically significant better than GA
Established Inconveniences and Possible Risks

- **Adverse effects**
  - Bradycardia, A-V block
  - Retinal edema
  - Infections: dermatomal zoster

- **Infrequent severe adverse effects**
  - Serious infections: disseminated varicella\(^+\), herpes encephalitis\(^+\)
  - Skin cancers
  - Single case of PML

Established Benefits

- Superior to IFN-β 1a
- Large effect on disease activity
- Moderate effect on disability progression
- One table daily
Established Inconveniences and Possible Risks
- Intravenous infusions
  - Rare infusion reactions
- Rare Nabs
- Infrequent severe adverse effects
  - PML in 2:1000 per year (after 2 years)

Established Benefits
- Profound effect on disease activity
- Significant effect on disability progression
- Improves QoL
- Good cost-effectiveness
- Risk stratification for PML possible

Natalizumab: Benefits > risks/inconveniences
Established Inconveniences and Possible Risks

- Infusion associated reactions
- Infections
- Immune thrombocytopenic purpura
- Immune thyroid disorders
- Immune nephropaties
- Cytopenias

Established Benefits

- Robust effect on disease activity and disability progression
- Infrequent administration
- Long-lasting efficacy
- Superiority to IFN-β 1a sc

Alemtuzumab: Benefits>risks/inconveniences
75-81% of Patients Treated in CLARITY were Relapse-Free after 2 Years vs No Additional Treatment

CLARITY EXT: Patients Free from Evidence of MRI Activity

Proportion of CP 3.5 mg/kg patients with no new T1 Gd+ lesions during CLARITY EXT (%)

<table>
<thead>
<tr>
<th>Period of treatment gap</th>
<th>CP 3.5 mg/kg group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 weeks (n=9)</td>
<td>87.5</td>
</tr>
<tr>
<td>&gt;4 weeks to ≤43 weeks (n=47)</td>
<td>77.3</td>
</tr>
<tr>
<td>&gt;43 weeks (n=42)</td>
<td>64.9</td>
</tr>
</tbody>
</table>

CLARITY: Effects of Cladribine 3.5 mg/kg on Time to 6-Month Confirmed EDSS Progression

Effects of cladribine 3.5 mg/kg vs placebo on the relative risk ratio of cumulative new T1 gd+ lesions in patient subgroups.

Effects of cladribine tablets 3.5 mg/kg vs placebo on the relative risk ratio of cumulative active T2 lesions in patient subgroups.
CLARITY: Brain Volume Loss in Patients with Relapsing MS

Treatment Effect of Placebo and Cladribine Tablets on Annualized PBVC Rate

- 3.5 mg/kg or 5.25 mg/kg showed significantly less brain atrophy than placebo.
- Brain volume changes showed a correlation between brain atrophy and disability progression.
- Treatment with cladribine tablets was associated with a significantly lower risk of disability progression compared with placebo.

Stefano ND et al. ECTRIMS Abstract 547 September 2016.
ORACLE-MS: Long-Term Follow-Up Analysis of Patients

Worst Post-Baseline CTCAE Grade in Patients Not Treated During Long Term Follow Up

Leist T et al ECTRIMS Abstract 609 September 2016.
Conclusions

• **MS is a disease that has far-reaching negative implications**
  – Mortality, disability, unemployment, divorce, suicide cognitive impairment, etc.

• **Era of Individualised Profiling**
  – Prognosis, risk, treatment and monitoring

• **New treatment paradigm**
  – Maintenance vs. induction therapy
  – Early highly-effective treatments are now a first-line option
  – Improved risk mitigation tools
  – New treatment paradigm of treat-2-target of NEDA (No Evidence of Disease Activity)

• **Is it fair to make patients wait 20 years for the outcome of an ongoing experiment?**