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

Maintenance-escalation

Choose therapy

Initiate or Switch or Escalate Rx

Rebaseline

Monitoring

Treatment failure?

Induction

Choose therapy

Complete course / Re-treat

Rebaseline

Monitoring

Breakthrough disease

Rebaselining:
- MS prognosis based on clinical and MRI indices
- Life style and goals
- Shared goals for therapy
- Patient’s preferences?
- Your choice?
- Only one licensed induction therapy at present

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

Choose therapy

X

Y

Z

A

B

C

X

Z

Y

A

B

C

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

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

HR=0.532 (95% CI: 0.314–0.902)
46.8% reduction in hazard ratio
Log rank, $P=0.0173$
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>
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</thead>
<tbody>
<tr>
<td>Active lesions (3)</td>
<td>5</td>
<td>11,236±2775</td>
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<tr>
<td>Chronic active lesions (4)</td>
<td>13</td>
<td>3138±688</td>
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<tr>
<td>Edge</td>
<td>5</td>
<td>875±246</td>
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<tr>
<td>Core</td>
<td>11</td>
<td>17±2.8</td>
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<tr>
<td>Nonlesion white matter (5)</td>
<td>11</td>
<td>0.7±0.7</td>
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<tr>
<td>Control white matter (4)</td>
<td>5</td>
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</tbody>
</table>

11,000 to 1

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

What is NEDA?

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

Treat-2-target

Gd, gadolinium.
Microscopic or biochemical pathology

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

Biomarkers

Clinical activity

Focal MRI activity

Hidden focal and diffuse MRI activity
Risk vs Benefit
Theoretical Model: Treat Early and Effectively

- **Time is brain**
- **Later treatment**
- **Treatment at diagnosis**
- **Natural course of disease**
- **Later intervention**
- **Intervention at diagnosis**
Early – Highly Active Treatment Enhances Outcome

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.


**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

All data are from 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>Newer DMT</th>
<th>Established DMT</th>
<th>No DMT</th>
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<tr>
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D, disease-modifying therapy.

1–3

0 20 40 60 80 100

All people with MS (%)
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
- Real-world evidence

Generate Consult

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

- Neuro-restoration
- Remyelination
- Neuroprotection
- Anti-inflammatory

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
- Alemtuzumab
- Teriflunomide
- Dimethyl fumarate

Timeline:
- 1996
- 1998
- 2000
- 2006
- 2011
- 2013
- 2014
Disease modifying drugs: Benefit/risk evaluation

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

Established Benefits
• Treatment efficacy

Risk Minimization
Interferon Beta: Benefit/Risk Evaluation

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
Fingolimod: Risks/Inconveniences>Benefits

Established Inconveniences and Possible Risks

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

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

Established Benefits

- Superior to IFN-\(\beta\) 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
75-81 % of Patients Treated in CLARITY were Relapse-Free after 2 Years vs No Additional Treatment

CLARIETY EXT: Patients Free from Evidence of MRI Activity

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

- ≤4 weeks (n=9): 87.5%
- >4 weeks to ≤43 weeks (n=47): 77.3%
- >43 weeks (n=42): 64.9%

Proportion with no new T1 Gd+ lesions in the cladribine 3.5 mg/kg group

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

CLARITY: Benefits of Cladribine on MRI Outcomes in Pooled Double-Blind Data - T1 gd+ lesions

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

CLARITY: Benefits of Cladribine on MRI Outcomes in Pooled Double-Blind Data – T2 lesions

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

- 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?**