The importance of early intervention – clinician perspective

Øivind Grytten Torkildsen
«You can never diagnose MS too late»

Neuroradiologist from Norway, early 1990s
Prognosis in untreated MS
Early diagnosis

Cerebral Volume

Relapses and Disability

MRI Lesion Load

MRI Activity

RIS | CIS | RRMS | SPMS

Employment in untreated MS

Probability of Remaining in Active Employment After Onset of MS

- Control Persons
- MS Patients

Employment Change with EDSS Score Increase

Adapted from Kobelt G et al. J Neurol Neurosurg Psychiatry. 2006;77:918-926.
Quality of life decreases with increasing EDSS-score

- 0.82 = mean utility of normal population
- 0.82 = mean utility of aging patients with osteoporosis, no fracture
- 0.72 = mean utility of patients with rheumatoid arthritis at stage 1
- 0.58 = mean utility of patients with Parkinson’s disease
- 0.55 = mean utility of patients with MS
- 0.48 = mean utility of severe hemophilia patients with inhibitors

Utility (EQ-5D: 0=Death; 1=Full Health)

EDSS Score

0.0–1.0: 1.00 Best Possible Health Status
0.0–9.0: 0.00 Worst Possible Health Status
Survival in untreated MS

8 years decreased survival
In other words...
After 10 years:

• 1/4 of MS-patients have died from the disease

• 1/4 are still employed

• 1/2 are not employed, with different degrees of disability
What happens in MS

Acute damages
Normal White Matter
Active Lesion

Chronic Active Lesion

Chronic Inactive Lesion

Transected axons in different MS-lesions

![Bar graph showing the number of transected axons per mm³ in different MS-lesions.

- Active: 11236
- Chronic Active Edge: 3138
- Chronic Active Core: 875
- NAWM: 17
- Control: 0.7

Number of damaged axons by disease duration

What happens in progressive MS?
Late Motor Decline After Accomplished Remyelination: Impact for Progressive Multiple Sclerosis

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Mitochondrial damage?
Prognosis with treated MS
Early treatment significantly reduced the risk of EDSS-progression
Survival in MS
A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial

**A**

![Kaplan-Meier curve for IFNβ-1b 250 µg vs Placebo](image1)

- **HR = 0.532 (95% CI 0.314-0.902)**
- 46.8% reduction in hazard rate
- Log-rank, *p* = 0.0173

**B**

![Kaplan-Meier curve for IFNβ-1b 50 µg vs Placebo](image2)

- **HR = 0.540 (95% CI 0.318-0.915)**
- 46.0% reduction in hazard rate
- Log-rank, *p* = 0.0202

At risk (n):
- **IFNβ-1b 250 µg**: 124, 124, 121, 118, 104
- **Placebo**: 123, 120, 117, 109, 88

Predictors of Long-Term Outcome in Multiple Sclerosis Patients Treated with Interferon Beta

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![Graph showing odds ratio of advancing into the worst quartile of EDSS change after 15 years for different conditions.

- Early disease activity: Gd+, New T2, Relapse.
- Interferon-β-1a: IM IFNβ-1a.
- Placebo.

Odds ratio (confidence interval) and P values:

- Gd+: 8.96 (2.53, 31.65) < 0.001
- New T2: 2.89 (0.88, 9.54) 0.080
- Relapse: 4.44 (1.43, 13.85) 0.010
- Gd+: 1.79 (0.62, 5.16) 0.284
- New T2: 2.62 (0.93, 7.43) 0.069
- Relapse: 1.53 (0.56, 4.19) 0.408

Ann Neurol. 2013 Jan;73(1):95-103
New MRI-lesions during MS-treatment predict disability progression

*Sustained disability progression was defined as a ≥1.0-point increase in EDSS score confirmed at 6 months. Mean follow-up was 4.8 years. Prosperini L et al. *Eur J Neurol.* 2009;16:1202-1209.
The window of therapeutic opportunity in multiple sclerosis
Evidence from monoclonal antibody therapy
Summary

- Early treatment $\rightarrow$ most effective

- Disease activity during treatment $\rightarrow$ poorer prognosis
Goals of Therapy

**Introduction of RRMS Therapies in the EU**

- SC IFNβ-1b 1995
- IM IFNβ-1a 1997
- SC IFNβ-1a 1998
- GA 2001
- Mitoxantrone 2000
- Natalizumab 2006
- Fingolimod 2010
- Alemtuzumab 2013
- DMF Peginterferon Beta-1a 2014

**Outcome Measures**

- Address Symptoms
- Slow Disease Progression
- Stop Disease Progression
- Repair

**No Evidence of Disease Activity (NEDA)**

- 2009

**Sustained Improvement**

- 2011

No Evidence of Disease Activity (NEDA)

- Relapses
  - No relapses
- EDSS-progression
  - No EDSS progression
- MRI activity
  - No new T2-lesions
  - No new Gd+-lesions

Imitola J, Racke MK. JAMA Neurol. 2015;72:145-147;
Stangel M et al. Ther Adv Neurol Disord. 2015;8:3-13.
Early Treatment vs Later Treatment

Adapted from Miller JR. *J Manag Care Pharm.* 2004;10(suppl S-b):S4-S11.
Early Treatment vs Later Treatment

- **Window of opportunity**
- **Effective treatment at diagnosis**
- **Late treatment**
- **Natural course of MS**

Adapted from Miller JR. *J Manag Care Pharm.* 2004;10(suppl S-b):S4-S11.
Summary

• MS is a serious disease, if untreated.

• Early and effective treatment can alter the prognosis.
"When you change the way you look at things, the things you look at change."

Max Planck