Progress in the field

Eva Havrdová

Department of Neurology and Centre of Clinical Neuroscience
Charles University in Prague
1st Medical Faculty and General University Hospital

Disclosures

- Dr. Havrdová has received consulting fees from Actelion, Biogen Idec, Merck, Novartis, Receptos, Roche, Teva, and is supported by Czech Ministry of Education, project PRVOUK P26/LF1/4

Historical notes

- Scientific description by J.- M. Charcot 1860 preceded by pathologists description
- Immunology did not exist that time
- No understanding of underlying pathological processes
- No treatment
- Speculation on Viking’s genes?

Historical notes

August d'Este 1794-1848

Diary with exact descriptions of attacks, progression of disability and inability of physicians to help

Modern Tx

- Steroids for relapse Tx (1961 - ....)
- Standard immunosuppression (azathioprine, cyclophosphamide, methotrexate) – 1969 -....
- 1993: IFNB 1b followed by IFNB 1a
- 1999: glatiramer acetate
- 2002: mitoxantrone
- 2006: natalizumab
- 2008: fingolimod
- 2013: teriflunomide, dimethyl fumarate, alemtuzumab
- ? ocrelizumab, daclizuab, cladribine

Changes of Tx paradigm

- Injectables: 1993 - 6: proven to decrease number of relapses
- Suboptimal response was expected
- Few believed that there is any impact on disease progression – why?
  - Clinical trials: 2 yrs of follow-up, pts with EDSS 0-5.5, variable disease duration, relatively low efficacy

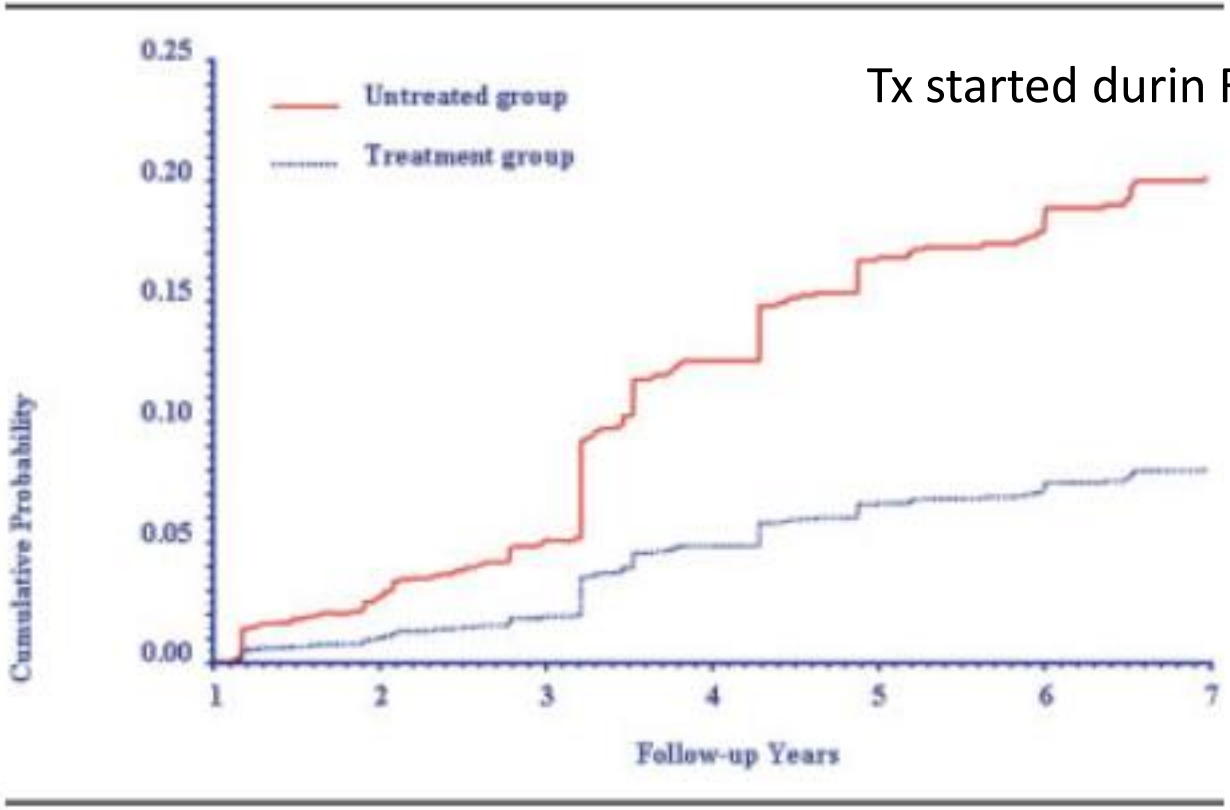
How to choose?

- Criteria in respective countries
- Reimbursement rules
- Shared decisions with patient
- Variety of side effects
- Pregnancy planning
- Concommitant diseases
- Adherence issues

Objectives

- Early diagnosis and early Tx
- Defining sub-optimal response based on close monitoring to reach:
- NEDA-concept;
- Switch to more effective Tx
- Collecting data in real clinical practice registries

First reports from real world clinical practice (Italian Registry)



Tx started durin RR MS

Age of reaching EDSS 4 – delayed by 4.6 yrs
Age of reaching EDSS 6 – delayed by 11.7 yrs

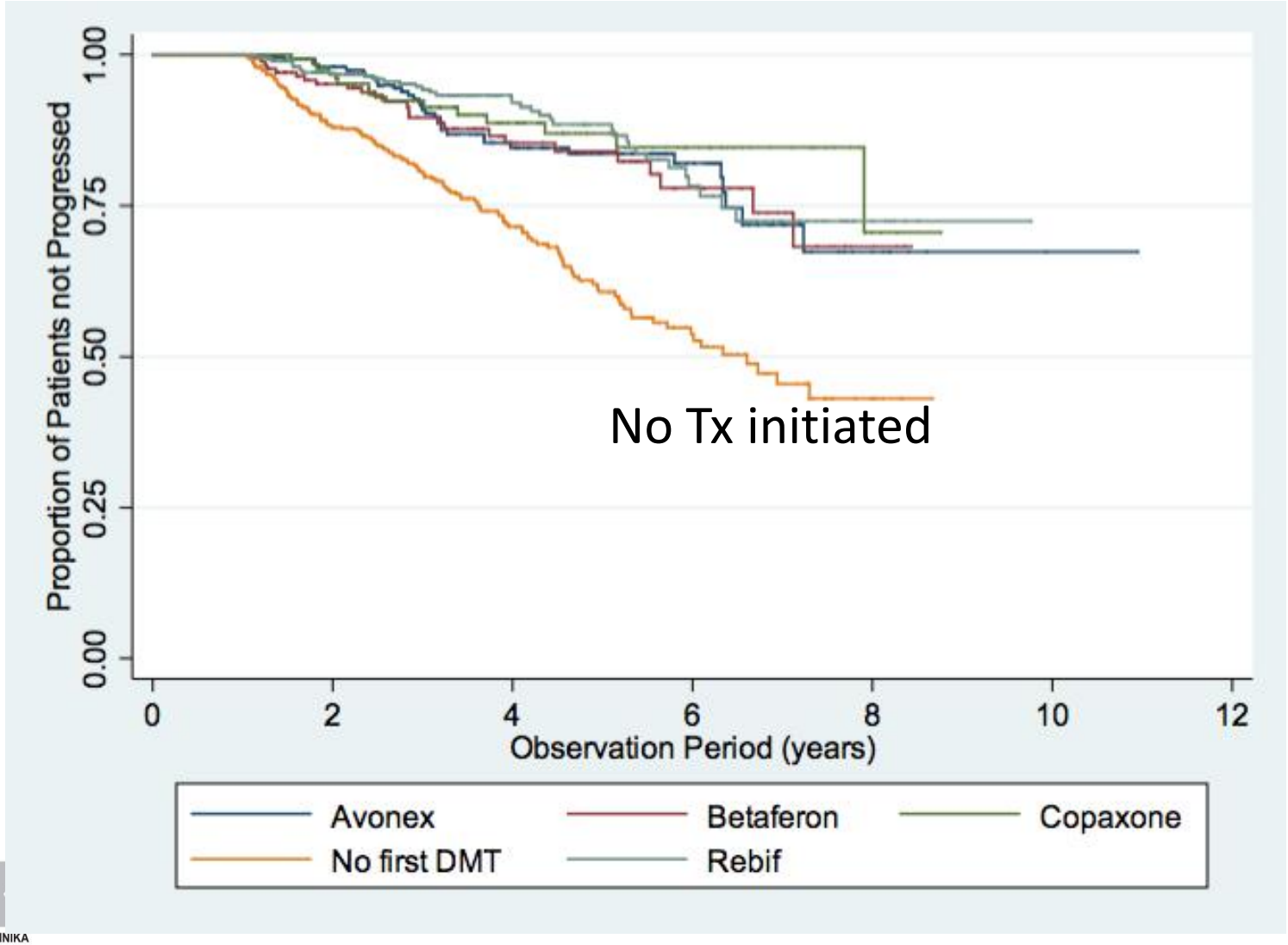
Trojano, Ann Neurol 2007 – new natural history with IFNB

Additional factor showed in CIS studies

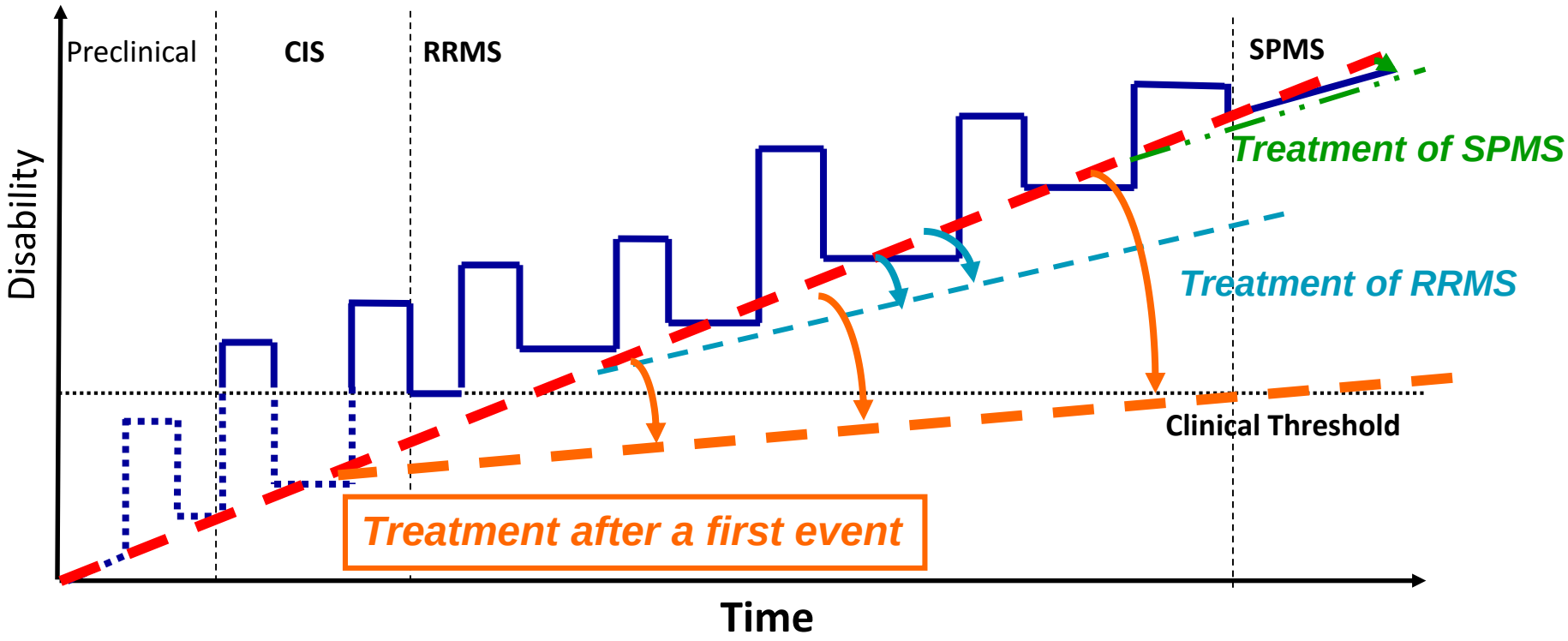
- When Tx is started MATTERS
- Confirmed by follow up of RW pts in registries

MSBase: RW patients

No Tx is the strongest predictor of disability



Treatment initiated at different stages of MS can affect outcomes



(Model)

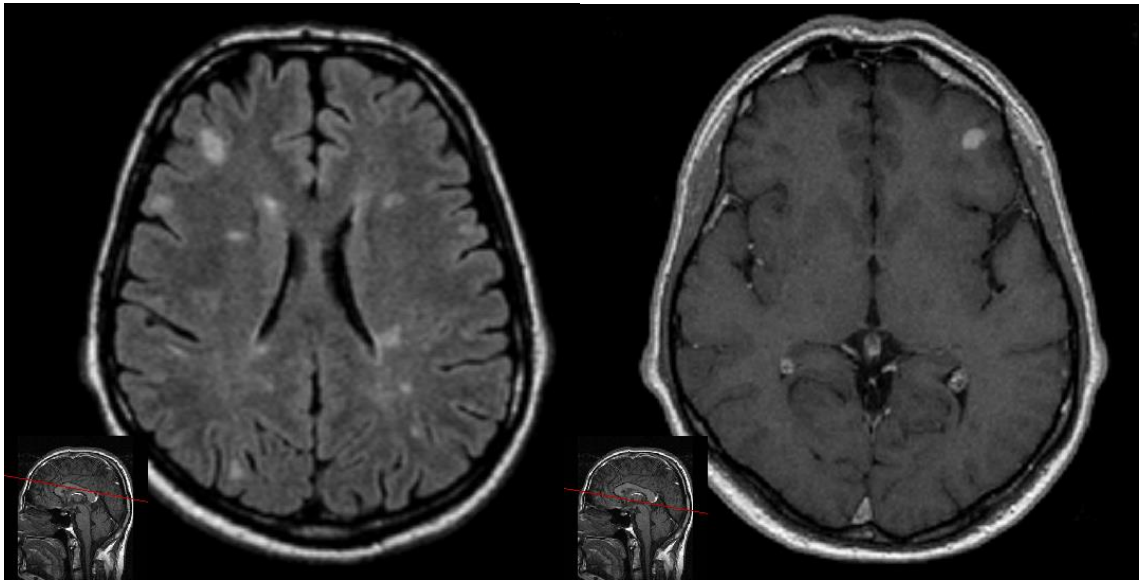
Routine follow up of MS pts

- Relapses – severity, type, response to steroid Tx
- EDSS – disability progression, (MSFC - rarely)
- MRI – not consistently, mostly if pt worsens or experiences severe relapse
- Cognition – rarely
- QoL, ADL – rarely
- Fatigue – rarely

On injectables:

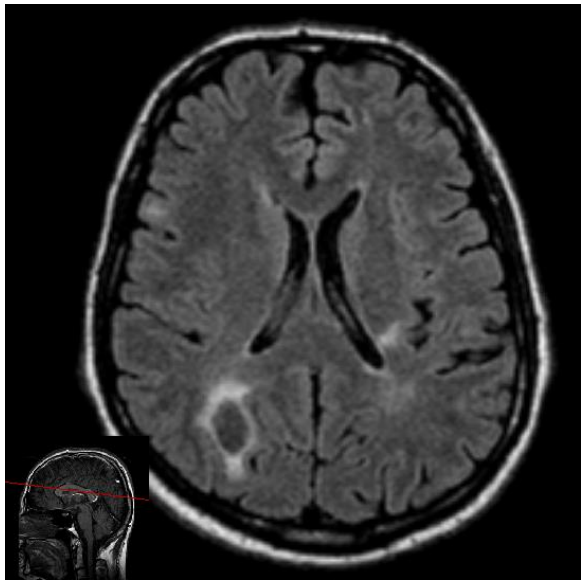
- 62% to 75% pts relapse within 2 yrs
- 20% to 27% pts worsen by ≥1 point on EDSS within 2 yrs

ECTRIMS 2015, ePoster No EP1276

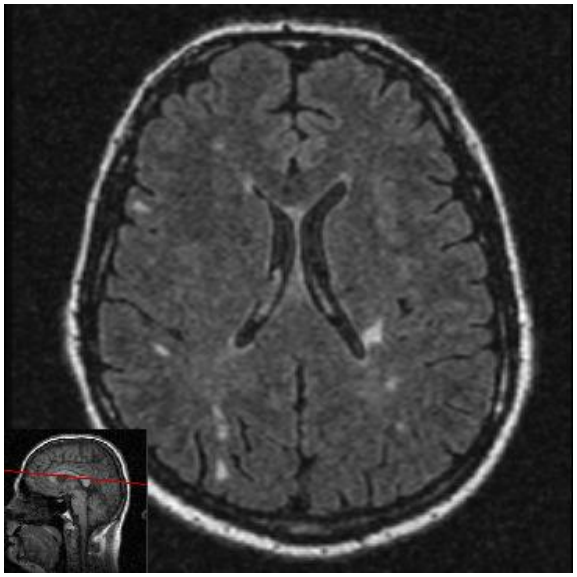


23.7.2008

14.1.2015



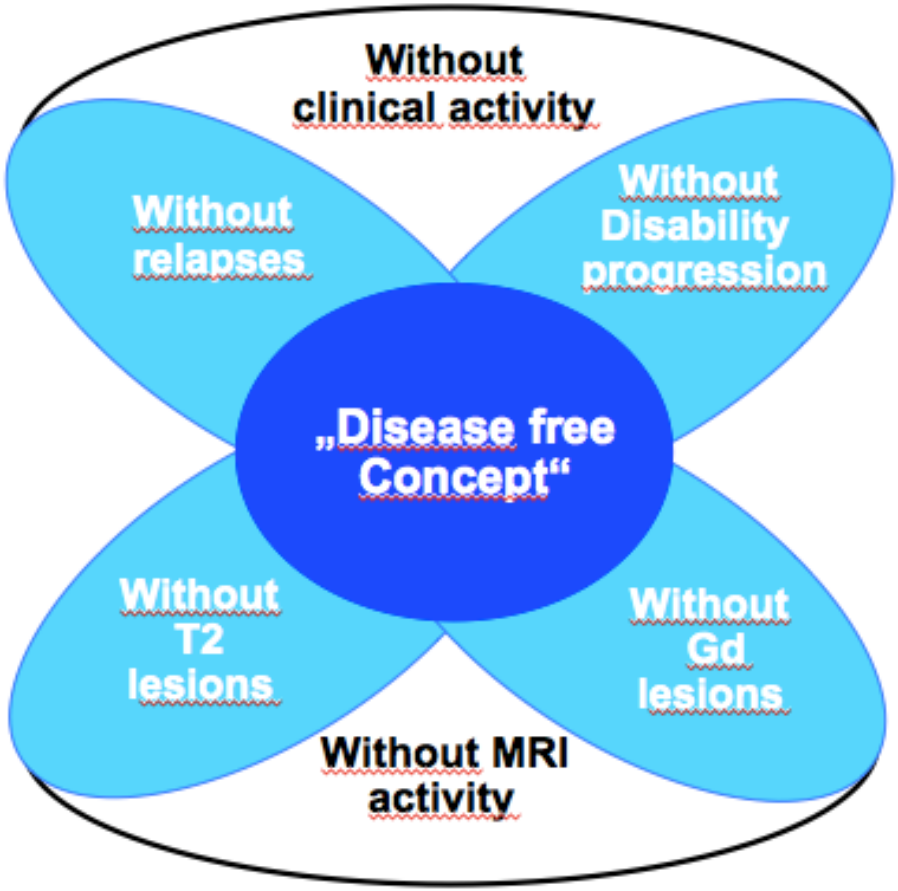
4.11.2008



NEUROLOGICKÁ KLINIKA
1. LF UK a VFN V PRAZE

Department of Neurology and Centre of Clinical Neuroscience
Charles University in Prague, 1st Medical Faculty and General University Hospital

Goal of Tx today – freedom from disease activity (NEDA)

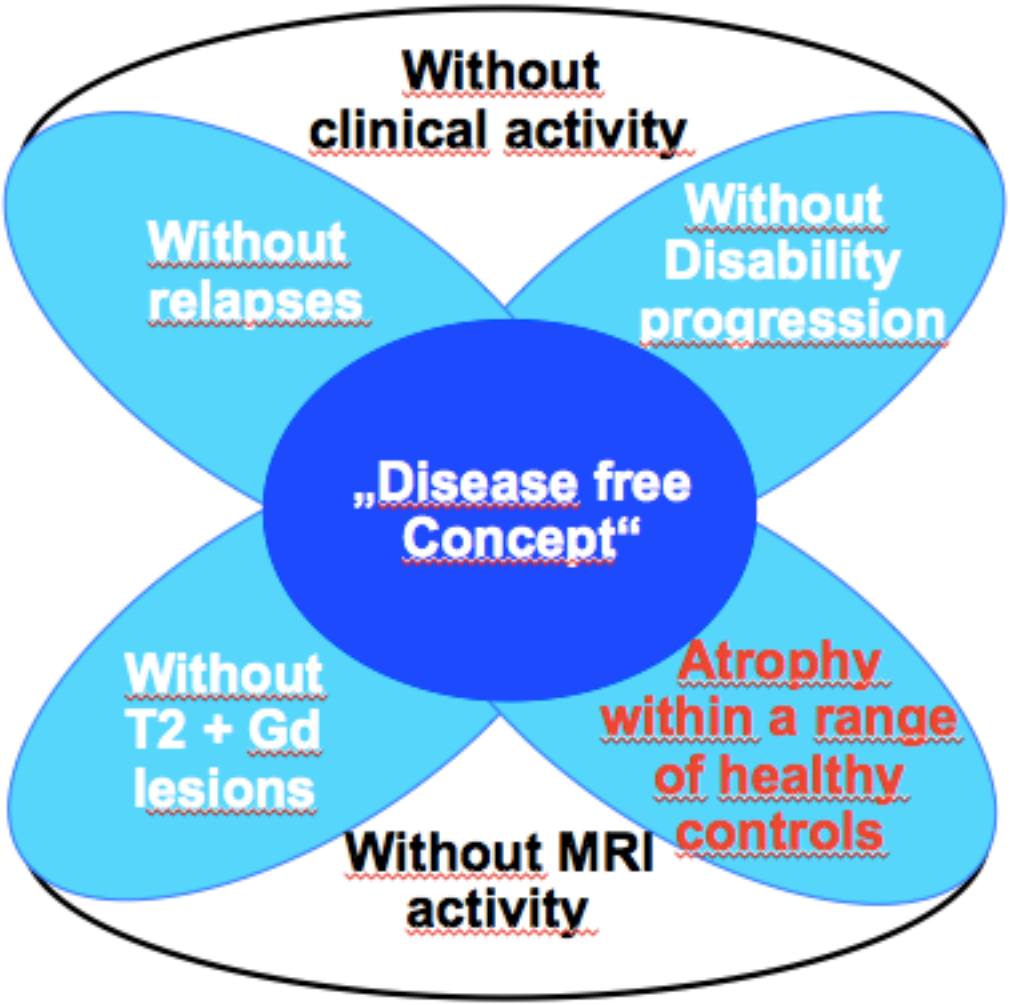


Havrdová E et al.
Lancet Neurol 2009

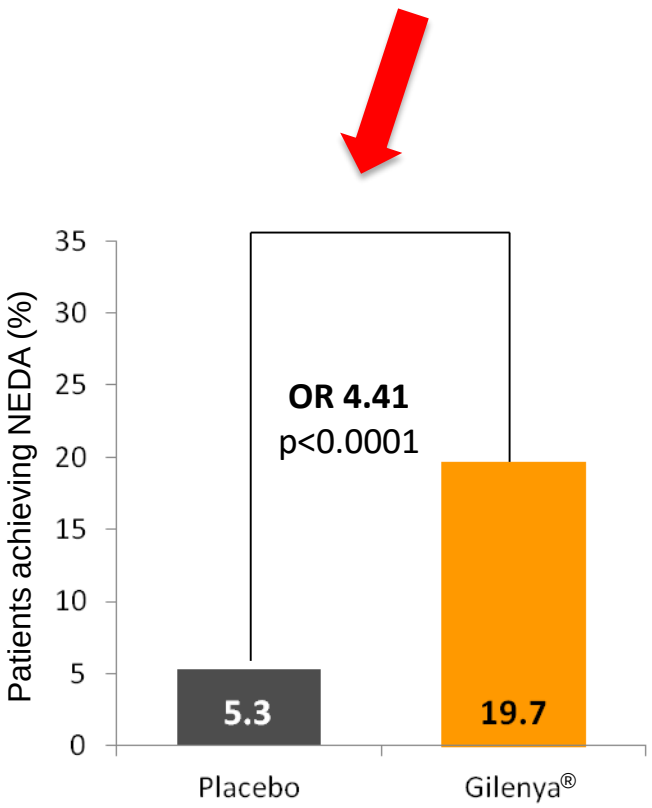
NEUROLOGICKÁ KLINIKA
1. LF UK a VFN V PRAZE

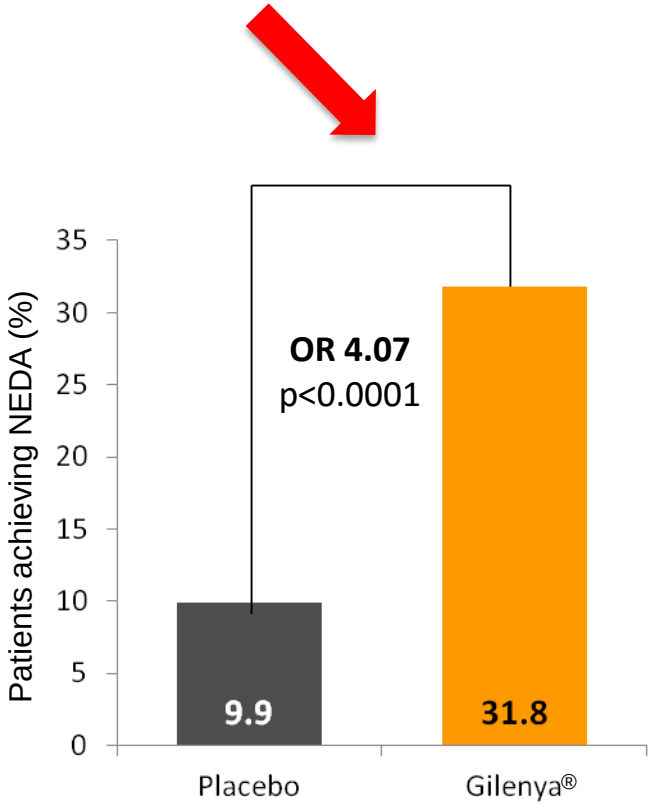
Department of Neurology and Centre of Clinical Neuroscience
Charles University in Prague, 1st Medical Faculty and General University Hospital

NEDA 3 ➔ 4


Without clinical activity
Without relapses
Without Disability progression
„Disease free Concept“
Without T2 + Gd lesions
Atrophy within a range of healthy controls
Without MRI activity

NEDA 4 versus NEDA 3

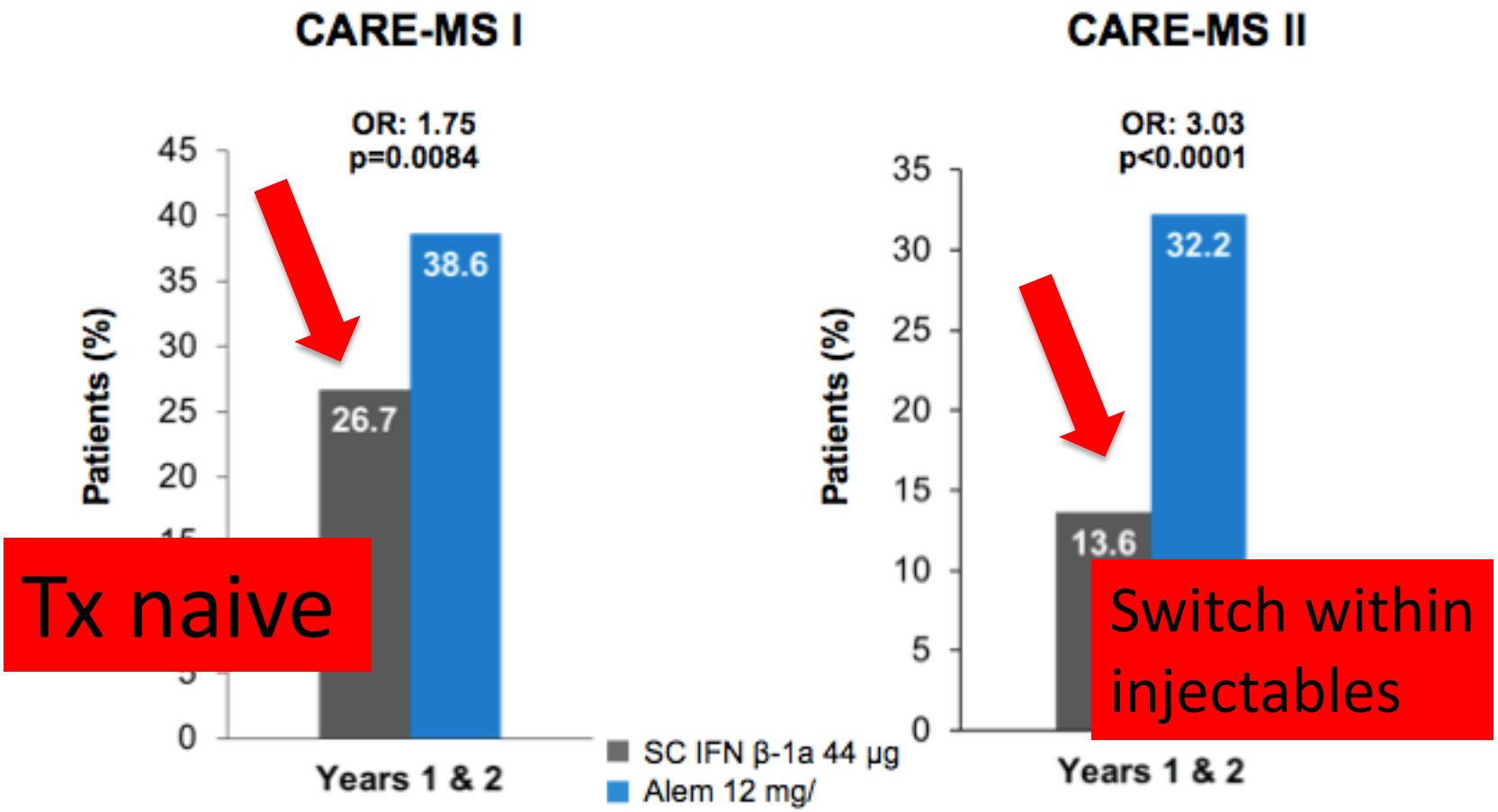




Kappos, L, et al. Presented at ECTRIMS 2014, 10-13 September. Boston, USA (Presentation FC1.5)

Can we reach freedom from disease activity (NEDA - 3) with old fashioned injectables?

Indirect evidence



1. Cohen et al. Lancet. 2012 Nov 24;380(9856):1819-28 2. Coles et al. Lancet. 2012 Nov 24;380(9856):1829-39.

No of NEDA pts is decreasing in time

Figure 2. Percentages of patients with no evidence of disease activity.

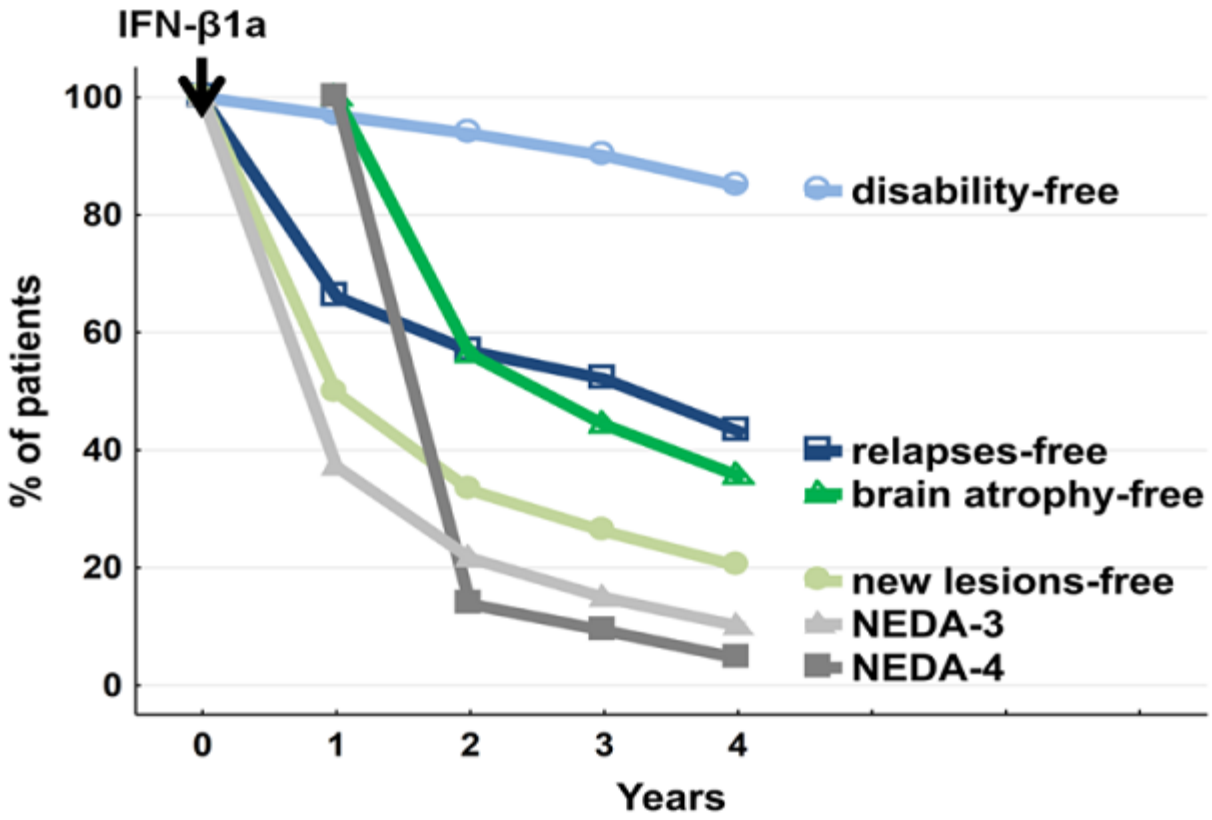


Table 2. Percentages of patients with no evidence of disease activity.

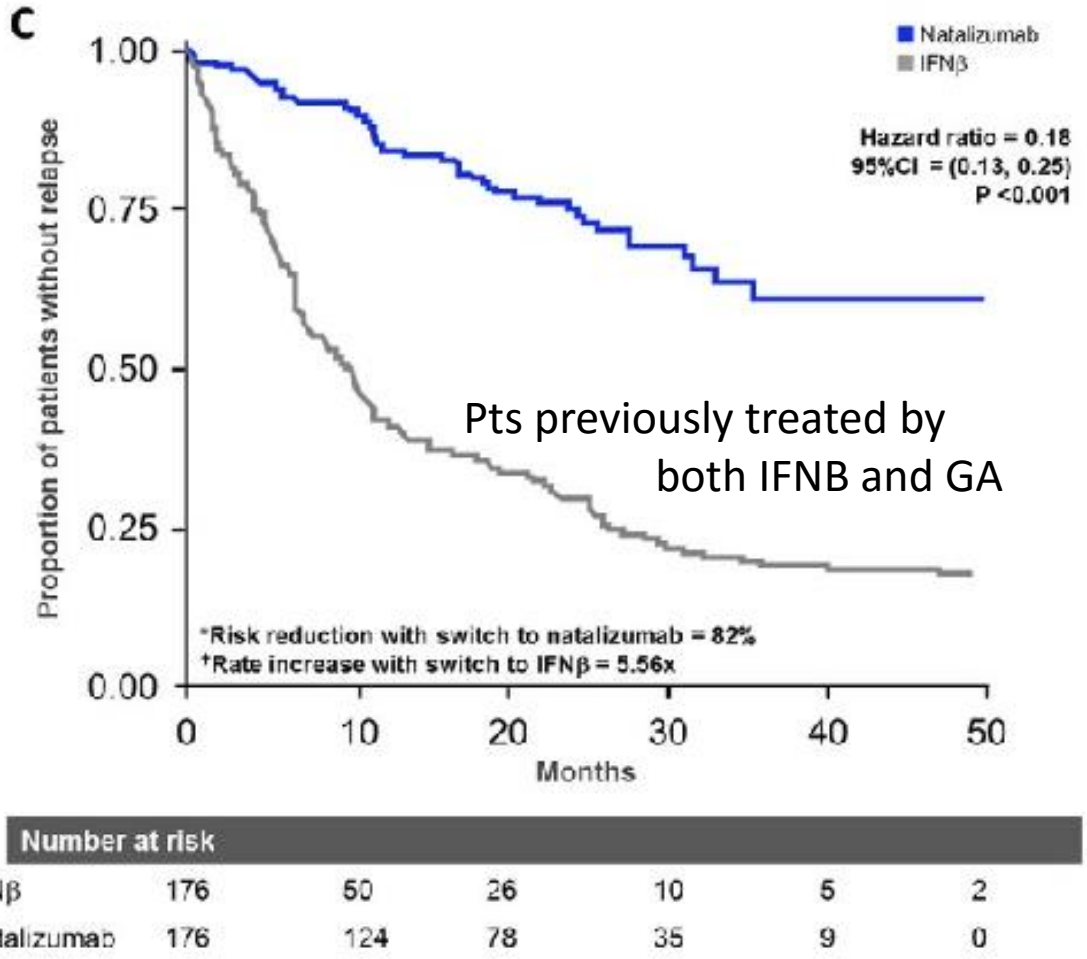
SET Study
210 CIS pts (MRI + OCBs)

All started IFNB-1a i.m. within 4 months from symptoms onset

Uher T et al. ECTRIMS 2015, poster A-733-0005-00476

Loosing time

Switching within 1st line DMDs versus 2nd line



RW data from MSBase + TOP:

ARR
Time to first relapse
Disability progression

Spelman et al. Ann Clin Transl Neurol 2015 Apr;2(4):373-87

Not to loose time

Switching within 1st line DMDs versus 2nd line

Patients who switched to natalizumab had a 26% reduction in the risk of 3-month confirmed **disability progression**.

ARR was higher in patients who switched to another BRACE therapy (mean, 0.58; SD, 0.86) than in those who switched to natalizumab (mean, 0.20; SD, 0.52) ($P < 0.0001$), representing a 66% relative reduction in ARR for patients who switched to natalizumab.

RW data from MSBase + TOP:

ARR
Time to first relapse
Disability progression

Spelman et al. Ann Clin Transl Neurol 2015 Apr;2(4):373-87

Treatment decision

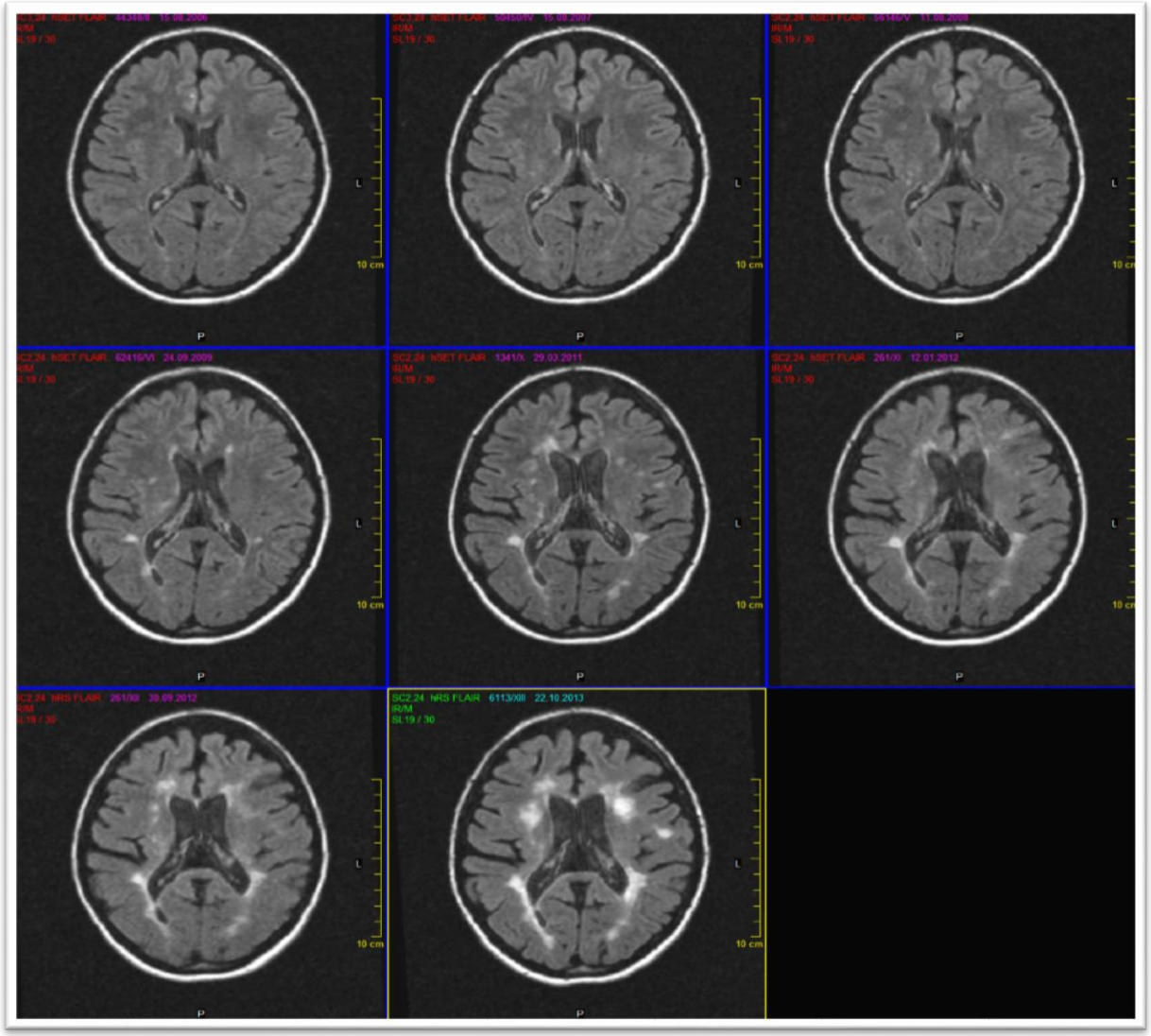
- SWITCH WITHIN injectables: intolerability, adherence issues, NABs (injectables to orals)

- SWITCH to HIGHER EFFICACY DRUGS:
- Severity of relapses and magnitude of MRI findings
- Risk/benefit – discussion and education
- Other factors: pregnancy planning, co-morbidities, JCV Abs positivity, lymphopenia

Brain atrophy development

16 Aug 2006

11 Aug 2008



24 Sep 2009

12 Jan 2012

30 Sep 2012

22 Oct 2013

Brain atrophy and other measures

- Proven correlation with disability development
- More inflammation leads to more atrophy (less reparative processes in action)
- Healthy persons loose 0.1-0.3% of brain tissue / year
- MS patients loose over 0.4% / year
- Not easy to measure in everyday clinical practice

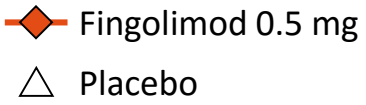
Drugs able to normalize rate of brain atrophy

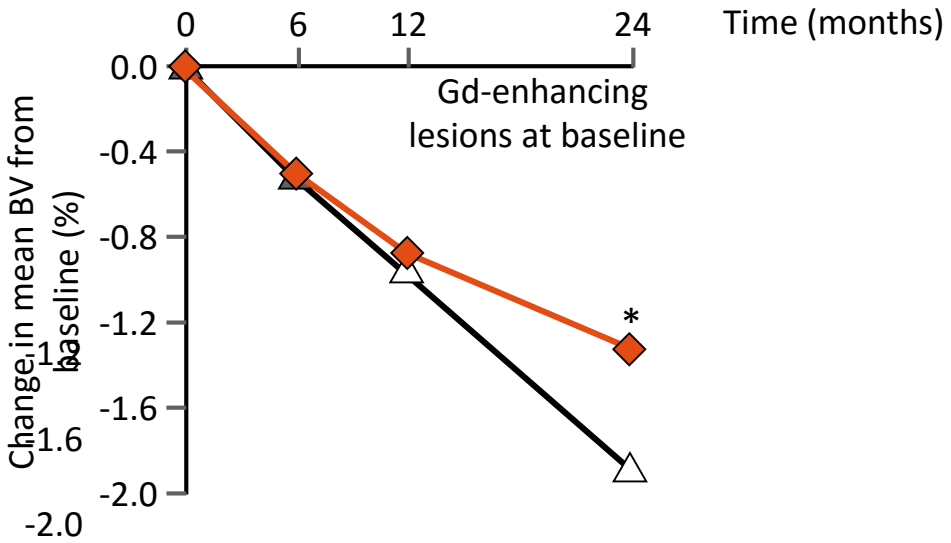
- **Teriflunomide**
- **Fingolimod**
- **Alemtuzumab**

- Dimethyl fumarate (?)
- Natalizumab (?)

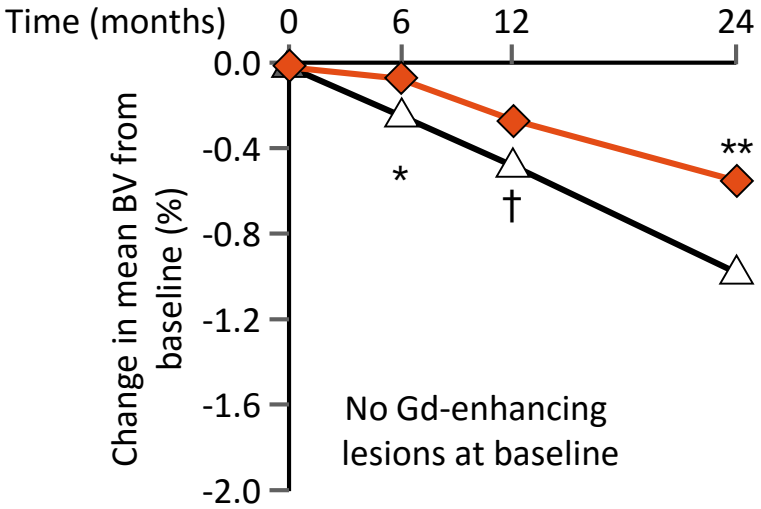
- Ocrelizumab (in registration process)

Fingolimod: Atrophy development according to initial inflammation: FREEDOMS – 2 yrs data





Atrophy rate decreased in both groups,
in pts without G+ lesions at baseline atrophy rate normalized in 6 months

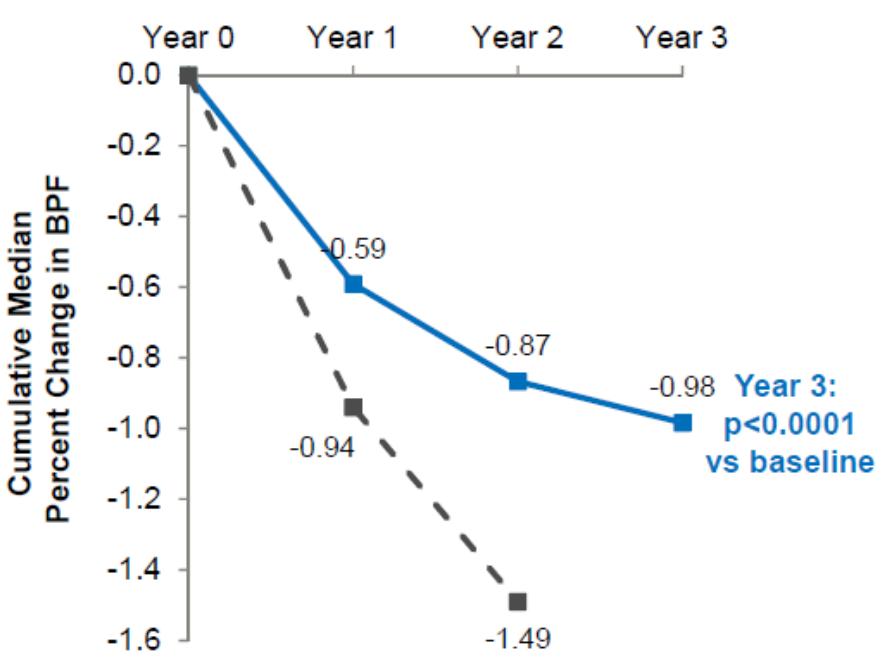


*p<0.05, **p<0.01, ***p<0.001 vs placebo; †p = 0.061 vs placebo; p-values are for comparisons over Months 0-6, Months 0-12, Months 0-24; patient numbers at baseline were 425 (n = 161 with Gd-enhancing lesions; n = 263 without Gd-enhancing lesions) and 418 (n = 154; n = 262) for fingolimod 0.5 mg and placebo, respectively; Gd, gadolinium; Radue E *et al.* Poster P05.064 presented at *AAN* 2011

CARE-MS Extension: brain tissue loss

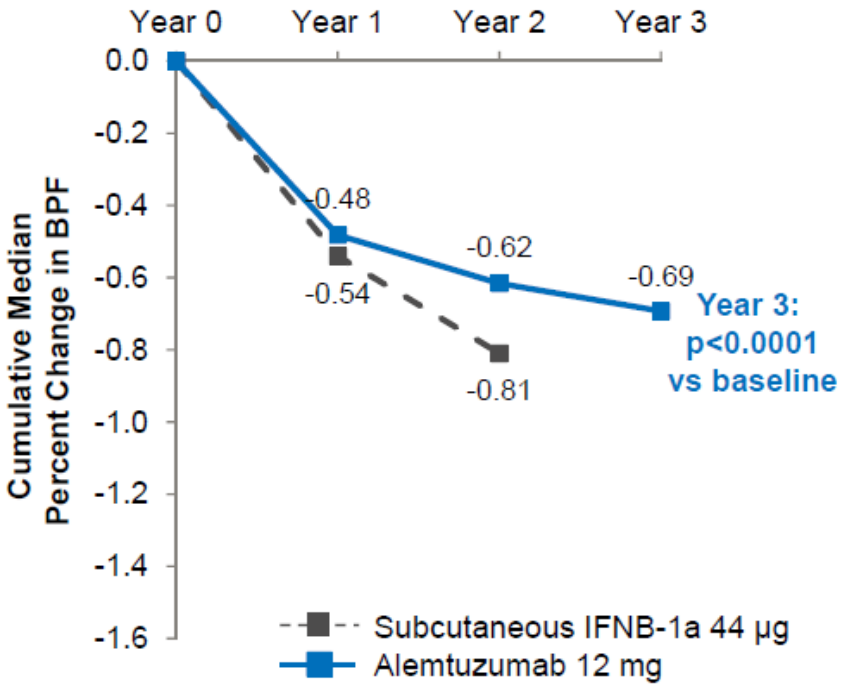
Treatment-naïve

(CARE-MS I: Percentage Change in BPF Over 3 Years)1-3



Relapsed on Prior Therapy

(CARE-MS II: Percentage Change in BPF Over 3 Years)1,3,4



- Alemtuzumab **slowed the yearly rate of brain volume loss** over 3 years in both treatment-naive patients and those who relapsed on prior therapy[1-4]
  - The mean annual rate of brain volume loss in healthy individuals is 0.1-0.4%[5,6]

BPF=brain parenchymal fraction. 1. Data on file; 2. Arnold DL et al. Presented at AAN 2012:Platform; 3. Arnold DL et al. AAN 2014:P008; 4. Arnold DL et al. Presented at ECTRIMS 2012:P877; 5. Fotenos AF et al. Arch Neurol 2008; 65:113-20; 6. Miller DH Brain 2002;125:1676-95.

Brain health

Time matters in multiple sclerosis

Gavin Giovannoni
Helmut Butzkueven
Suhayl Dhib-Jalbut
Jeremy Hobart
Gisela Kobelt
George Pepper
Maria Pia Sormani
Christoph Thalheim
Anthony Traboulsee
Timothy Vollmer

EMBARGOED
00:01 GMT Wednesday, 7 October, 2015

Preparation of the report and its recommendations was funded by an educational grant from F. Hoffmann-La Roche, who had no influence on the content

Tasks

- For physicians: early diagnosis, early treatment, monitoring of the disease activity, early escalation, multidisciplinary team of MS specialists
- For patients:
  - **Fight for access to this high quality care**
  - **Introduce healthy life style: no smoking, no obesity, decreased amount of salt, exercise, stress management**
  - **Support of registries to collect real world data**

Conclusions

- MS has become a treatable disease
- We can change the natual course of MS and decrease the rate of progression by EARLY diagnosis followed by EARLY treatment
- We need drugs preventing brain loss and disability

... we never ever give up hope !

NEUROLOGICKÁ KLINIKA
1. LF UK a VFN V PRAZE

Department of Neurology and Centre of Clinical Neuroscience
Charles University in Prague, 1st Medical Faculty and General University Hospital

Acknowledgments:

To all patients enrolled in our studies

To my team (MS Center, Dpt of Neurology, First Medical Faculty, Charles University in Prague

To our radiological team MRI Dpt., First Medical Faculty, Charles University in Prague