Progress in the field

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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, daclizumab, 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
- Concomitant 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)

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

- Treatment of RRMS
- Treatment of SPMS
- Treatment after a first event
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
Goal of Tx today – freedom from disease activity (NEDA)

Havrdová E et al. Lancet Neurol 2009
NEDA 3 ➞ 4

- Without clinical activity
- Without relapses
- Without Disability progression
- Without T2 + Gd lesions
- Disease free Concept
- Atrophy within a range of healthy controls
- Without MRI activity
NEDA 4 versus NEDA 3

Patients achieving NEDA (%)

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

CARE-MS I
- OR: 1.75
- p=0.0084

CARE-MS II
- OR: 3.03
- p<0.0001


Tx naive

Switch within injectables
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

Pts previously treated by both IFNB and GA

RW data from MSBase + TOP:

ARR
Time to first relapse
Disability progression

Apr;2(4):373-87
Not to lose 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.

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

24 Sep 2009

30 Sep 2012

11 Aug 2008

12 Jan 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
Alemtuzumab slowed the yearly rate of brain volume loss over 3 years in both treatment-naive patients and those who relapsed on prior therapy\textsuperscript{1-4}

- The mean annual rate of brain volume loss in healthy individuals is 0.1-0.4\%\textsuperscript{5,6}
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

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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 natural 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!
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