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Studi real life: terapie HEET vs Escalation

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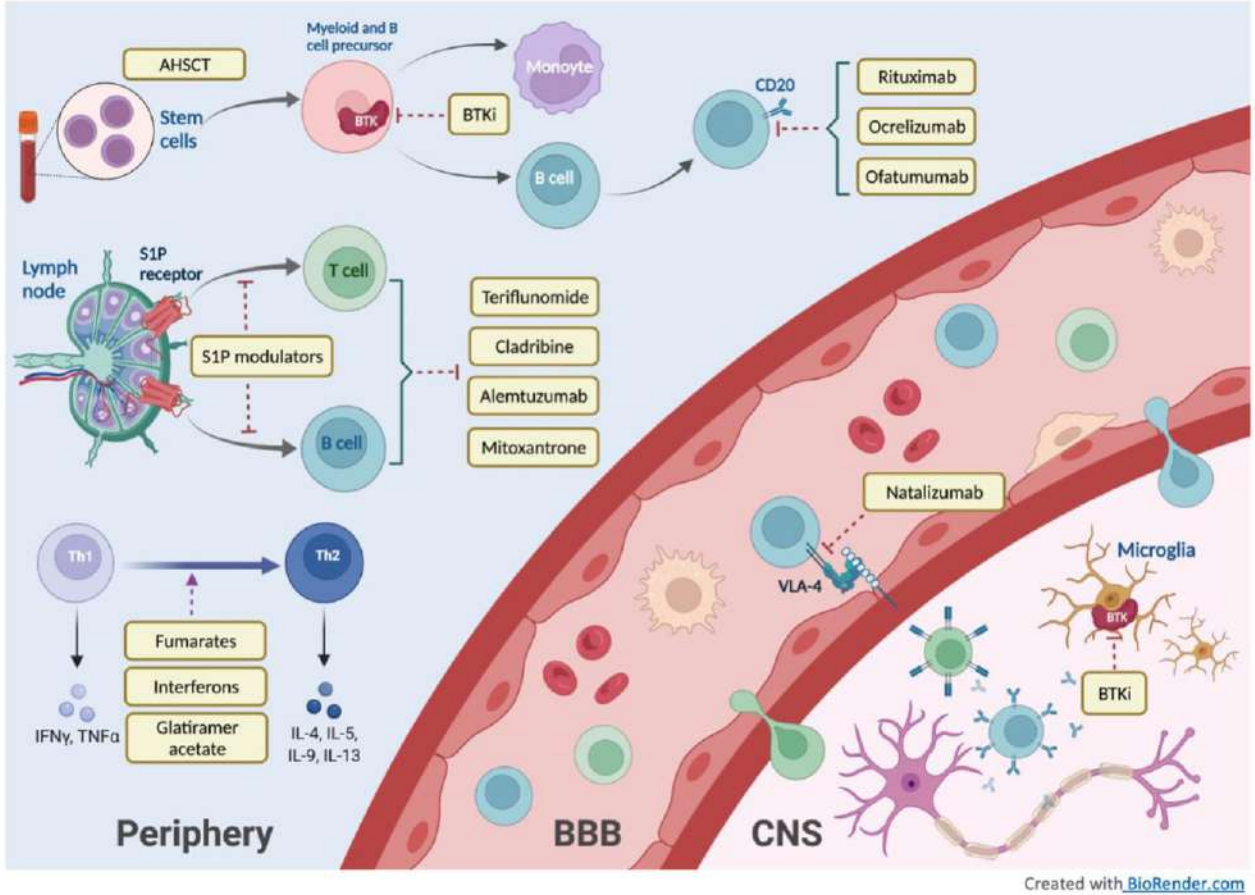
HEET=High Efficacy Early Treatment

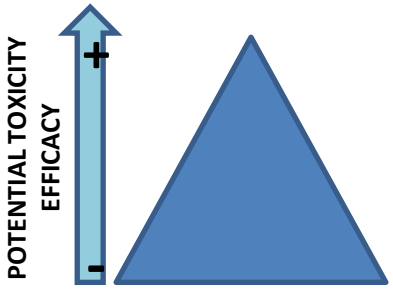
Disclosures

Iaffaldano P. has served on scientific advisory boards for Biogen Idec, Bayer, Teva, Roche, Merck Serono, Novartis and Genzyme and has received funding for travel and/or Speaker honoraria from Sanofi Aventis, Genzyme, Biogen Idec, Teva, Merck Serono and Novartis.

Treatment landscapes / Currently DMTs



Escalation vs HEET strategy – treatment algorithms in MS



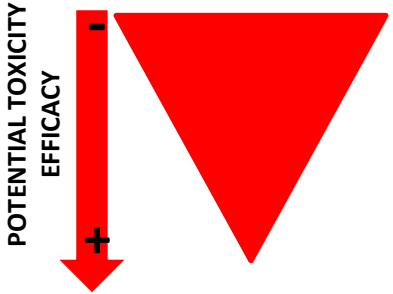
SAFETY FIRST

Escalating treatment means to start with the safest MS drugs. If they failed, the escalation to more aggressive second line is warranted

Advantages: to allow many patients to have a satisfying control of the disease while receiving relatively safe drugs.

Disadvantage: to expose some patients to the risk of losing precious years spent receiving a treatment that was not potent enough and potentially leading to sustained accumulation of disability

Challenge: the key to escalation therapy success is to define upfront with the patient ***the exact suboptimal response threshold*** at which the next-level therapeutic option should be introduced



EFFICACY FIRST

HEET means to start with a strong immunointervention.

Advantages: this facilitates an earlier achievement of a "No Evidence of Disease Activity", which is the gold standard for MS treatment.

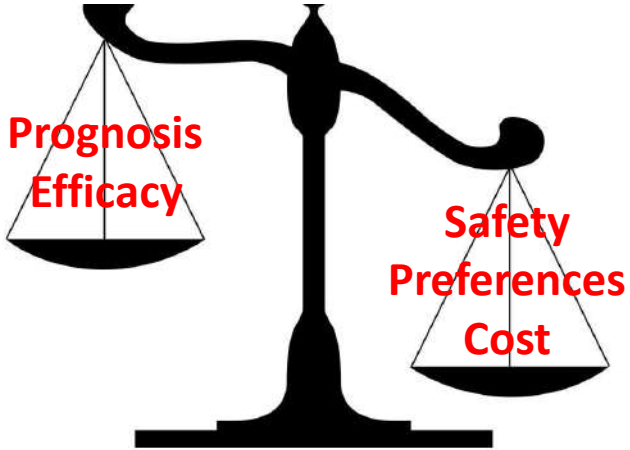
Disadvantages: some patients may be needlessly to serious side effects.

Challenge: the key to HEET strategy success is ***to use immunosuppressants for the right patient***

Escalation vs HEET strategy – treatment algorithms in MS

Reasons for starting with an immunomodulator

- Favourable prognostic factors
- Long-term safety
- Patient's preferencs
    - Route of administration
    - Comfort with risk
- Cost and coverage



Escalation vs HEET strategy – treatment algorithms in MS

Reasons for starting with an HEET

- Unfavourable prognostic factors
- Long-term disability accumulation

Journal of Neurology
https://doi.org/10.1007/s00415-022-11193-w

ORIGINAL COMMUNICATION

Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion

Massimo Filippi[1,2,3,4,5] · Maria Pia Amato[6,7] · Diego Centonze[8,9] · Paolo Gallo[10] · Claudio Gasperini[11] · Matilde Inglese[12,13] · Francesco Patti[14,15] · Carlo Pozzilli[16] · Paolo Preziosa[1,2] · Maria Trojano[17]

Received: 7 April 2022 / Revised: 12 May 2022 / Accepted: 13 May 2022

HE-DMTs: defining high efficacy

A drug should be defined as HE-DMT if its substantial therapeutic effect can be proven on ≥ 1 outcome of inflammation/demyelination but also on ≥ 1 outcome of disease progression.

A therapy can be defined as HE-DMT if a therapeutic effect can be proven on

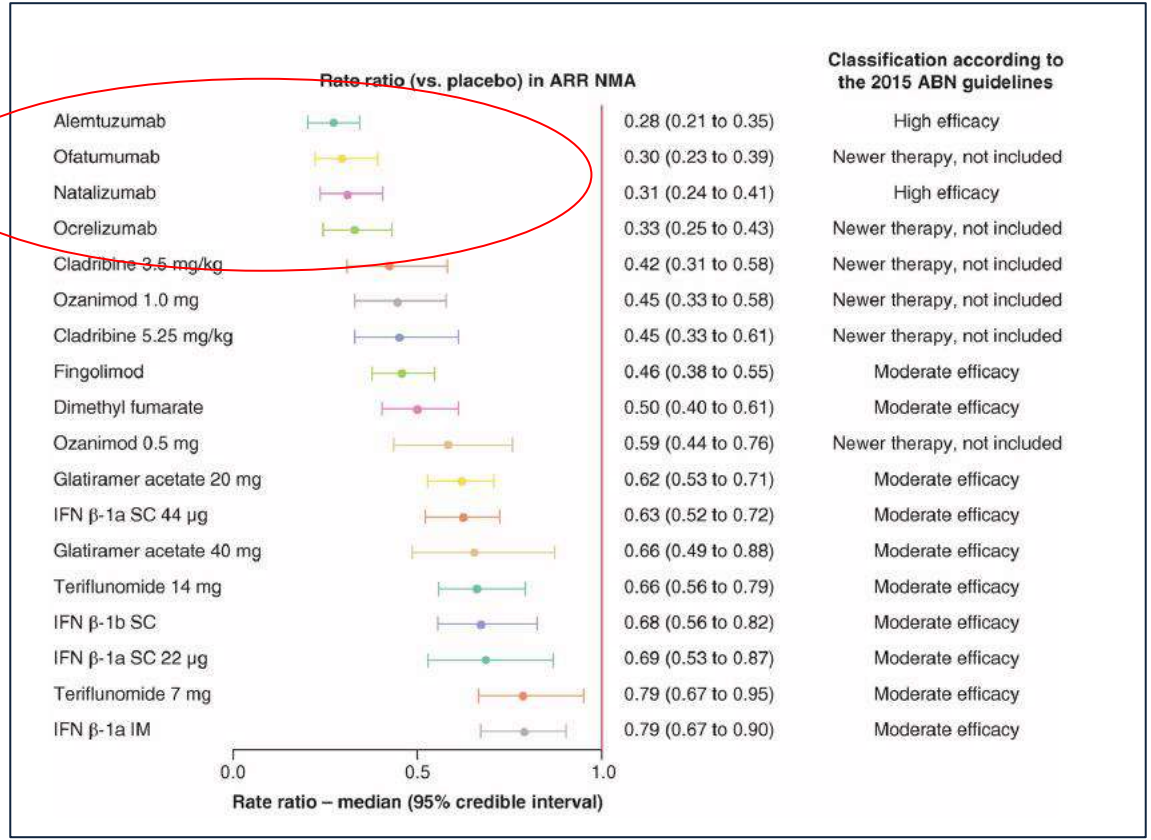
- ≥ 1 outcome of inflammation
  - Substantial decrease of annualized relapse rate and/or
  - Substantial decrease of MRI activity (new/enlarging T2-hyperintense lesions and/or Gd-enhancing lesions)

AND

- ≥ 1 outcome of disease progression:
  - Substantial decrease of clinical disability progression: confirmed worsening of EDSS score and its functional system scores, cognitive deterioration, composite scores (e.g., MSFC, EDSS worsening plus ≥ 20% minimum threshold change for T25FWT and 9HPT)
  - Substantial effect on MRI measures of neurodegeneration: global or regional brain and spinal cord atrophy
  - Substantial effect on body fluid biomarkers: neurofilament light chain levels PROs

Filippi M, Amato MP, Centonze D, Gallo P, Gasperini C, Inglese M, Patti F, Pozzilli C, Preziosa P, Trojano M. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol. 2022 May 24. doi: 10.1007/s00415-022-11193-w.

HE-DMTs: defining high efficacy

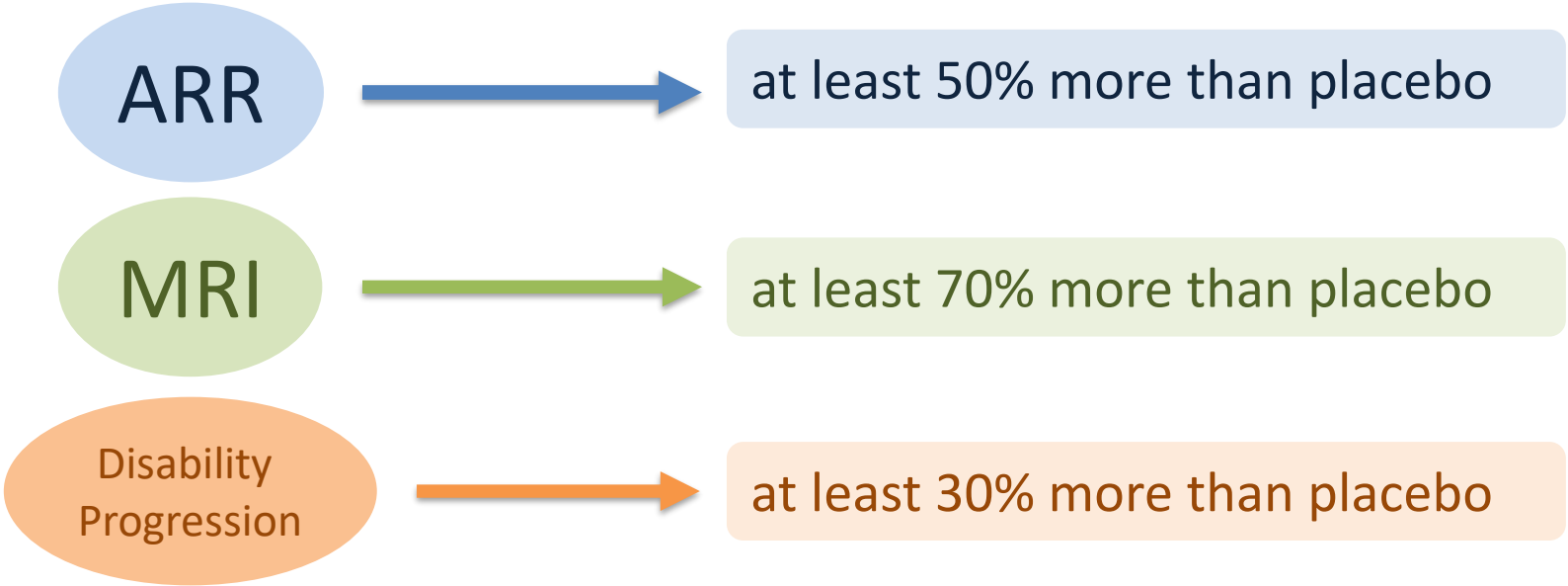


Annualized relapse rate network meta-analysis forest plot (versus placebo) with efficacy class for each disease-modifying therapies (2015 Association of British Neurologists guidelines).

Samjoo IA, Worthington E, Drudge C, Zhao M, Cameron C, Hring DA, Stoneman D, Klotz L, Adlard N. Efficacy classification of modern therapies in multiple sclerosis. J Comp Eff Res 2021; 10(6): 495–507. https:// doi. org/ 10. 2217/ cer- 2020- 0267.

HE-DMTs: defining high efficacy

According to the results from RCTs and observational studies HEDMTs should determine a substantial decrease of the ARR, MRI activity and disability progression.
Experts suggest to consider as HE-DMTs those treatments having an average reduction of each of these parameters.



Filippi M, Amato MP, Centonze D, Gallo P, Gasperini C, Inglese M, Patti F, Pozzilli C, Preziosa P, Trojano M. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol. 2022 May 24. doi: 10.1007/s00415-022-11193-w.

Therapeutic paradigm shift

MULTIPLE SCLEROSIS JOURNAL | MSJ

Editorial

Paradigm shifts: Early initiation of high-efficacy disease-modifying treatment in multiple sclerosis

Hans-Peter Hartung, Sven G Meuth and Alan J Thompson

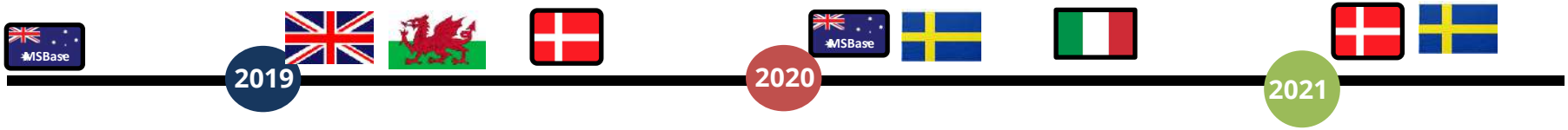
Multiple Sclerosis Journal

2021, Vol. 27(10) 1473–1476

DOI: 10.1177/13524585211033190

RW observational studies in MS enable to perform comparisons between different treatment strategies

Brown J et al JAMA 2019	Harding K et al JAMA Neurol 2019	Buron MD et al. Neurology 2020	He A et al. Lancet Neurol 2020	Iaffaldano P et al. TAND 2021	Spelman et al. JAMA Neurol 2021
First DMT: • fingolimod, alemtuzumab, or natalizumab (n=235); • Injectables (n=380)	Early Intensive Therapy (EIT) (n=104) vs Escalation (ESC) (n=488)	Initial treatment with High efficacy DMT (n=194) or medium efficacy DMT (n=194).	Rituximab, Ocrelizumab, MTX, Alemtuzumab, or Natalizumab either 0-2 years (early) (n=213) or >4 years (late) (n=253) after clinical disease onset.	Early Intensive Therapy (EIT) (n=363) vs Escalation (ESC) (n=363)	To investigate the association of national differences in disease-modifying treatment (DMT) strategies for RRMS with disability outcomes.
5.8 years	Up to 6.9 years	4 years	7.8 years	8.5 years	Up to 7 years
Time to SP conversion (data-driven definition)	5-year change in EDSS.; time to Sustained Accumulation of Disability (SAD).	Time to 6-month confirmed EDSS worsening and to first relapse	EDSS at 6 to 10 years and cumulative hazard of confirmed disability progression	Disability trajectories at 10 years by using longitudinal models	Time to 24-week confirmed disability worsening



Initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion to SP than initial treatment with injectables.	Mean 5-year change in EDSS was lower in the EIT group than the ESC group. EIT better than ESC to reduce the risk of reaching SAD.	Initial therapy with high efficacy DMT was associated to a lower risk of confirmed disability worsening and a first relapse.	High-efficacy therapy commenced within 2 years of disease onset is associated with less disability after 6–10 years than when commenced later in the disease course.	EIT strategy is more effective than ESC strategy in controlling disability progression over time.	There is an association between differences in treatment strategies for RRMS and disability outcomes at a national level.

Key messages:

- **Early initiation of highly effective therapy may provide more benefit than an escalation approach**

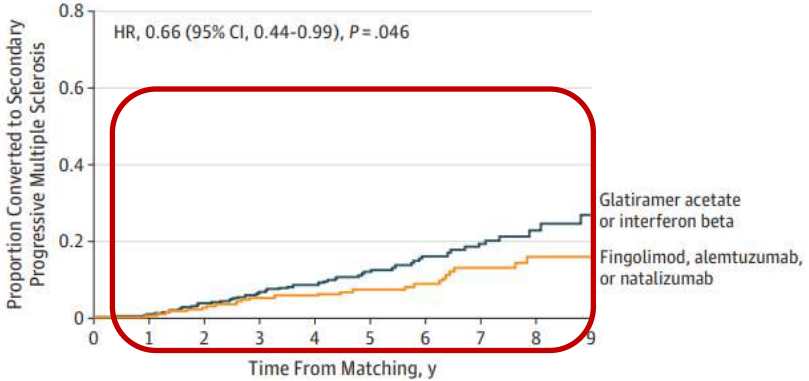
Early intensive therapy and conversion to SPMS

- Cohort study with prospective data from 68 neurology centers in 21 countries
- 1555 patients with RRMS

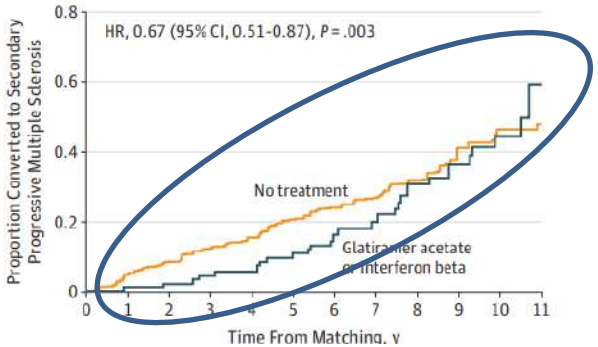
MSBase Neuro-Immunology Registry

Initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of SP conversion than initial treatment with glatiramer acetate or interferon beta (HR, 0.66; 95% CI, 0.44-0.99; P = .046); 5-year absolute risk, 7% [16 of 235] vs 12% [46 of 380]; median follow-up, 5.8 years [IQR, 4.7-8.0]).

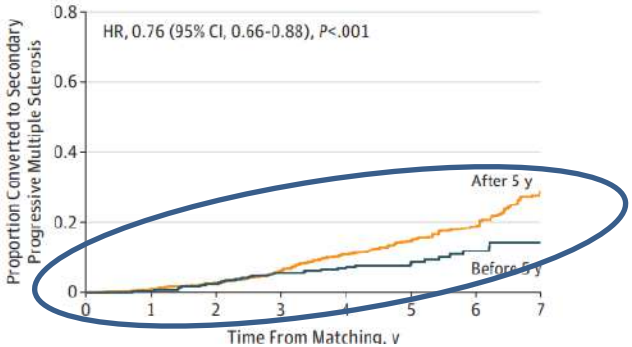
Comparison of Cumulative Hazard of Conversion to SPMS



C Treatment with glatiramer acetate or interferon beta between 5 y and 10 y vs no treatment



D Escalation from glatiramer acetate or interferon beta treatment to fingolimod, alemtuzumab, or natalizumab treatment ≤5 y vs >5 y of onset



"Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis" Brown et al. – 2019 JAMA

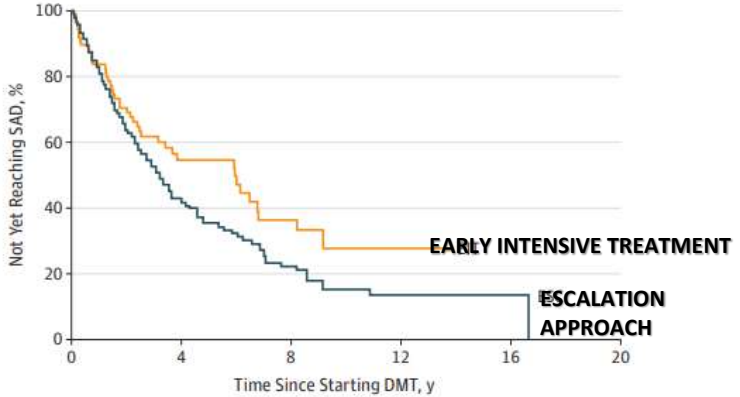
Early intensive therapy: long term outcomes

- Cohort study with prospective data
- 592 patients, classified in EIT and ESC
- Primary outcome was 5-year change in EDSS. Secondary outcome was time to SAD.

Table 2. Association of First-Line DMT Strategy and Change in EDSS Score at 5 Years: Adjusted Linear Regression Model[a]

Covariate	β Estimate (95% CI)	*P* Value
Unadjusted model		
EIT treatment strategy	−0.92 (−1.45 to −0.41)	<.001
Final adjusted model		
EIT treatment strategy	−0.85 (−1.38 to −0.32)	.002
Age at starting DMT	0.03 (−0.002 to 0.05)	.03

Time to Sustained Accumulation of Disability (SAD) by Initial Treatment Strategy



Mean (SD) 5-year change in Expanded Disability Status Scale score **was lower in the EIT group than the ESC group** (0.3 [1.5] vs 1.2 [1.5]). This remains significant after adjustment for relevant covariates (β = −0.85; 95%CI, −1.38 to −0.32; *P* = .002).

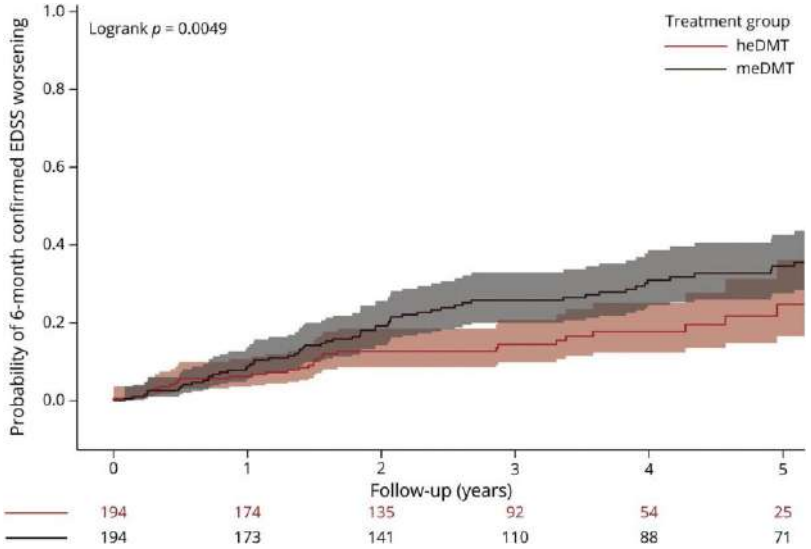
Median (95% CI) time to SAD was **6.0 (3.17-9.16) years for EIT** and **3.14 (2.77-4.00) years for ESC** (P = .05). For those within the ESC group who escalated to high-efficacy DMT as second-line treatment, median (95% CI) time to SAD was 3.3 years (1.8-5.6; compared with EIT group log-rank test P = .08).

In a real-life setting, long-term outcomes were more favorable following early intensive therapy vs first-line moderate-efficacy DMT.

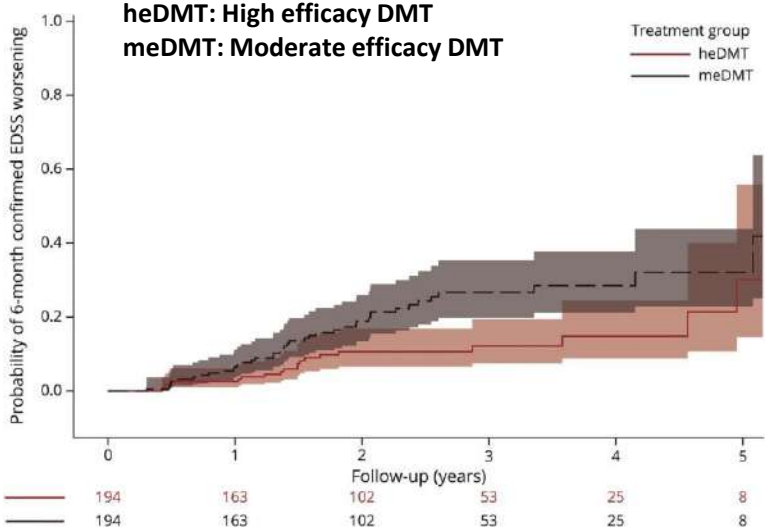
"Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis" K. Harding et al. – JAMA Neurology 2019

Initial high efficacy DMT

Probability of 6-month confirmed EDSS worsening. 1-Kaplan-Meier estimates



heDMT: High efficacy DMT
meDMT: Moderate efficacy DMT



- 388 patients from the Danish Multiple Sclerosis Registry
- heDMT: natalizumab, fingolimod, alemtuzumab, cladribine, daclizumab, or ocrelizumab
- meDMT: interferon-β, teriflunomide, dimethyl fumarate, or glatiramer acetate
- Propensity score matching

A **47% lower rate of EDSS worsening in the heDMT-group** compared with the meDMT-group (hazard ratio (HR) 0.53, 95% CI 0.33-0.83, p=0.006).

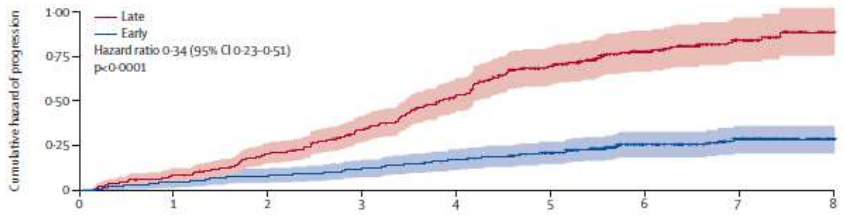
Patients initiating heDMT also had **a lower probability of a first relapse** (HR 0.50, 95% CI 0.37-0.67).

"Initial high-efficacy disease-modifying therapy in multiple sclerosis: A nationwide cohort study" Buron et al. – Neurology 2020

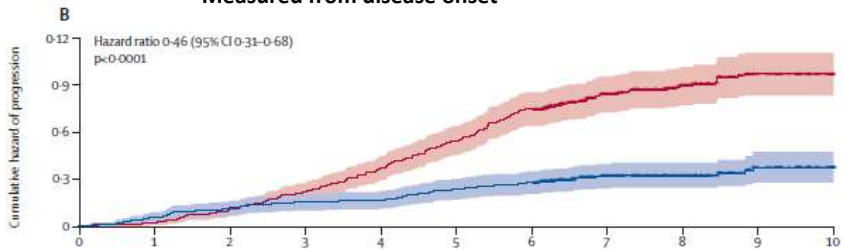
Timing of high efficacy therapy

Cumulative hazard of confirmed disability progression

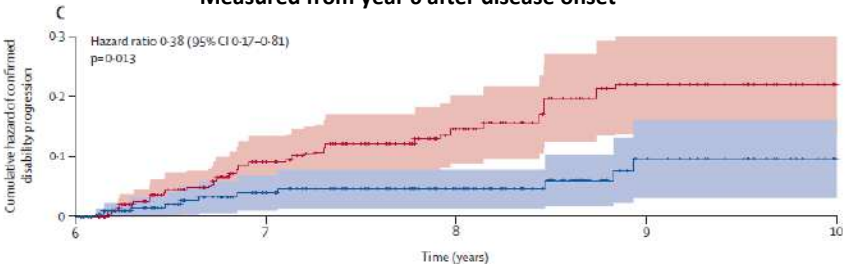
From commencement of first disease-modifying therapy



Measured from disease onset



Measured from year 6 after disease onset



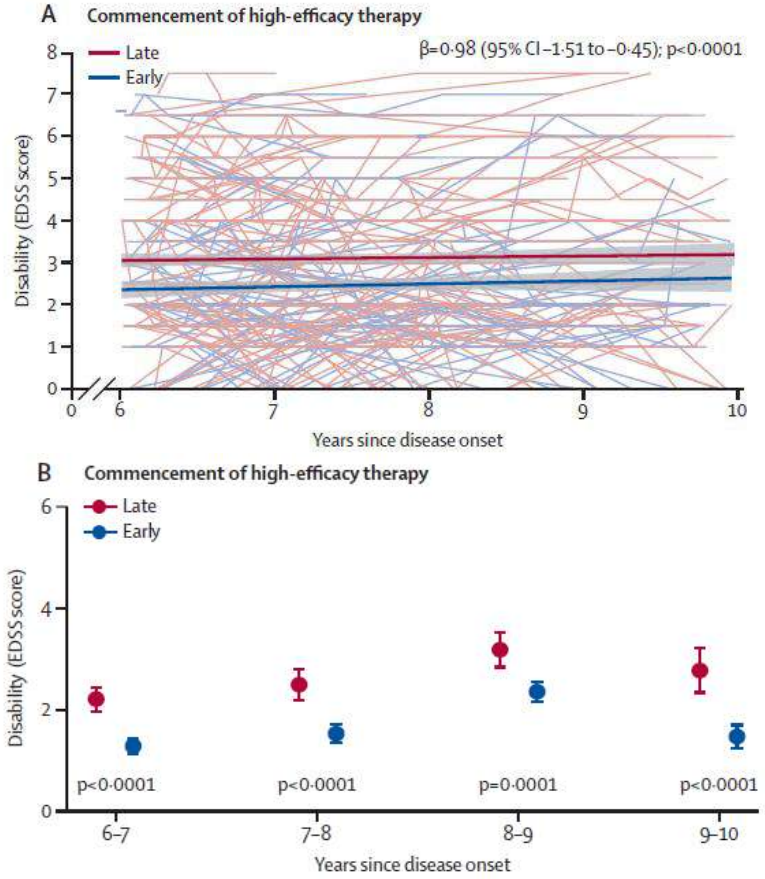
- Data from MSBase and Swedish MS Registry
- Patients with RRMS who commenced high-efficacy DMT (**Rituximab, Ocrelizumab, MTX, Alemtuzumab, Natalizumab**) either 0-2 years (early) or >4 years (late) after clinical disease onset.
- Outcomes were assessed at years 6 to 10 after onset: EDSS and cumulative hazard of confirmed disability progression. Assessing with a linear mixed-effects model.

Patients in the early treatment group had a lower hazard of confirmed disability progression than those in the late treatment group. This pattern was seen when cumulative hazards were compared from the date of starting first disease-modifying therapy (HR 0.34, 95% CI 0.23–0.51; p<0.0001) and when compared from the date of disease onset (0.46, 0.31–0.68; p=0.0001; figure 3) and after 6 years (HR 0.38, 95% CI 0.17–0.81; p=0.013).

«Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study» A. He – Lancet Neurology 2020

Timing of high efficacy therapy

Disability trajectories 6–10 years after disease onset in patients with RRMS treated early versus late with high-efficacy therapy

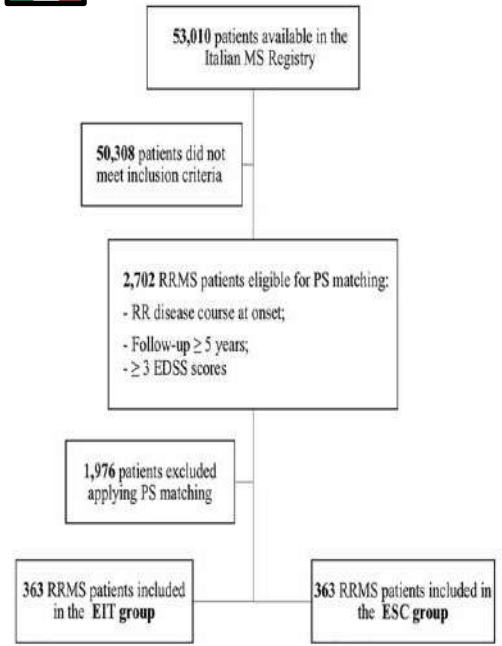


In the sixth year after disease onset, the **mean EDSS score was 2.2 (SD 1.6) in the early group compared with 2.9 (SD 1.8) in the late group (p<0.0001).** This difference persisted throughout each year of follow-up until the tenth year after disease onset (mean EDSS score 2.3 [SD 1.8] *vs* 3.5 [SD 2.1]; p<0.0001), with a difference between groups of –0.98 (95% CI –1.51 to –0.45; p<0.0001, adjusted for proportion of time on any disease-modifying therapy) across the 6–10 year follow-up period.

High-efficacy therapy commenced within 2 years of disease onset is associated with less disability after 6–10 years than when commenced later in the disease course.

«Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study» A. He – Lancet Neurology 2020

Early intensive therapy: Long-term disability trajectories



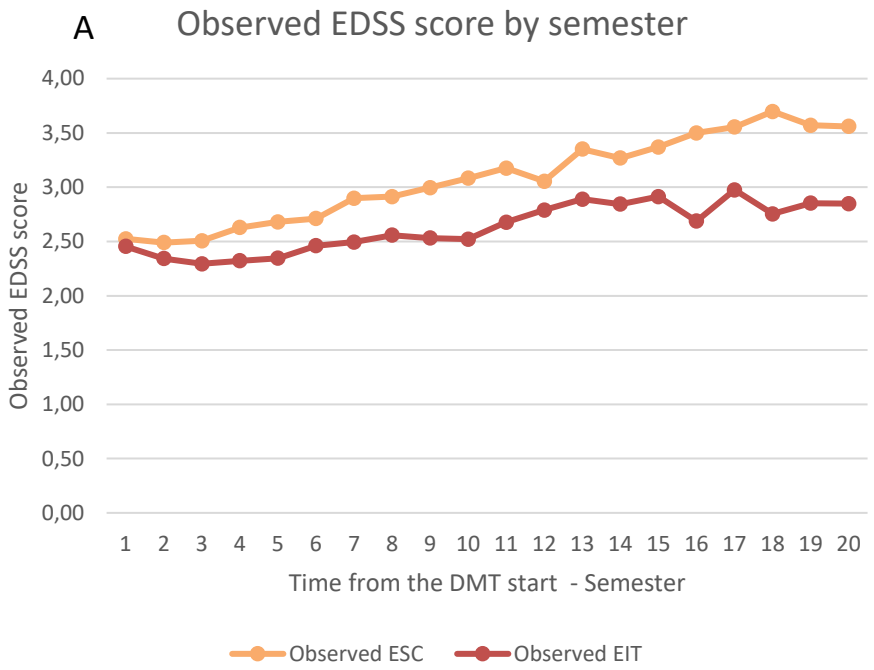
- The study has been conducted **using longitudinal design** derived from respectively acquired **clinical data extracted from the IMSR**
- **EIT group** included patients who received, as first DMT, **fingolimod, natalizumab, mitoxantrone, alemtuzumab, ocrelizumab or cladribine.**
- **ESC group** included those who received the **high efficacy DMT after ≥1 year of glatiramer acetate, interferons, azathioprine, teriflunomide or dimethylfumarate treatment.**

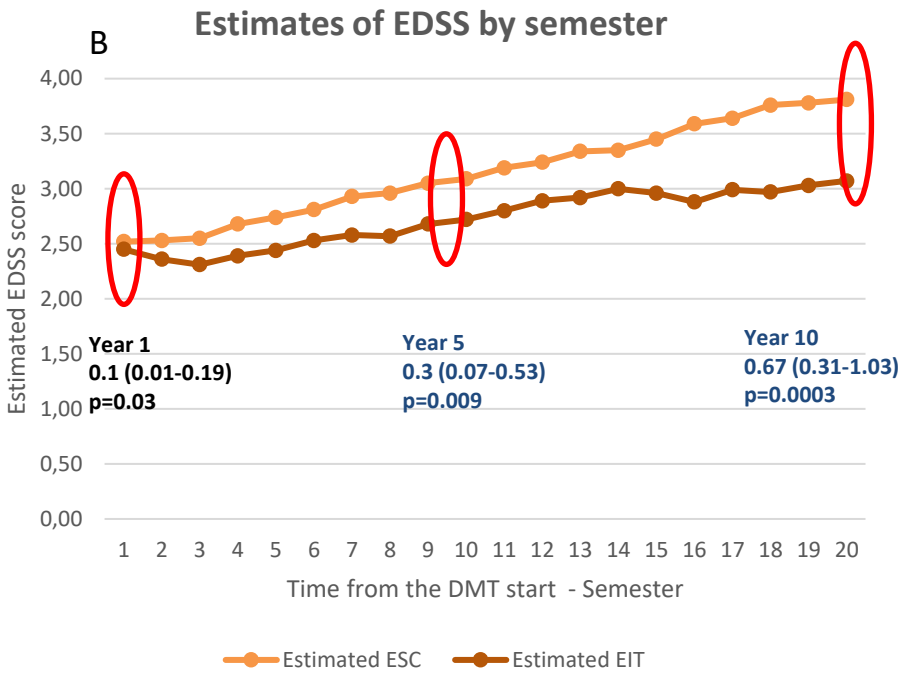
Table 1. Comparison of clinical and demographic features between ESC and EIT groups before and after PS matching.

Variable	Before PS matching			After PS matching		
	ESC *n* = 2337	EIT *n* = 365	SMD	ESC *n* = 363	EIT *n* = 363	SMD
Female sex, *n* (%)	1541 (65.94)	240 (65.75)	−0.39	222 (61.16)	240 (66.12)	10.32
Age at first DMT, mean (SD), years	29.37 (9.22)	31.13 (10.06)	18.19	30.28 (9.26)	31.04 (10.02)	7.84
Time to first DMT, mean (SD), months	14.04 (9.64)	12.69 (9.61)	−14.10	12.92 (9.74)	12.73 (9.61)	−1.87
EDSS at the DMT start, mean (SD)	1.85 (1.26)	2.63 (1.60)	54.60	2.63 (1.54)	2.61 (1.57)	−1.24
Number of EDSS evaluations from the first DMT, mean (SD)	24.43 (16.75)	21.99 (15.71)	−15.01	22.24 (15.03)	22.05 (15.72)	−1.24
Number of patients with relapses in the last 2 years before DMT start, mean (SD)	2007 (85.88)	315 (86.30)	-	308 (84.85)	313 (86.23)	-
Onset type, mean (SD)						
Monofocal	1992 (85.24)	315 (86.30)	3.05	296 (81.54)	314 (86.50)	13.56
Multifocal	345 (14.76)	50 (13.70)	-	67 (18.46)	49 (13.50)	-

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EIT, early intensive treatment; ESC, escalation approach; *N*, number; PS, propensity score; SD, standard deviation; SMD, standardized mean difference.

Comparison of disability trajectories of the observed (A) and of the estimated (B) EDSS scores by semester between the ESC and EIT groups.





The mean delta-EDSS differences between the two groups tend to increase from 0.1 at year 1, to 0.3 at year 5 and to 0.67 at year 10.

"Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies" P. Iaffaldano et al. – Ther Adv Neurol Disord 2021

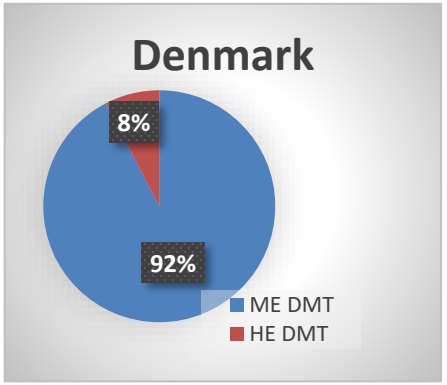
Comparison of treatment strategies at national level

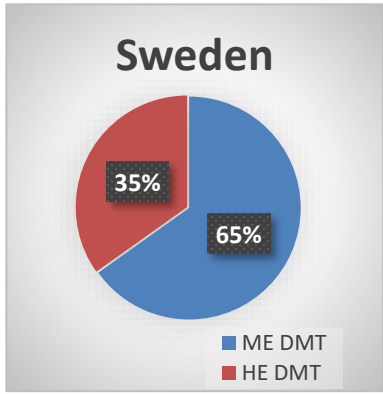
JAMA Neurology | Original Investigation

Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients With Relapsing-Remitting Multiple Sclerosis

Data From 2 Different National Strategies

Tim Spelman, PhD, MD; Melinda Magyari, PhD, MD; Fredrik Piehl, PhD, MD; Anders Svenningsson, PhD, MD; Peter Vestergaard Rasmussen, PhD, MD; Matthias Kant, PhD, MD; Finn Sellebjerg, PhD, MD; Hanna Joensen, BScScientBibl, GradDipB; Jan Hillert, PhD, MD; Jan Lycke, PhD, MD





Key Points

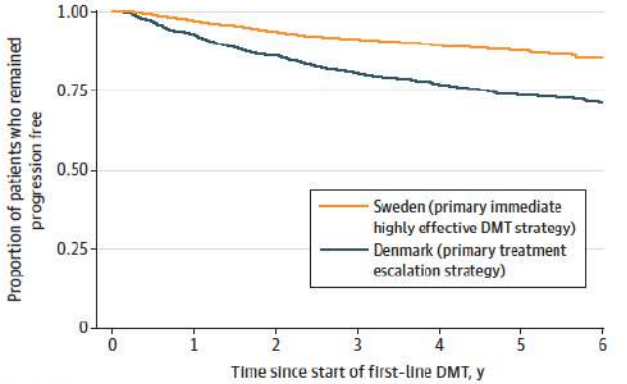
Question How are differences in national treatment strategies for multiple sclerosis associated with clinical outcomes?

Findings In this cohort study comparing patients in the Danish and Swedish multiple sclerosis registries, the use of highly effective disease-modifying treatment was far more frequent in the Swedish cohort and was associated with significant reductions in the rate of confirmed disability worsening and relapse outcomes.

Meaning This study suggests that escalation of treatment was inferior to using a more effective disease-modifying treatment as initial treatment for multiple sclerosis.

Selection criteria:
First DMT 2013-2016

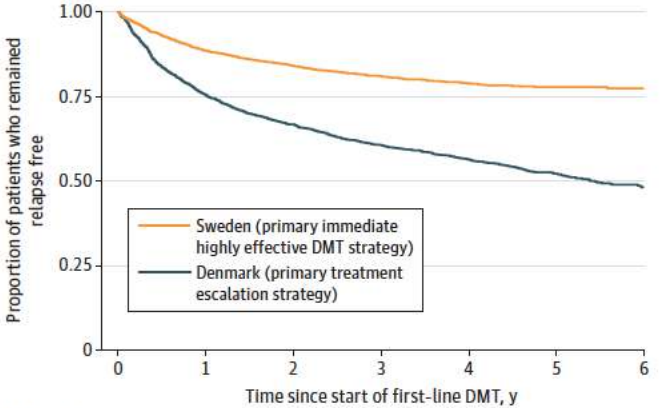
Figure 1. Time to Confirmed Disability Progression by Treatment Strategy Cohort



No. at risk

Denmark	2161	1941	1745	1459	1029	587	256
Sweden	2700	2378	2047	1434	860	368	57

Figure 2. Time to First Relapse by Treatment Strategy Cohort



No. at risk

Denmark	2161	1579	1361	1097	758	441	174
Sweden	2700	2216	1922	1380	842	390	69

Conclusions

The superiority of high-efficacy DMTs in comparison to the traditional first-line MS therapies have been consistently proven by different randomized clinical trials (RCTs) and/or observational studies.

Indirect comparisons from extension arms and subgroup analyses of randomized trials suggest that high-efficacy therapies are associated with improved control of relapse activity when initiated earlier after MS onset.

Recent observational studies showed evidence that early initiation of highly effective therapy in RRMS may provide more benefit that an escalation approach in decreasing the risk of developing secondary progression and disability accrual up to 10 years of follow-up.