IX NAPLES MEETING - 1 Dicembre 2023 - Napoli

II Sessione – Towards new therapeutic Strategies

DMT Start

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Disclosures

Carlo Pozzilli has served on scientific advisory boards for Bristol Meyer, Novartis, Merck, Biogen, Roche, Janssen, Alexion, Almirall and has received research support from Merck, Biogen , Bristol Meyer, Novartis and Roche.

THE LANCET

Published: November 07, 2023DOI:https://doi.org/10.1016/S0140-6736(23)01473-3

Multiple Sclerosis I

Multiple sclerosis remains one of the most common causes of neurological disability in the young adult population (aged 18–40 years).

Novel pathophysiological findings underline the importance of the interaction between genetics and environment.

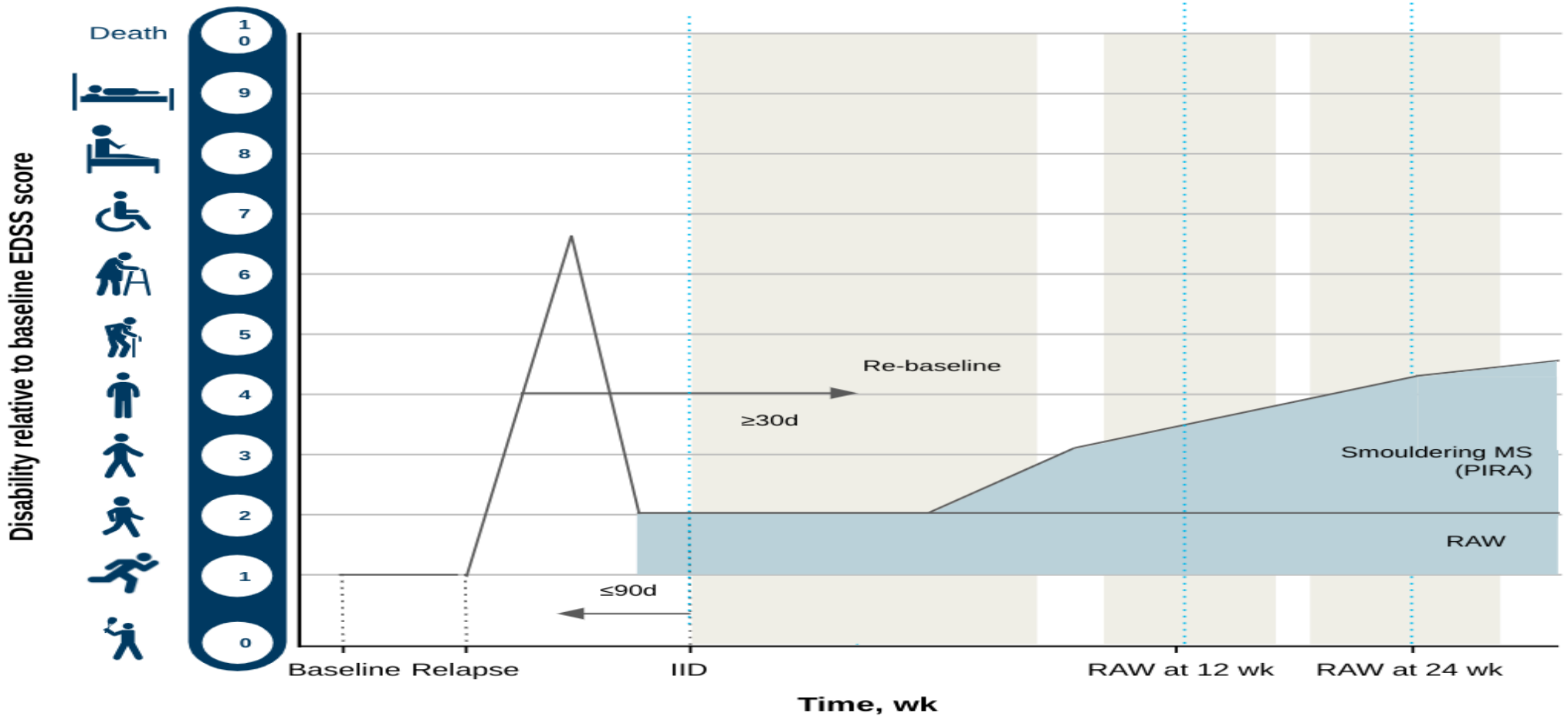
Improvements in diagnostic criteria, harmonised guidelines for MRI, and globalised treatment recommendations have led to more accurate diagnosis and an earlier start of effective immunomodulatory treatment than previously.

Multiple sclerosis II

Understanding and capturing the long prodromal multiple sclerosis period would further improve diagnostic abilities and thus treatment initiation, eventually improving long-term disease outcomes.

The large portfolio of currently available medications paved the way for personalised therapeutic strategies that will balance safety and effectiveness. Incorporation of cognitive interventions, lifestyle recommendations, and management of non-neurological comorbidities could further improve quality of life and outcomes.

Giovannoni et al. Smouldering multiple sclerosis: the 'real MS'. Ther Adv Neurol Disord 2022, Vol. 15: 1–18.

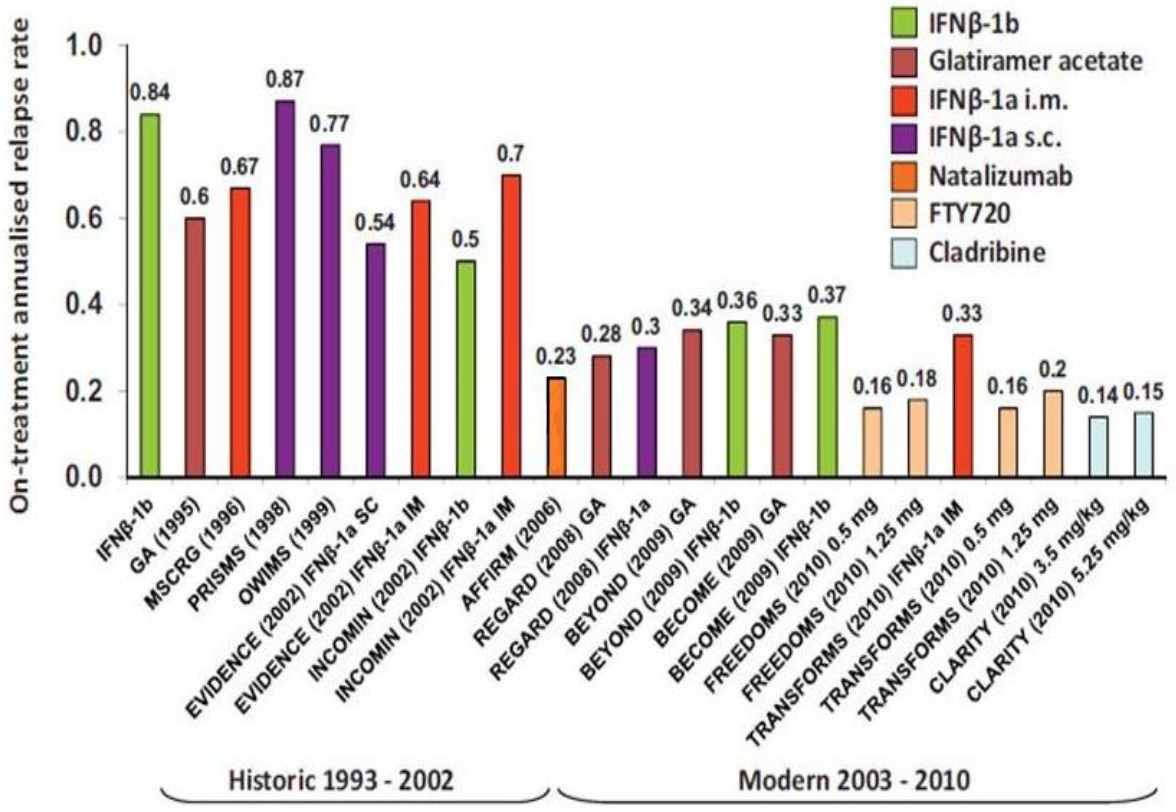


EDSS indicates Expanded Disability Status Scale; IID indicates initial increase of disability; MS, multiple sclerosis.

The new natural history of multiple sclerosis

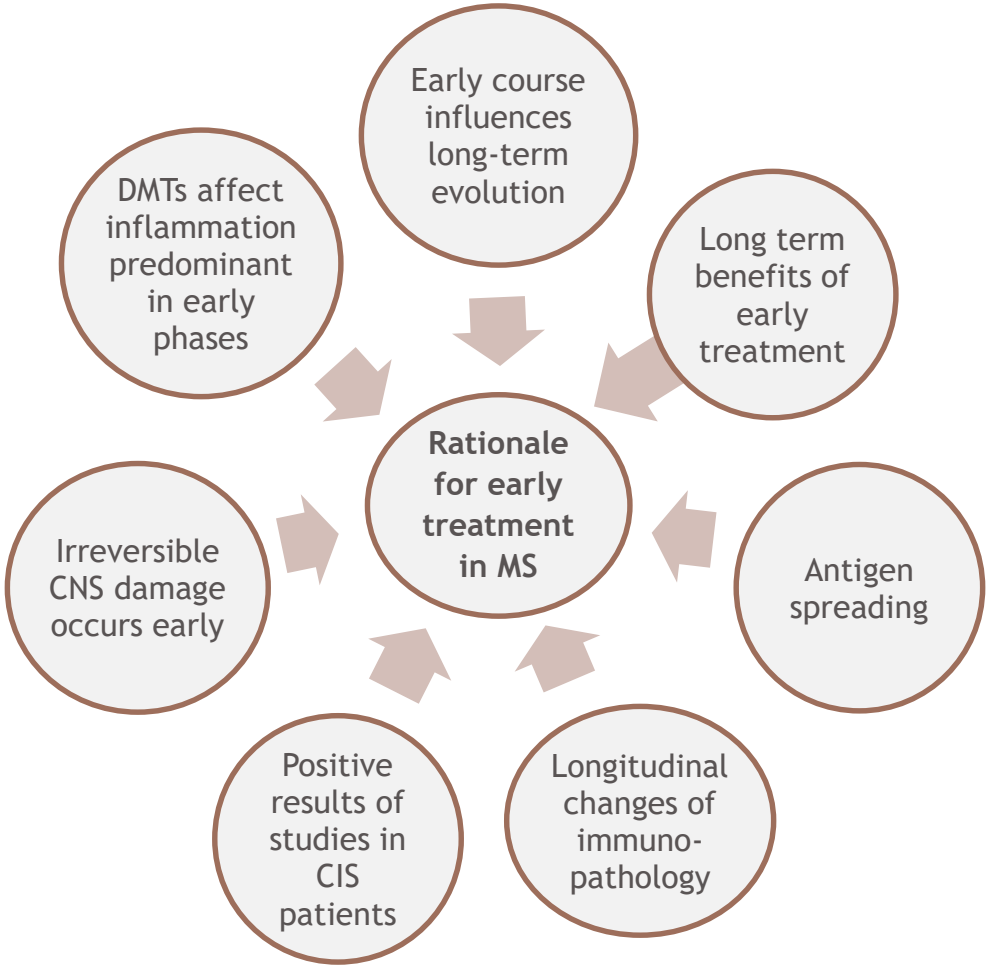
- In RRMS, disability accumulation was thought to result from incomplete recovery from relapses, until relapse-independent disability occurs [1]
- **Effective therapies have reduced attacks in most patients, however, a "silent progression" independent of relapse activity still may occur and is now evident in RRMS** [1,2]
- The effectiveness of the DMTs against silent progression and on associated measures of brain atrophy is likely to represent a key determinant of their relative value [2]

Where have all the relapses gone?



S. Wolinsky, ACTRIMS 2008.

Rationale for early treatment of multiple sclerosis



Disease severity and recovery mechanisms that may become less effective during the course of MS are also considered as a rationale for early treatment

CIS, clinically isolated syndrome; CNS, central nervous system; DMTs, disease modifying therapies; MS, multiple sclerosis

Comi G et al. *Lancet*. 2017;389(10076):1347-1356. Figure adapted with permission from *lancet*

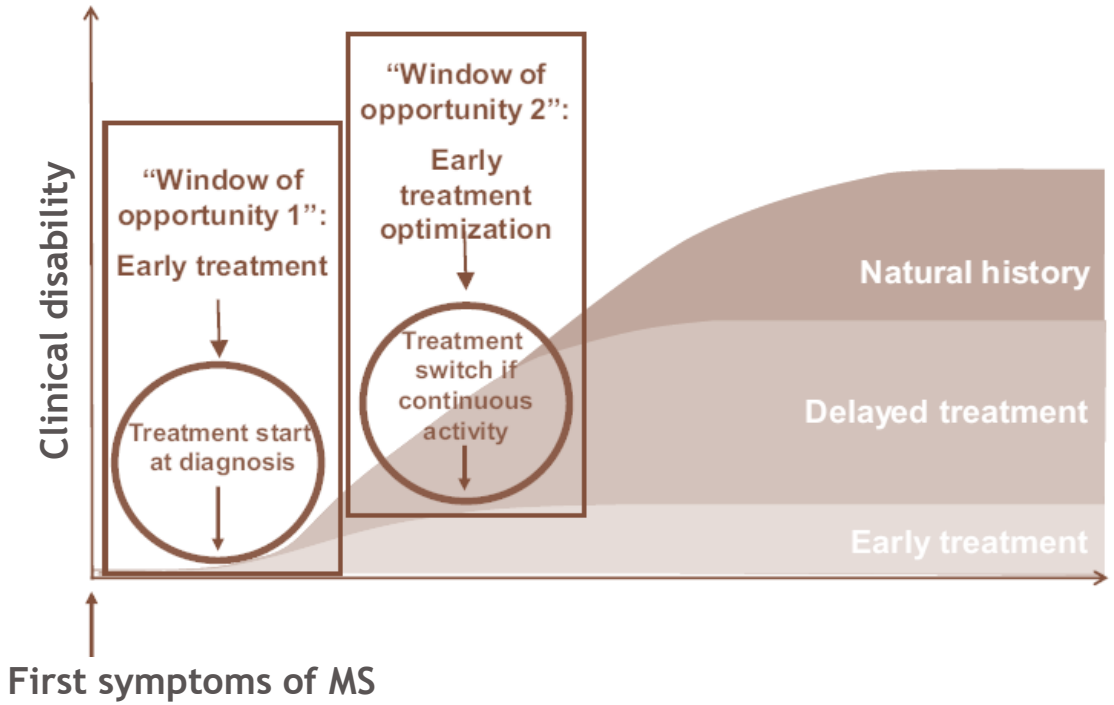
The window of therapeutic opportunity in multiple sclerosis

The benefit-risk profile for a given treatment is not constant during the course of MS[1]

Benefits tend to be greater in the earlier phases, whereas risks tend to increase with disease evolution, age and comorbidities[1]

Early initiation of more efficacious DMTs has shown benefits in different clinical studies in MS suggesting a "window of opportunity" for treatment to achieve better results and long-term clinical outcomes [2,3,4,5,6,7,8]

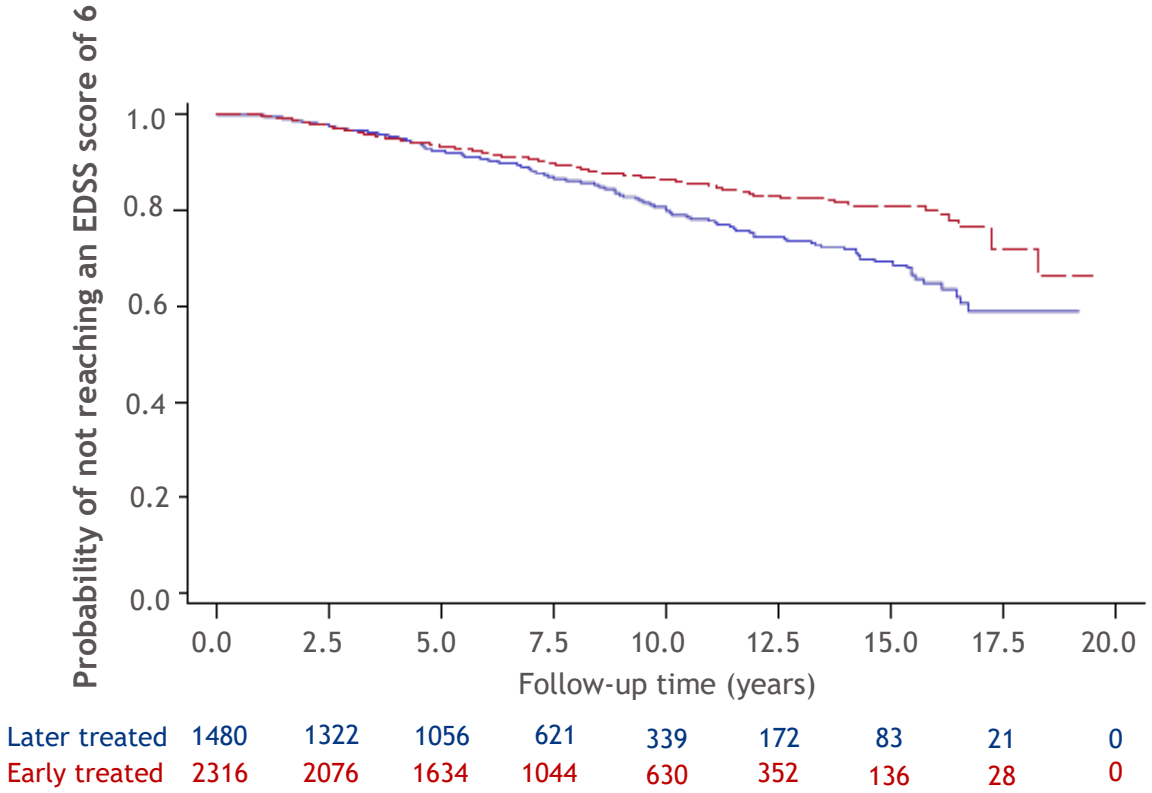
The window of opportunity for treatment in MS [8]



DMTs, disease-modifying therapies; MS, multiple sclerosis

1. Comi G et al. *Lancet*. 2017;389(10076):1347-1356. 2. Coban H et al. *Mult Scler Relat Disord*. 2021;47:102631. 3. Kavaliunas A et al. *Mult Scler*. 2017;23(9):1233-1240. 4. Brown JWL et al. *JAMA*. 2019;321(2):175-187. 5. He A et al. *Lancet Neurol*. 2020;19(4):307-316. 6. Iaffaldano P et al. *Mult Scler*. 2021;27(10):1543-1555. 7. Harding K et al. *JAMA Neurol*. 2019;76(5):536-541. 8. Ziemssen T et al. *J Neurol*. 2016;263(6):1053-1065. Figure reproduced with permission from *J Neurol*.

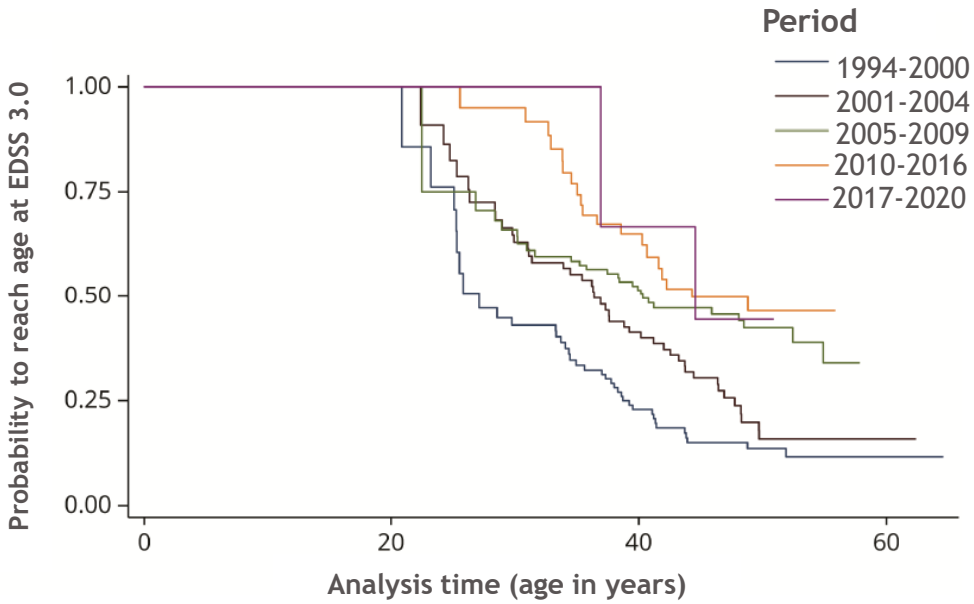
Early DMTs initiation from clinical onset might delay long-term disability in RRMS



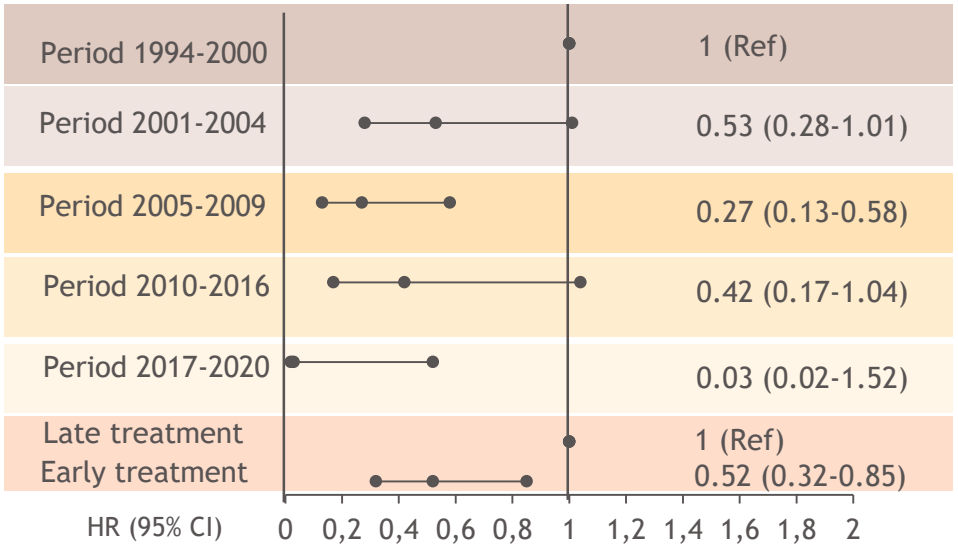
- A register-based cohort study compared long-term treatment effectiveness of DMT initiated early in RRMS patients (within 2 yrs. from clinical onset; 2316 patients) vs. later (2-8 yrs. from clinical onset; 1479 patients)
  - 10.2% of early-treated patients reached EDSS 6 vs. 16.5% of later-treated patients during a median follow-up of 7 and 6.9 yrs, respectively
  - Patients with later treatment showed 42% increased hazard of reaching an EDSS score of 6 compared with the early-treated patients [HR, 1.42; 95% CI, 1.18–1.70; $P < .001$]

Data prospectively collected from the Danish Multiple Sclerosis Treatment Register (DMSTR) and The Danish Multiple Sclerosis Registry for 3795 RRMS patients treated with DMT from the first drug approval in 1996 to October 2015. CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HR, hazard ratio; vs. versus; RRMS, relapsing remitting multiple sclerosis; yrs., years
Chalmer TA et al. *Eur J Neurol*. 2018;25(10):1262-e110. Figure reproduced with permission from *Eur J Neurol*.

Earlier treatment initiation with recent diagnostic criteria in MS may lower risk of reaching disability in CIS patients



Multivariate Cox regression analysis, applying McDonald 2017 criteria

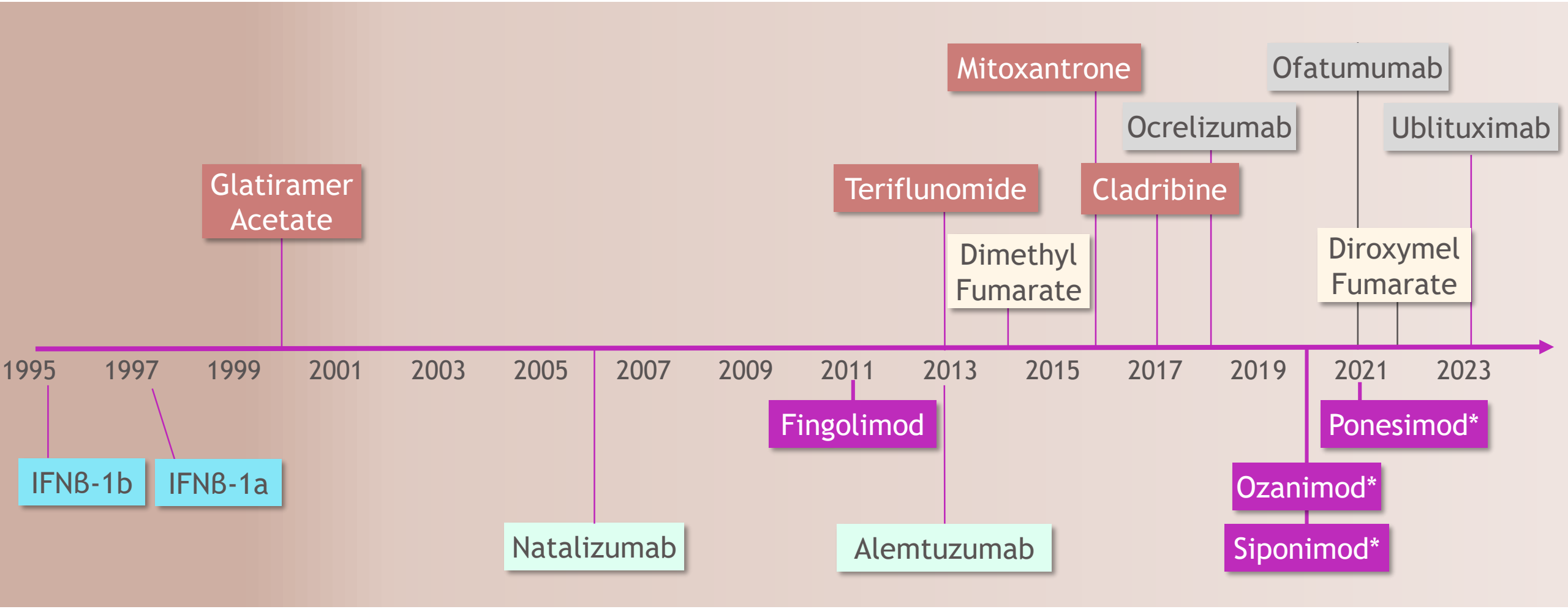


- Retrospective cohort study in CIS assessed whether time to MS diagnosis, time to treatment initiation, and age at which CIS patients reached an EDSS ≥ 3.0 changed according to different diagnostic criteria periods; 62.6% of patients had an MS diagnosis at any time (N = 1174)
- From the Poser (1994-2000) to the McDonald 2017 period (2017-2020),
  - **Proportion of patient with MS diagnosis increased from 25.2% to 55.1%, while median time to MS diagnosis and time to treatment initiation was reduced by 77% and 82%, respectively**
  - **Early-treatment was independently related to a lower risk of reaching ≥ EDSS 3.0 vs late-treatment patients (adjusted HR 0.53 [95% CI, 0.33-0.85])**

Barcelona-CIS cohort between 1994 and 2020 included 1174 CIS patients. Patients were classified into five periods according to different MS diagnostic criteria:

Ref,reference Tintore M et al. *Neurology.* 2021;97(17):e1641-e1652. Figures reproduced with permission from *Neurology*

The Evolving MS Treatment Landscape-EMA Approvals



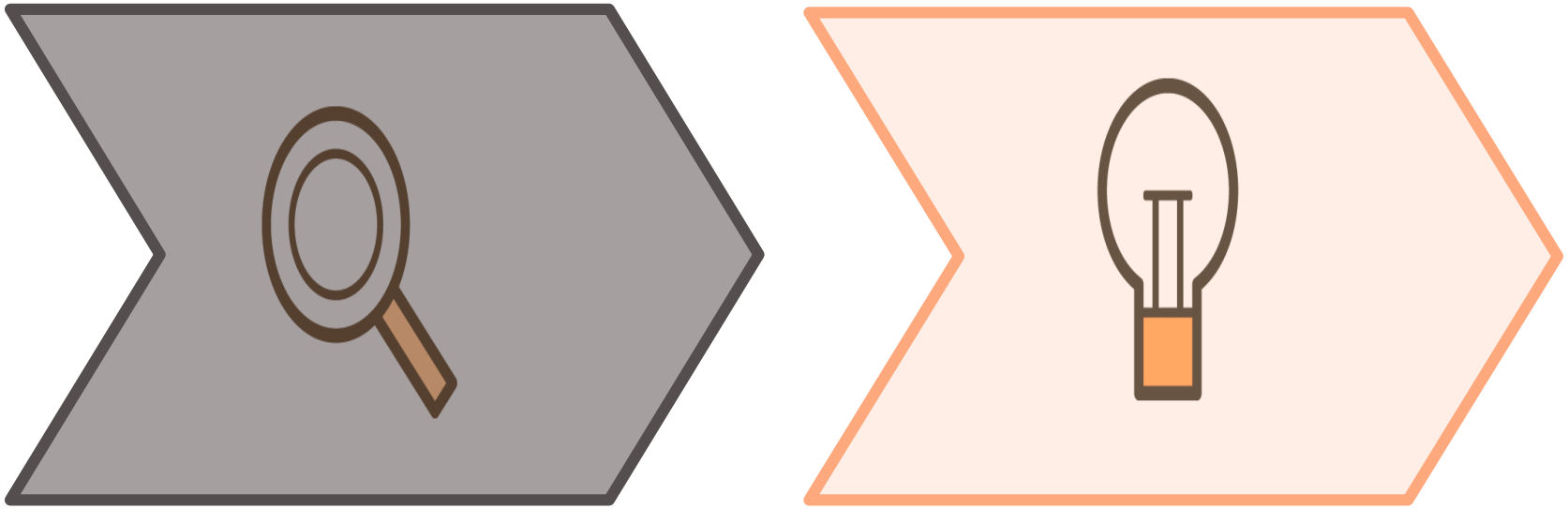
*Second generation sphingosine-1-phosphate receptor modulator. Image adapted from EMA Drug Approvals at www.ema.europa.eu; Faissner S and Gold R. 2022 CNS Drugs; Coyle PK, et al. 2018 Int J MS Care.

Towards a tailored approach to guide the therapeutic algorithm

Personalization of MS therapy involves two key components

Prediction of prognosis

Initial treatment decision



DMTs, disease modifying therapies; MS, multiple sclerosis . Rotstein D et al. *Nat Rev Neurol*. 2019;15(5):287-300.

Different predictors of poor prognosis in MS

Male gender[1]

Older age at onset[1]

Higher rate of relapse[1]

Shorter time between relapses[1]

Poor recovery & increased rate of progression[1]

Primary progressive disease course[1]

Higher EDSS score at diagnosis[1]

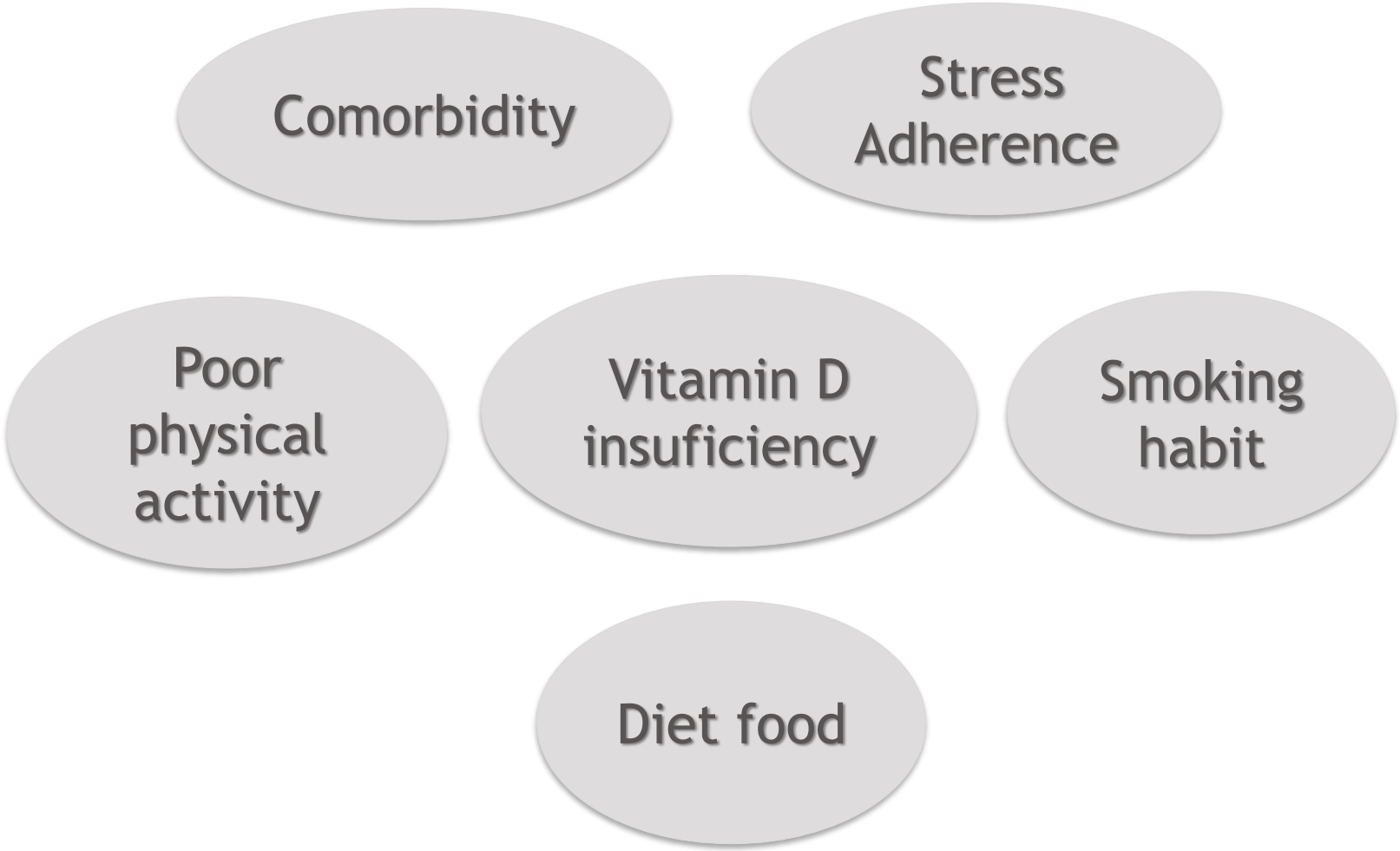
Polysymptomatic onset
Early cognitive deficits[1]

High number of T2 lesions
High T2 lesion volume
WB or GM atrophy
Spinal cord lesions[1] or atrophy[2]

High NfL levels[a]
IgG, IgM[b]
High chitinase levels[b]

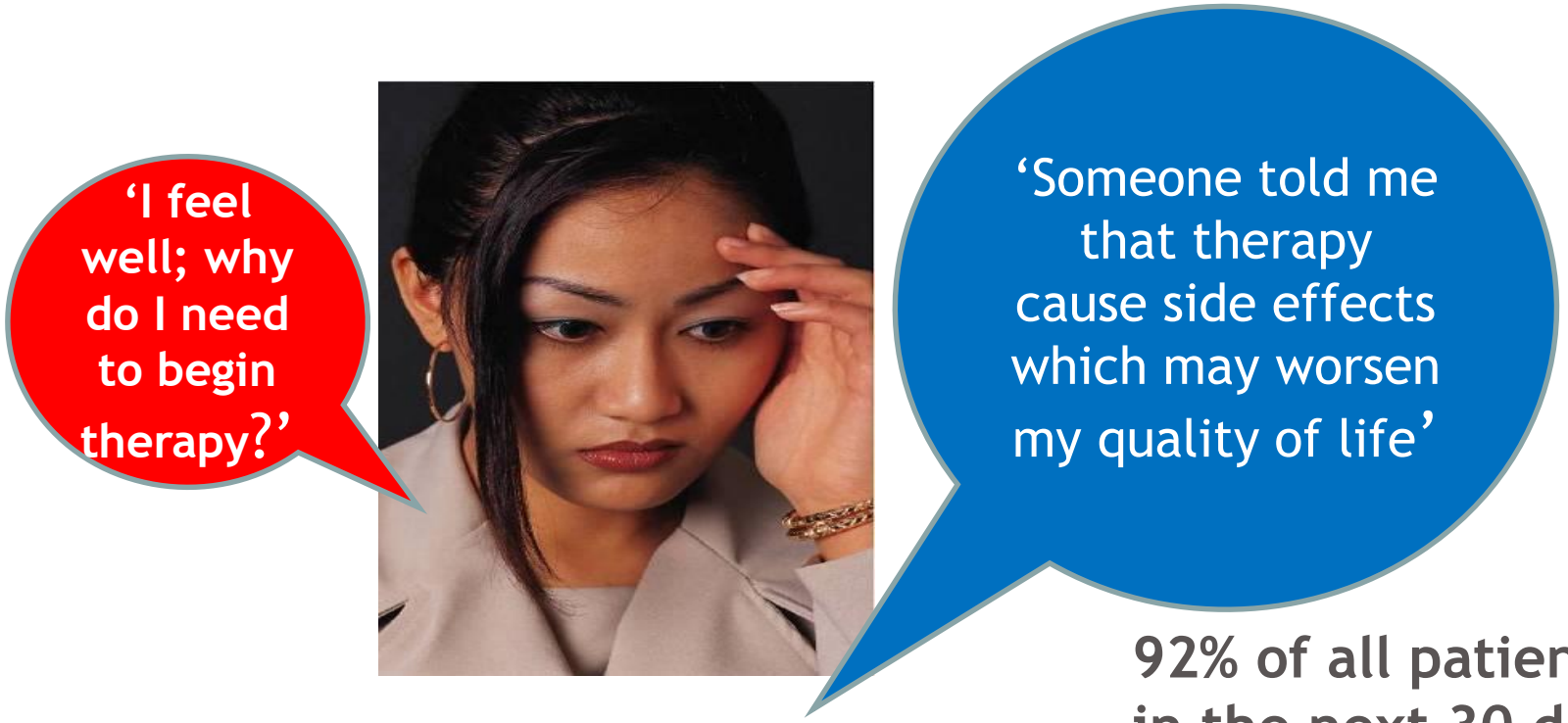
[a] in serum and CSF; [b] in the CSF
CSF, cerebrospinal fluid; EDSS, Expanded disability status scale; GM, gray matter; MS, multiple sclerosis; NfL, neurofilament light chain; WB, whole brain.
1. Rotstein D, Montalban X. *Nat Rev Neurol*. 2019;15(5):287-300. 2. Bischof A et al. *Ann Neurol*. 2022;91(2):268-281.

Poor outcome (prognostic factors)



Predictive Adherence Targeting

Swoop, a New York-based consumer health data company, has launched a first-of-its-kind targeting algorithm designed to predict the likelihood of patients becoming non adherent. **The methodology, called Predictive AI Adherence Targeting, applies machine learning (ML) and artificial intelligence (AI) approaches .**



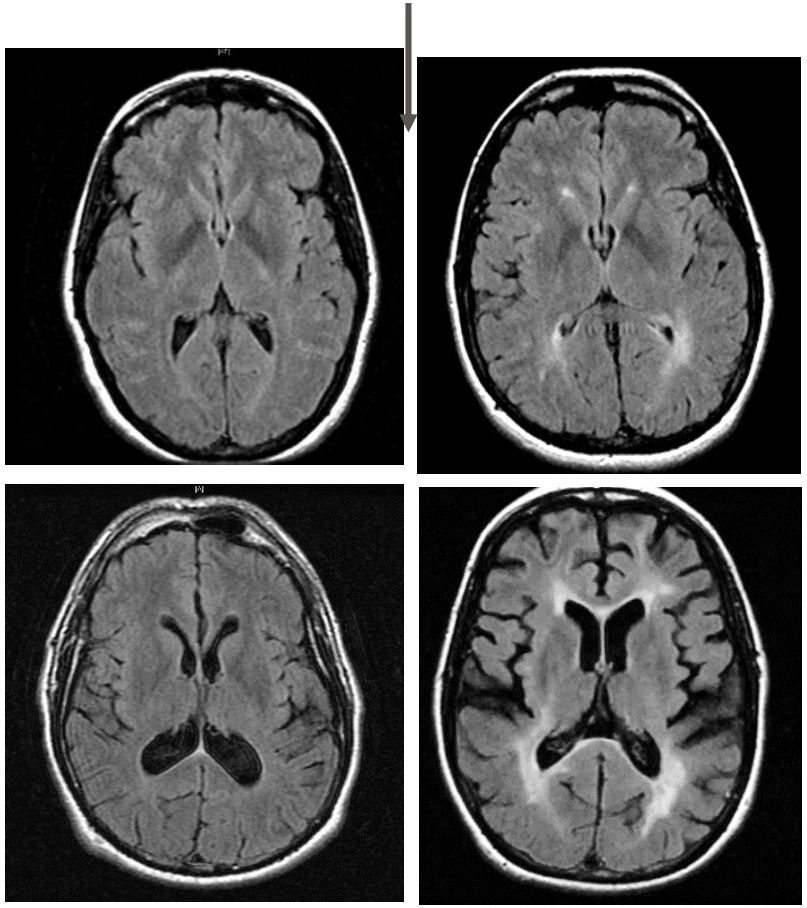
According to the World Health Organization, an estimated 50% of patients with chronic conditions are non adherent with their treatments or medications. Non adherence contributes to treatment failure and raises healthcare costs.

92% of all patients who became non-adherent in the next 30 days were accurately predicted for a multiple sclerosis treatment

Predict therapeutical response based on MRI imaging pathology

T2-hyperintense lesion volume

Type I
-Low atrophy
-Low T2LV



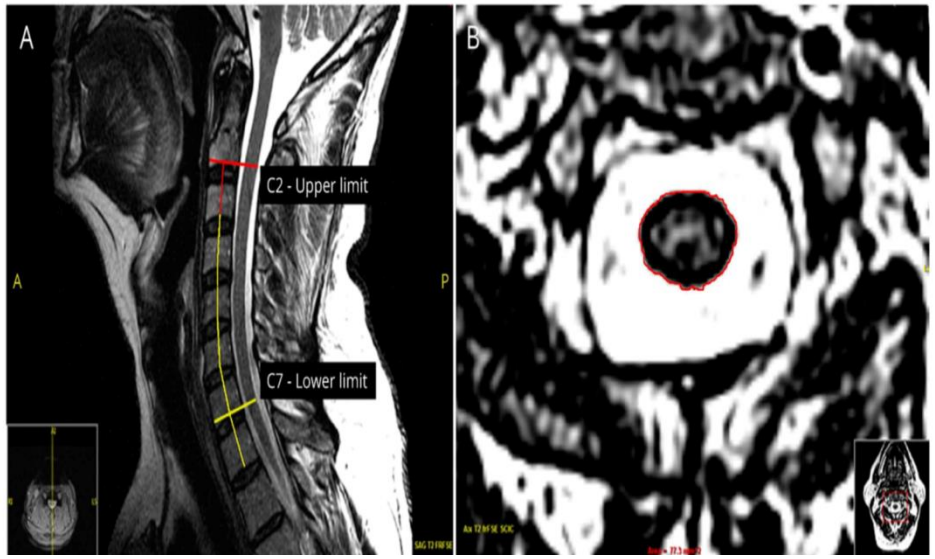
Type II
-Low atrophy
-High T2LV

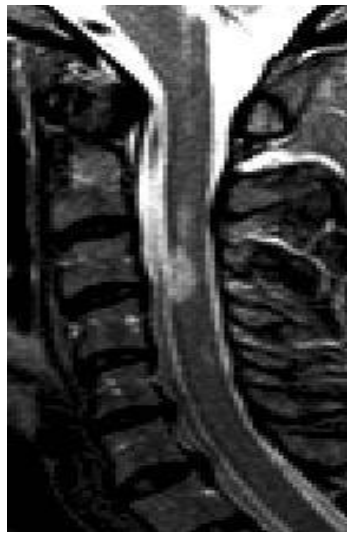
Type III
-High atrophy
-Low T2LV

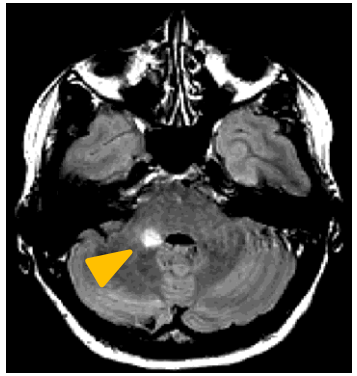
Type IV
-High atrophy
-High T2LV

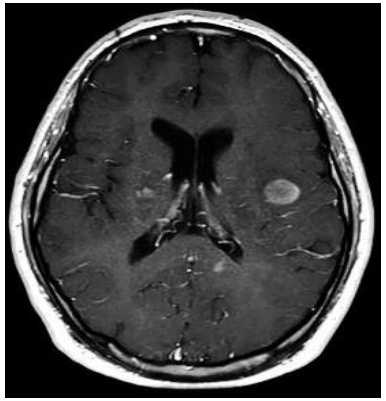
Tauhid S et al. MRI phenotypes based on cerebral lesions and atrophy in patients with multiple sclerosis. J Neurol Sci 2014;346:250-4.

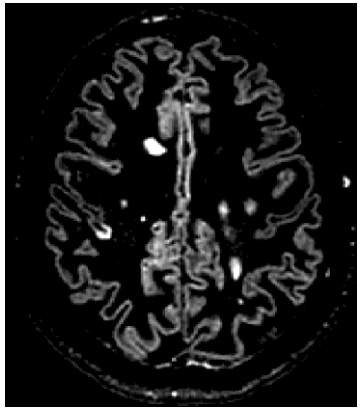
MRI negative prognostic factors in MS











Neuroradiological factors
Higher number and volume of T2-hyperintense lesions
Brainstem and cerebellar lesions
Spinal cord lesions (especially affecting the central GM)
T1-hypointense lesions (“black-holes”)
Cortical lesions
Presence of gadolinium-enhancing lesions
New T2 lesions formation in the first 5 years
Chronic active lesions (paramagnetic iron rim or slowly-expanding)
Brain atrophy (especially GM)
Spinal cord atrophy (especially GM)

Filippi et al. J Neurol 2022 et al,

Age and Spinal cord lesions predict progression independent relapse activity (PIRA) but not relepse activity Worsening (RAW) in the long term period.

Table 3 Competing Risk Regression Analyses for RAW and PIRA on 224 Patients With No Evident Disease Activity After the First 2 Years of Treatment

	RAW (n = 31)		PIRA (n = 27)	
	Adjusted SHR (95% CIs)	*p* Value	Adjusted SHR (95% CIs)	*p* Value
Male sex	1.84 (0.89–3.82)	0.10	0.77 (0.28–2.08)	0.60
Age (each y)	1.02 (0.97–1.07)	0.51	1.05 (1.01–1.10)	0.036
Comorbidity	0.78 (0.26–2.29)	0.65	1.88 (0.84–4.26)	0.13
Efferent symptom onset	1.72 (0.62–4.64)	0.29	1.06 (0.44–2.56)	0.89
Disease duration (each y)	1.00 (0.91–1.08)	0.93	1.03 (0.96–1.10)	0.46
EDSS score (each step)	0.79 (0.49–1.26)	0.32	1.37 (0.77–2.41)	0.28
Annualized relapse rate (each unit)	1.25 (0.56–2.76)	0.58	0.99 (0.39–2.52)	0.98
>9 brain lesions	3.92 (1.36–11.29)	0.012	0.88 (0.20–3.86)	0.87
Infratentorial lesions	1.28 (0.49–3.12)	0.61	1.52 (0.66–3.53)	0.33
Spinal cord lesions	1.11 (0.46–2.70)	0.81	4.08 (1.29–12.87)	0.016
Contrast-enhancing lesions	2.38 (1.01–5.63)	0.047	0.62 (0.26–1.49)	0.29
Treatment interruption (time-varying covariate)	1.11 (1.02–1.21)	0.015	1.04 (0.94–1.16)	0.43

Abbreviations: CIs = confidence intervals; EDSS = Expanded Disability Status Scale; PIRA = progression independent from relapse activity; RAW = relapse-associated worsening; SHR = subdistribution hazard ratio.

Prosperini L et al, Neurol Neuroimmunol Neuroinflamm 2021

Both the number and volume of SC lesions on MRI are associated with future accumulation of disability largely independent of relapses.

Multiple sclerosis

OPEN ACCESS

Original research

Prognostic value of spinal cord lesion measures in early relapsing-remitting multiple sclerosis

Markus Lauerer [1,2] Julian McGinnis [1,3] Matthias Bussas,[1,2] Malek El Husseini,[4] Viola Pongratz,[1,2] Christina Engl,[1] Alexander Wuschek,[1] Achim Berthele,[1] Isabelle Riederer,[4] Jan S Kirschke [4] Claus Zimmer,[4] Bernhard Hemmer [1,5] Mark Mühlau [1,2]

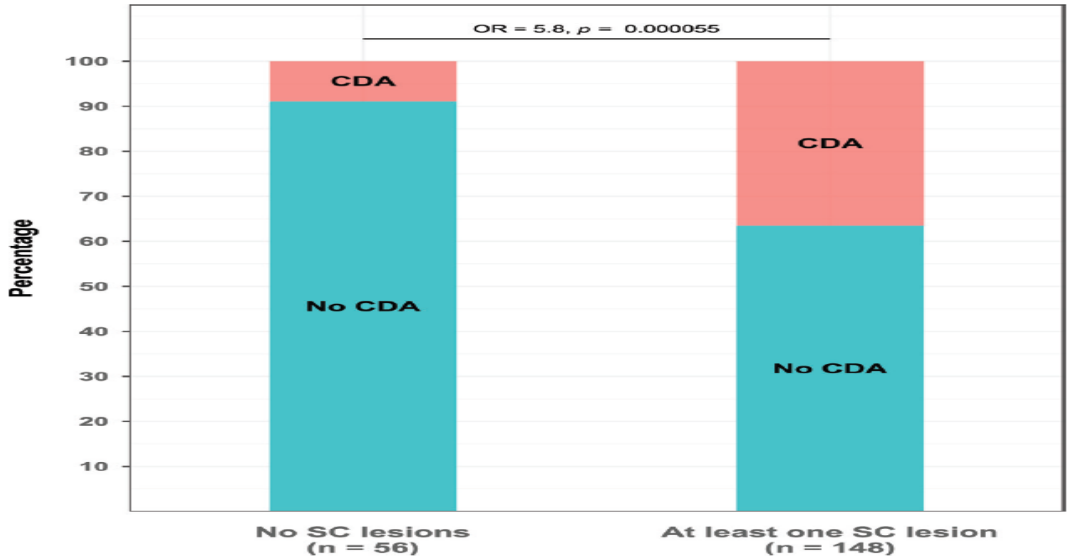
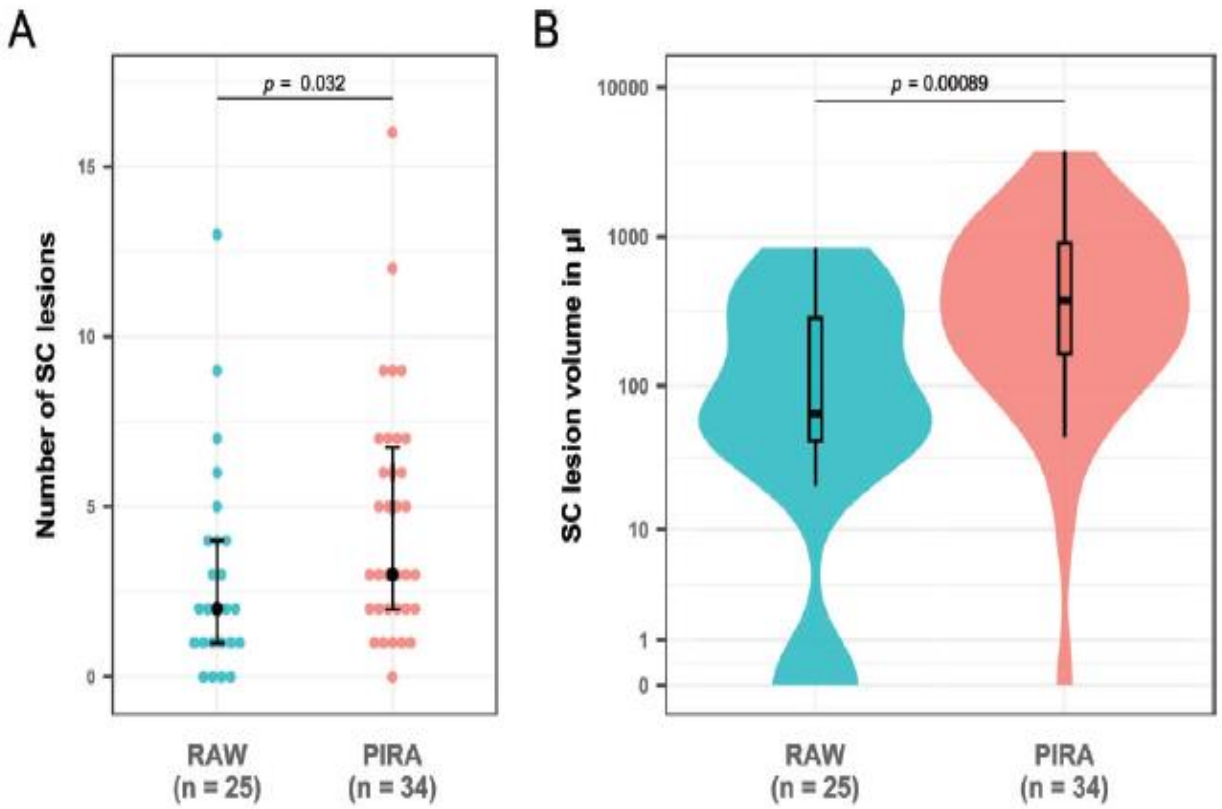


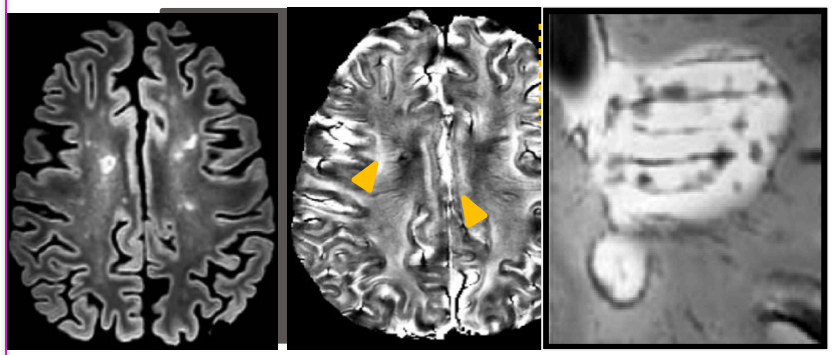
Figure 2 Rate of CDA on follow-up in patients with and without SC lesions. Bar plot showing percentages of disability worsening in both groups. Fisher's exact test was performed for between-group comparison. CDA, confirmed disability accumulation; SC, spinal cord.



Laurer M.J. Neurol. Neurosurg. Psychiatry 2023

Promising MRI markers to identify PIRA

Slowly-evolving lesions. Slowly-evolving lesions have been suggested as one of the pathological substrates contributing to disability progression in MS .



≥ 4 rim positive lesions
Having four or more rim lesions has been associated with more severe brain atrophy, earlier development of motor disability and cognitive impairment and a 3.2-fold higher prevalence of PMS.[1]

These lesions are characterized by a paramagnetic hypointense rim on susceptibility-based sequences, a slow rate of increase in size, more limited lesional repair, and lower T1 signal intensity compared to not evolving lesions.

[1] Absinta M et al, Jama Neurology 2019; [2]Derakhshan M et al, Human brain mapping 2014

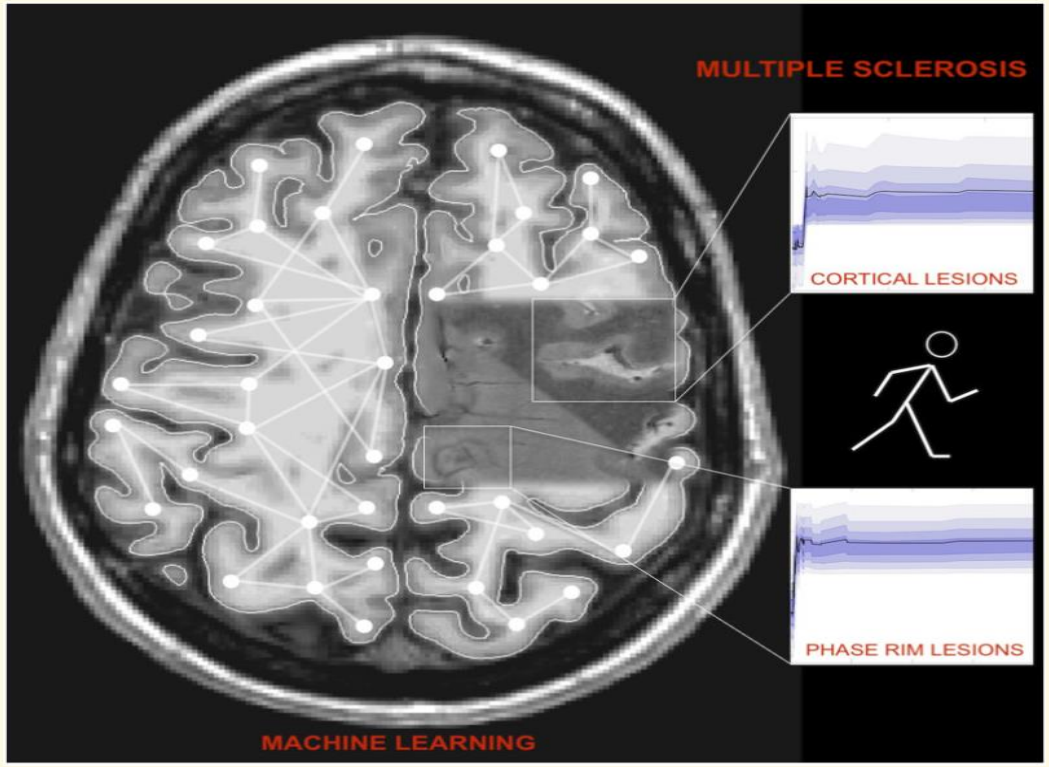
doi:10.1093/braincomms/fcab134 BRAIN COMMUNICATIONS 2021: Page 1 of 14 | 1

BRAIN COMMUNICATIONS

Cortical and phase rim lesions on 7 T MRI as markers of multiple sclerosis disease progression

Constantina A. Treaba,[1,2] Allegra Conti,[3] Eric C. Klawiter,[4] Valeria T. Barletta,[1,2] Elena Herranz,[1,2] Ambica Mehndiratta,[1] Andrew W. Russo,[4] Jacob A. Sloane,[5] Revere P. Kinkel,[6] Nicola Toschi[1,3,*] and Caterina Mainero[1,2,*]

Graphical Abstract



Using a modern machine learning algorithm the authors demonstrate that cortical lesions are extremely frequent in MS while rim lesions development occurs only in a subset of patients

Both, however persist over time and related to disease progression. Their combined assessment is needed to improve the ability of identifying MS patients at risk of progressive disease

JAMA Neurology | Original Investigation

Neurofilament Light Chain Elevation and Disability Progression in Multiple Sclerosis

Key Points

Question When does neuroaxonal pathology occur in people with multiple sclerosis (MS) who experience disability worsening?

Findings In this cohort study including 1899 individuals, serum neurofilament light chain elevation, as a sign of accelerated neuroaxonal injury, was detected approximately 1 year preceding disability worsening events associated with relapses and 1 to 2 years before worsening events independent of clinical relapses.

Meaning Pronounced neuroaxonal damage precedes disability worsening events with or without preceding clinical relapses in people with MS, providing novel insights into the mechanisms contributing to accumulated worsening, their timing, and defining a potential window of dynamic central nervous system pathology that can be targeted with abortive therapies.

Figure 2. Future Risk of Confirmed Disability Worsening With Clinical Relapses (CDW-R) Based on Neurofilament Light Chain (NfL) *z* Score

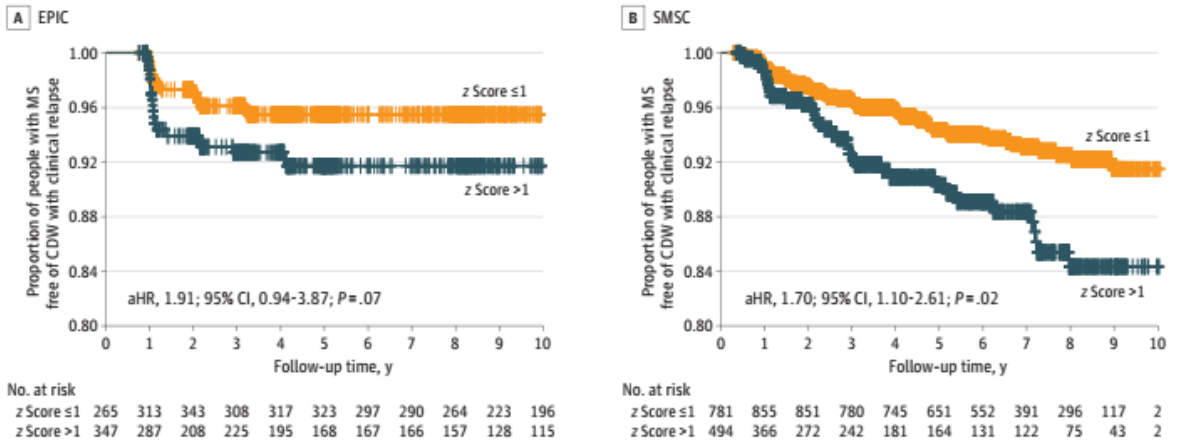
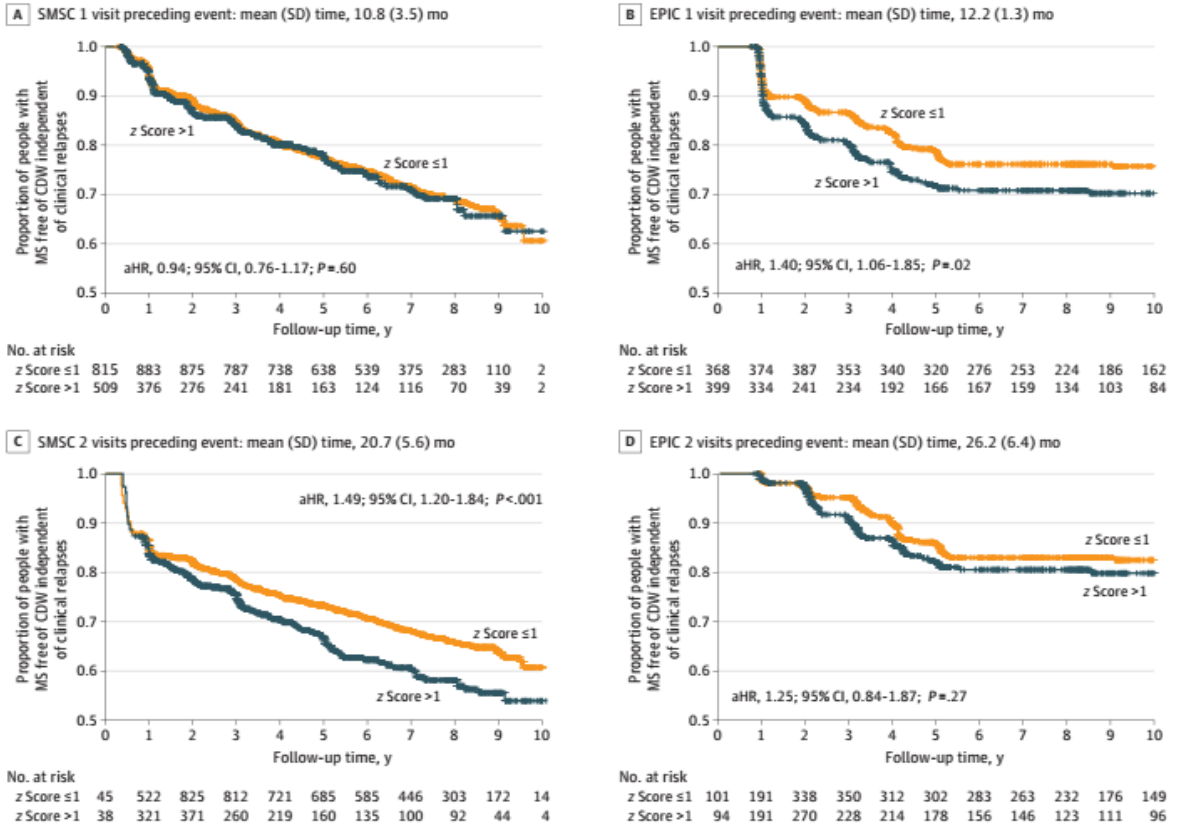


Figure 3. Future Risk of Confirmed Disability Worsening Independent of Clinical Relapses (CDW-NR) based on Neurofilament Light Chain (NfL) *z* Score



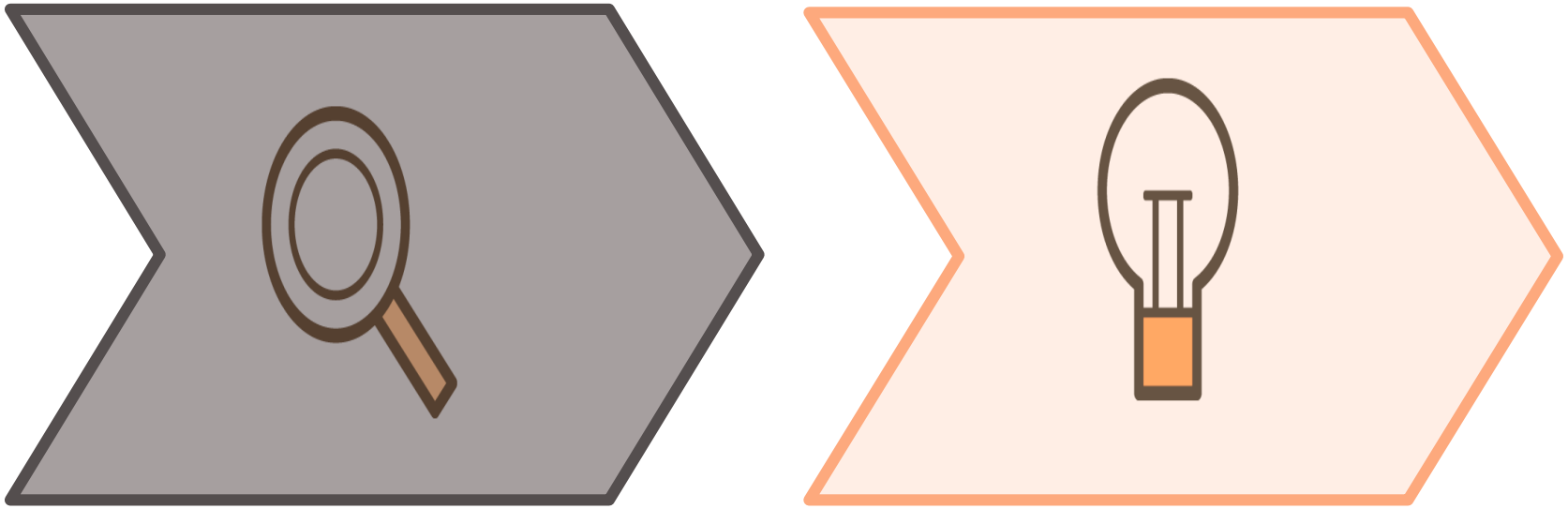
Abdelhak a.et al . Jama Neurology; Nov 6 2023

Towards a tailored approach to guide the therapeutic algorithm

Personalization of MS therapy involves two key components

Prediction of prognosis

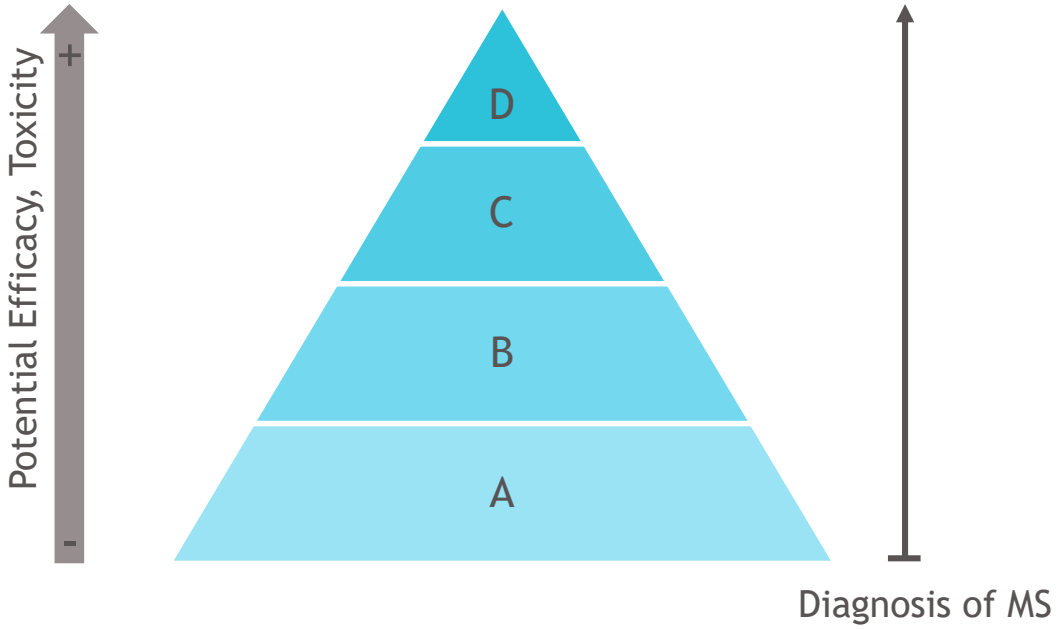
Initial treatment decision



DMTs, disease modifying therapies; MS, multiple sclerosis . Rotstein D et al. *Nat Rev Neurol*. 2019;15(5):287-300.

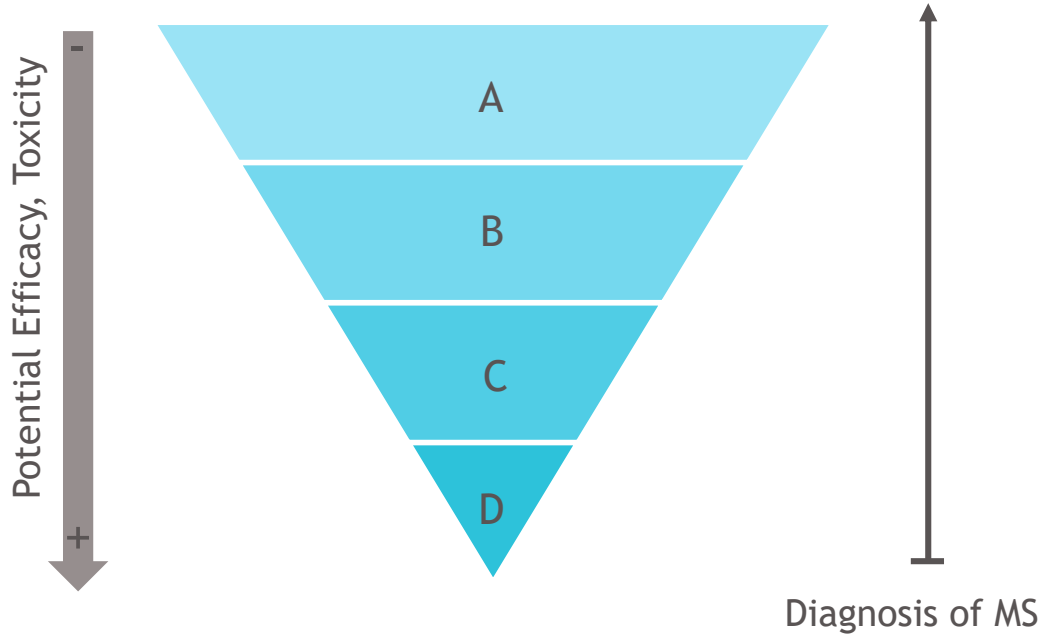
Treatment strategies in MS: escalation and induction

Escalation strategy



- This approach focuses on safety
- Treatment starts with lower-risk, lower-efficacy DMTs and only moves on treatments with higher risk if the disease activity occurs[1,2]

Induction strategy



- This approach prioritizes efficacy
- Treatment is based on the use of high-efficacy DMTs with strong immune effect from the diagnosis of MS [1,2]

A, B, C, D stand for different treatments
DMT, disease modifying therapy; MS, multiple sclerosis

1. Filippi M, Rocca MA. *Lancet Neurol*. 2020 Apr;19(4):281-282. 2. Ruggieri et al. *Multiple Sclerosis and Demyelinating Disorders (2018) 3:5*. https://doi.org/10.1186/s40893-018-0037-7.
Figure adapted with permission from *Mult Scler Demyelinating Disord*.

35TH Congress of the European Committee for Treatment and Research in Multiple Sclerosis

and

24TH Annual Conference of Rehabilitation in MS

ECTRIMS

11 – 13 SEPTEMBER

2019

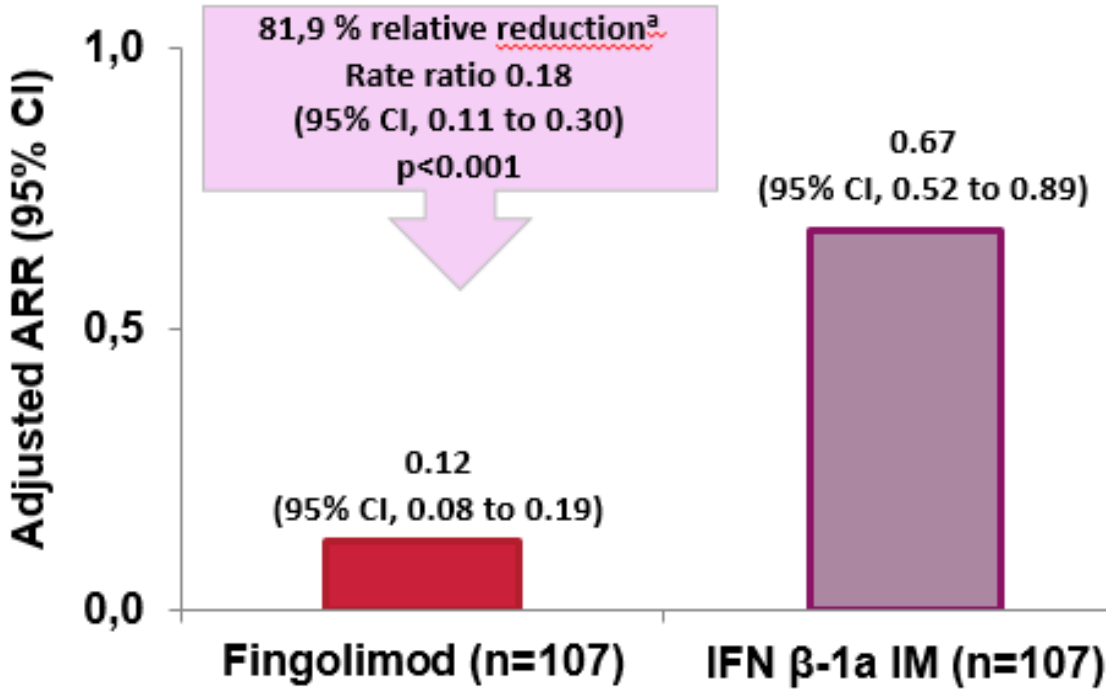
STOCKHOLM, SWEDEN

Burning Debate:

It is inappropriate to prescribe interferonbeta and glatiramer acetate for active relapsing MS.

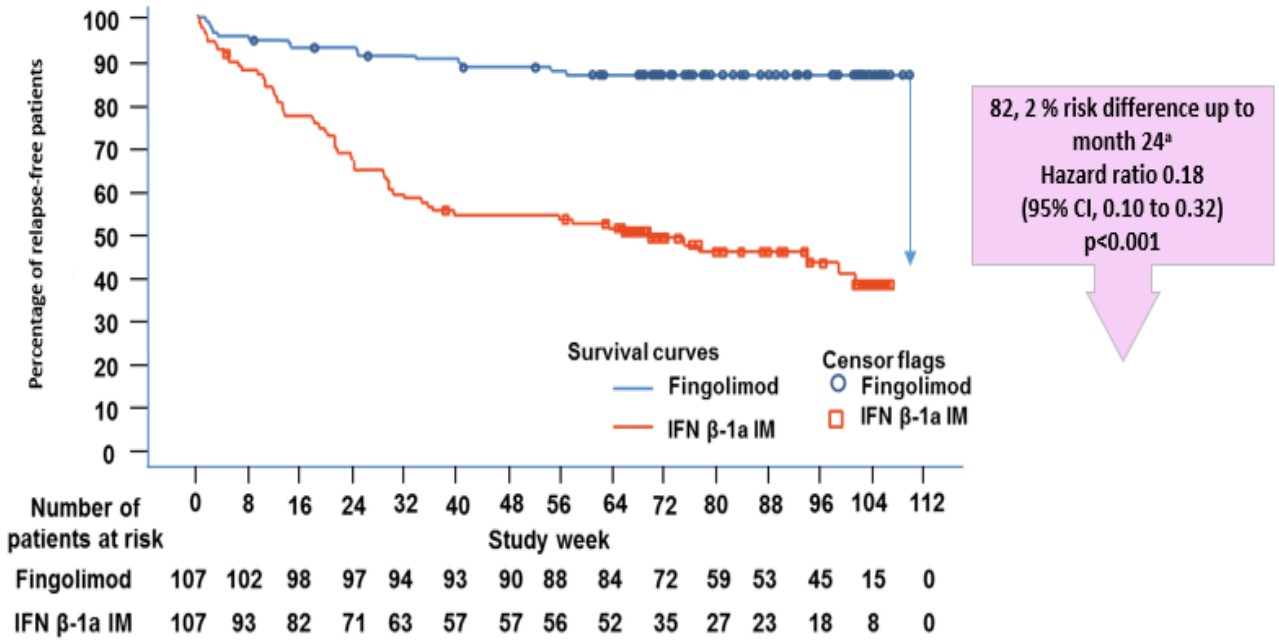
This burning debate will address the topical motion: From a healthcare provider perspective, it is now inappropriate to prescribe 1st generation injectables(interferon-beta and glatiramer acetate) to newly diagnosed patients with active relapsing MS.

ARR up to Month 24



Chitnis T, et al. *N Engl J Med* 2018;379:1017–1027.

Time-to-first confirmed relapse and proportion of patients free from relapse



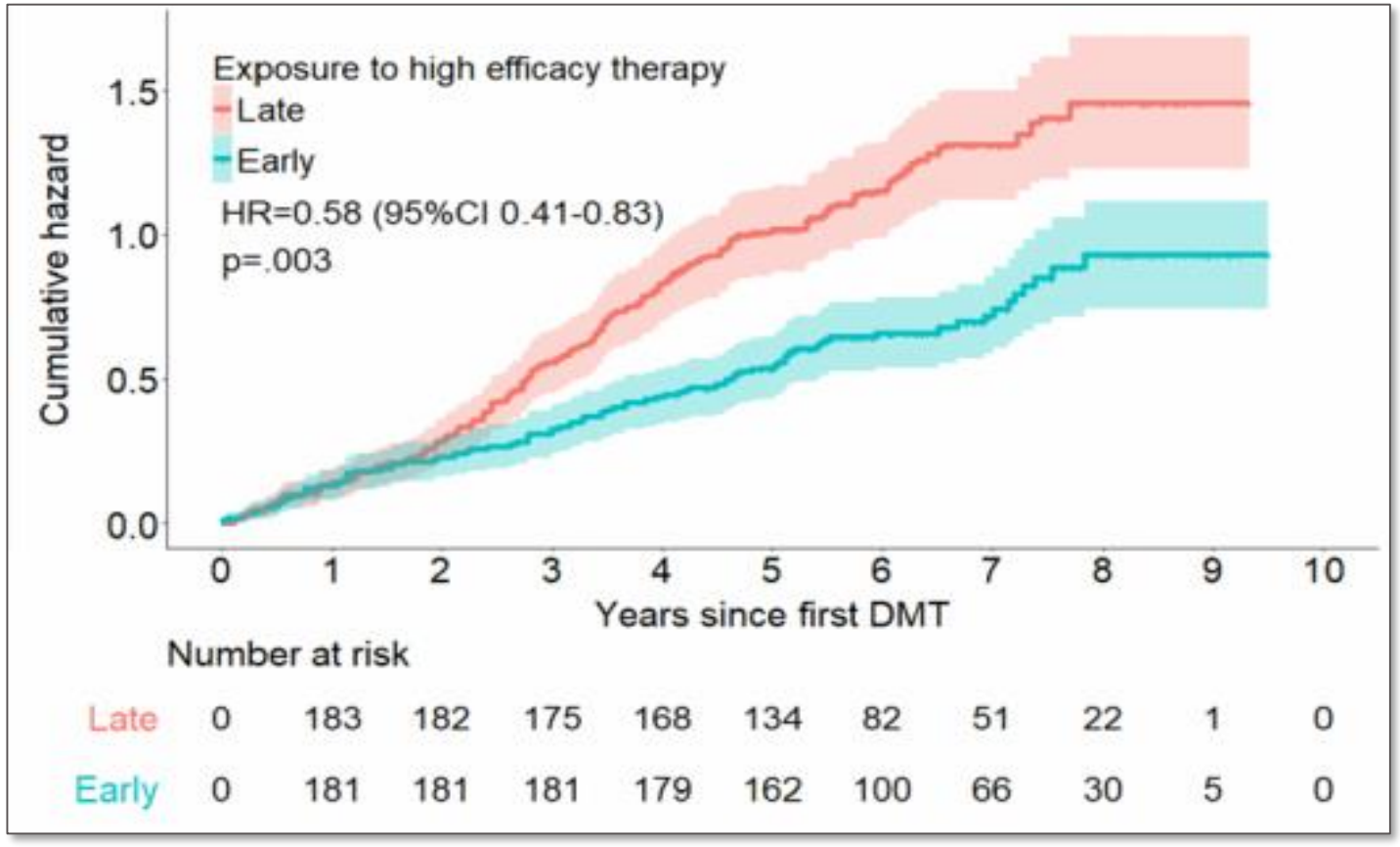
[a]Negative binomial regression model with a log link, adjusted for trial regimen, the number of relapses in the 2 years before randomization, pubertal status, and geographic region

Fingolimod was superior to IFN β-1a IM in reducing ARR up to Month 24 in pediatric patients with MS

Early initiation of higher-efficacy therapy

- MSBase analysis of RRMS patients who started a higher-efficacy therapy either Early (0-2 years after onset; n=170) or Late (>4 years after onset; n-578)

- Higher-efficacy DMDs: Rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab
- From Years 2-10, the risk of CDP was significantly lower in the Early group
- EDSS change from baseline to Year 6:*
  - Early: EDSS 2.3 to 2.5
  - Late: EDSS 2.3 to 3.4



*Propensity score match analysis, n=117 (Early) and n=181 (Late)CDP, confirmed disability progression

He A et al. Lencet Neurology 2020

Initial high-efficacy disease-modifying therapy in multiple sclerosis

A nationwide cohort study

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JAMA | Original Investigation

Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis

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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

Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis

Massimo Filippi[1,2] · Romano Danesi[3] · Tobias Derfuss[4] · Martin Duddy[5] · Paolo Gallo[6] · Ralf Gold[7] · Eva Kubala Havrdová[8] · Barbara Kornek[9] · Francesco Saccà[10] · Mar Tintoré[11] · Jörg Weber[12] · Maria Trojano[13]

JAMA Neurology | Original Investigation

Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis

Katharine Harding, PhD; Owain Williams, MBBCh; Mark Willis, PhD; James Hrastelj, MBBS; Anthony Rimmer, MBBS; Fady Joseph, MD; Valentina Tomassini, PhD; Mark Wardle, MD; Trevor Pickersgill, MRCP; Neil Robertson, MD; Emma Tallantyre, PhD

Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study

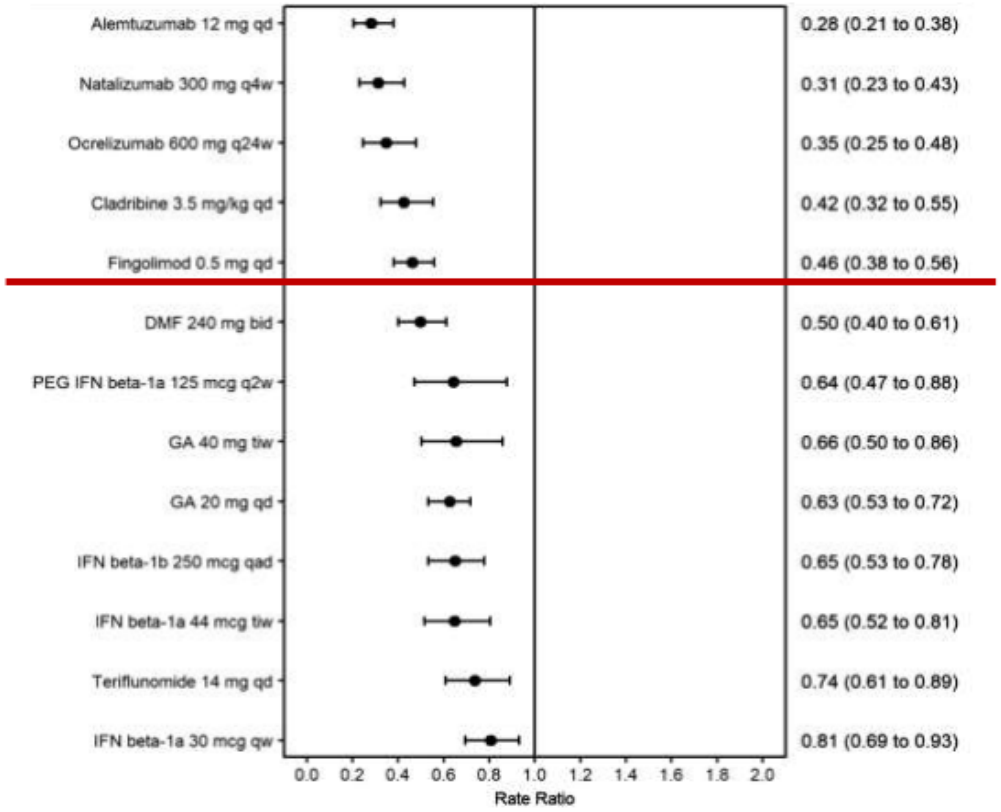
*Anna He, Bernd Merkel, James William L Brown, Lana Zhovits Ryerson, Ilya Kister, Charles B Malpas, Sifat Sharmin, Dana Horakova, Eva Kubala Havrdova, Tim Spelman, Guillermo Izquierdo, Sara Eichau, Maria Trojano, Alessandra Lugaresi, Raymond Hupperts, Patrizia Sola, Diana Ferraro, Jan Lycke, Francois Grand'Maison, Alexandre Prat, Marc Girard, Pierre Duquette, Catherine Larochelle, Anders Svenningsson, Thor Petersen, Pierre Grammond, Franco Granella, Vincent Van Pesch, Roberto Bergamaschi, Christopher McGuigan, Alasdair Coles, Jan Hillert, Fredrik Piehl, Helmut Butzkueven, Tomas Kalincik, on behalf of the MSBase study group**

Superior efficacy of HE DMTs in RCTs

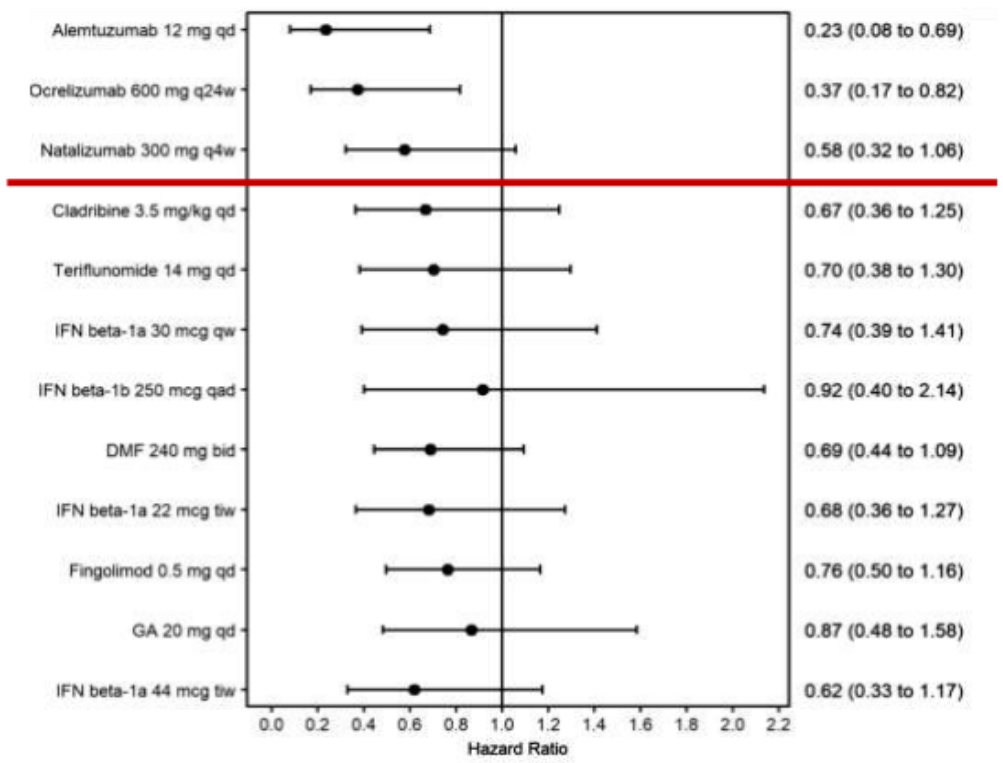
Network meta-analysis outcomes for ARR and CDP

Forest Plot – Active Treatments vs. Placebo (Rate Ratio)

Annualised relapse rate of all treatments relative to placebo



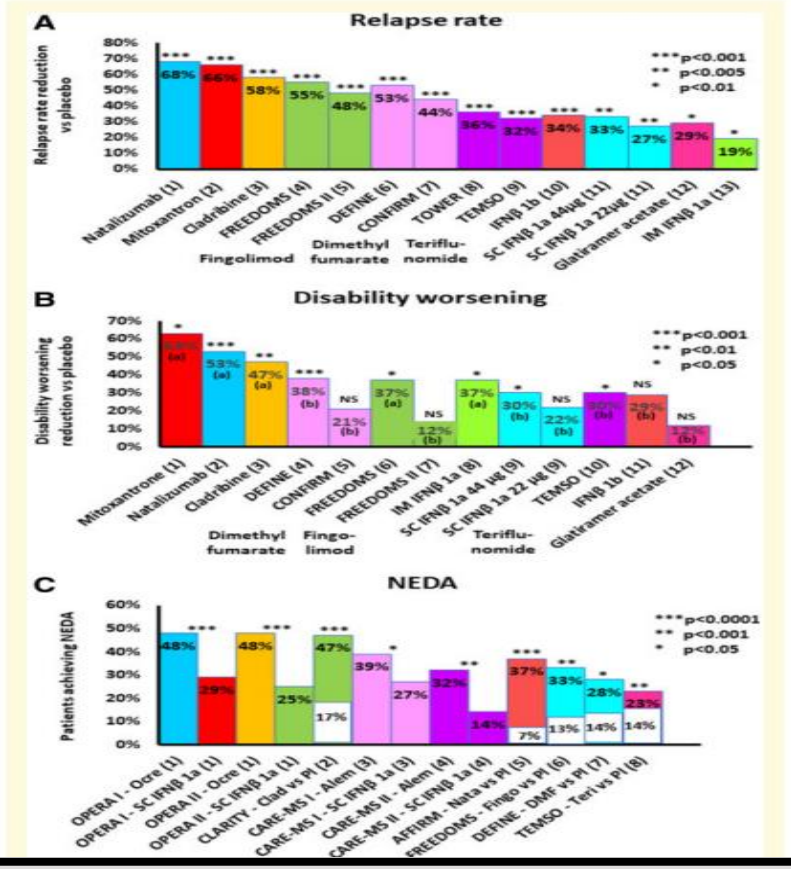
Disability progression confirmed after 3 months for all treatments relative to placebo



Giovannoni G, Neurol Ther 2020

REVIEW ARTICLE

The apparently milder course of multiple sclerosis: changes in the diagnostic criteria, therapy and natural history



VIEWS & REVIEWS | OPEN ACCESS

An argument for broad use of high efficacy treatments in early multiple sclerosis

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Neurol Neuroimmunol Neuroinflamm 2020;7:e636. doi:10.1212/NXI.0000000000000636

The effect of highly efficient drugs contributed to the decrease in disease activity and disability worsening observed during the last decade.

Sorensen et al. Brain 2020

Journal of Neurology (2022) 269:5382–5394
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]

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Abstract

Multiple sclerosis (MS) is a chronic and progressive neurological disease that is characterized by neuroinflammation, demyelination and neurodegeneration occurring from the earliest phases of the disease and that may be underestimated. MS patients accumulate disability through relapse-associated worsening or progression independent of relapse activity. Early intervention with high-efficacy disease-modifying therapies (HE-DMTs) may represent the best window of opportunity to delay irreversible central nervous system damage and MS-related disability progression by hindering underlying heterogeneous pathophysiological processes contributing to disability progression. In line with this, growing evidence suggests that early use of HE-DMTs is associated with a significant greater reduction not only of inflammatory activity (clinical relapses and new lesion formation at magnetic resonance imaging) but also of disease progression, in terms of accumulation of irreversible clinical disability and neurodegeneration compared to delayed HE-DMT use or escalation strategy. These beneficial effects seem to be associated with acceptable long-term safety risks, thus configuring this treatment approach as that with the most positive benefit/risk profile. Accordingly, it should be mandatory to treat people with MS early with HE-DMTs in case of prognostic factors suggestive of aggressive disease, and it may be advisable to offer an HE-DMT to MS patients early after diagnosis, taking into account drug safety profile, disease severity, clinical and/or radiological activity, and patient-related factors, including possible comorbidities, family planning, and patients' preference in agreement with the EAN/ECTRIMS and AAN guidelines. Barriers for an early use of HE-DMTs include concerns for long-term safety, challenges in the management of treatment initiation and monitoring, negative MS patients' preferences, restricted access to HE-DMTs according to guidelines and regulatory rules, and sustainability. However, these barriers do not apply to each HE-DMT and none of these appear insuperable.

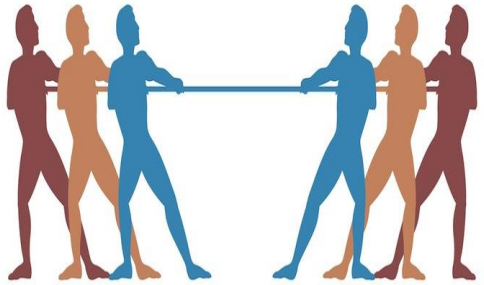
Keywords Multiple sclerosis · Disease-modifying drugs · Disease progression

- It is advisable to offer an early treatment with an HE DMT to all MS patients
- It is mandatory to offer early treatment initiation with an HE DMT in case prognostic factors are indicative of aggressive disease
- In evaluating treatment options, patient-related factors should be considered (e.g. comorbidities, preferences, family planning, etc.)

Reasons for treatment selection in MS

Age, Presence of comorbidities, Desire for pregnancy, Previous use of other immunosuppressants (for MS or other conditions), John Cunningham virus (JCV) antibody seropositivity, Sustainability, Patient/neurologist preferences

Risk of adverse events



Risk of inefficacious treatment strategy (disease worsening)

Safety concerns are the major factors impacting the decision for HE DMTs utilization[1,2,3] and long-term safety data of HE DMTs are needed to optimize MS treatment strategies in routine clinical practice [1]

Risk of infections is generally increased with age with an increased incidence of neoplasms especially over 45 years of age [4].

1. Filippi M et al. *J Neurol*. 2021;1-8.doi:10.1007/s00415-021-10836-8. 2. Stankiewicz JM et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;7(1):e636. 3. Wiendl H et al. *Ther Adv Neurol Disord*. 2021;14:17562864211039648 4. Prosperini L. et al. Mult Scler 2022

Risk in MS treatment – Therapeutic inertia

Factors influencing therapeutic inertia in MS care

Physicians factors	Patient-related factors	Health-care factors
• Failure to set clear goals	• Demographic (e.g., older age)	• Lack of guidelines
• Errors in risk assessment	• Misinterpretation of clinical activity (e.g., non-disabling attacks)	• Coverage and funding for disease-modifying therapies (DMTs) (government, HMOs, etc.)
• Failure to identify comorbid conditions influencing clinical outcomes	• Radiological activity	• Lack of visit planning
• Underestimation of patient's need	• Aversion to change	• Lack of contingency plans for patients experiencing new symptoms
• Low tolerance to uncertainty	• Concomitant mental illness (e.g., depression affecting self-care)	• Limited resources (e.g., MS clinic space, busy schedules, low clinic, and MRI capacity)
• Aversion to unknown risks/*status quo*	• Side effects of new DMTs	• High costs
• Herding (mistakenly following a colleague previous decision)	• Poor communication	• Lack of coordination of health-care services
• Nihilistic approach	• Lack of trust	
• Knowledge gaps (lack of awareness of clinical guidelines)		

High rate of therapeutic inertia among neurologists (60-70%)

Older age, Lower years of experience.

High patient volume; Time constraints: Limited training in risk management.

Saposnik G, Montalban X. Therapeutic inertia in the new land of multiple sclerosis care. *Front Neurol* 2018Cooke CE, et al. Review: clinical inertia in the management of chronic obstructive pulmonary disease. *COPD* 2012 Reach G, et al. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. *Diabetes Metab* 2017. Terzaghi MA, et al. Factors associated with therapeutic inertia among pharmacists caring for people with multiple sclerosis. *Mult Scler Relat Dis* 2020

Conclusions

We recommend making treatment decisions based on the individual patient's pattern of disease profile, as well as functional, clinical, and MRI parameters, rather than on their clinical phenotype

Data on the treatment of MS highlight the importance of assessing the extent of the ongoing inflammatory component of the disease, and the needs of an early treatment with high efficacy therapy

Successful MS treatment depends upon appropriate management of risk of both DMTs adverse events and delays/under treatment

Thank you