Quale futuro per le prime linee?

VIII | NapleSMeeting

www.naplesmeeting.it

Napoli, 25 novembre 2022

Emanuele D'Amico

Università degli studi di Foggia

Disclosures

Honoraria speaking from Merck-Serono, Sanofi-Genzyme, Roche, Biogen, Novartis, Bristol.

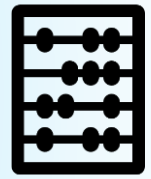
Agenda

- **First-line DMTs Prescription patterns:**

The past and the present

- **MS therapeutic approaches and first lines DMTs:**

What the future?



-*De-escalation*

-*Maintenance*

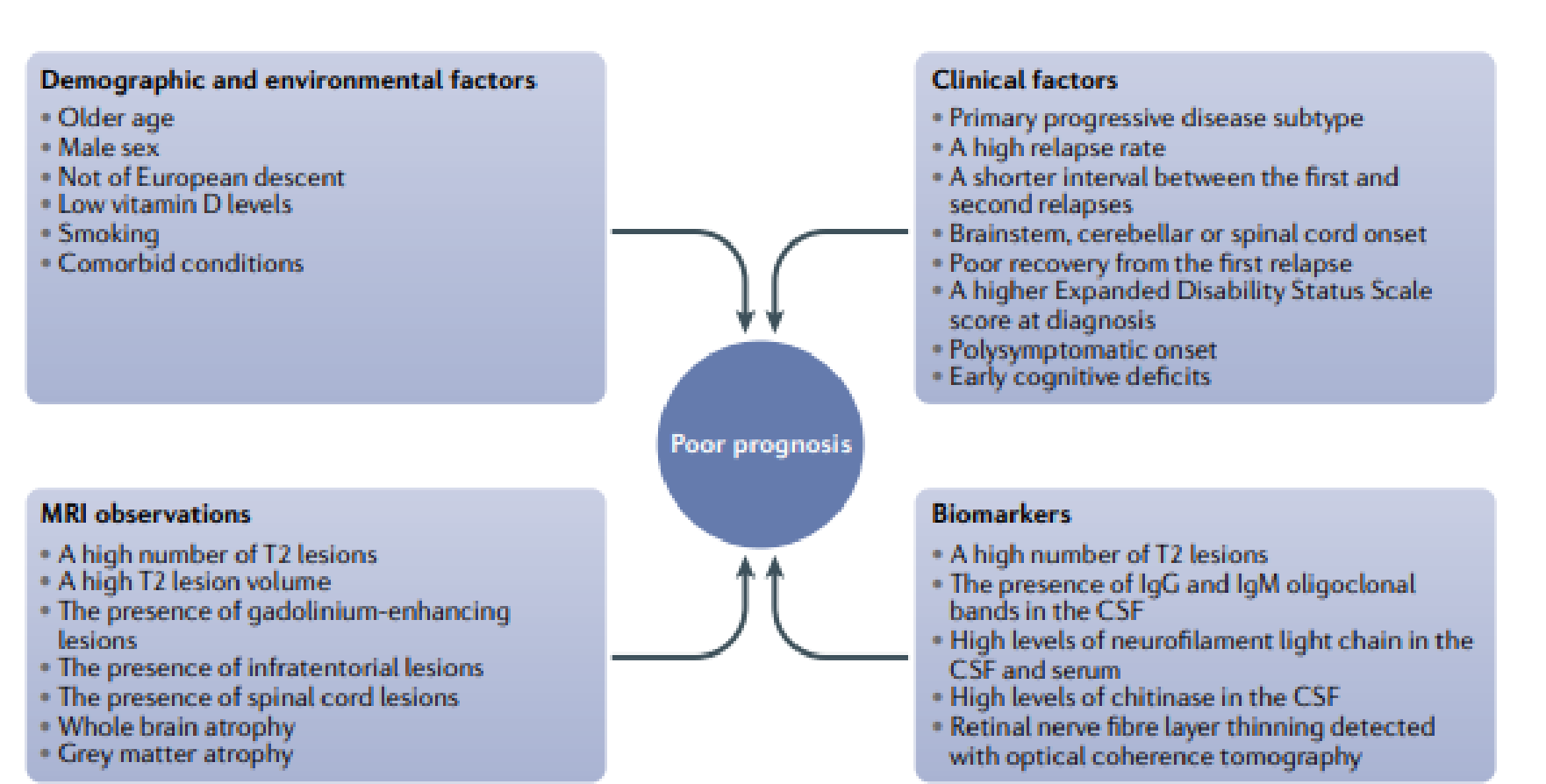
-*Early treatment (RIS)*

-*Pregnancy management*

- **Take home messages**

First-line DMTs Prescription patterns

Defining MS course: PROGNOSTIC FACTORS

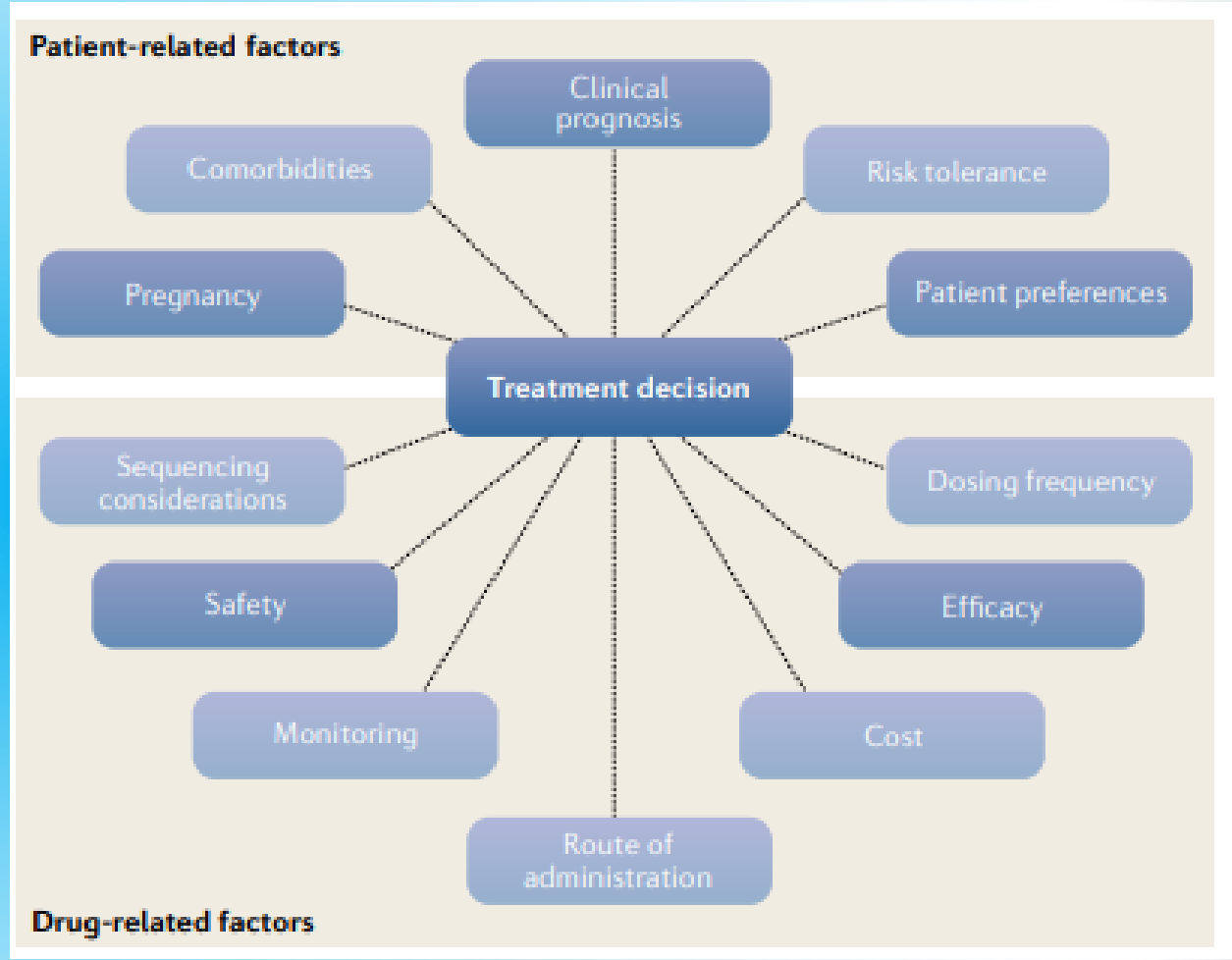


Rotsein et al. 2019

Patients and drug-related factors

Patient/related factors

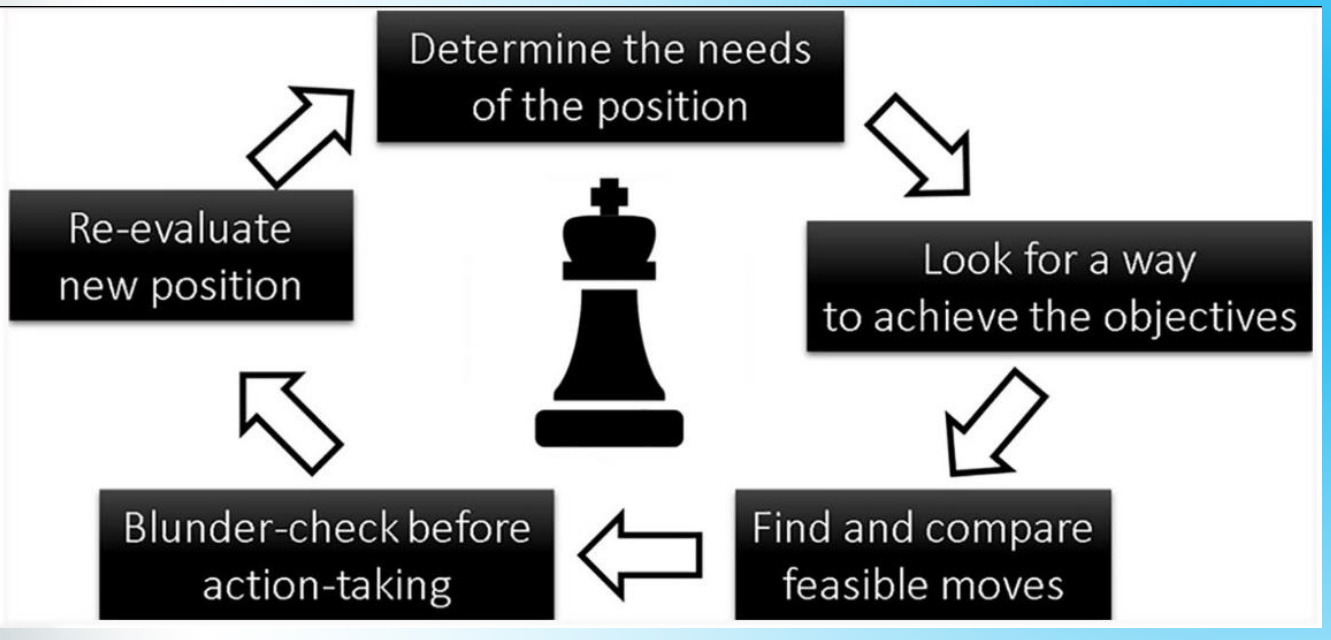
Disease Modifying Therapies/related factors



Rotsein et al. 2019

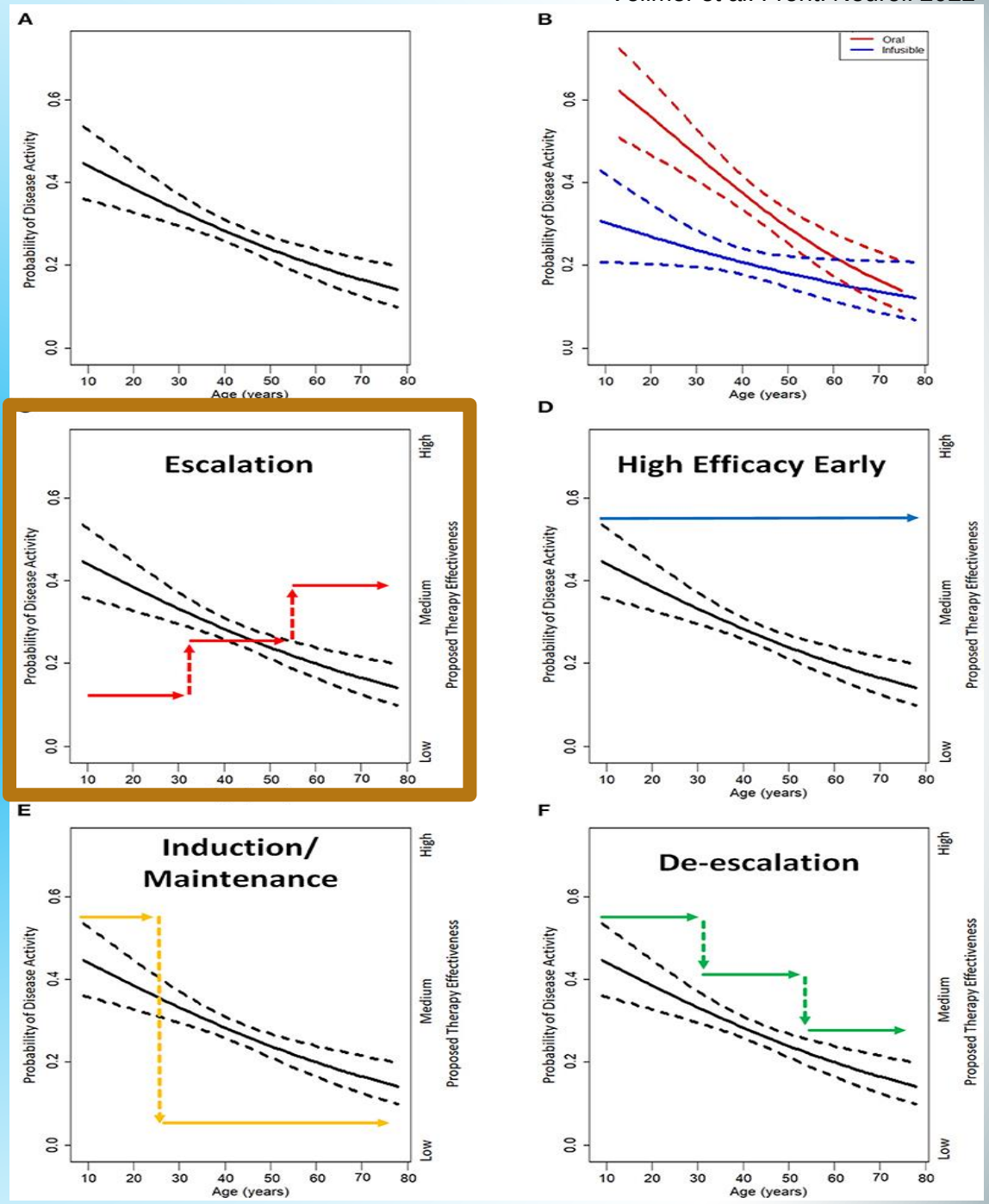
The ideal treatment approach should provide optimal disease management while not limiting future therapeutic options based on safety concerns. It should also recognize the possibility of combinations

When to prescribe FIRST-LINE DMTs



Inojosa et al, Therapeutic Adv in Chronic Diseases. 2022

Vollmer et al. Front. Neurol. 2022



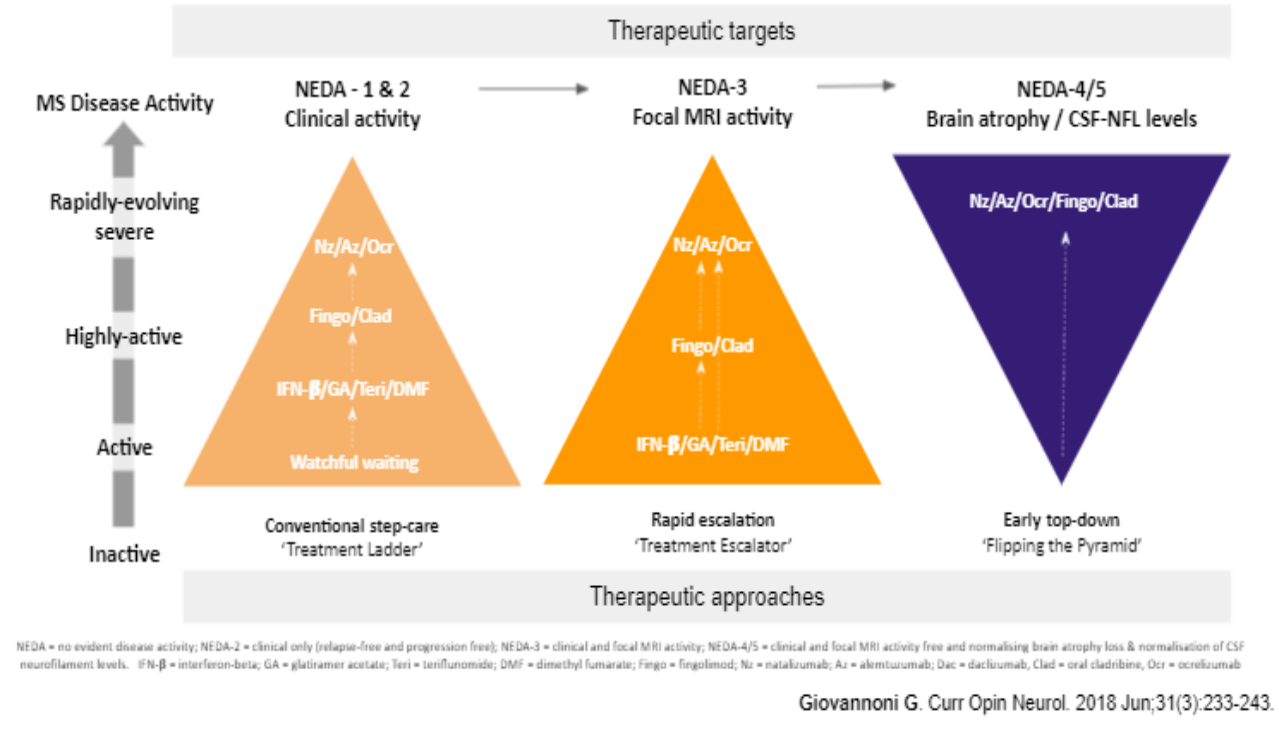
The past and the present

Escalation scheme

The concept of escalation and maintenance therapy represents a strategy that gives precedence to safety over efficacy and, if necessary, to sequentially advance in the treatment pyramid.

In this approach, individuals start with first-line agents and are switched to second- or even third-line agents if they exhibit breakthrough disease that pushes them from low to high in terms of the risk for imminent disease progression.

Sequential DMT monotherapy is currently the most common treatment strategy for RMS.

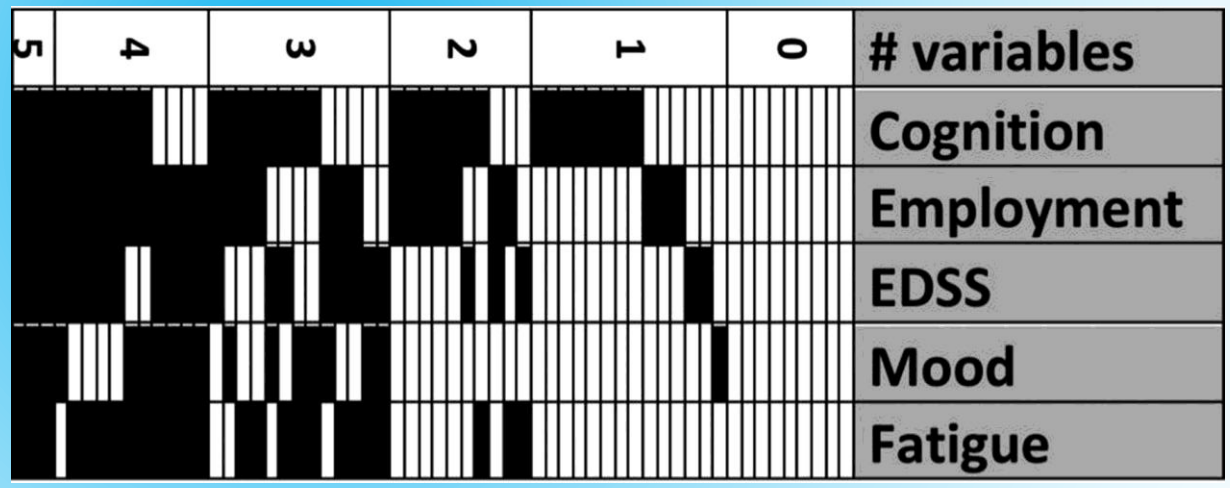


Giovannoni G. Curr Opin Neurol. 2018 Jun;31(3):233-243.

Benign MS

A report from Tallantyre et al. found that in a carefully examined untreated population with disease duration >15 years, only 9 patients in a cohort of 1,049 had "benign" disease as defined by an EDSS <3.0, no significant fatigue, mood disturbance, cognitive impairment, or disrupted employment.

A representation of the clinical cohort (n=60, selected based on disease duration >15 years and no history of DMT), according to whether an individual fulfilled (white) or failed to fulfil (black) each additional criterion for truly benign MS. Cognition: no cognitive impairment according to study criteria.

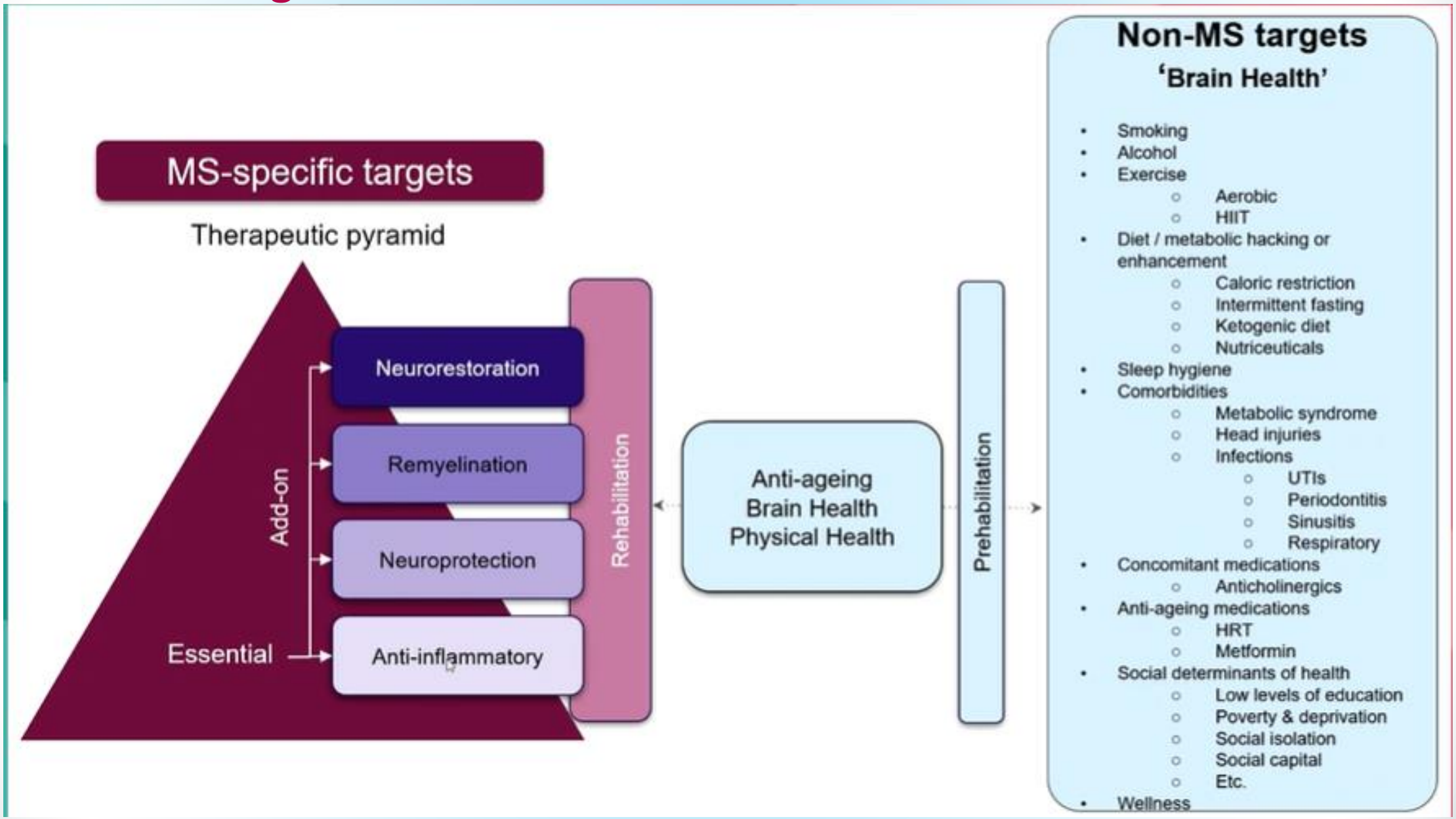


Emma Clare Tallantyre et al. J Neurol Neurosurg Psychiatry 2019;90:522-528

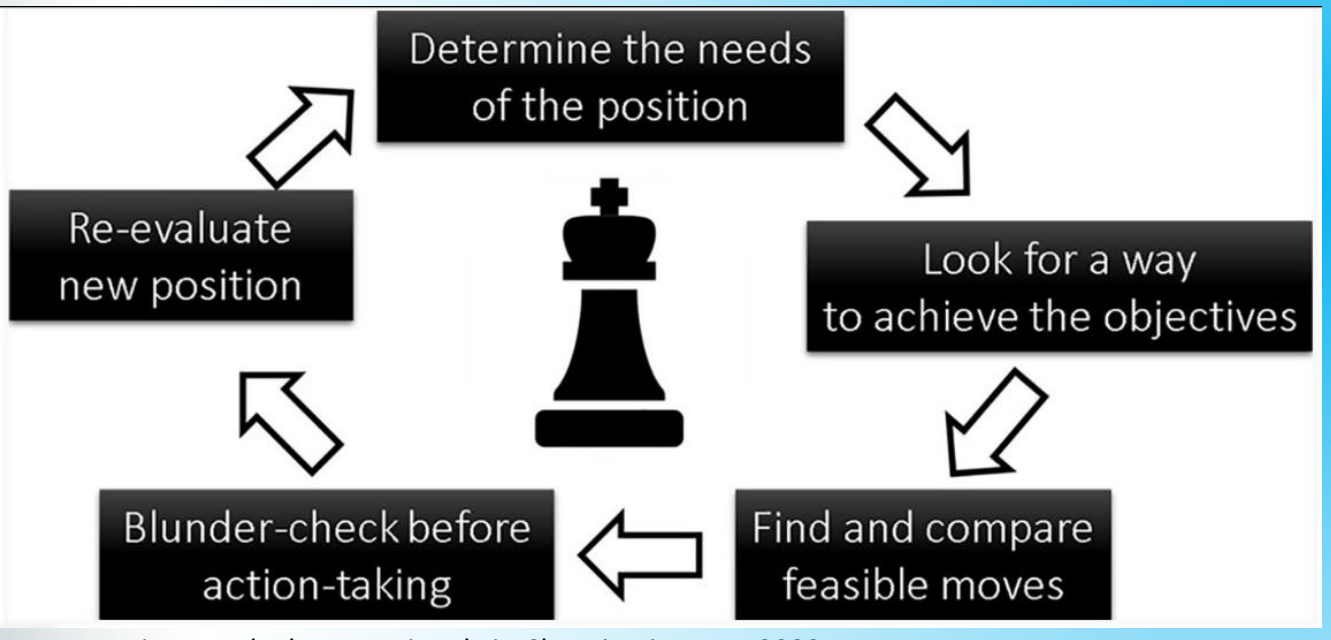
JNNP

What the future?

The holistic management of MS

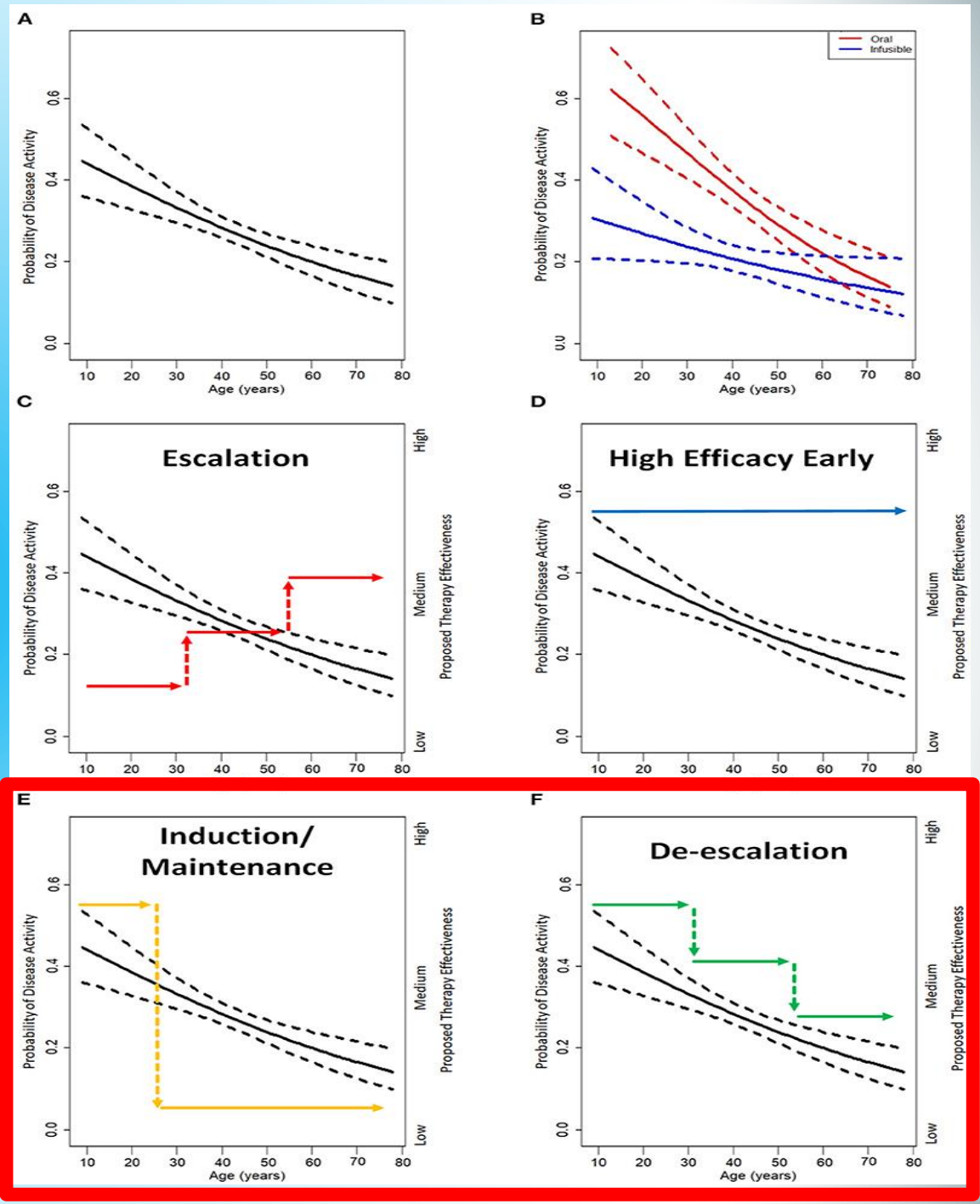


When to prescribe FIRST-LINE DMTs



Inojosa et al, Therapeutic Adv in Chronic Diseases. 2022

Vollmer et al. Front. Neurol. 2022



De-escalation

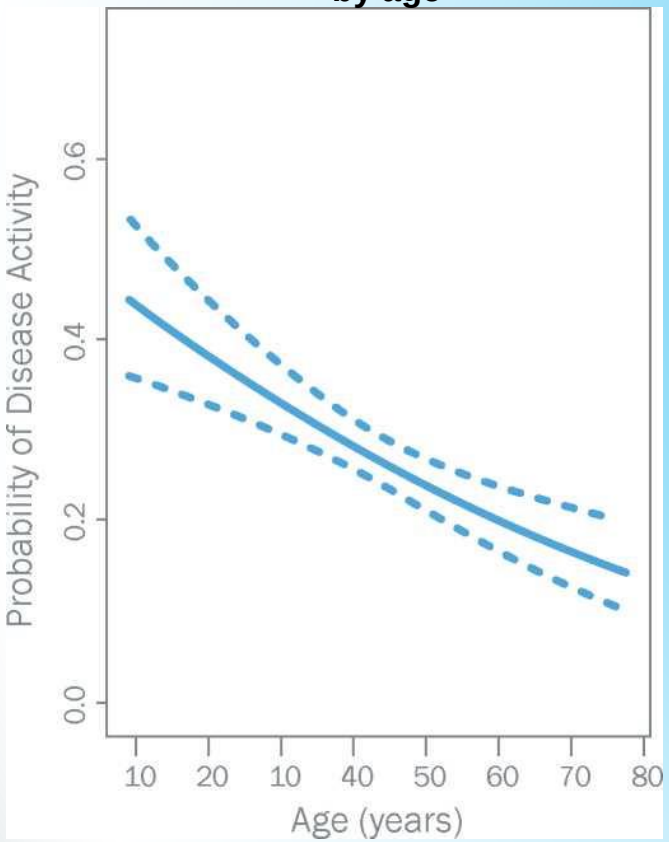
Reasons for de-escalate

- Patient's preference (concerns re infection risk or vaccine efficacy)
- Limited disease burden or activity pre-high efficacy DMT
- Severe adverse event
- JC virus antibody seroconversion
- Loss of infusion center access
- Poor venous access

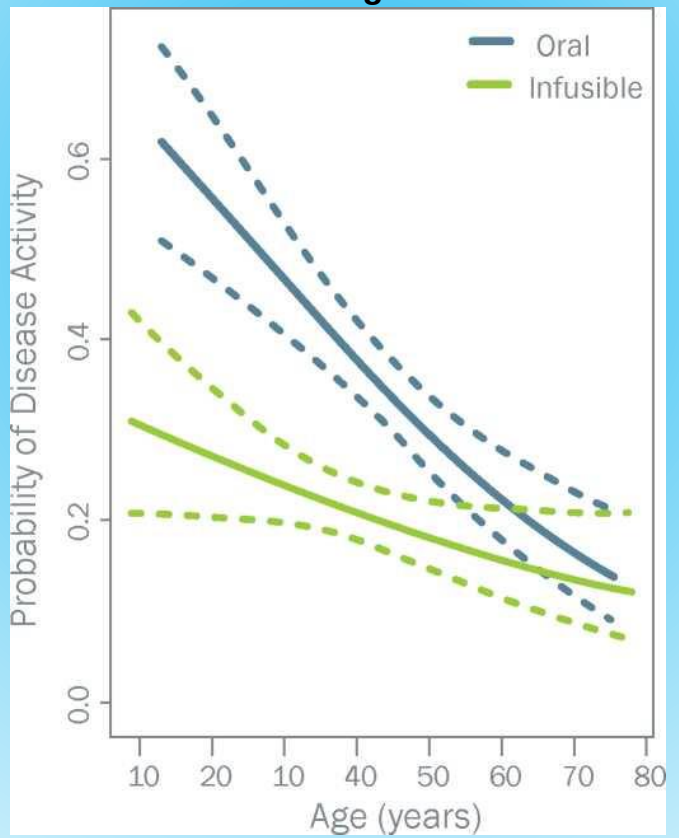
Is there evidence to support DMT de-escalation?

Reanalysis of data from a real-world cohort of 1,246 PwMS to model disease activity for oral DMT (n=613) and infusible DMT (n=633) by age

Probability of disease activity within 2 years of any DMT initiation by age



Probability of disease activity within 2 years by type of DMT by age



Statistically significant difference between oral and infusible DMTs is observed up to age 54.2

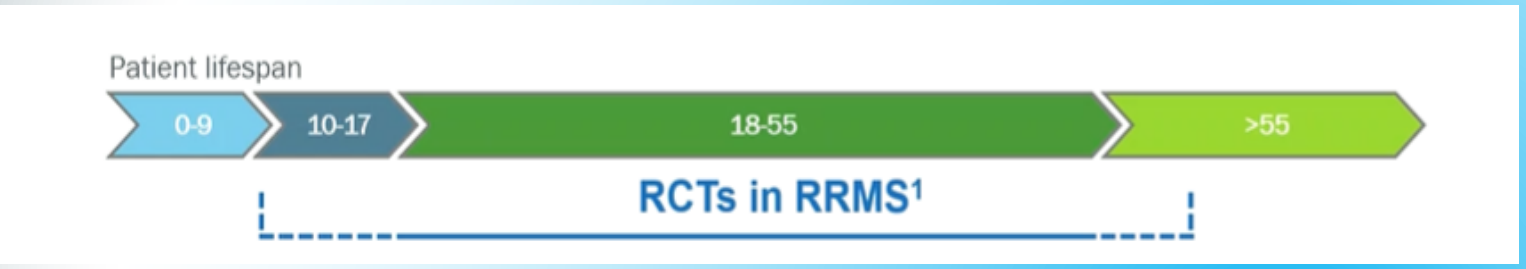
Among PwMS >45 years, patients receiving oral DMT had no significant difference in odds of disease activity vs patients on infusible DMT*

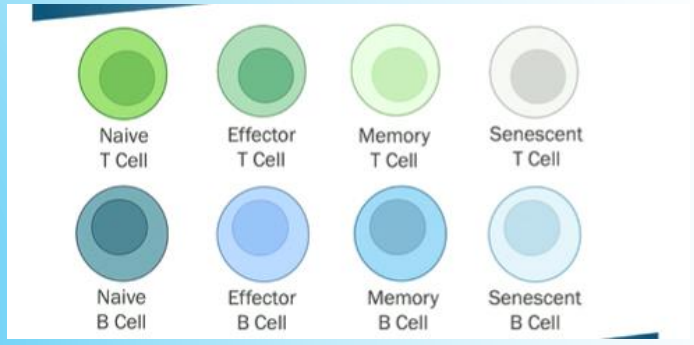
Stratified analysis. Adjusted odds ratio, 1.65 (0.99, 2.76), P=0.053. Figure adapted from Vollmer BL etal. Dashed lines represent 95% confidence interval. Patients were treated with rituximab, natalizumab, fingolimod or dimethyl fumarate at a single centre in the US. ***DMT,*** *disease-modifying therapy;* ***PwMS,*** *patients with multiple sclerosis. Adapted from ref 1.*

1. Vollmer BL et al. Front Neurol. 2022;12:799138.

De escalation: the role of age

MS changes across the lifespan
Real world evidence and treatment decision later in LIFE





Increasing FOCUS

- Long term efficacy and safety of newer high More patients are ageing on long-terms MS therapy efficacy DMTs

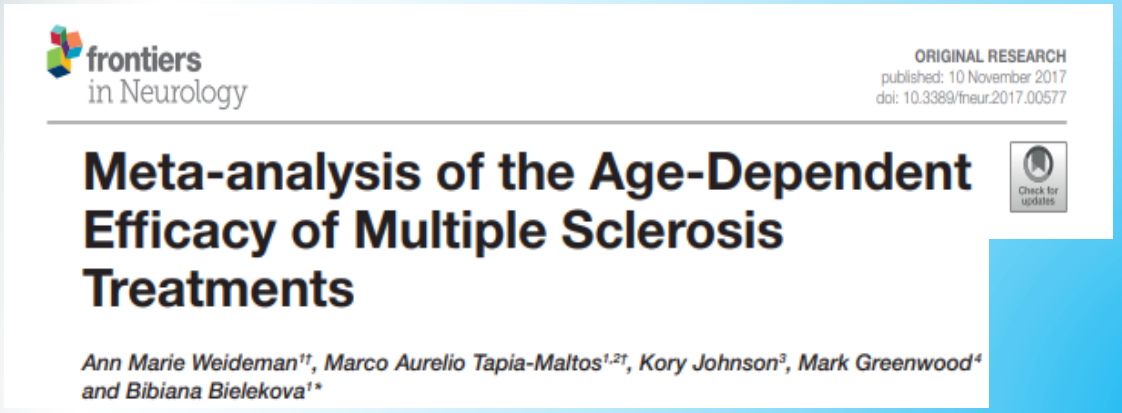
- Optimal approaches for aging patients who has controlled MS but increasing comorbidities.
- De escalation of therapy may provide equivalent efficacy and fewer risks than contiunuing EIT in patients reaching immunosenescence

Adaptive immunity and age

- The benefit/risk profile changes as people with MS age:
- Less need for immunosuppressant to manage disease activity
- Increased risk of infection with immunosenescence
- Potential dor more severe infection outcomes

1. Schweltzer et al. Curr Opin Neurol 2019; 2. Volmer BL et al Front Neurol 2022; 3 Marrie RA et al. Neurology 2016

De escalation: the role of age



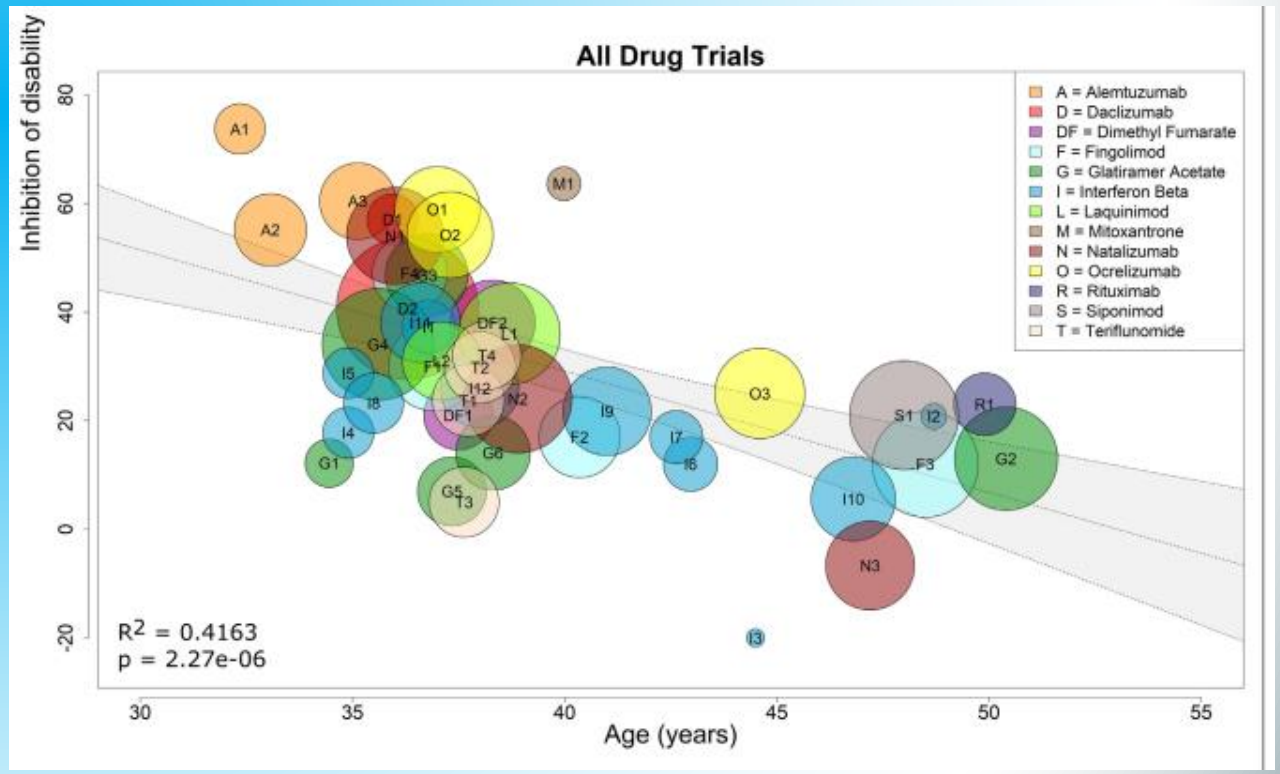
Efficacy of immunomodulatory disease-modifying therapies (DMTs) on MS disability progression is strongly dependent on age.

The efficacy of immunomodulatory DMTs on MS disability strongly decreased with advancing age ($R2 = 0.6757$, $p = 6.39e{-}09$).

The regression predicts zero efficacy beyond approximately age 53 years.

The comparative efficacy rank derived from the regression residuals differentiates high- and low-efficacy drugs.

High-efficacy drugs outperform low-efficacy drugs in inhibiting MS disability only for patients younger than 40.5 years



De-escalation from anti-CD20 DMTs in routine care

Baseline and 1 year data from 25 adult PwMS who switched from ocrelizumab (mean duration 26 ± 8 months) to DRF due to concerns about immune suppression during the COVID-19 pandemic

	Baseline values on ocrelizumab													Post 1-year values on DRF											
	IgG	IgA	IgM	IgG 1	IgG 2	IgG 3	IgG 4	CD4 %	CD4 Abs	CD8 %	CD8 Abs	CD4 / CD8	% CD 19	IgG	IgA	IgM	IgG 1	IgG 2	IgG 3	IgG 4	CD4 %	CD4 Abs	CD8 %	CD8 Abs	CD4 / CD8	% CD 19
Avg	873	203	85	464	263	41	24	56	743	20	264	4	1	846	216	48	452	264	32	25	52	733	21	270	4	8
SD	222	171	116	146	100	18	15	12	305	9	149	2	2	195	188	38	138	99	9	17	11	339	17	199	3	10

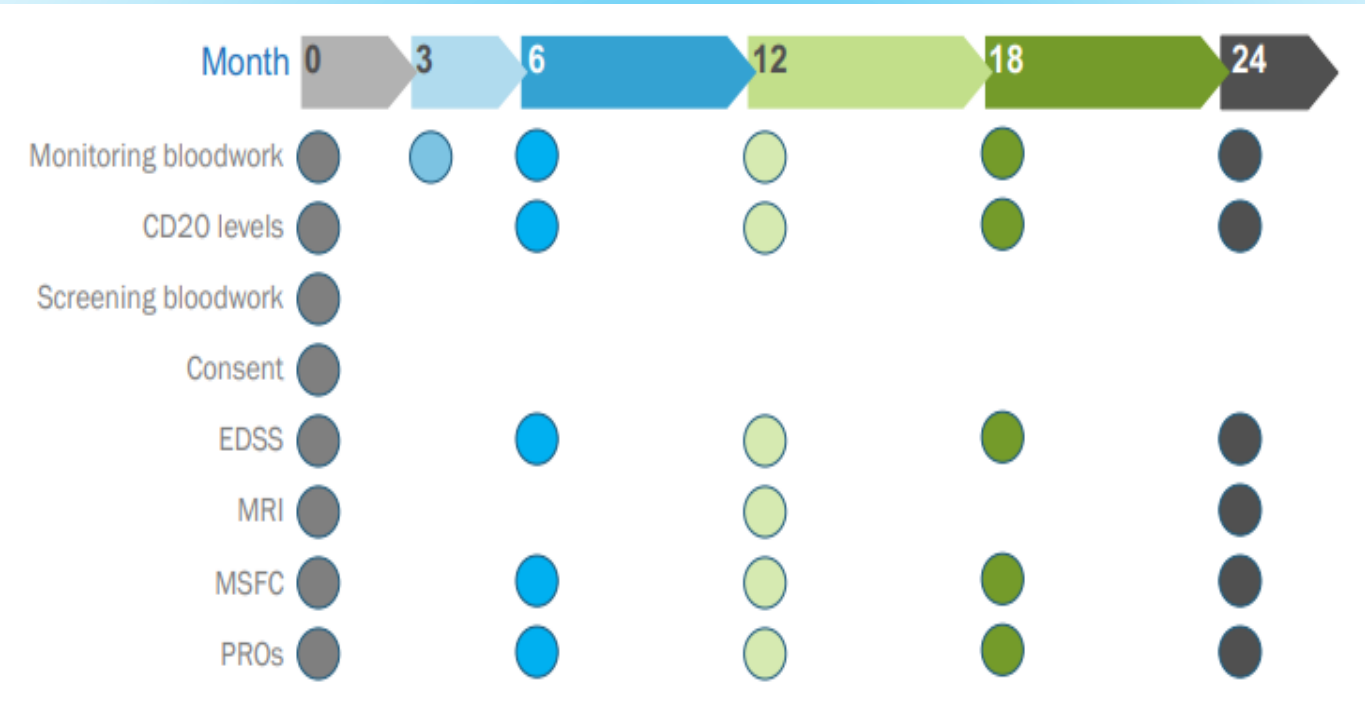
B cell repopulation

- No patients relapsed on DRF
- PROs showed no significant difference from baseline
- All patients remained persistent on DRF

DRF, diroximel fumarate; PROs, patient-reported outcomes; PwMS, people with multiple sclerosis. Figure adapted from ref 1. 1. Kaczmarek 0, et al. Presented atACTRIMS 2022. Poster P129.

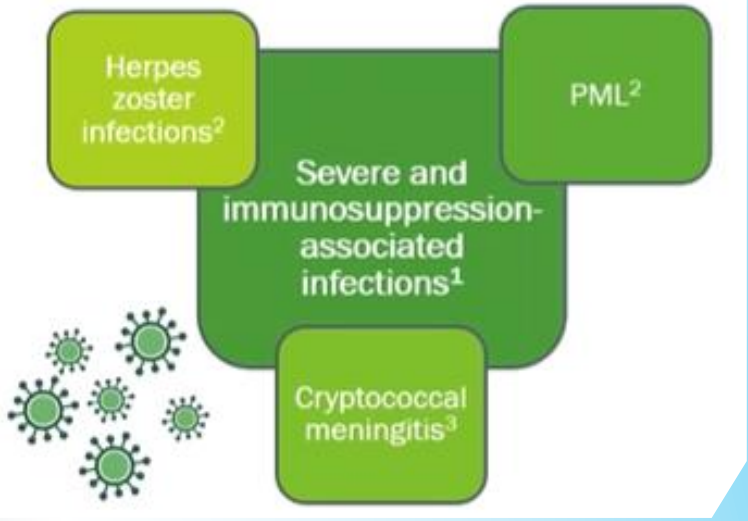
Prospective evaluation of de-escalation from anti-CD20 therapies to Diroximel fumarate (DRF)

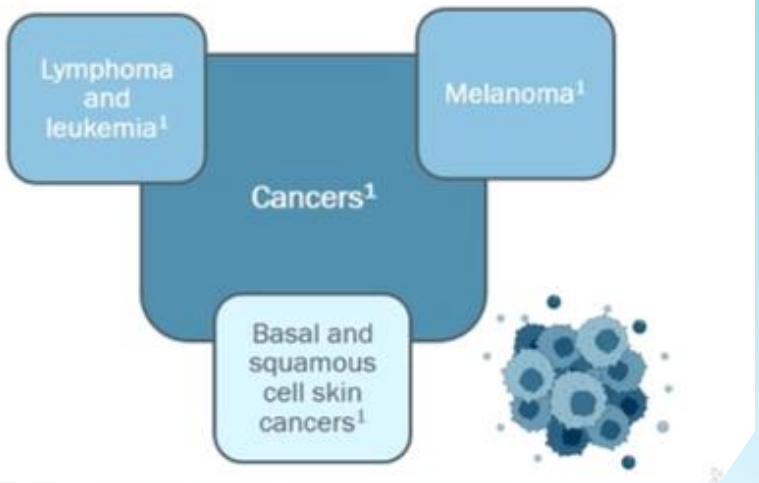
Patients stable on anti-CD20 switched to DRF 6-12 months from last anti-CD20 treatment and evaluated as shown



DRF, diroximel fumarate; EDSS, expanded disability status scale; MRI, magnetic resonance imaging; MSFC, multiple sclerosis functional composite; PROs, patient-reported outcomes. 1. Speaker's experience as principal investigator of this study.

De escalation: safety concerns





Post-approval studies with real-world data (in red patiens from Msbase)

CLARION[1,2] 2018–2034**	MANUSCRIPT[2] 2019–2029**	TYSABRI SWITCH[2,3] 2017–2024**
patients newly initiating: ○ fingolimod (n=~4,000; n=658) or ○ cladribine (n=~4,000; n=546)	patients exposed to: ○ ocrelizumab (n=~5,000; n=1,897) or ○ other DMTs (n=~3,500; n=3,303)	patients (80,327) receiving natalizumab after: ○ IFN or GA (n=1,069) ○ fingolimod (n=500) ○ DMF (n=142) or ○ teriflunomide(n=58)

1. Butzkueven et al. Curr. ,Med Res Opin. 2022.38.1167:76. 2, Eupas Register number EUPASS24484. 3. eupass reister number 28619; 4 EUPAS regster number 19800; NCT03399981

1.Jalk G. et al. Vaccines (Basel) 2020; 9:12. 2.Pianas R et al. Patient related outcome Meas 2014; 25-33:3. 3Wienemann T. et al. BMC Neurol. 2020;20.158.

Maintenance

Pulsed therapies and long term management

Maintenance/escalation therapy		Immune reconstitution therapy-like action	
Immunostimulation/ immunomodulation	Continuous immunosuppression	More selective[a]	Less selective[a]

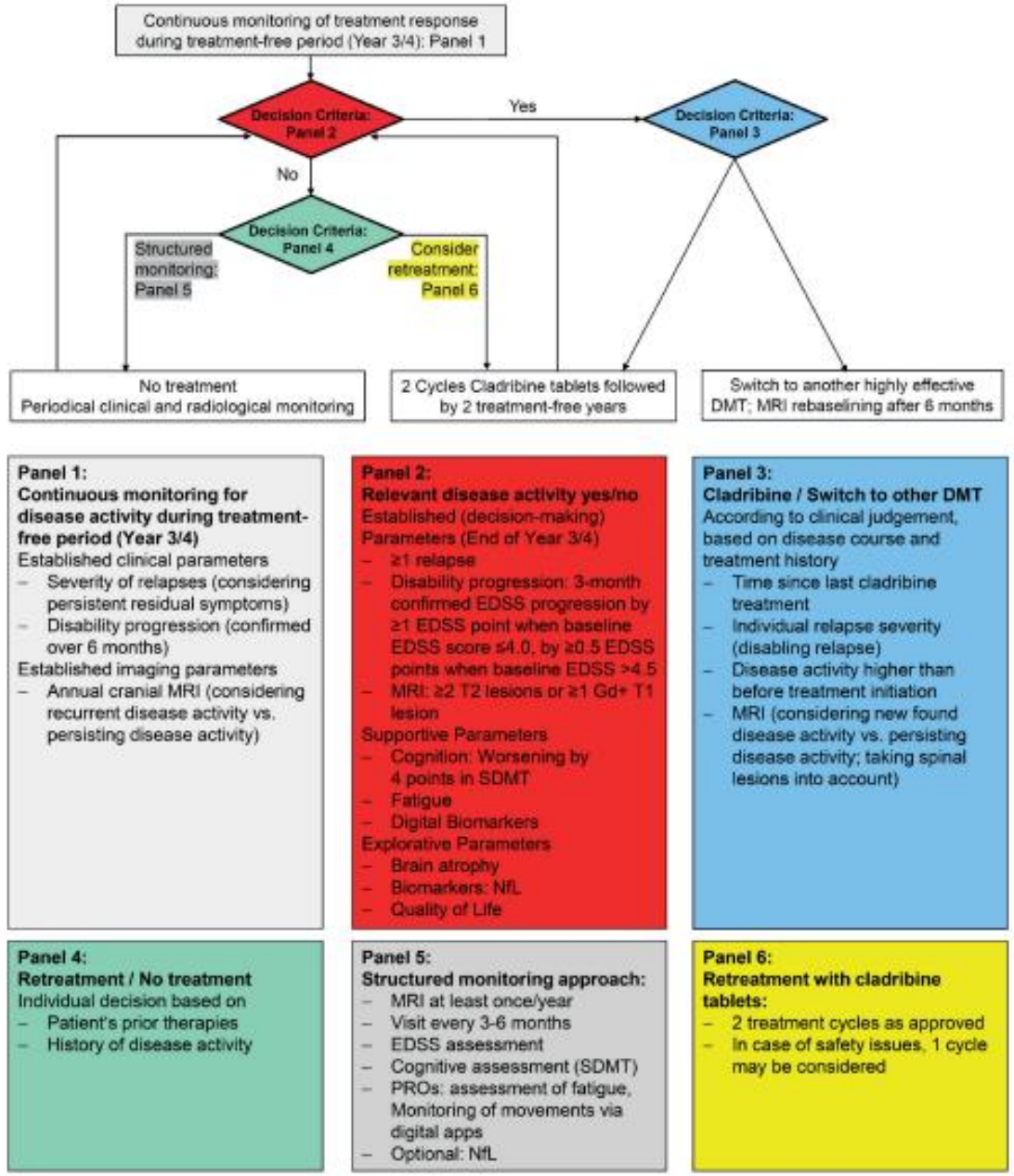
Modern classification of DMTs used in the management of active relapsing remitting Multiple Sclerosis, with reference to the mechanism of action.

a)Refers to balance of effect on adaptive immunity and innate immunity, with more selective implying a greater effect on the former and a lesser effect on the latter.

AlSharoqi, I.A et al, *Neurol Ther* **9**, 55–66 (2020). https://doi.org/10.1007/s40120-020-00187-3

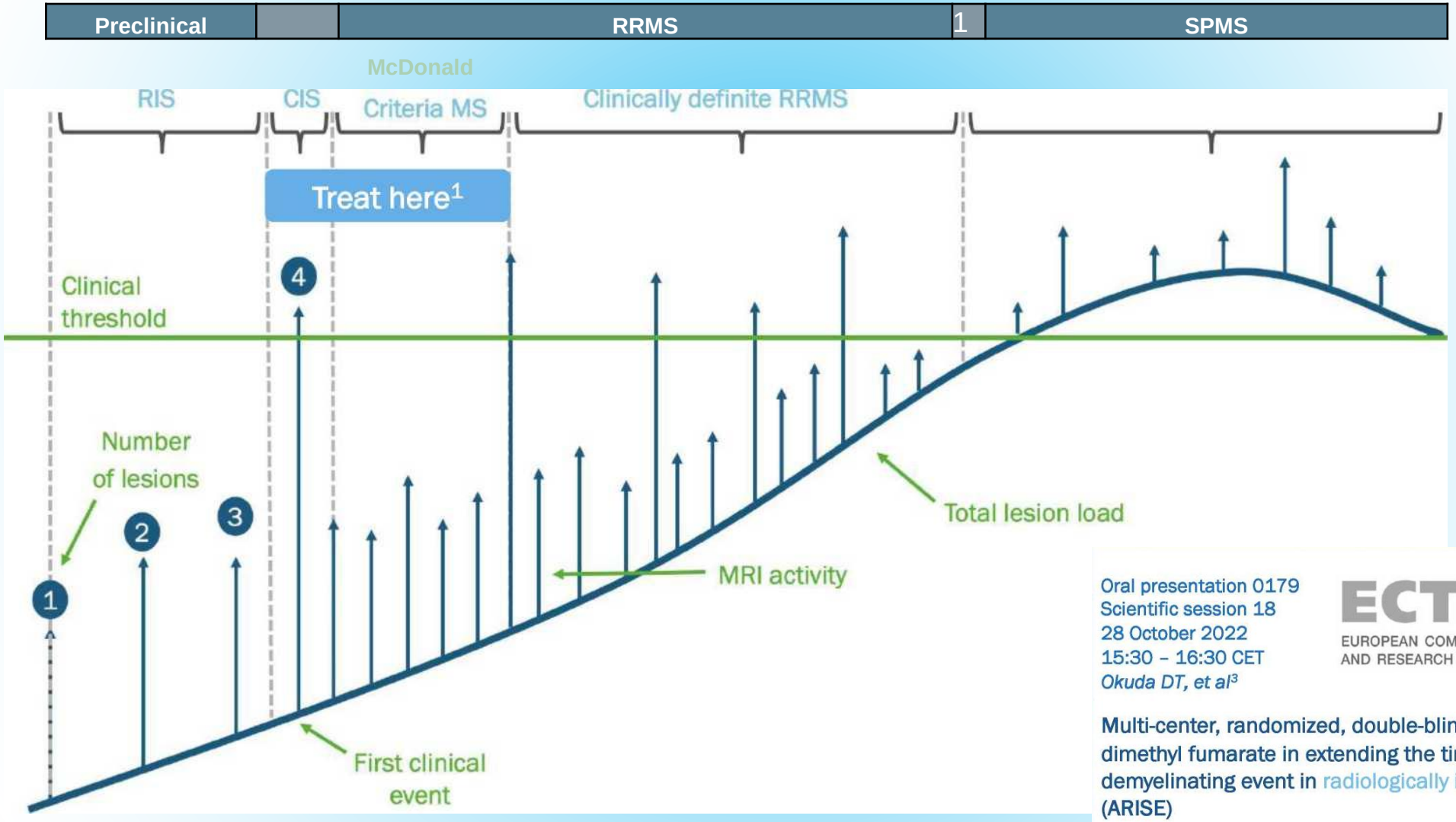
Maintenance

Pulsed therapies and long term management



Meuth S et al. Expert Opinion on Pharmacotherapy, 23:13, 1503-1510, DOI: 10.1080/14656566.2022.2106783

Early treatment- Radiologically isolated syndrome



Oral presentation 0179
Scientific session 18
28 October 2022
15:30 – 16:30 CET
Okuda DT, et al[3]

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

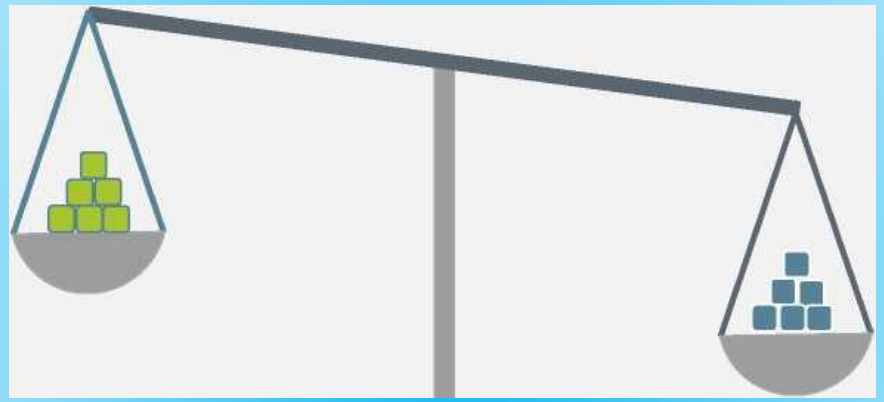
Multi-center, randomized, double-blinded assessment of dimethyl fumarate in extending the time to a first clinical demyelinating event in radiologically isolated syndrome (ARISE)

CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; MS, multiple sclerosis; RIS, radiologically isolated syndrome; RRMS, relapsing remitting MS; SPMS, secondary progressive MS. Figure adapted from ref 2.1. Montalban X et al. Mult Scler. 2018;24:96-120. 2. Adapted from Nicholas R, et al. Drug Design, Dev Ther. 2011;5:255-74.

Pregnancy management

When contemplating DMT use during pregnancy, considerations exist for both mother and baby...[1'2]

CONSIDERATIONS FOR THE MOTHER



CONSIDERATIONS FOR THE BABY

Relapse control during pregnancy and post-partum, with desire to breastfeed[1'3]

Potential teratogenic effects[1'2] Potential haematological abnormalities[1'2] Potential B-cell depletion[1'2] Potential for inadequate vaccine response[4'5]

DMT, disease-modifying therapies.

1. Krysko KM, et al. Curr Treat Options Neurol. 2021;23(4):11; 2. Villaverde-Gonzalez R. Degener Neurol Neuromuscul Dis. 2022;12:1-21; 3. Dobson R, et al. Pract Neurol. 2019;19:106-114; 4. LingJ & Koren G. Expert Rev Vaccine. 2016;15:2, 239-256. 5. Speaker's clinical opinion.

Pregnancy management

DMTs teratogenic effects and use in pregnancy

DMT	Teratogenic effects?	Pregnancy consideration
Injectables		
Interferon-beta[1-4]	No association (n=797 throughout pregnancy)[6]	
Glatiramer acetate[5]	No association (n>2,500 1st trimester[7], n=7468 throughout pregnancy)[8]	

But many patients are now on more efficacious therapies[9], what is the current knowledge for these agents?

Care *should be taken when prescribing in pregnancy as medicines can cross the placenta and may affect the foetus.*

DMT, disease-modifying therapy.

1. Interferon beta-la SmPC. March 2021; 2. Interferon beta-la SmPC. Jan. 2021; 3. Interferon beta-lb. SmPC. December 2021; 4. Peginterferon beta-la SmPC. March 2021; 5. Glatiramer acetate PI. April 2022; 6. Hakkarainen KM, etal. Ther Adv Neurol Disord. 2020;13:1756286420951072; 7. Krysko KM, etal. Curr Treat Options Neurol. 2021;23:11; 8. Sandberg-Wollheim M, et al. IntJ MS Care. 2018;20(1):9-14. 9. Speakers opinion.

Pregnancy management: DMTs teratogenic effects and use in pregnancy

DMT	Teratogenic effects?	Pregnancy consideration
Oral therapies		
Cladribine[1]	Potential risk cannot be ruled out (**n=16 1st trimester**) 10 ET, 3 healthy newborns[2]	✕
Dimethyl fumarate[3]	No association* (**n=374 1st trimester**[4])	**EMA: Continue in pregnancy if clearly needed and if the potential benefit justifies the risk**
Diroximel fumarate[5]	Unknown but likely similar to dimethyl fumarate	? **Limited data, registry study ongoing**[9]
Fingolimod[6]	2-fold higher risk of major CA (**n=113 1st trimester**)[7]	✕
Siponimod[7]	Unknown but likely similar to fingolimod	✕
Teriflunomide[7,10]	May cause birth defects, slight increase in abortion possible (**n=222 1st trimester**)[8]	✕

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Pregnancy management: DMTs teratogenic effects and use in pregnancy

DMT	Teratogenic effects?	Pregnancy consideration
Infusion		
Natalizumab	Slightly increased abortive and teratogenic risk unlikely, but cannot be ruled out (n=355 1st trimester)*	May be considered up to conception and beyond after careful risk-benefit evaluation§
Ocrelizumab	Risk for SA likely not elevated, stillbirth 3% (n=118 1st trimester)†	? ‖
Rituximab‡	Reduced B-cell count in newborns if treated in pregnancy, risk for SA and CA likely not elevated (n=102 1st trimester)† However recent study with ~30% SA and 1/38 live births with peri-natal ischemic stroke (n=74 last RTX 9.5 months pre-conception)†	? ‖
Alemtuzumab	Slightly increased abortive risk cannot be ruled out (n≈200 1st trimester)²	? ‖

But many patients are now on more efficacious therapies[9], what is the current knowledge for these agents?

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Take home messages

- ✓ Place-in Therapy For First Lines DMTs is changing.
- ✓ The therapeutic landscape now includes not only new drugs, but also next-generation versions of established therapies.
- ✓ High efficacy DMTs are disproportionately more efficacious early in the disease course arguing for early use. For these reasons, the benefit of high efficacy DMT is front-loaded.
- ✓ Due to decreasing DMT efficacy and increasing risks, as patients approach 40-55 years, de-escalating should be contemplated.
- ✓ Less need for immunosuppression to manage disease activity (Increasing risk of infections with immunosenescence/Potential for more severe infection outcomes).

Take home messages

- ✓ In addition to age, disability (especially in patients who require bilateral support or are wheelchair-bound) should be considered, as should DMT-specific factors that increase infection risk such as JCV seroconversion for natalizumab, or hypogammaglobulinemia for B-cell depleting therapies.

- ✓ This process should be discussed with patients and adjusted based on comfort level and desire for aggressive treatment.

- ✓ First lines therapies in early disease course-RIS-could improve long term outcomes.

- ✓ Pregnancy management and family planning becomes an important consideration and should be factored into DMT choices.