Individualizing long-term treatment and care in active MS: How are therapeutic sequencing options evolving to address unmet needs?

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Factors guiding the use of high-efficacy DMTs in the management of active MS

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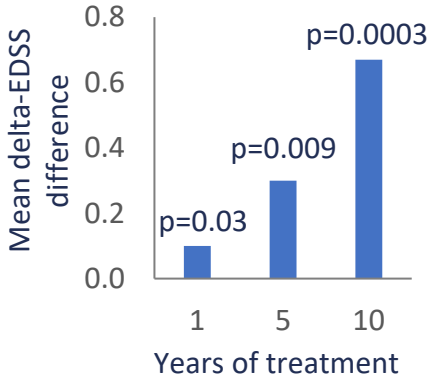
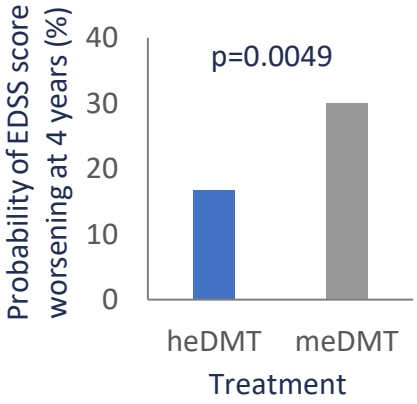
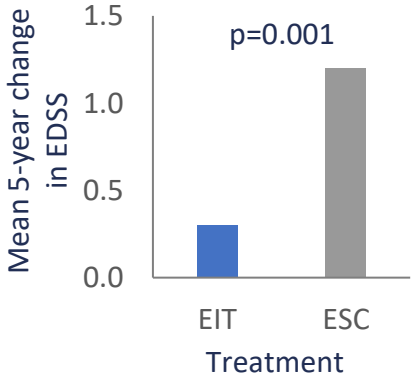
High-efficacy DMTs are most effective in delaying disease progression



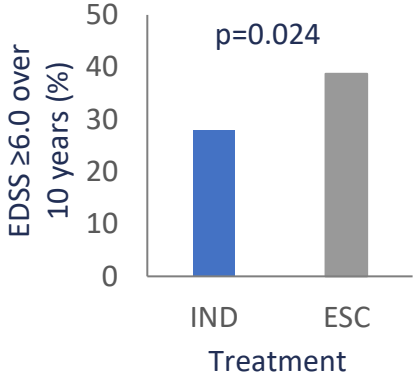
- High-efficacy (EIT) vs escalation approach[1]
- RRMS (N=2,702)



- High efficacy vs medium efficacy initial DMT*[2]
- MS (N=388)



- High-efficacy (EIT) vs escalation approach[3]
- MS (N=592)



- High-efficacy (IND) vs escalation approach†[4]
- RRMS (N=150)

*Medium-efficacy DMTs were defined as interferon-β, teriflunomide, dimethyl fumarate or glatiramer acetate;
†Induction immunosuppression was defined as intravenous immunosuppression (mitoxantrone or cyclophosphamide), followed or not by maintenance treatments.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EIT, early intensive treatment; ESC, escalation to higher-efficacy DMT; heDMT, high-efficacy DMT; IND, induction; meDMT, medium-efficacy DMT; MS, multiple sclerosis; RRMS, relapsing–remitting MS.

1. Iaffaldano P, et al. *Ther Adv Neurol Disord*. 2021;14:17562864211019574; 2. Buron MD, et al. *Neurology*. 2020;95:e1041–51;
3. Harding K, et al. *JAMA Neurol*. 2019;76:536–41; 4. Prosperini L, et al. *Neurotherapeutics*. 2020;17:994–1004.

Factors for initiating high-efficacy DMTs[1–6]

Patient characteristics

- Age
- Sex
- Family planning
- Expected adherence
- Personal preference

Existing comorbidities

- Comorbidity decreases the likelihood of initiating DMT

Side effects

- Considerations should be given to monitoring measures

Accessibility

- Cost of the therapy and the possibility of reimbursement

DMT, disease-modifying therapy.

1. Wiendl H, et al.. *Ther Adv Neurol Disord.* 2021;14:17562864211039648; 2. Montalban X, et al. *Mult Scler*. 2018;24:96–120; 3. Rae-Grant A, et al. *Neurology*. 2018;90:777–88; 4. Fillipi M, et al. *J Neurol*. 2022;269:5382–94; 5. Del Río-Muñoz B, et al. *J Neurosci Nurs*. 2022;54:220–5; 6. Zhang T, et al. *Neurology.* 2016;86:1287–95.

Current approaches and safety considerations relating to DMT switching and sequencing in MS

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Guidelines in the event of breakthrough disease activity or inadequate response to current DMT

MSTCG[1]

- Determinants of treatment failure:
  - ≥3 new T2 lesions and 1 relapse OR
  - ≥2 relapses in last 6–12 months*
- After initiating high-efficacy DMTs:
  - A cerebral MRI scan should be performed yearly

AAN[2]

- Determinants of treatment failure (in last 12 months):
  - ≥1 relapse
  - ≥2 new MRI-detected lesions
  - Increased disability
- Before natalizumab discontinuation:
  - Patients should know the risks (e.g. increased risk of relapse within 6 months)

Making an informed decision regarding switching DMTs is complex – physician judgement and patient preferences are critical[1,2]

*Independent of MRI activity.

AAN, American Academy of Neurology; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; MSTCG, Multiple Sclerosis Therapy Consensus Group.

1. Wiendl H, et al. *Ther Adv Neurol Disord.* 2021;14:17562864211039648; 2. Rae-Grant A, et al. *Neurology*. 2018;90:777–88.

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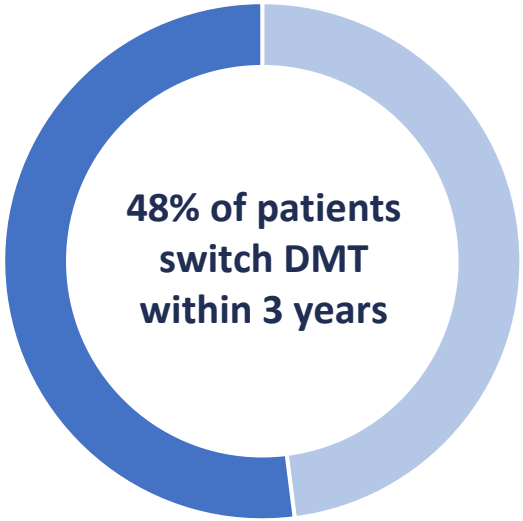
Real-world data: Switching DMT in the event of poor tolerability or inadequate response



- Observational study of patients with RRMS (N=2,954)
- Switch risk for lack of efficacy of other DMTs vs interferons
  - Fingolimod (HR=0.50; p=0.009)
  - Natalizumab (HR=0.13; p<0.001)
  - Dimethyl fumarate (HR=0.60; p=0.037)
  - Teriflunomide (HR=0.21; p=0.031)

DMT, disease-modifying therapy; HR, hazard ratio; RRMS, relapsing–remitting multiple sclerosis.

Saccà F, et al. *Mult Scler.* 2019;25:1263–72.

Approaches needed to support women of child-bearing age living with MS through family planning and beyond

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Guidelines for the use of DMTs in pregnancy

MSTCG[1]

- Only interferons and glatiramer acetate are approved
- For highly active disease, control of disease activity should be a priority and postponement of a planned conception is advised
- For pregnancies in patients with highly active disease, natalizumab may be given up to week 32
- Use of DMTs can be resumed after delivery, taking into account requirements and restrictions during breastfeeding

AAN[2]

- Stop use of DMT before conception for planned pregnancies unless the risk of disease activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy
- DMTs should not be initiated during pregnancy unless the risk of disease activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy

AAN, American Academy of Neurology; DMT, disease-modifying therapy; MSTCG, Multiple Sclerosis Therapy Consensus Group.

1. Wiendl H, et al. *Ther Adv Neurol Disord.* 2021;14:17562864211039648; 2. Rae-Grant A, et al. *Neurology*. 2018;90:777–88.

Real-world data: Pregnancy DMT exposure

DMT	First trimester exposure	Pregnancy exposure	Rebound risk
Ofatumumab	Limited data (n=30) with no congenital anomalies reported in 17 livebirths	No data	None
Natalizumab	Probably no increased risk of spontaneous abortion or congenital abnormality (n>500)	Haematological abnormalities in <60 neonates	Yes
Glatiramer acetate	No association with negative pregnancy outcomes (n>2,500)	No association with negative pregnancy outcomes (n>100)	None
Interferon betas	No association with negative pregnancy outcomes (n>2,500)	No association with negative pregnancy outcomes (n<100)	None

DMT, disease-modifying therapy.

Krysko KM, et al. *Lancet Neurol*. 2023;22:350–66.

Real-world data: Pregnancy DMT exposure

DMT	First trimester exposure	Pregnancy exposure	Rebound risk
Immune modulators*	Potential increase in spontaneous abortion with teriflunomide and cladribine	Limited data	• Limited data • Case reports outside of pregnancy with teriflunomide
S1P receptor modulators	Suspected increased risk of congenital abnormalities (limited data)	Limited data	• Fingolimod: Yes • No data for other agents
Anti-CD20 antibodies	Increased risk of spontaneous abortion or congenital abnormality unlikely	Probable risk for reduced B-cell count in neonates	None

These agents are not recommended during pregnancy by the EMA and FDA

*Teriflunomide, cladribine, and dimethyl fumarate and diroximel fumarate.
DMT, disease-modifying therapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; S1P, sphingosine-1-phosphate.
Krysko KM, et al. *Lancet Neurol*. 2023;22:350–66.