Treatment sequencing in multiple sclerosis: The benefits of disease-modifying therapies

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Expert panel

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Learning objectives

- Explain the factors that drive therapeutic inertia in MS
- Analyse the evidence for starting DMT early in patients with MS
- Perform adverse event management for patients receiving DMT

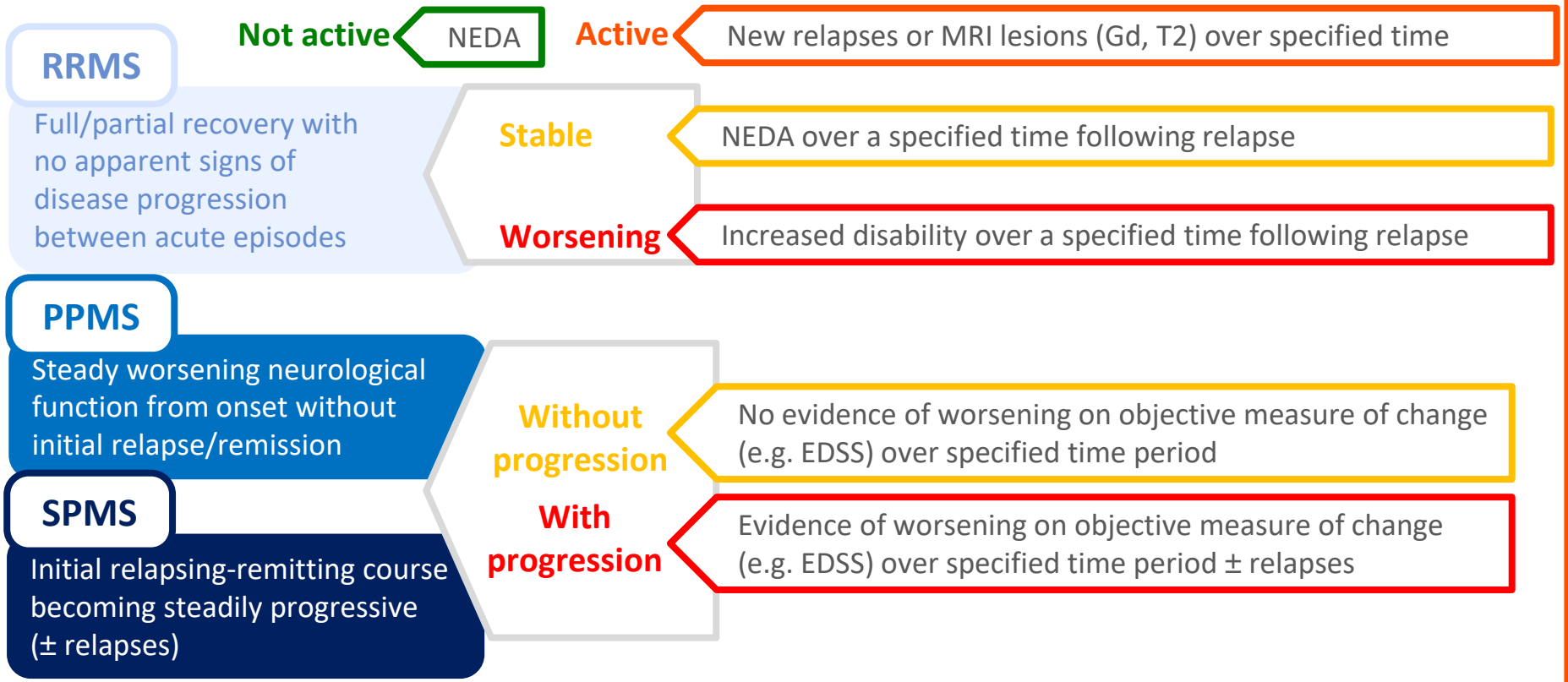
DMT, disease-modifying therapy; MS, multiple sclerosis.

Towards effective and meaningful monitoring of disease activity in multiple sclerosis

Prof. Gavin Giovannoni

Professor of Neurology,
Blizard Institute, Queen Mary University of London, UK

Defining disease activity in multiple sclerosis



EDSS, expanded disability status scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; T2, transverse relaxation time.

1. Lublin FD, et al. *Neurology.* 2014;83:278–86; 2. Fox E, et al. 2018. Available at: bit.ly/3OfpciL (accessed 16 June 2022).

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Assessing disease activity in multiple sclerosis

Imaging[1,2]

MRI

- Gd-positive lesions
- T2-enhanced lesions
- BVL

Functionality[3,4]

Patient perspective

PROMs

- UKNDS
- FSMC
- WPAI:MS
- EQ-5D

Physician perspective

Clinical assessments

- EDSS
- MSFC
- SDMT
- CGI

Biomarkers[5]

CSF, blood, plasma

- NF, IgM, CHIT1
- Innate immunity (myeloid lineage)
- Inflammatory markers
- miRNA

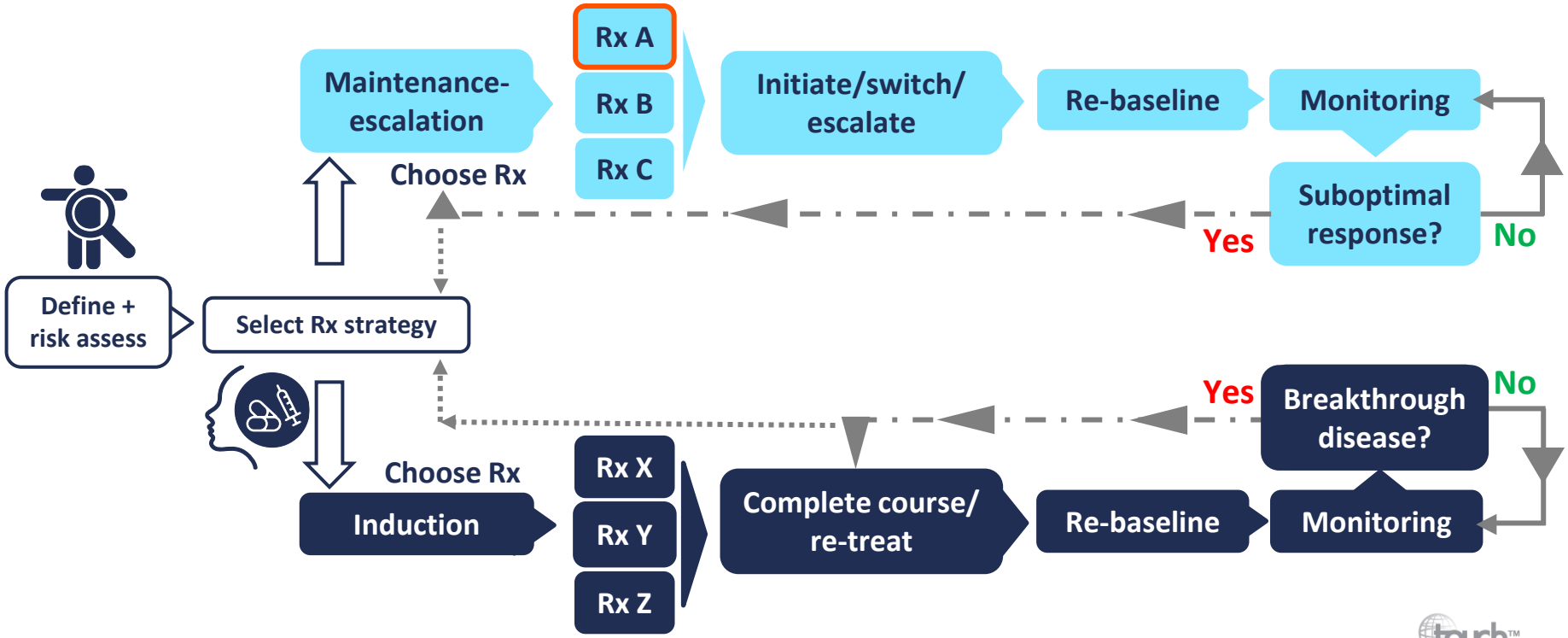
MRI alone does not capture underlying disease mechanisms (e.g. neurodegeneration, de/remyelination, microglial activation, astrogliosis, inflammation) that may contribute to subclinical disease activity[3,5]

BVL, brain volume loss; CGI, Clinical Global Impression; CHIT1, chitinase-1; CSF, cerebral spinal fluid; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol- 5 dimension; FSMC, Fatigue Scale for Motor and Cognitive Functions; Gd, gadolinium; Ig,M immunoglobulin M; miRNA, microRNA; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; NF, neurofilament; PROMs, patient reported outcome measures; SDMT, Symbol Digit Modalities Test; T2, transverse relaxation time; UKNDS, UK Neurological Disability Scale; WPAI-MS, Work Productivity and Activity Impairment Questionnaire: MS.

1. Lublin FD, et al. *Neurology.* 2014;83:278–86; 2. Scolding N, et al. *Pract Neurol.* 2015;15:273–79; 3. Bou Rjeily N, et al. 2022. Available at: bit.ly/3MhY7Kl (accessed 16 June 2022); 4. Ziemssen T, et al. *BMC Neurology.* 2016;16:124; 5. Harris VK, et al. *Degener Neurol Neuromuscul Dis.* 2017;7:19–29.

Multiple sclerosis activity status and clinical management

BARTS-MS TREAT-2-TARGET-NEDA algorithm for MS management



DMT, disease-modifying therapy; MS, multiple sclerosis; NEDA, no evidence of disease activity; Rx, treatment/therapy.
Giovannoni G, et al. *Mult Scler Relat Disord.* 2015;4:329–33.

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Optimizing individualized management in an expanding therapeutic landscape

Prof. Gavin Giovannoni

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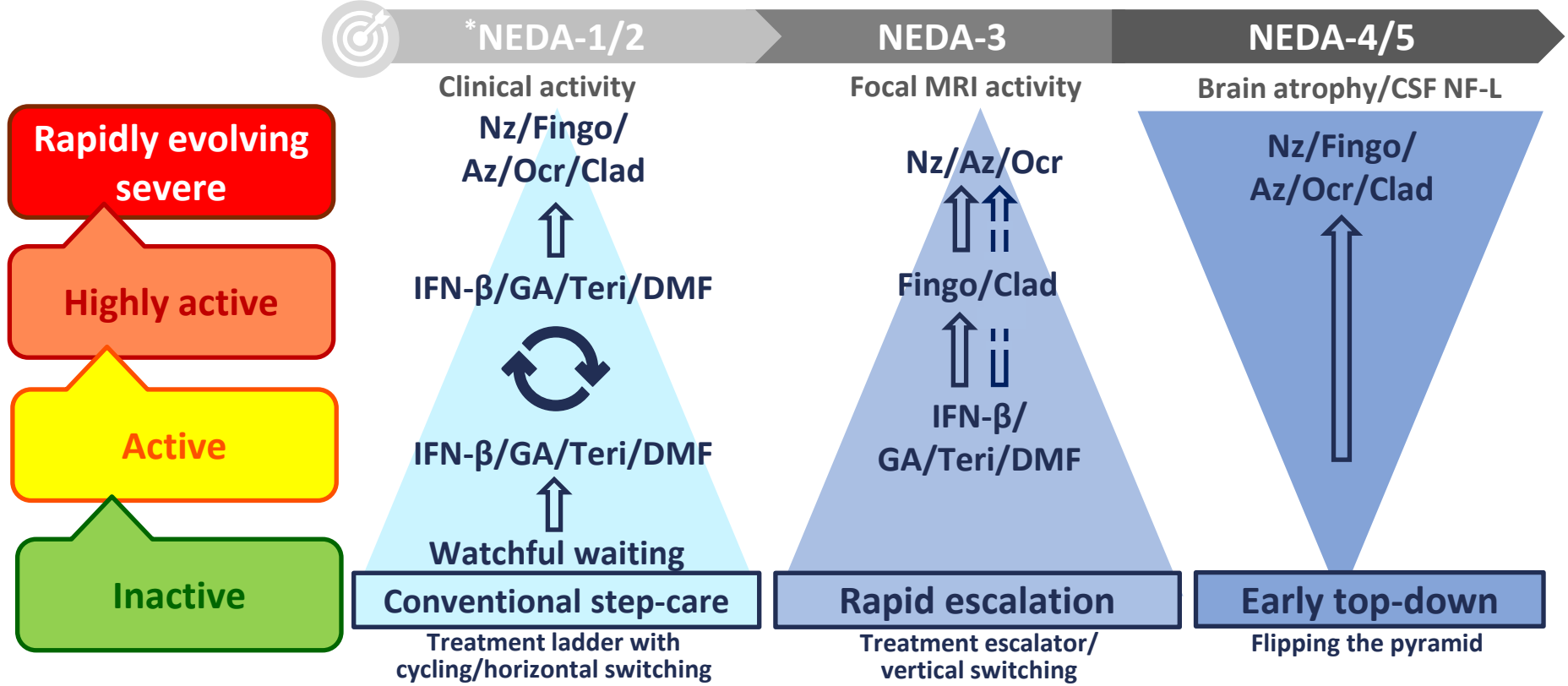
NEDA as a treatment target in multiple sclerosis



*NEDA, no evident disease activity; NEDA-2, clinical only (relapse free + progression free); NEDA-3, clinical + focal MRI activity; NEDA-4/5, clinical + focal MRI activity free + normalizing brain atrophy loss + CSF NF-L level normalization. Az, alemtuzumab; Clad, oral cladribine; CSF, cerebral spinal fluid; DMF, dimethyl fumarate; Fingo, fingolimod; GA, glatiramer acetate; IFN-β, interferon-beta; MRI, magnetic resonance imaging; MS, multiple sclerosis; NF-L, neurofilament (light chain); Nz, natalizumab; Ocr, ocrelizumab; Teri, teriflunomide. Giovannoni G. *Curr Opin Neurol.* 2018;31:233–43.

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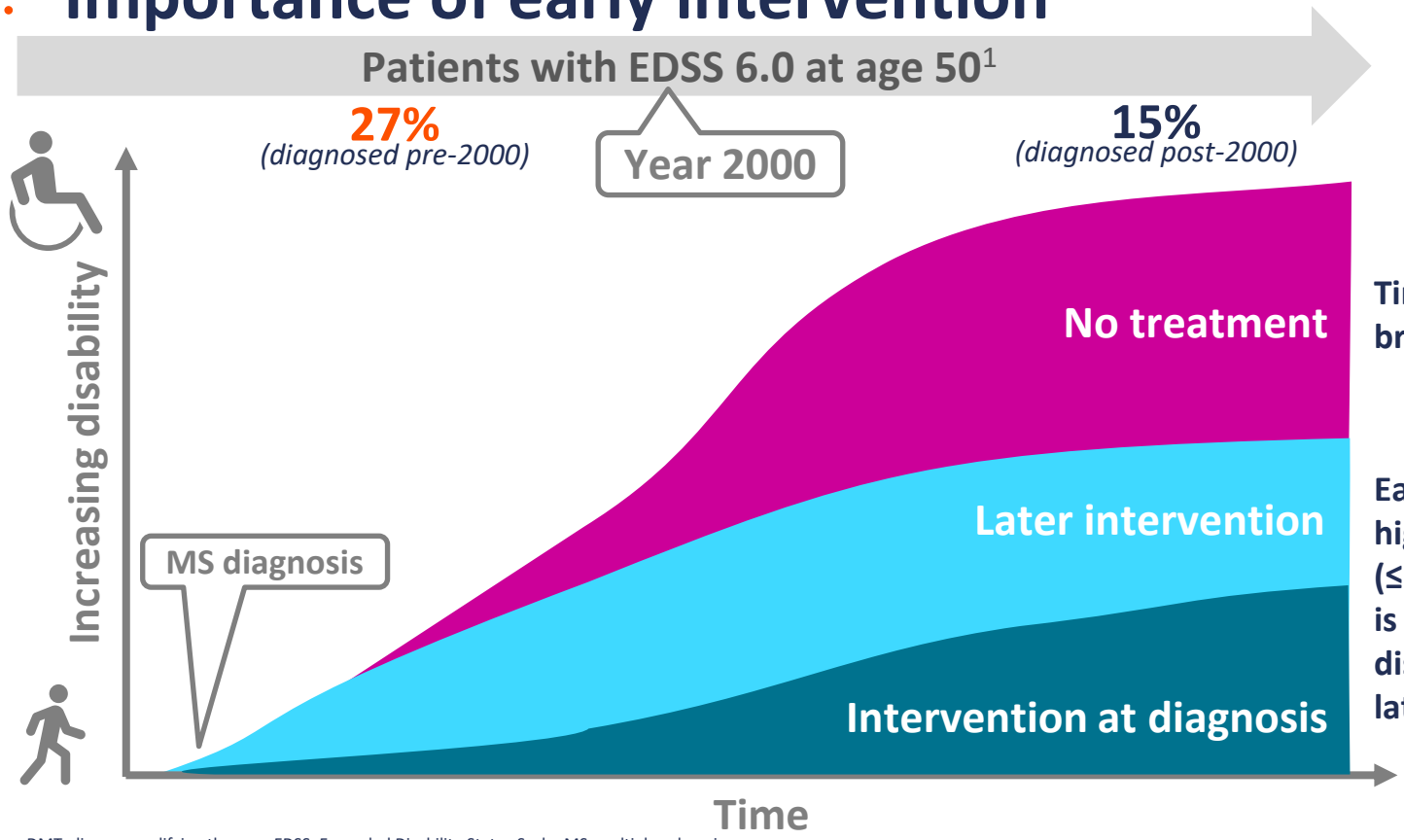
Importance of early intervention



'Time is brain'

Time matters for brain health in MS[2]

MS Base Registry

Early initiation of high-efficacy DMT (≤2 years of disease onset) is associated with less disability compared with later DMT initiation[3]

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Image reproduced with permission from Giovannoni G, et al. Brain health: Time matters in multiple sclerosis. 2015 Available at www.msbrainhealth.org/report (accessed 20 June 2022).

1. Capra R, et al. *Mult Scler.* 2017;23:1757–61; 2. Giovannoni G, et al. *Mult Scler Relat Disord.* 2016;9(Suppl. 1):S5–S48; 3. He A, et al. *Lancet Neurol.* 2020;19:307–16.

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Case study: Immune status and treatment decisions

- 24-year-old female
- Early active RRMS

- One relapse in the last year
- New lesions on MRI compared with 2 years ago; no Gd-enhancing lesions

- Started on DMF
- Six-monthly bloods: lymphopenia (0.7×10^9/L); repeated 1 month later and now 0.68×10^9/L

DMF, dimethyl fumarate; Gd, gadolinium; MRI, magnetic resonance imaging; RRMS, relapsing remitting multiple sclerosis.

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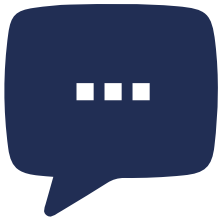
Case study: Patient considerations in decision-making

- 51-year-old woman
- Active RRMS

- Received ocrelizumab (in OPERA-1 and extension study)
- NEDA for 43 months



- Left breast lesion found on routine mammogram
- Fine needle biopsy reveals DCIS, and patient undergoes lumpectomy
- Misses one ocrelizumab infusion due to surgery

- No new lesions on MRI
- Patient is keen to continue on ocrelizumab

DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; RRMS, relapsing remitting multiple sclerosis.

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Safety and immunologic considerations associated with disease modifying therapies

Prof. Gavin Giovannoni

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Reasons for disease modifying therapy sequencing

Treatment related

- Efficacy
- Side effects
- Tolerability
- AEs

Wider health needs

- Lymphopenia
- Malignancy
- Infection(s)
- Risks

Patient centric

- Preference
- Ageing
- Pregnancy
- Breast feeding

Healthcare framework

- Guidelines
- Vaccinations
- Reimbursement
- Costs

Appropriate treatment sequencing is imperative to mitigate risks, notably risk of PML associated with natalizumab and alemtuzumab

AE, adverse event; PML, progressive multifocal leukoencephalopathy.
Personal communication with Prof. Gavin Giovannoni (May 2022).

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Case study: Immune-management in multiple sclerosis

- 28-year-old male
- RES RRMS is NEDA on natalizumab

- Previously JCV negative
- After 3 years of treatment has seroconverted to JCV positive
- Anti-JCV antibody index now 2.8

JCV, John Cunningham virus (human polyomavirus 2); MS, multiple sclerosis; NEDA, no evidence of disease activity; RES RRMS, rapidly evolving severe relapsing remitting MS.

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Case study: Family planning in multiple sclerosis

- 37-year-old female

- NEDA for 3 years on fingolimod
- Previously failed on IFN-β

- She wants to start a family

IFN-β, interferon-beta; NEDA, no evidence of disease activity.

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