Disease modifying drugs for neurological disorders

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- Evolving disease modifying drugs (focus on MS/NMOSD)
- Current treatment algorithm of MS/NMOSD
- Monitoring plan for drug use
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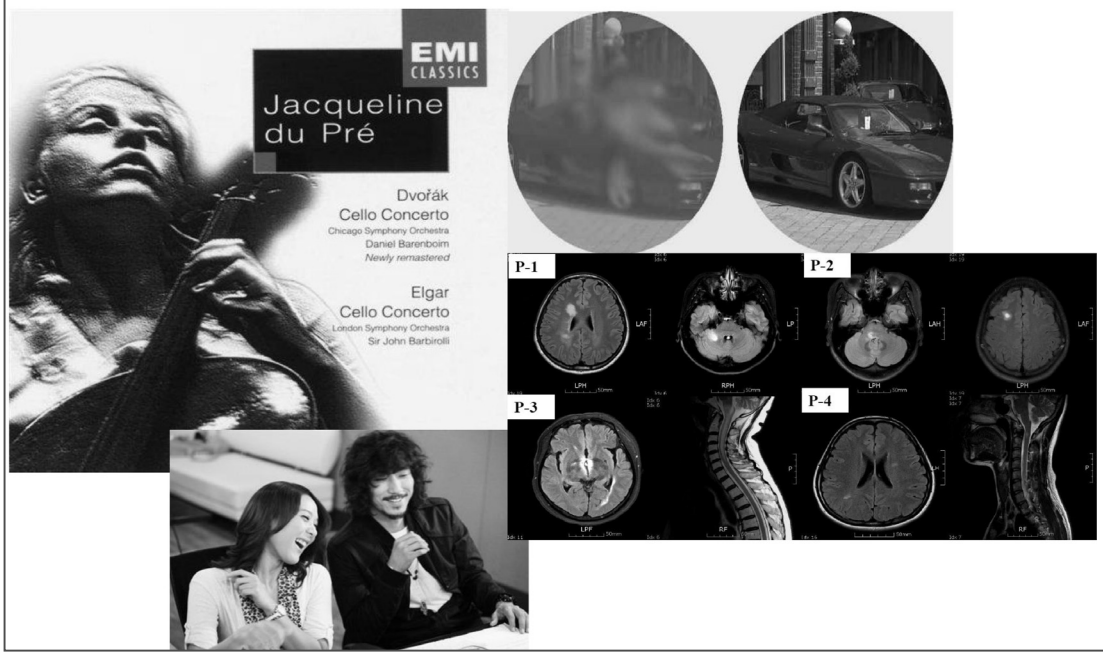
Multiple Sclerosis & Neuromyelitis optica spectrum disorder



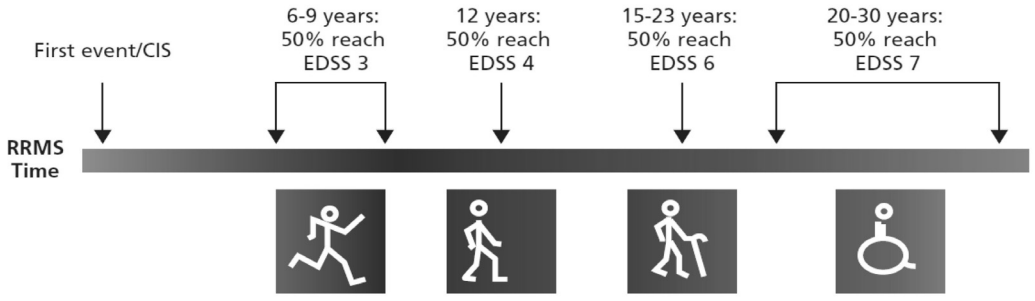
VIEWS & REVIEWS

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

- International Panel for NMO Diagnosis (IPND)
- Nomenclature
  - ***NMOSD***: unifying term, NMO & NMOSD
  - Monophasic NMOSD : criteria not defined
    - Panel recommendation:>5 years relapse-free from index
  - Relapse: Interval longer than 4wks between attack
  - OSMS: superseded term as NMOSD

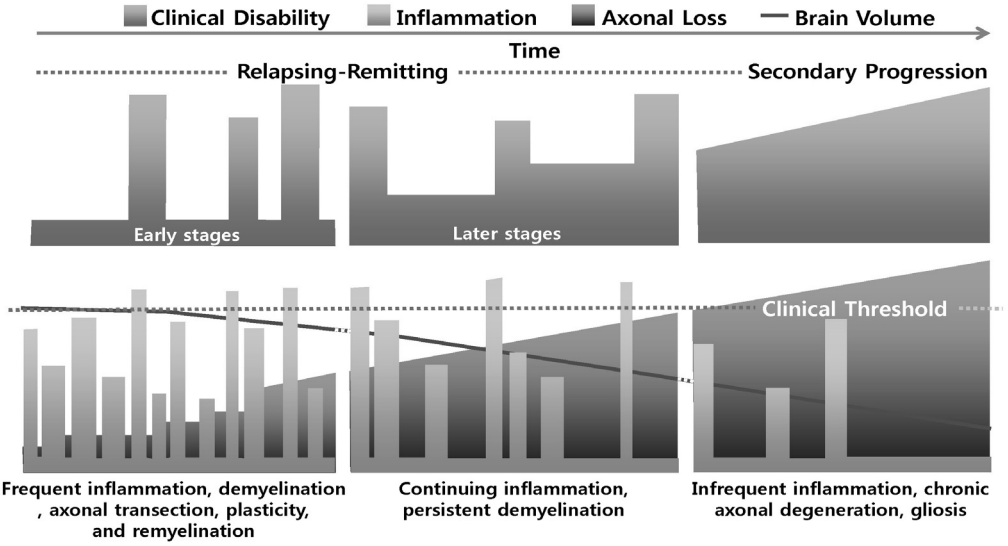
Wingerchuk et al., Neurology, 2015

Natural Course of MS: Milestones of Disability



- Cognitive impairment is present in 26-75% of patients
  - More prevalent and severe in patients with higher EDSS

Relapsing-Remitting and Secondary Progressive Forms of MS Are Characterized by Inflammation and Axonal Loss



Compston A et al. *Lancet*. 2008;372:1502-1517; Compston A et al. *Lancet*. 2002;359:1221-1231.

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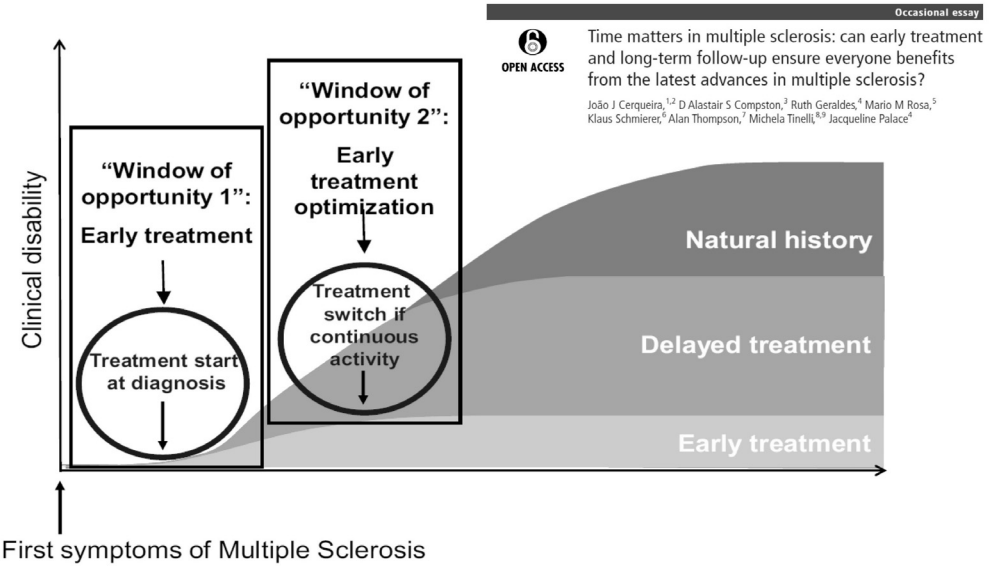
Time is brain in MS



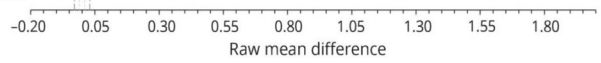
Current available options for MS in Korea

Treatment options		Availability (Reimbursement status)	Korean Indications	Approved administration
SC INFβ-1b	Betaferon®	1998 (-); 1999(+)	RRMS, CIS	250ug SC injection, EOD
SC INFβ-1a	Rebif®	2000 (+)	RRMS, CIS	22ug, 44ug SC injection, TIW
Mitoxantrone	Novantrone®	2005 (+)	RRMS/SPMS	12mg/m^2 IV, Q3M
Glatiramer Acetate	Copaxone®	2011 (+)	RRMS, CIS	30mg SC injection, QD
IM INFβ-1a	Avonex®	2013 (+)	RRMS	30ug IM injection, QW
Teriflunomide	Aubagio®	2013 (+)	RRMS	14mg oral, QD
Natalizumab	Tysabri®	2014; 2015(+)	Highly active RRMS	300mg IV, Q4W
Alemtuzumab	Lemtrada®	2014; 2015(+)	Highly active RRMS	12mg IV, Yearly
Dimethyl Fumarate	Tecfidera®	2016	RRMS	240mg Oral, BID
Fingolimod	Gilenya® Fytarex®	2011 (holding) 2017 (+)	RRMS	0.5mg Oral, QD
SC PegINFβ-1a	Plegridifin®	2017(+)	RRMS	125mcg, 2/Month

Ocrelizumab (Ocrevus®), Clardribine (Mavenclad®) Coming Soon..

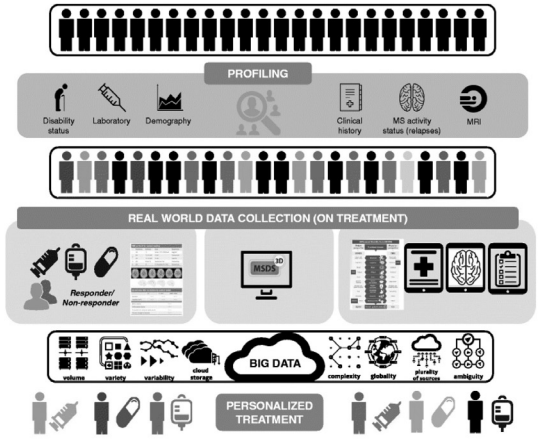
DMT Outcome: ARR, RRMS

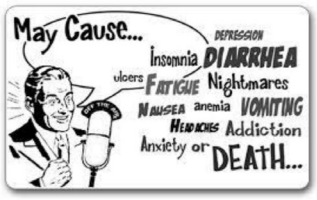
Drug	RM	LCL	UCL	Studies	Confidence
Cyclophosphamide	1.80	0.56	3.04	1 III	Low
Azathioprine	0.49	0.07	0.91	1 II	Moderate
Betaseron	0.43	0.24	0.62	1 II	Moderate
Natalizumab	0.41	0.31	0.51	1 I	High
IVIg	0.37	-0.21	0.94	2 I, 2 II	Very low
Rituximab	0.30	-0.07	0.67	1 II	Very low
Alemtuzumab[a]	0.26	0.22	0.29	1 I, 1 II	High
Daclizumab[b]	0.25	0.13	0.37	1 I	High
Interferon + pulsed corticosteroids	0.24	0.02	0.47	2 II	Moderate
Fingolimod	0.21	0.16	0.26	2 I, 2 II	High
Cladribine	0.19	0.14	0.24	3 II	High
Dimethyl fumarate	0.19	0.13	0.25	1 I, 1 II	High
Glatiramer	0.18	0.09	0.28	2 I, 1 II	High
Teriflunomide	0.18	0.11	0.25	3 II	High
Ocrelizumab	0.13	0.09	0.18	2 I	High
Pegylated interferon	0.11	0.01	0.21	1 I	High
Avonex	0.08	0.01	0.15	1 I	Moderate
Pulsed corticosteroids	0.00	-0.24	0.24	1 IV	Very low



Rae-Grant et al., Neurology, 2018

Time for precision, personalized treatment on MS



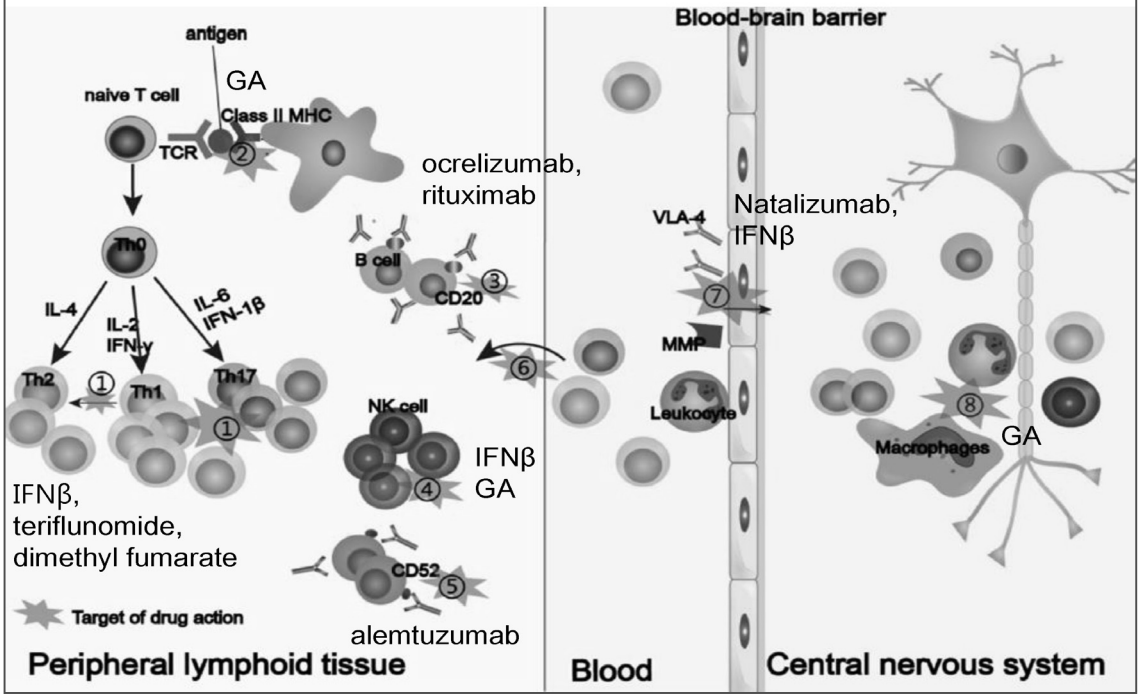


Clinicians must incorporate preferences (safety, routine of adm., AE, tolerability) in choice of DMT in MS patients (Level A)

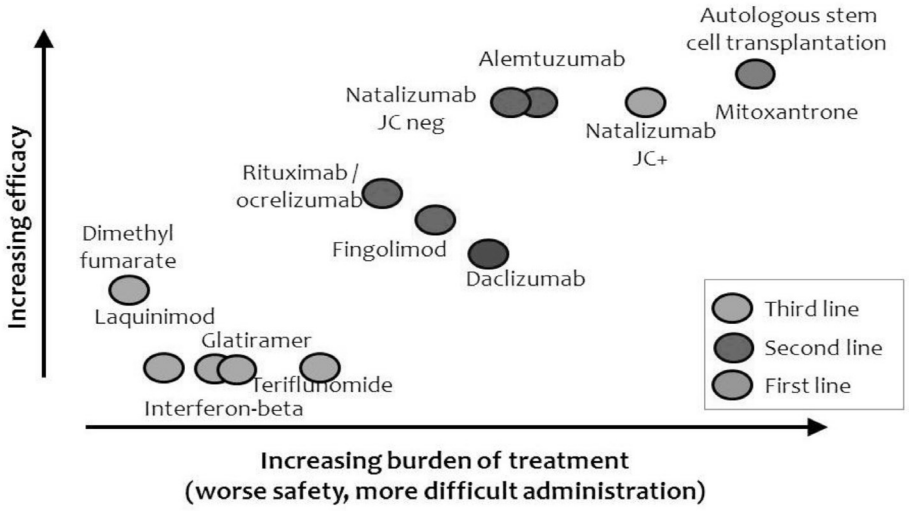
Rae-Grant et al., Neurology, 2018

NEW DRUGS FOR MS & NMOSD

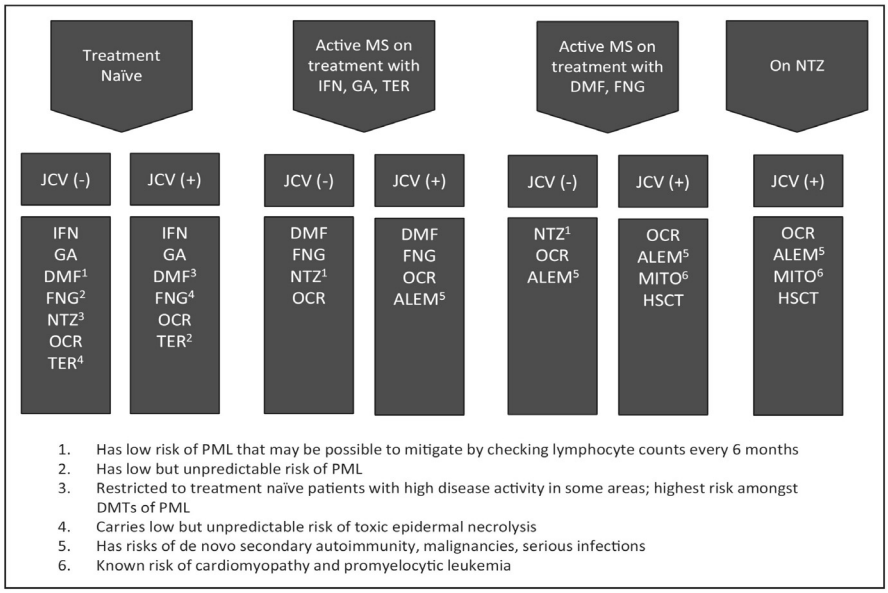
Targets & Mechanism of DMT



Drug potency



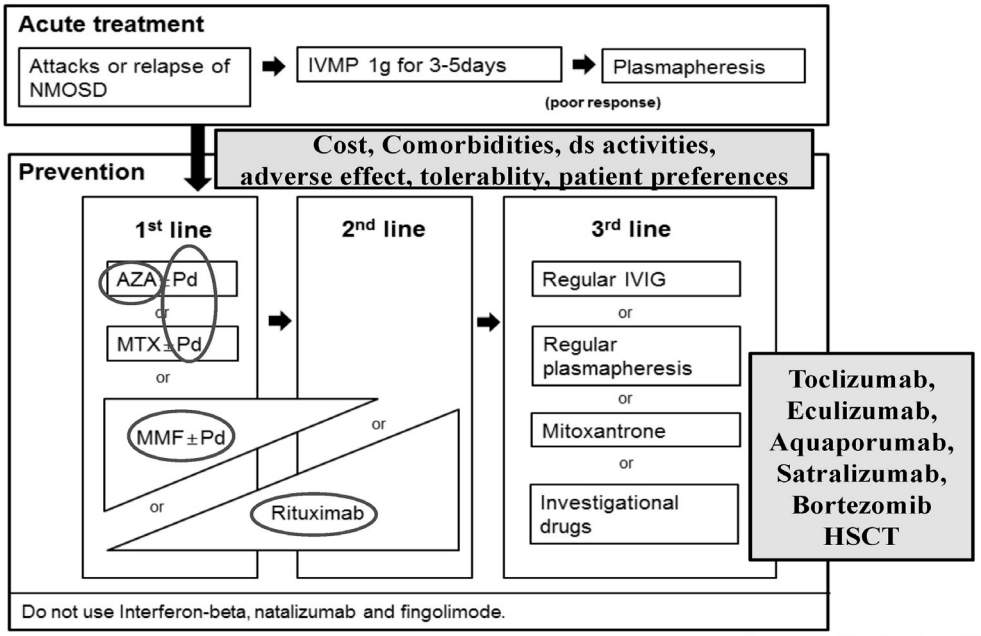
Maintenance treatment of MS



1. Has low risk of PML that may be possible to mitigate by checking lymphocyte counts every 6 months
2. Has low but unpredictable risk of PML
3. Restricted to treatment naïve patients with high disease activity in some areas; highest risk amongst DMTs of PML
4. Carries low but unpredictable risk of toxic epidermal necrolysis
5. Has risks of de novo secondary autoimmunity, malignancies, serious infections
6. Known risk of cardiomyopathy and promyelocytic leukemia

Bruce et al., Curr Opin, 2019

Maintenance treatment for NMOSD



Heo et al., J Mult Scler 2015

SE & monitoring for DMT (MS) (1)

Drug	Dosing/ Route	Baseline Monitoring	On-Therapy Monitoring	Special Considerations	Common Adverse Effects	Potentially Serious Adverse Effects
Interferon beta-1a/1b	Variable; IM/ subcutaneous	Complete blood cell count, liver function tests, thyroid function tests	Complete blood cell count, liver function tests, thyroid function tests every 3 months for 6 months then annually	Development of neutralizing antibodies	Injection site reaction, flulike symptoms, fatigue	Anemia, leukopenia, thrombocytopenia, depression, liver injury, skin necrosis
Glatiramer acetate	20 mg/d; 40 mg 3 times a week; subcutaneous	None	None	Postinjection systemic reaction (flushing, tightness of chest, shortness of breath, anxiety)	Injection site reaction, lipoatrophy, vasodilation, rash	Skin necrosis
Fingolimod	0.5 mg/d; oral	Complete blood cell count, liver function tests, varicella-zoster virus titer, macular optical coherence tomography	Macular optical coherence tomography (at 3 months); complete blood cell count, liver function tests every 3–6 months; skin examinations regularly	First-dose observation; varicella-zoster virus immunity	Diarrhea, mild blood pressure increase, headache, back pain, cough	Progressive multifocal leukoencephalopathy (PML) fungal infection, shingles, liver injury, macular edema, pulmonary function test changes
Dimethyl fumarate	Initiate at 120 mg 2 times a day and titrate up to 240 mg 2 times a day; oral	Complete blood cell count, liver function tests	Complete blood cell count, liver function tests every 3–6 months	Consider slow titration to lessen side effects; can use H2 blockers or proton pump inhibitors for gastrointestinal symptoms; can use aspirin for flushing	Flushing, abdominal pain, diarrhea, nausea, pruritus	PML, lymphopenia, liver injury, anaphylaxis
Teriflunomide	14 mg once a day; oral	Complete blood cell count, liver function tests, tuberculosis test, pregnancy test	Liver function tests monthly for 6 months; complete blood cell count every 3–6 months	Pregnancy category X; accelerated elimination procedure (cholestyramine or activated charcoal)	Alopecia, diarrhea, nausea, headache, paresthesia	Toxic epidermal necrosis/Stevens-Johnson syndrome, teratogenicity, infection, interstitial lung disease, peripheral neuropathy, hypertension

SE & monitoring for DMT (MS) (2)

Drug	Dosing/ Route	Baseline Monitoring	On-Therapy Monitoring	Special Considerations	Common Adverse Effects	Potentially Serious Adverse Effects
Natalizumab	300 mg every 4 weeks; IV	Complete blood cell count, liver function tests, JC virus antibody	JC virus antibody testing every 3–6 months; complete blood cell count and liver function tests every 6 months	Risk Evaluation and Mitigation Strategy; antinatalizumab antibodies	Infusion reactions, headache, urticaria, diarrhea, mild leukocytosis, eosinophilia	PML, anaphylaxis
Alemtuzumab	12 mg/d for 5 days; 1 year later, 12 mg/d for 3 days; IV	Complete blood cell count, serum creatinine, urinalysis, thyroid function tests, varicella-zoster virus titer, hepatitis B virus core antibody and surface antigen, hepatitis C virus, human immunodeficiency virus (HIV), tuberculosis test, skin examination	Skin examinations and human papilloma virus screening annually; complete blood cell count, serum creatinine, and urinalysis monthly until 48 months after last infusion; thyroid function tests every 3 months until 48 months after infusion	Risk Evaluation and Mitigation Strategy; varicella-zoster virus immunity; antiherpes treatment starting on day 1 for 2 months or until CD4+ count >200	Infusion reactions	Autoimmune diseases (thyroid, idiopathic thrombocytopenic purpura, Goodpasture syndrome), anaphylaxis, infections, malignancy, arterial dissection, and stroke
Ocrelizumab	Initial doses: 300 mg × 2 (2 weeks apart); IV Subsequent doses: 600 mg every 6 months; IV	Complete blood cell count, comprehensive metabolic profile, lymphocyte subsets, hepatitis B virus core antibody and surface antigen, hepatitis C virus, HIV, tuberculosis test, serum immunoglobulins	Complete blood cell count, comprehensive metabolic profile, lymphocyte subsets every 6 months, immunoglobulins every 6–12 months	Antivirals for hepatitis B virus carrier; treatment for latent tuberculosis	Infusion reactions, respiratory infections, urinary tract infections, herpes infections	Neutropenia, hypogammaglobulinemia

SE & monitoring drug for NMOSD(1)

DRUG	MECHANISM	DOSE	SIDE EFFERCTS	EFFICACY
Corticosteroids	Bind to glucocorticoid receptor, Induce gene expression and modulates immune function	**Acute attack:** methylprednisolone 1,000 mg, 3–5 days **Prophylaxis: prednisone** 2.5–20 mg/d	Insomnia, mood changes, weight gain,glaucoma, osteoporosis, diabetes, hypertension, growth impairment, insomnia	Reduced ARR from 1.48 to 0.49 EDSS was stable
Azathioprine	Acts as immunosuppressive antimetabolite by interfering with proliferation of T and B lymphocytes and alterations in antibody production	2 $mg \cdot kg^{-1} \cdot d^{-1}$	Bone marrow suppression, leukopenia, nausea, hepatotoxicity, diarrhea, hair loss, fatigue	Reduced ARR from 2.20–1.13 to 0.40–0.60 EDSS was stable

SE & monitoring drug for NMOSD(2)

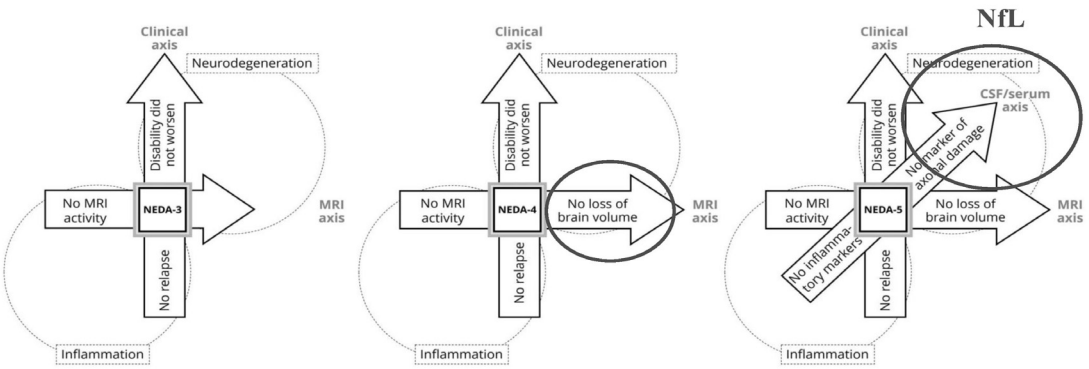
DRUG	MECHANISM	DOSE	SIDE EFFERCTS	EFFICACY
Mycophenolate	Reversible inhibitor of inosine monophosphate dehydrogenase that is involved in guanosine nucleotide synthesis Proliferation of T and B lymphocytes is impaired by interruption of guanosine synthesis	2,000 mg/d, range 750–3,000 mg	Leukopenia, skin malignancy, lymphoma, PML, headache, hair loss, diarrhea, constipation, bruising, anxiety	Reduced ARR from 1.28 to 0.09 EDSS was stable
Methotrexate	Inhibitor of dihydrofolate reductase and purine and thymidine synthesis Inhibits proliferation of T and B lymphocytes	17.5–50 mg/wk	Leukopenia, pancytopenia, infections, hepatotoxicity, joint pain, stomatitis, nausea, diarrhea	Reduced ARR from 1.39 to 0.18 EDSS was stable

SE & monitoring drug for NMOSD(3)

DRUG	MECHANISM	DOSE	SIDE EFFERCTS	EFFICACY
Mitoxantrone	Intercalates with DNA and inhibits topoisomerase II Suppresses development of T and B lymphocytes and macrophages	max. cumulative doses 120mg/m^2 3–6 monthly cycles of 12 mg/m^2 followed by 6–12 mg/m^2 maintenance doses	Cardiotoxicity, leukemia, hepatotoxicity, leukopenia, nausea, stomatitis, diarrhea	Reduced ARR from 2.8 to 0.7 Reduced EDSS from 5.6 to 4.4
Rituximab	Chimeric anti-CD20 monoclonal antibody Depletes B cells from pre-B cells through memory lineages	Initiation with 375 mg/m^2 weekly for 4 wk, 1,000 mg twice biweekly, maintenance (1,000 mg) either fixed or upon recurrence of B cells	Infusion reactions, infections, (e.g. recurrent herpes zoster, respiratory infections, urinary tract infects), fatigue, transient leukopenia and transaminase elevation, PML	Reduced ARR from 1.7–2.6 to 0.0–0.93 EDSS stabilized or improved

QUESTIONS FROM PATIENTS..

1. What is my goal of using DMT: NEDA



NEDA difficult to sustain long with platform Tx (<10% over 7-10 yrs)

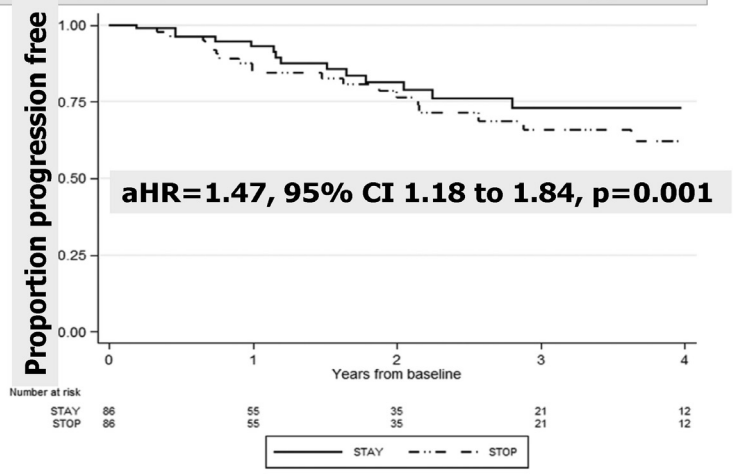
Gasperini et al., Neurology, 2019

2. Can I Stop DMT (MS)?

- No RCT for whether, when, why stop

5 y stop IFN/GA,: No diff relapse free
Survival time to disability progression, shorter in DMT stoppers

1 Prospective cohort study(RRMS)



Kister et al., JNNP, 2016

DMT stop (MS)

ECTRIMS/EAN

- Continue DMT if stable (clinically, MRI), no safety/tolerability issue (weak)

AAN

- RRMS, stable on DMT, wish to discontinue: periodic re-evaluation in discontinuation (B)
- Advocate stable MS on DMT to continue DMT (B)
- CIS: review associated risk
- Consider likelihood future relapse in SPMS (age, ds duration, relapse hx, MRI activity)
- May discontinue DMT in SPMS with no relapse, not ambulatory (EDSS ≥7) for ≥ 2yr

3. Special situation in immunosuppressive therapy(IST)

- Previous HBV, HCV infection
- Previous/latent tuberculosis (TB)
- Vaccinations

5-1. Hepatitis B

- 1) HBsAg (+) or 2) HBsAg(-) and anti-HBc (+): HBV reactivation risk ↑
- Level of risk of HBV reactivation: depends serological profile, medical conditions, drug types.
- Do not give IST to active HBV hepatitis. Test HBVsAg, HBVcAb, LFT in all, prior to starting IST
- Positive serology: refer specialist for prophylactic antiviral therapy (continued for the duration of therapy)
- Monitor serial HBV DNA titres, LFT, HBVsAg (if HBVsAg negative at baseline).

5-2. Hepatitis C

- Information is conflicting but reactivation of HCV seems less common than HBV
- Screening HCV antibody prior to starting IST. Positivity is not contraindication (Consultation with hepatology & monitored for HCV activity (HCV RNA titres, LFT)

5-3. Previous/latent tuberculosis (TB)

- Do not give IST on active TB.
- Although routine TB screening may be unnecessary, screen for latent TB with QuantiFERON-TB Gold or tuberculin skin testing in high-risk patients (eg, from endemic regions).

5-4 Vaccine

- Theoretical risk that live vaccines (eg, yellow fever, varicella-zoster) may cause infection.
- Standard inactivated vaccines are safe (less effective after IST)
- Give all routine vaccinations ≥ 4 weeks prior IST (≥ 8 weeks prior for live vaccines).
- Do not give live vaccines to patients treated IST
- Recommend annual influenza vaccine and five-yearly pneumococcal vaccine throughout Tx