MULTİPL SKLEROZDA TEDAVİ SEÇİMİ ve DEĞİŞİMİ

Dr. Murat TERZİ

Ondokuz Mayıs Üniversitesi Tıp Fakültesi Nöroloji AD.

15.02.2019 - Ankara

MS tedavisinden beklenen

Etkinlik

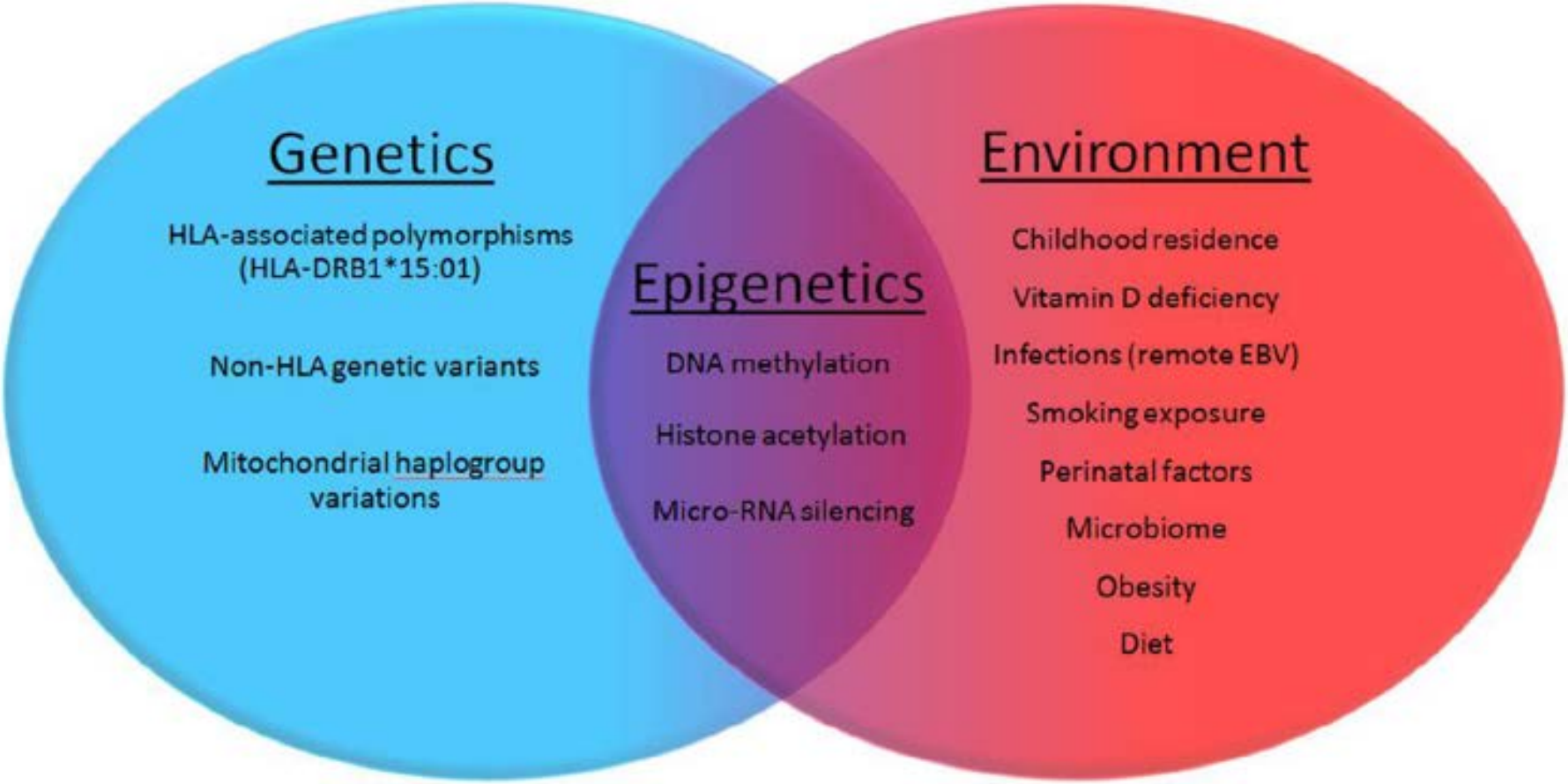
Özürlülük üzerine etki

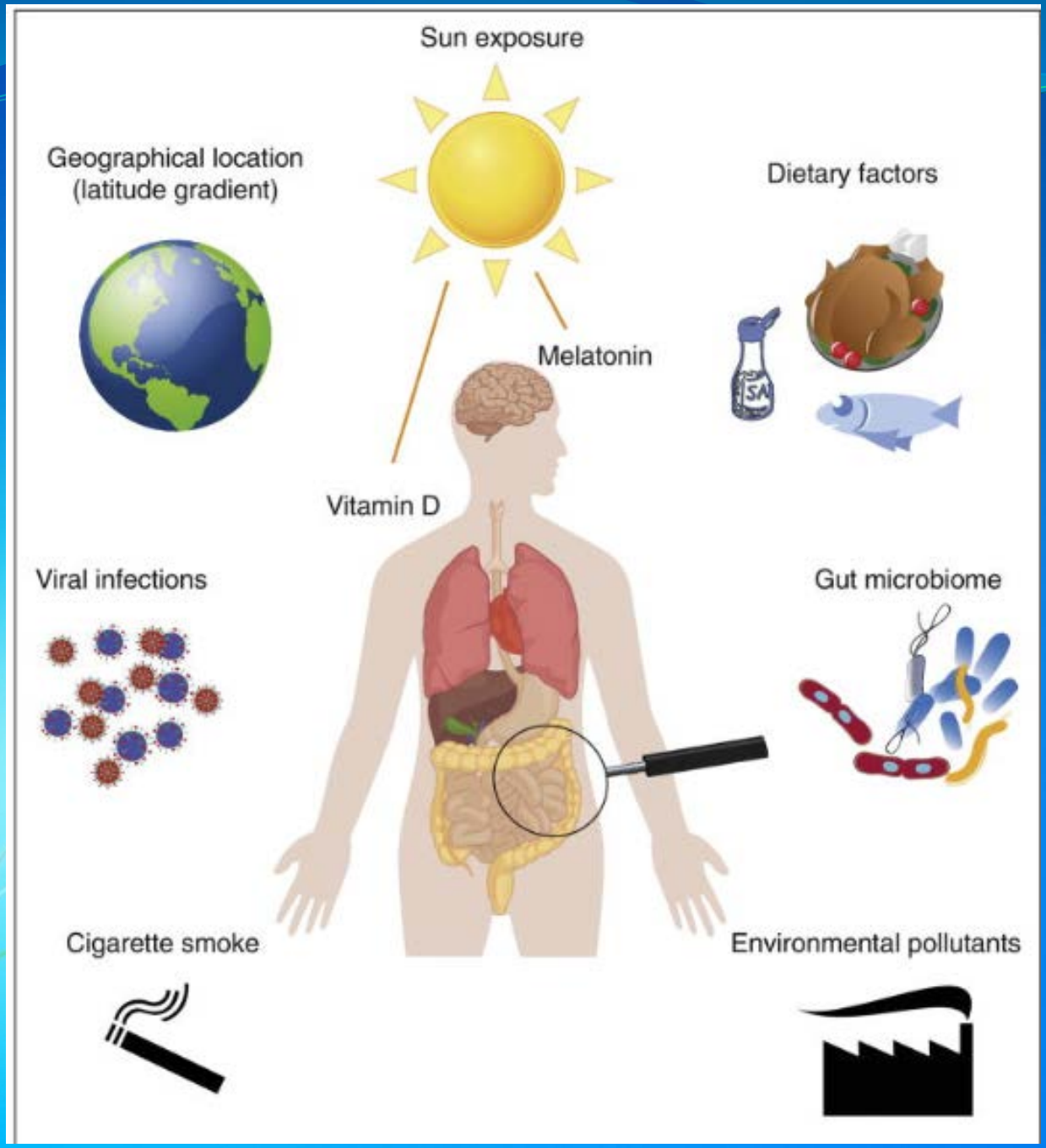
Erken başlayan etki

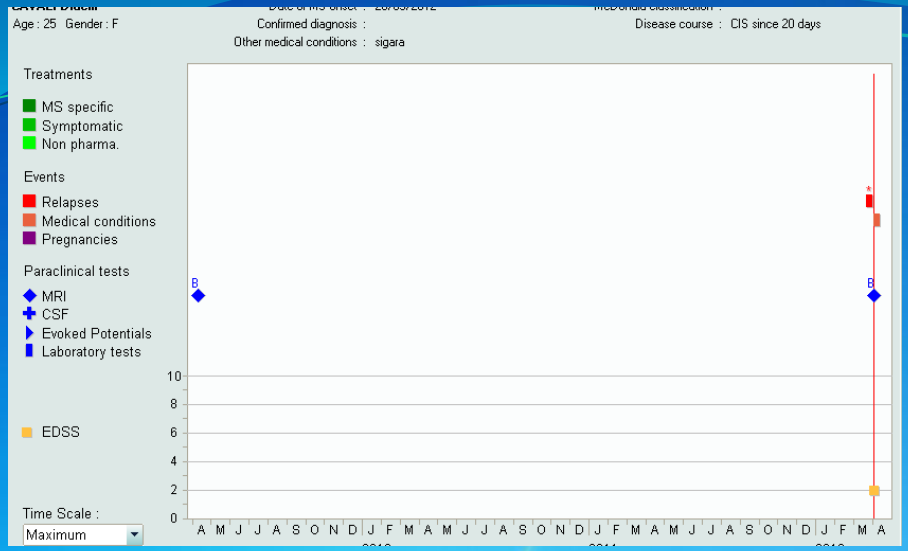
Uzun dönem güvenlilik

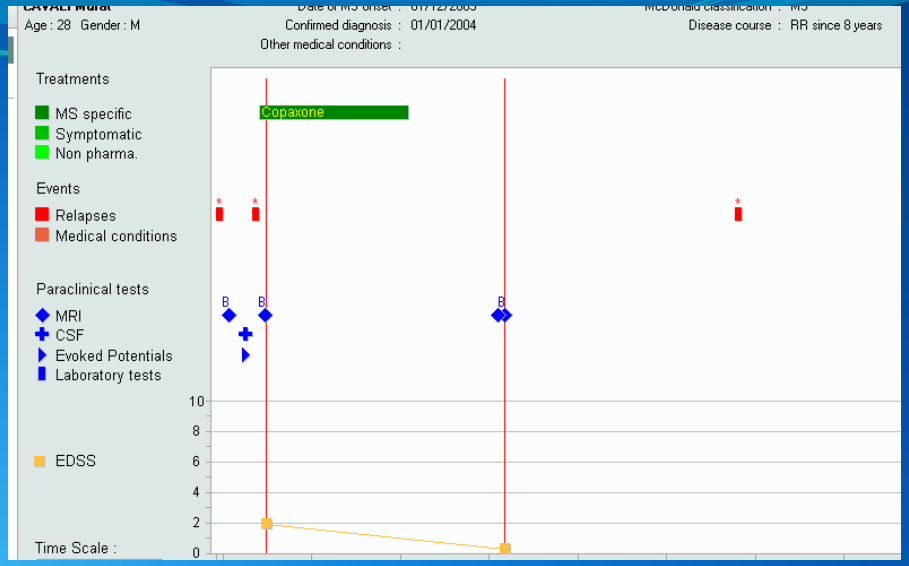
Hasta uyumunu iyileştirmek

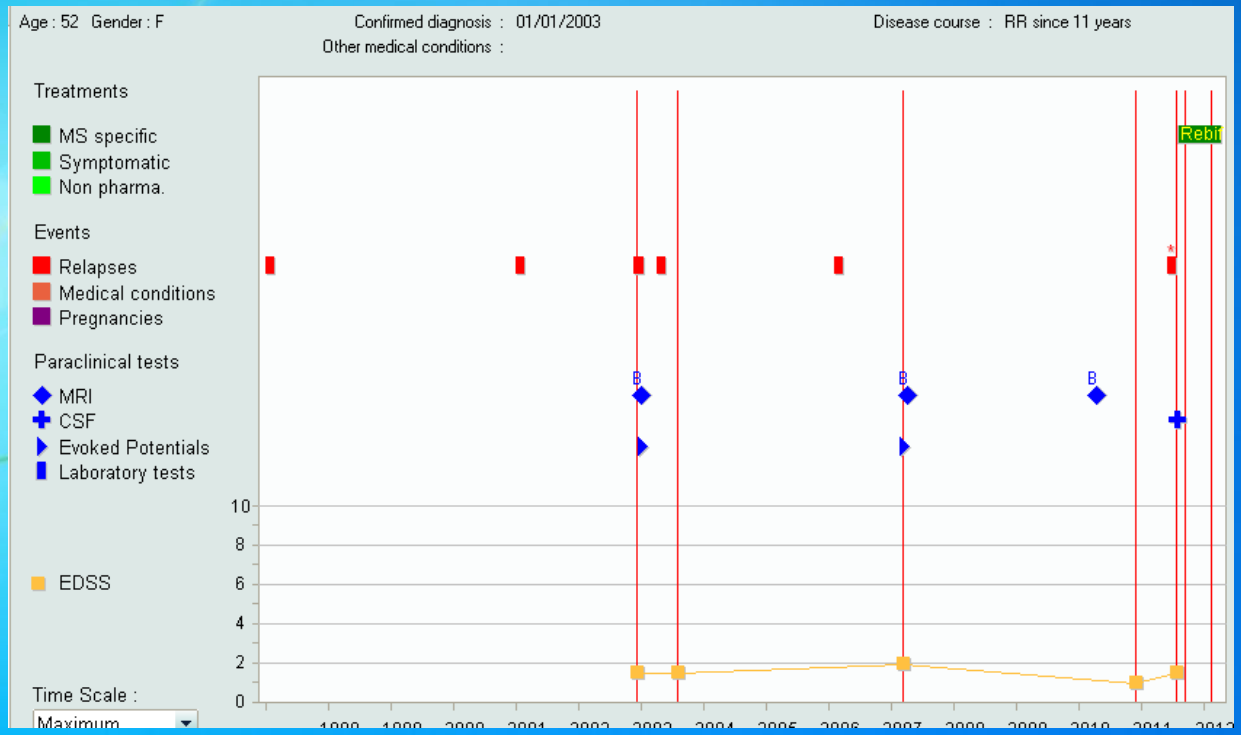
Gebelik


Genetics
HLA-associated polymorphisms (HLA-DRB1*15:01)
Non-HLA genetic variants
Mitochondrial haplogroup variations
Epigenetics
DNA methylation
Histone acetylation
Micro-RNA silencing
Environment
Childhood residence
Vitamin D deficiency
Infections (remote EBV)
Smoking exposure
Perinatal factors
Microbiome
Obesity
Diet


Sun exposure
Geographical location
(latitude gradient)
Dietary factors
Melatonin
Vitamin D
Viral infections
Gut microbiome
Cigarette smoke
Environmental pollutants

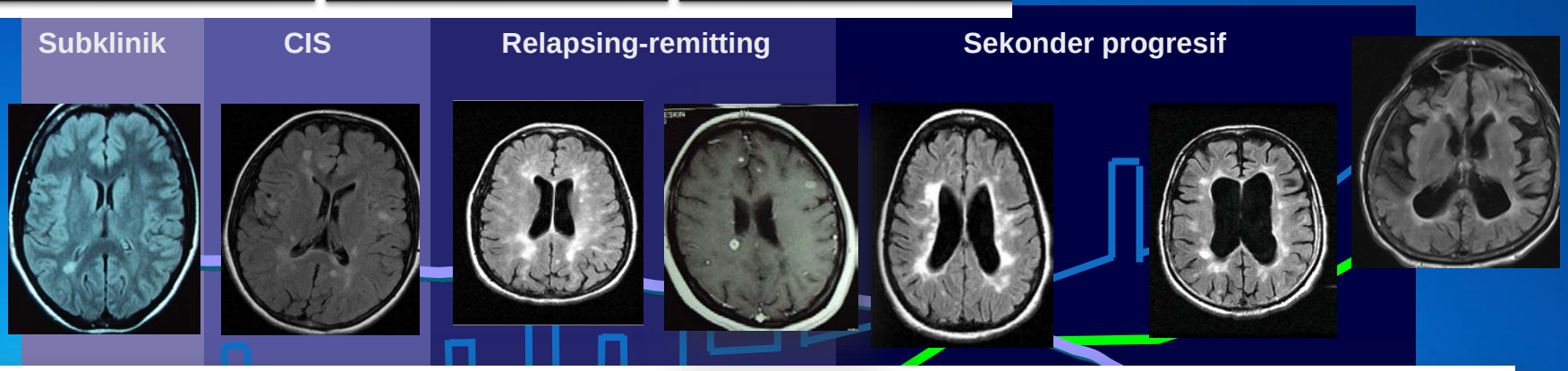

Age : 25 Gender : F
Confirmed diagnosis :
Other medical conditions : sigara
Disease course : CIS since 20 days
Treatments
MS specific
Symptomatic
Non pharma.
Events
Relapses
Medical conditions
Pregnancies
Paraclinical tests
MRI
CSF
Evoked Potentials
Laboratory tests
EDSS
Time Scale :
Maximum

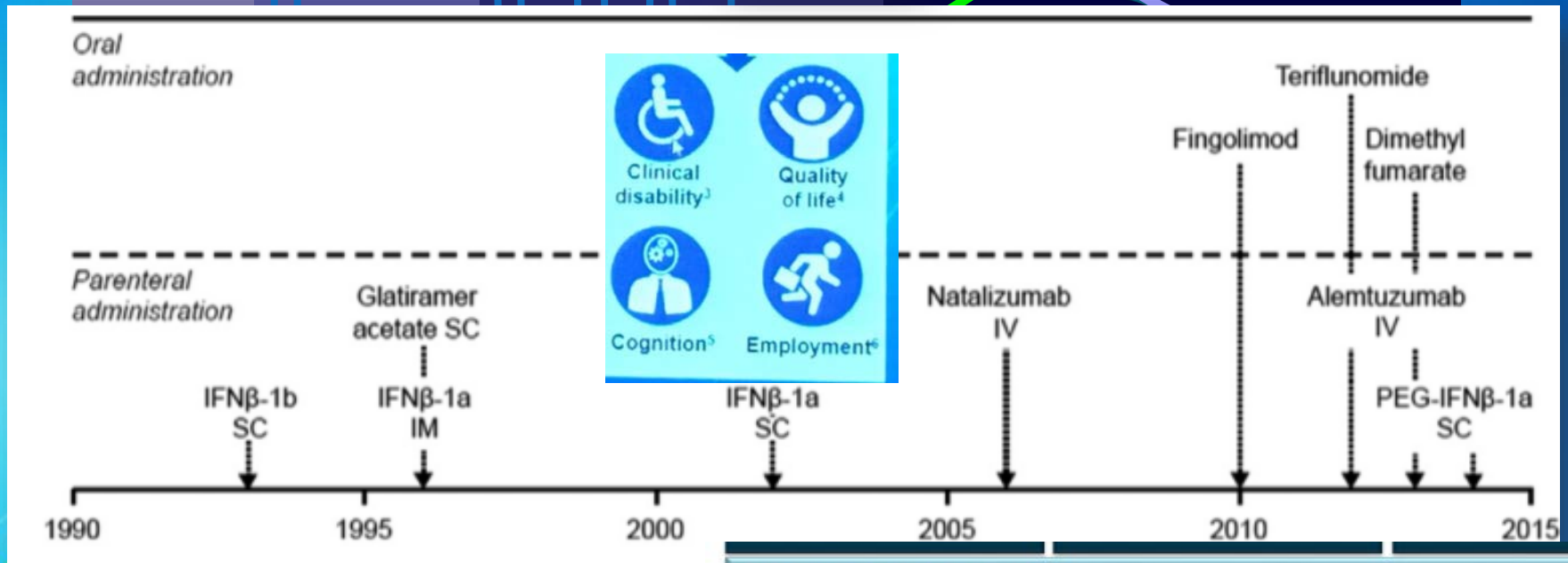

Age : 28 Gender : M
Confirmed diagnosis : 01/01/2004
Other medical conditions :
Disease course : RR since 8 years
Treatments
MS specific
Symptomatic
Non pharma.
Copaxone
Events
Relapses
Medical conditions
Paraclinical tests
MRI
CSF
Evoked Potentials
Laboratory tests
EDSS
Time Scale :


Age : 52 Gender : F
Confirmed diagnosis : 01/01/2003
Other medical conditions :
Disease course : RR since 11 years
Treatments
MS specific
Symptomatic
Non pharma.
Rebif
Events
Relapses
Medical conditions
Pregnancies
Paraclinical tests
MRI
CSF
Evoked Potentials
Laboratory tests
EDSS
Time Scale :
Maximum

MS prevention

- Vitamin D
- Smoking
- EBV

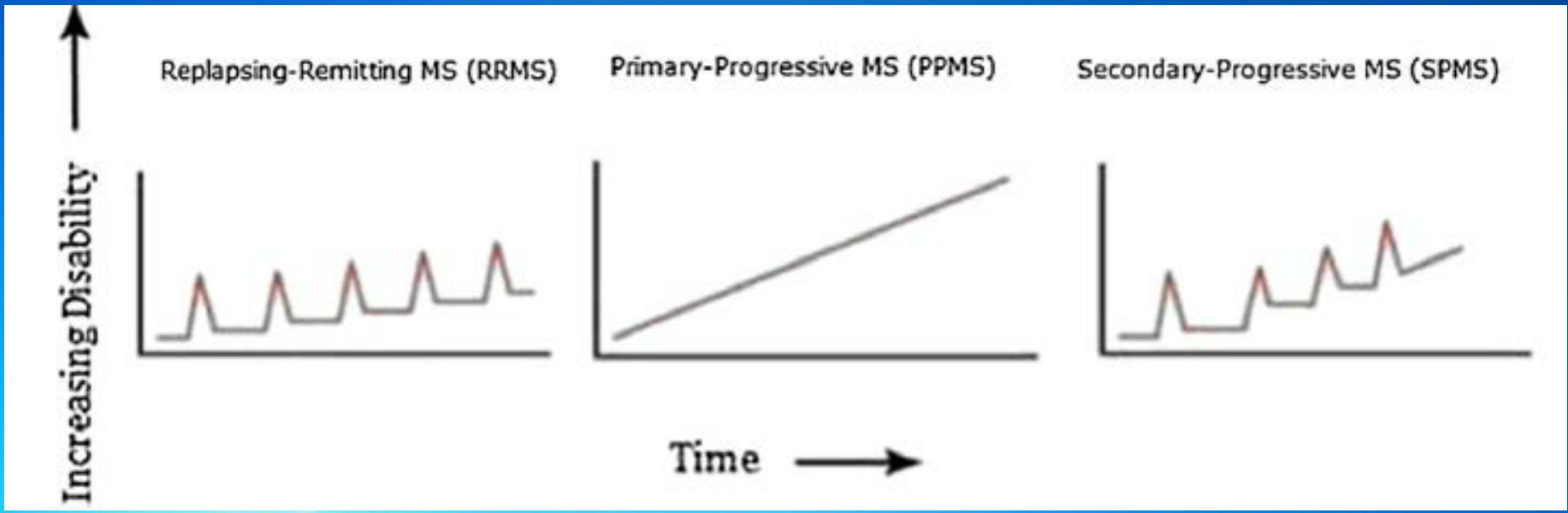




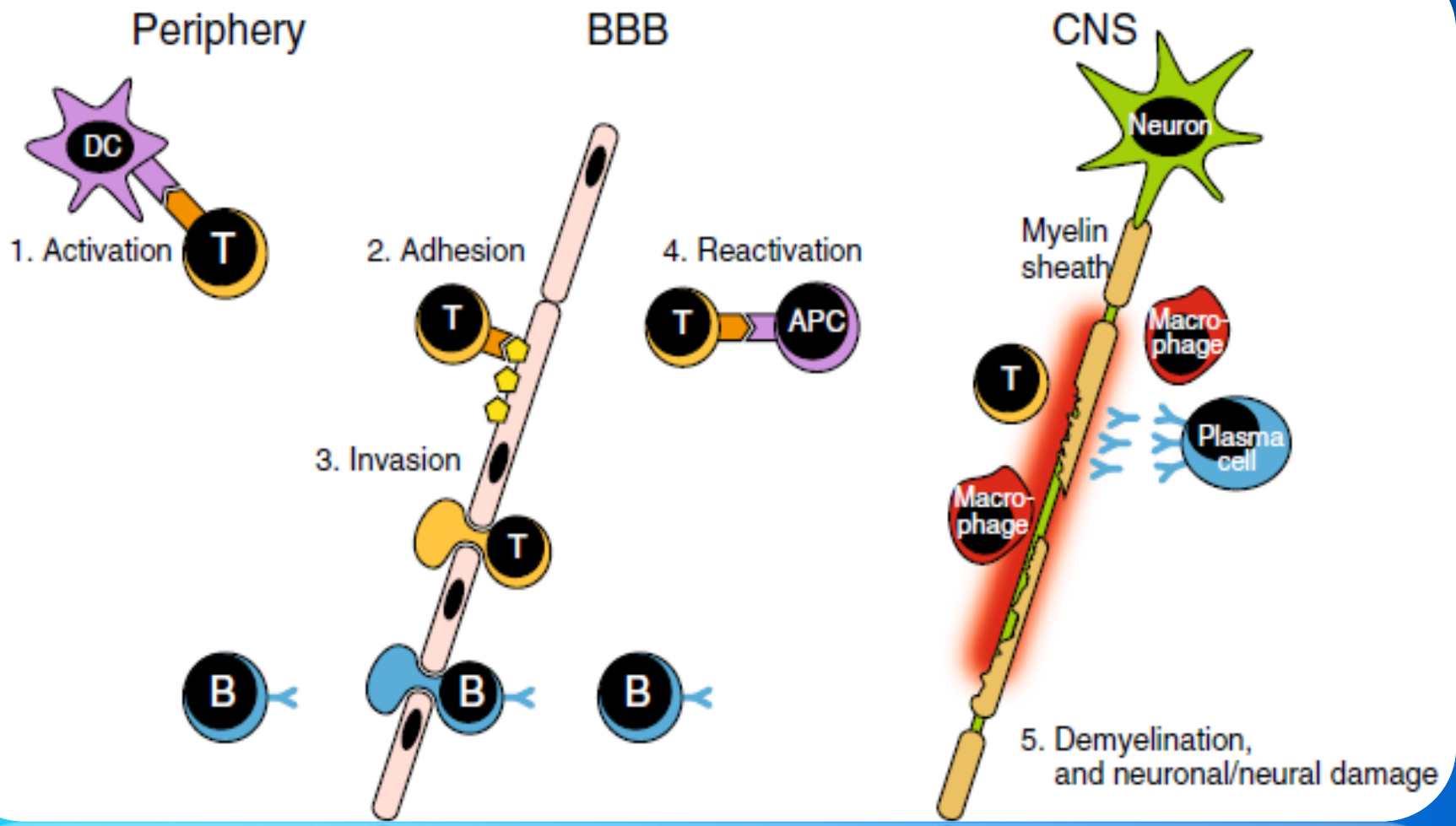
- Anti-inflammatory strategies
- Neuroprotective strategies
- Neurorestorative strategies

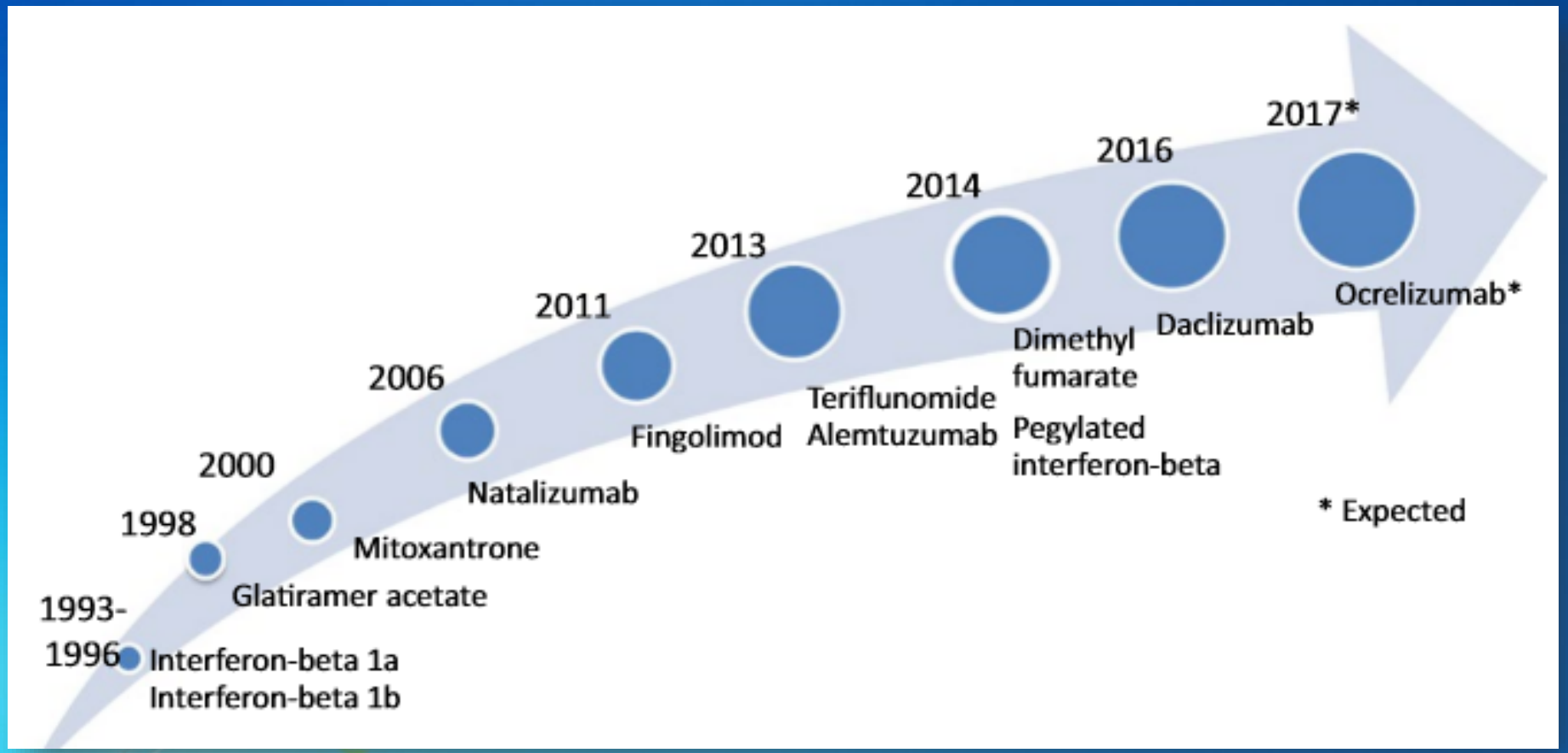
Symptomatic therapies

- Cognition
- Fatigue
- Spasticity
- Bladder/Bowel
- Mobility
- Mood

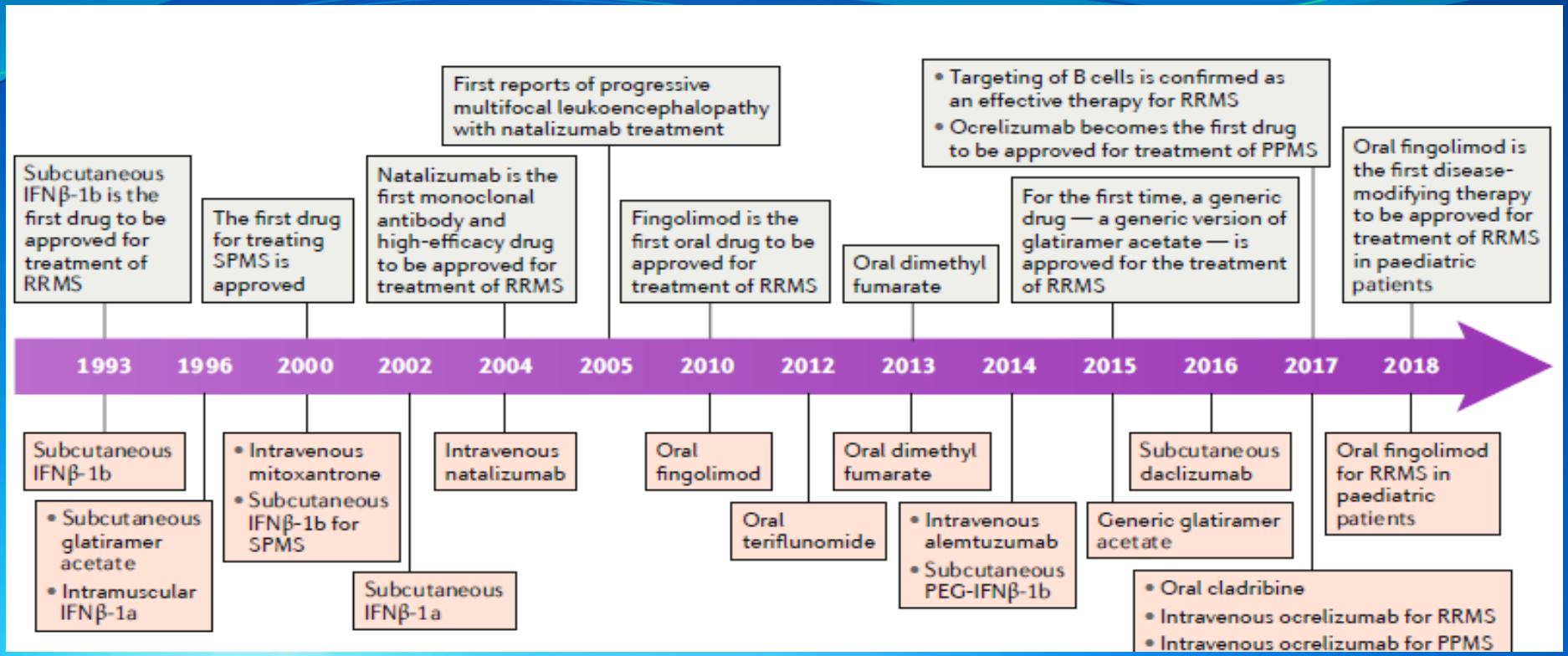


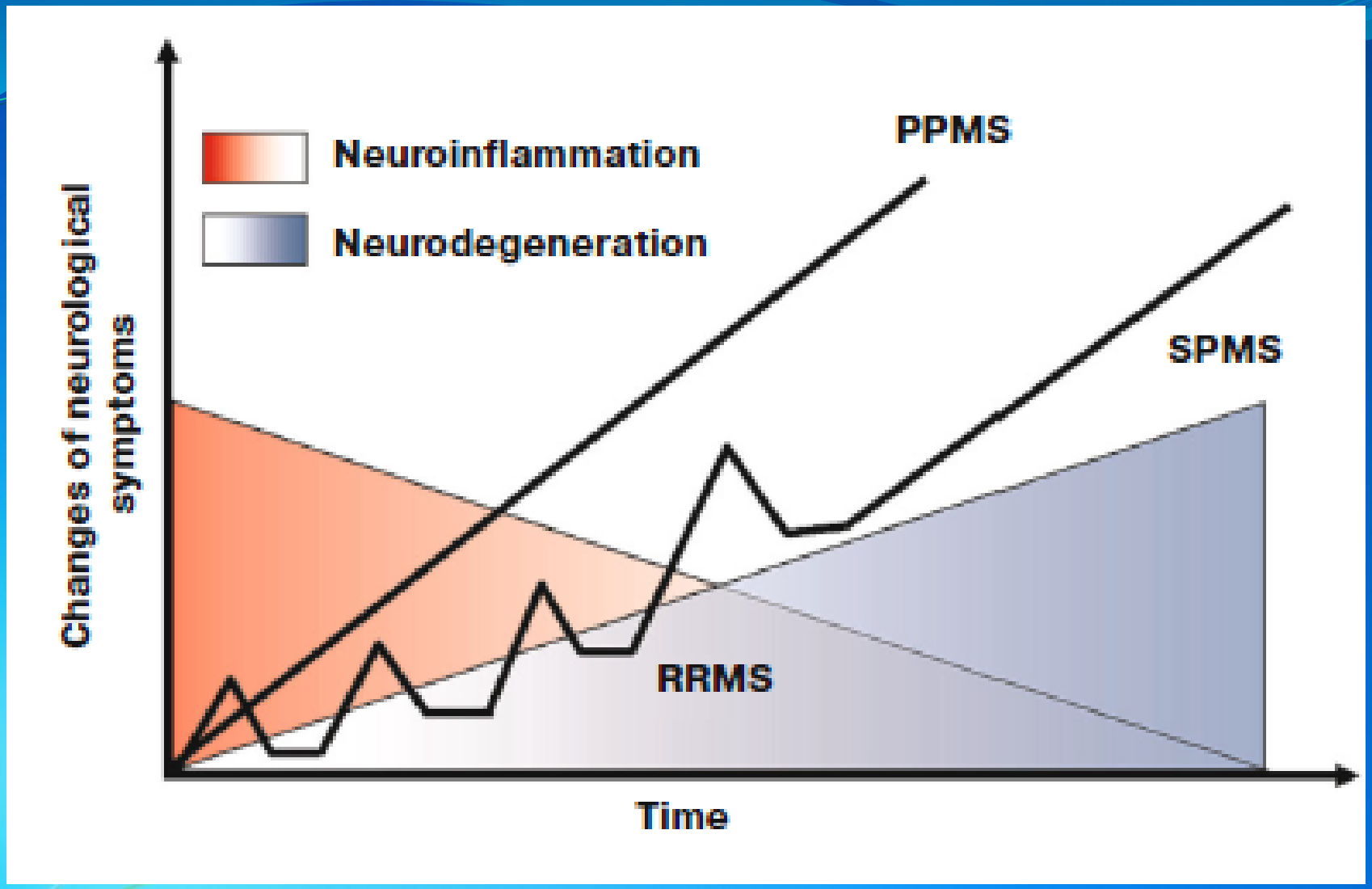
Journal of the Neurological Sciences 349 (2015) 10–14


Periphery
BBB
CNS
DC
1. Activation
T
2. Adhesion
T
3. Invasion
T
B
B
4. Reactivation
T
APC
B
Neuron
Myelin sheath
Macro-phage
T
Plasma cell
Macro-phage
5. Demyelination, and neuronal/neural damage

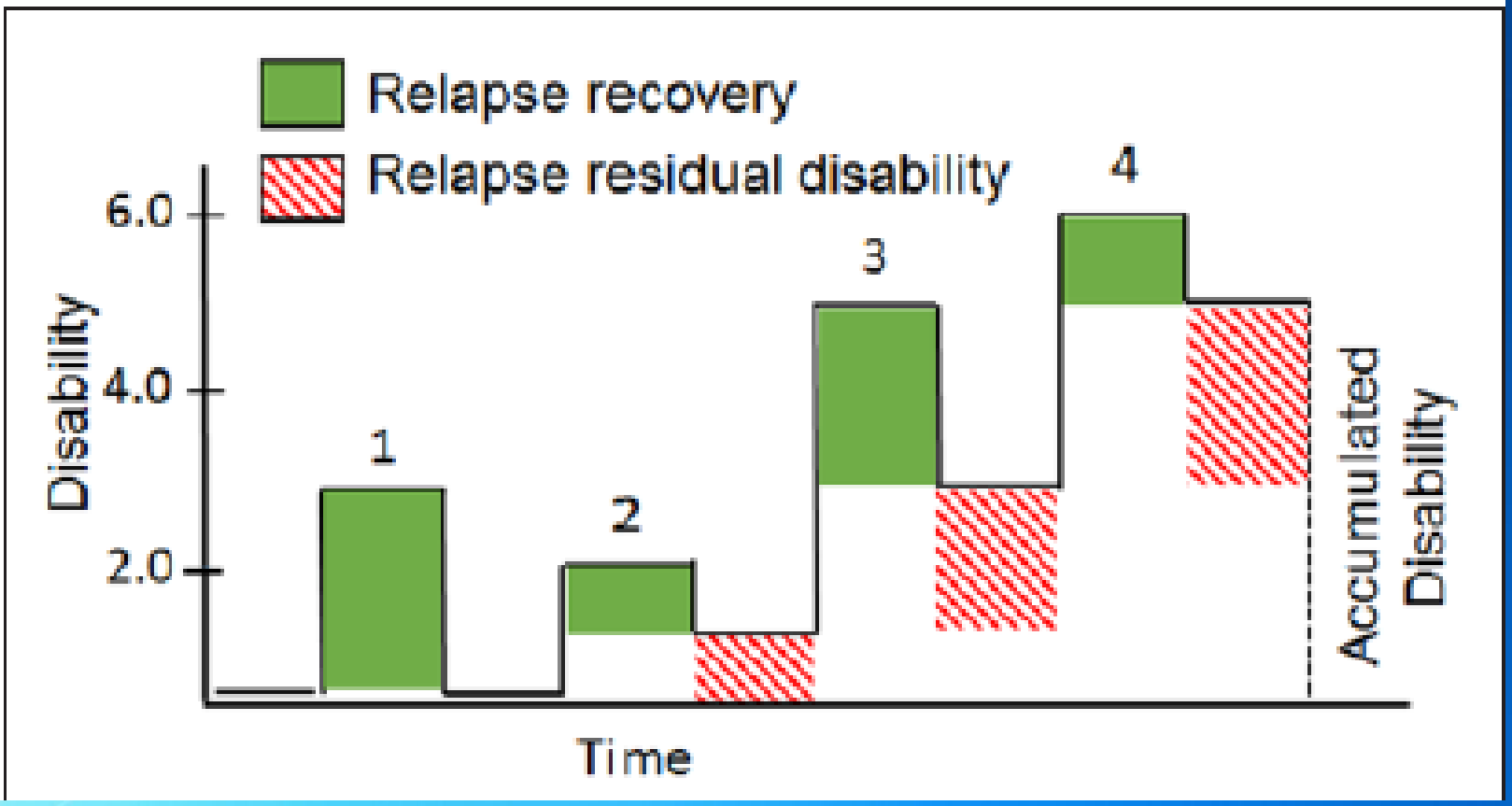


Acta Neurol Scand 2016; 1–19

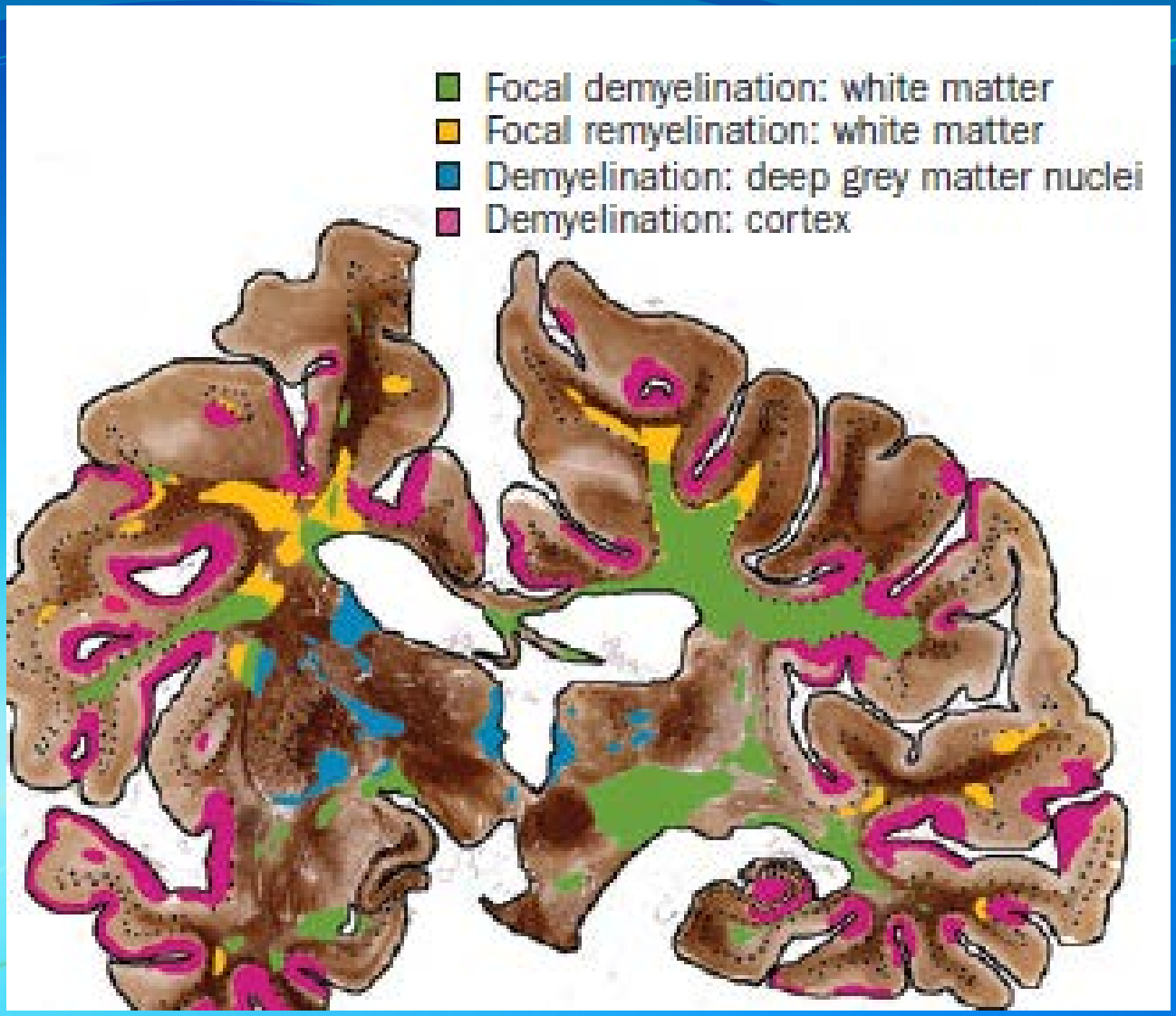

Subcutaneous IFNβ-1b is the first drug to be approved for treatment of RRMS
The first drug for treating SPMS is approved
Natalizumab is the first monoclonal antibody and high-efficacy drug to be approved for treatment of RRMS
First reports of progressive multifocal leukoencephalopathy with natalizumab treatment
Fingolimod is the first oral drug to be approved for treatment of RRMS
Oral dimethyl fumarate
• Targeting of B cells is confirmed as an effective therapy for RRMS
• Ocrelizumab becomes the first drug to be approved for treatment of PPMS
For the first time, a generic drug — a generic version of glatiramer acetate — is approved for the treatment of RRMS
Oral fingolimod is the first disease-modifying therapy to be approved for treatment of RRMS in paediatric patients
1993
1996
2000
2002
2004
2005
2010
2012
2013
2014
2015
2016
2017
2018
Subcutaneous IFNβ-1b
• Subcutaneous glatiramer acetate
• Intramuscular IFNβ-1a
• Intravenous mitoxantrone
• Subcutaneous IFNβ-1b for SPMS
Subcutaneous IFNβ-1a
Intravenous natalizumab
Oral fingolimod
Oral teriflunomide
Oral dimethyl fumarate
• Intravenous alemtuzumab
• Subcutaneous PEG-IFNβ-1b
Generic glatiramer acetate
Subcutaneous daclizumab
• Oral cladribine
• Intravenous ocrelizumab for RRMS
• Intravenous ocrelizumab for PPMS
Oral fingolimod for RRMS in paediatric patients



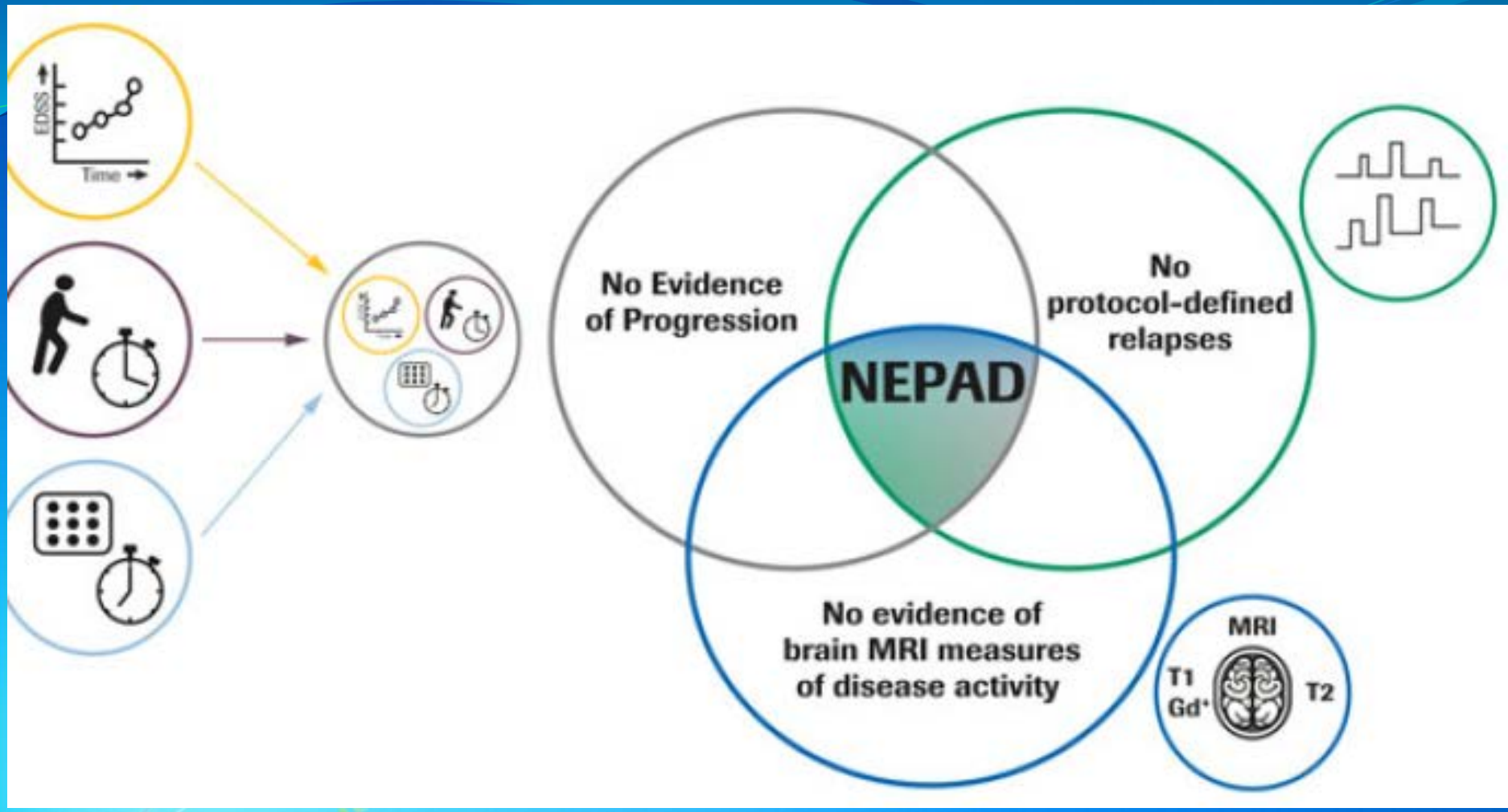
BIOCHEMISTRY (Moscow) Vol. 83 No. 7 2018



*Multiple Sclerosis Journal*1–8DOI: 10.1177/1352458518809903

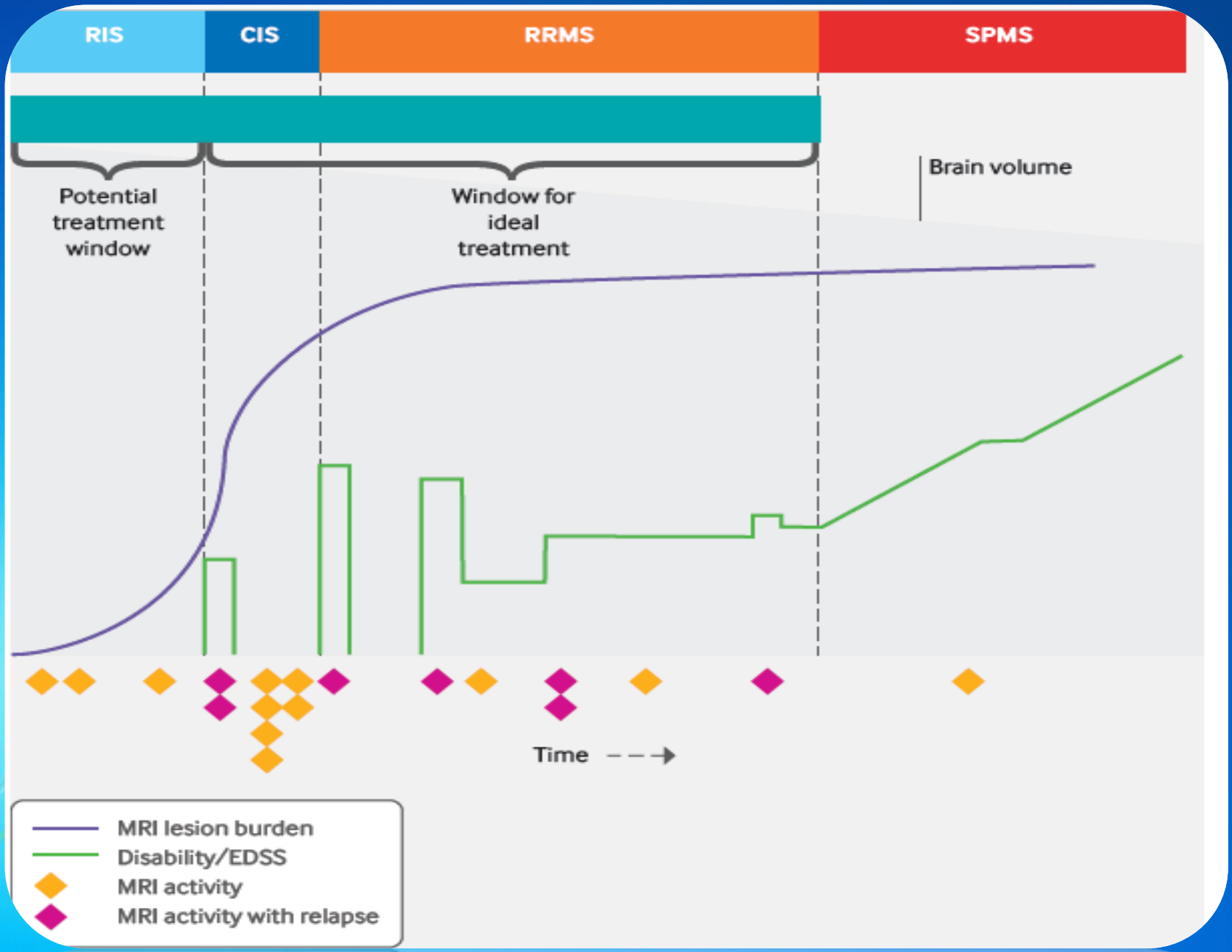


Nat. Rev. Neurol. 8, 647–656 (2012

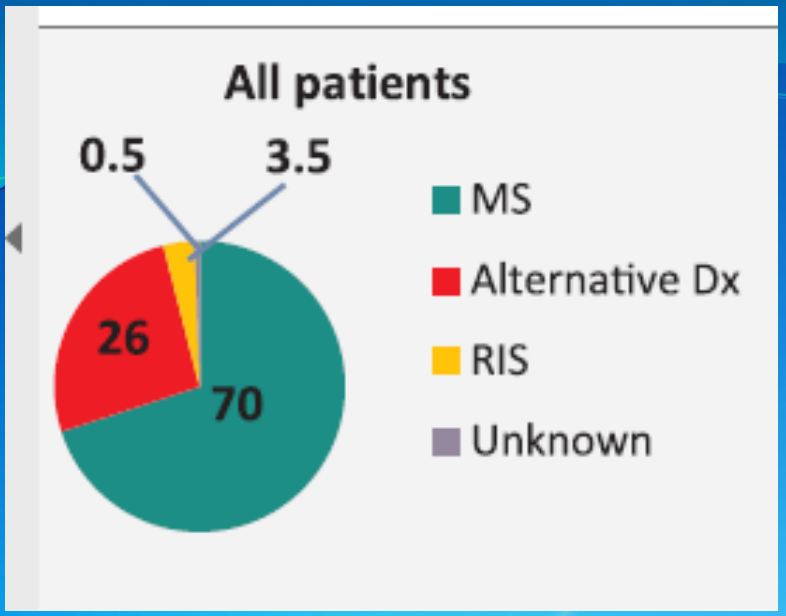

EDSS
Time
No Evidence of Progression
No protocol-defined relapses
NEPAD
No evidence of brain MRI measures of disease activity
MRI
T1 Gd+
T2

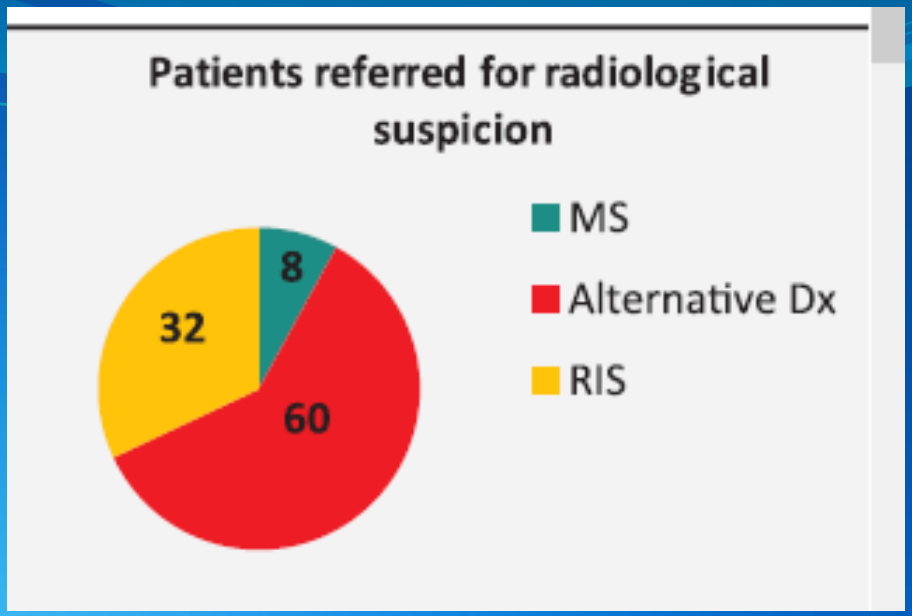
NEDA status[25] • NEDA 1–3 • NEDA 4 • NEDA 5 • NEDA 6 • NEDA 7 • NEDA 8	Clinical event, EDSS, MRI Brain atrophy Cognitive impairment CSF neurofilament level Patients related outcome Oligoclonal bands
BIOMARKERS[7,8] Related to cells, structures, metabolic pathways, and inflammatory and degenerative cascades.	OCB, NAA, Glutamate, IL-12, IL-23, Enolase, NfL, CXCL13, IL-8, ATP break down products, GFAP, MMP9, MMP3, Th17, Th1/Th17, Chitinase 3, IFN-ϒ, TNF-α, Fetuin-A, Osteopontin, PET (microglia), non-conventional MRI. Others.

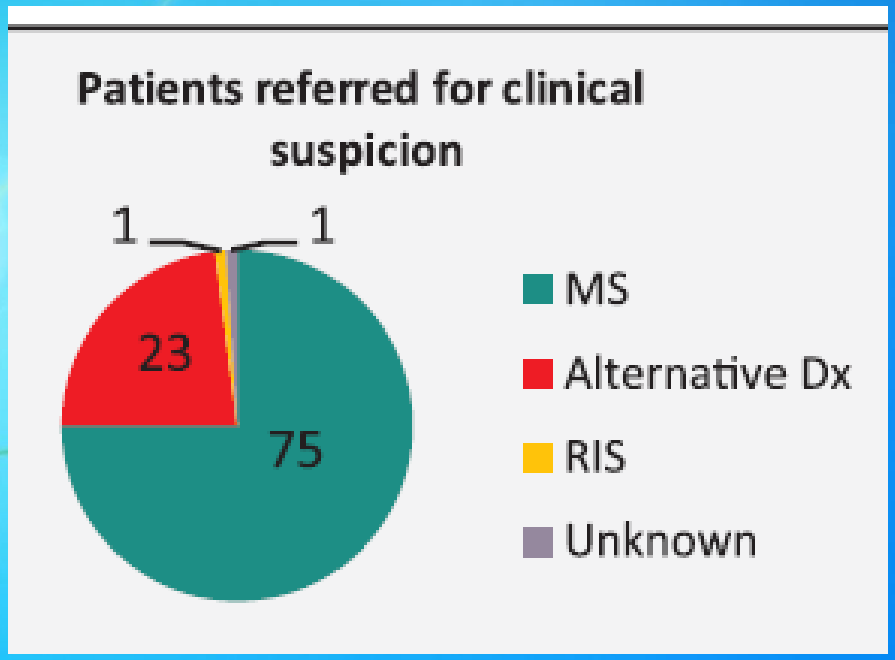
F1000Research 2017, 6:566 Last updated: 20 JUN 2017



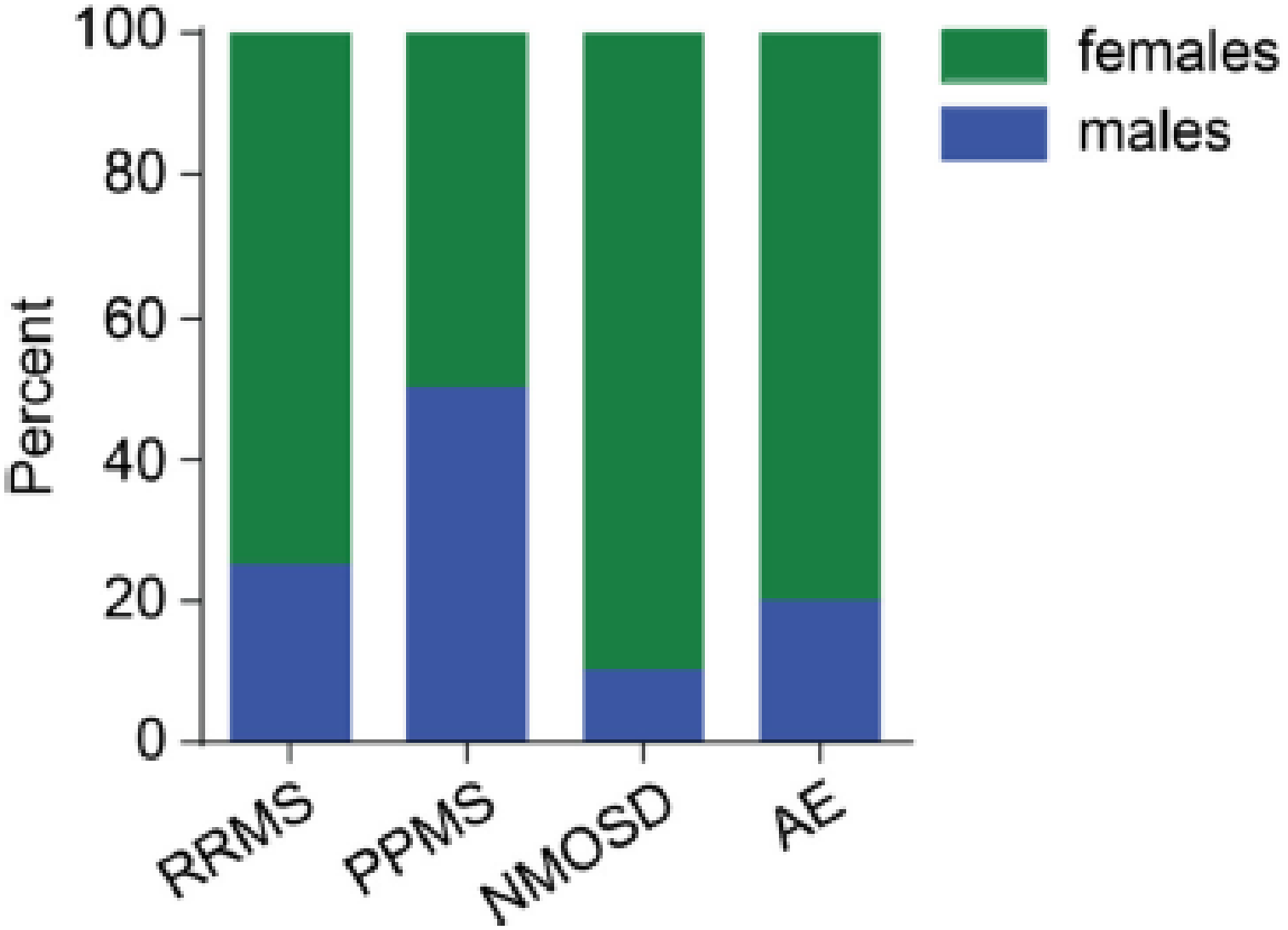
BMJ 2016;354:i3518







Multiple Sclerosis and Related Disorders 18 (2017) 85–89

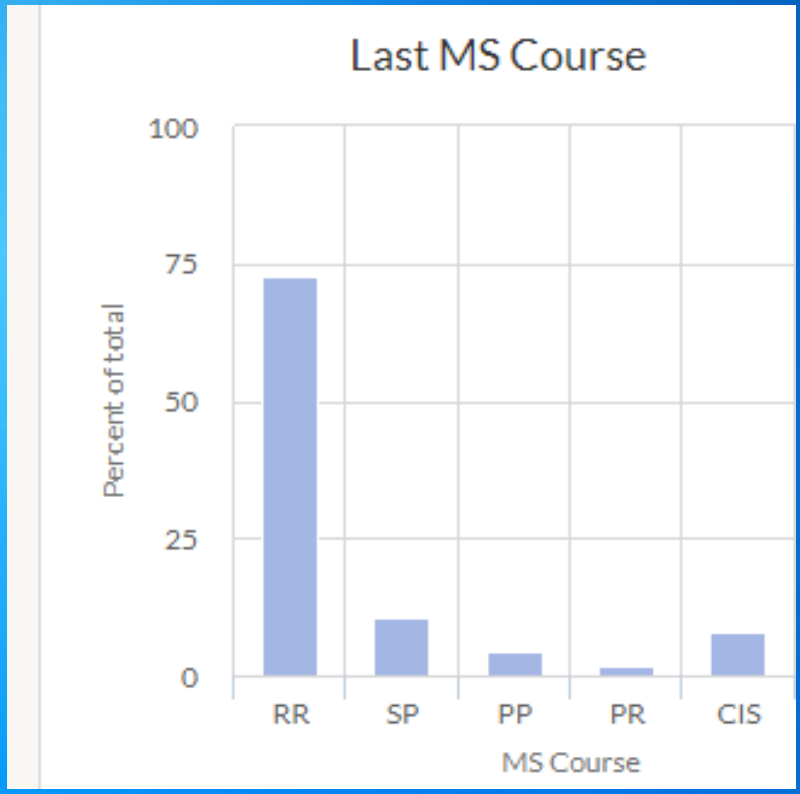


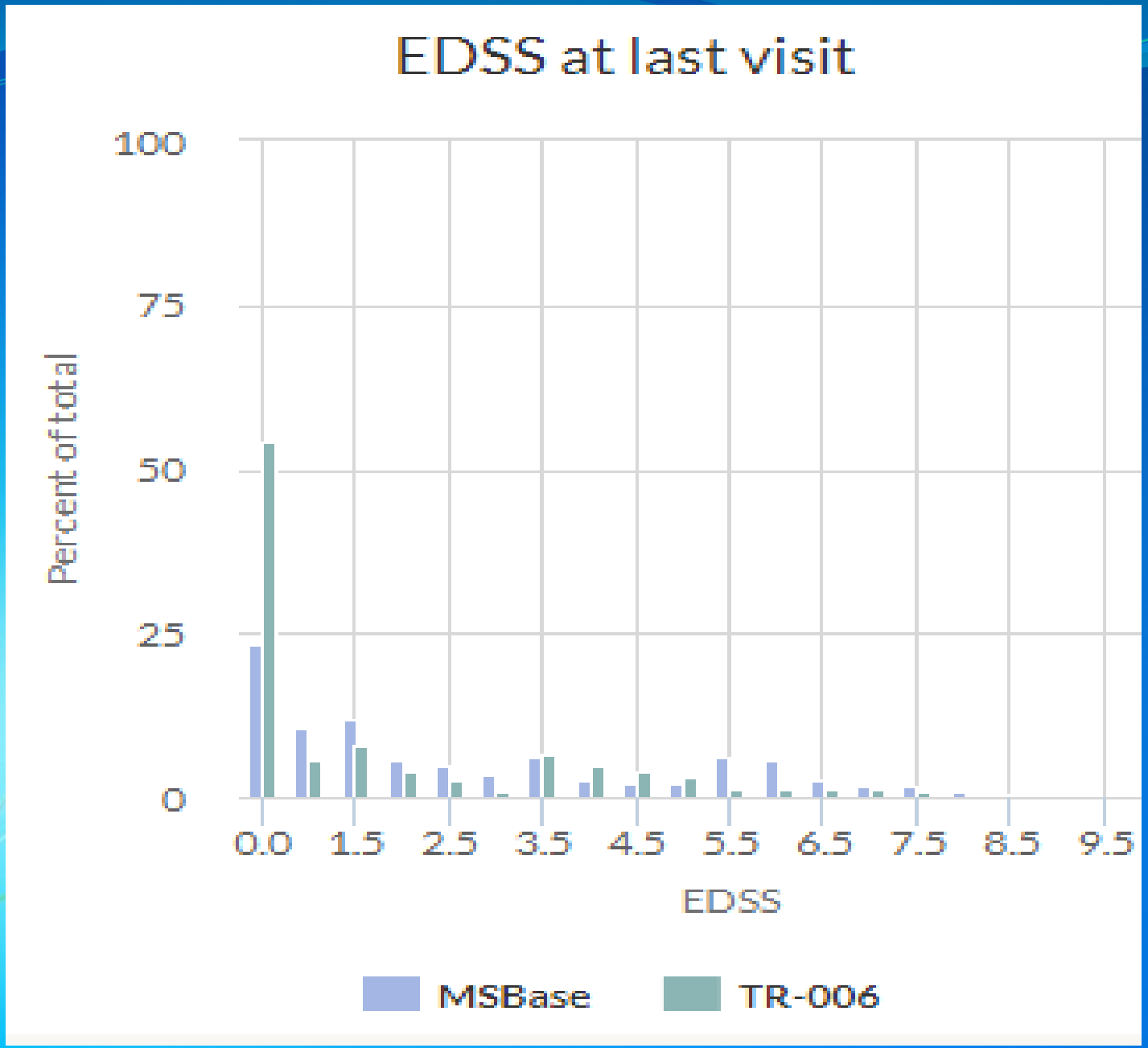
Seminars in Immunopathology
https://doi.org/10.1007/s00281-018-0723-8

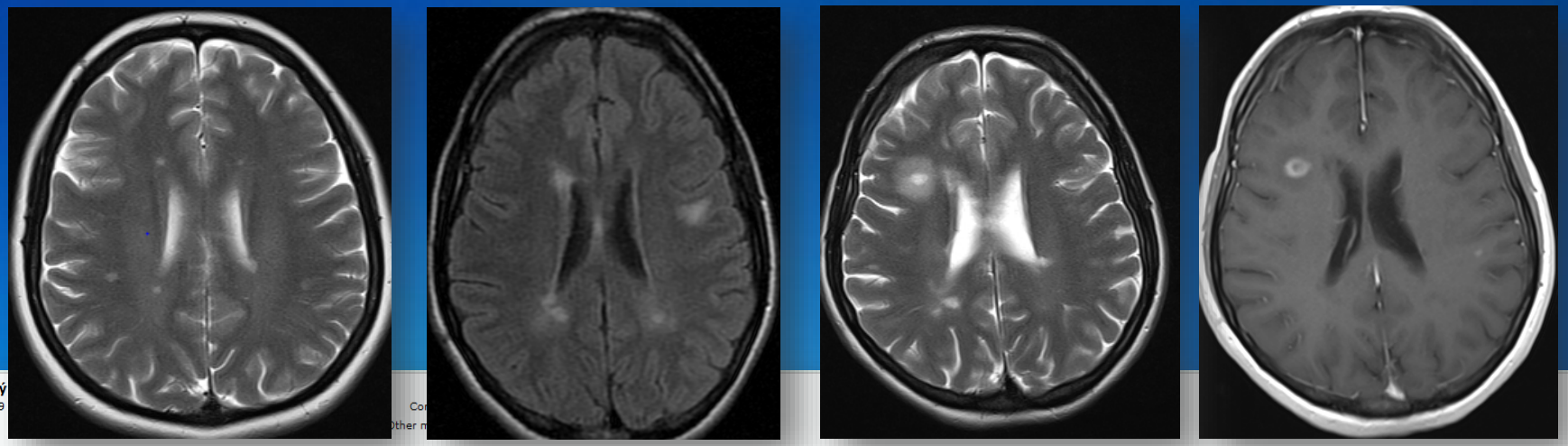
Drug (generic name)	Fertility	Pregnancy	Lactation
Interferon-β	No effects	Exposure was associated with a lower mean birth weight, shorter mean birth length and preterm birth	Excretion in human milk is not well established; the transfer should be limited by the molecular weight; the drug is not orally bioavailable
Glatiramer acetate	No effects	No major concerns after drug exposure during pregnancy	Excretion in human milk is not well established; the transfer should be limited by the molecular weight; the drug is not orally bioavailable
Natalizumab	Reduced fertility in animal studies; no information in humans	Limited information in humans; haematological alterations, lower birth weight, shorter birth length and risks of malformations and miscarriage have been reported	Excretion in human milk has been reported; the drug is not orally bioavailable
Fingolimod	No effects	Limited information in humans; increased risks of miscarriage and malformations have been reported	Excretion in rat milk has been reported; the drug is orally bioavailable
Mitoxantrone	Amenorrhoea and transient azoospermia have been reported	Limited information in humans; increased risk of malformations has been reported	Excretion in human milk has been reported
Cyclophosphamide[a]	Amenorrhoea and azoospermia have been reported	Limited information in humans; increased risk of malformations has been reported	Excretion in human milk has been reported
Teriflunomide	No effects	Embryotoxicity in animal studies in the human therapeutic range	Excretion in rat milk has been reported
Dimethyl fumarate	No effects	Limited information in humans	Excretion in human milk is unknown
Alemtuzumab	No effects	Limited information in humans; thyroid diseases and malformations have been reported	Excretion in mouse milk has been reported

CNS Drugs (2015) 29:207–220

Last MS Course	MSBase	
MS Course	Count	%
RR	45675	72.82 %
SP	6753	10.77 %
PP	2881	4.59 %
PR	1091	1.74 %
CIS	4844	7.72 %




EDSS at last visit
100
75
50
25
0
Percent of total
0.0
1.5
2.5
3.5
4.5
5.5
6.5
7.5
8.5
9.5
EDSS
MSBase
TR-006



CAVALý
Age : 29

Treatments

- MS specific
- Symptomatic
- Non pharma.

Events

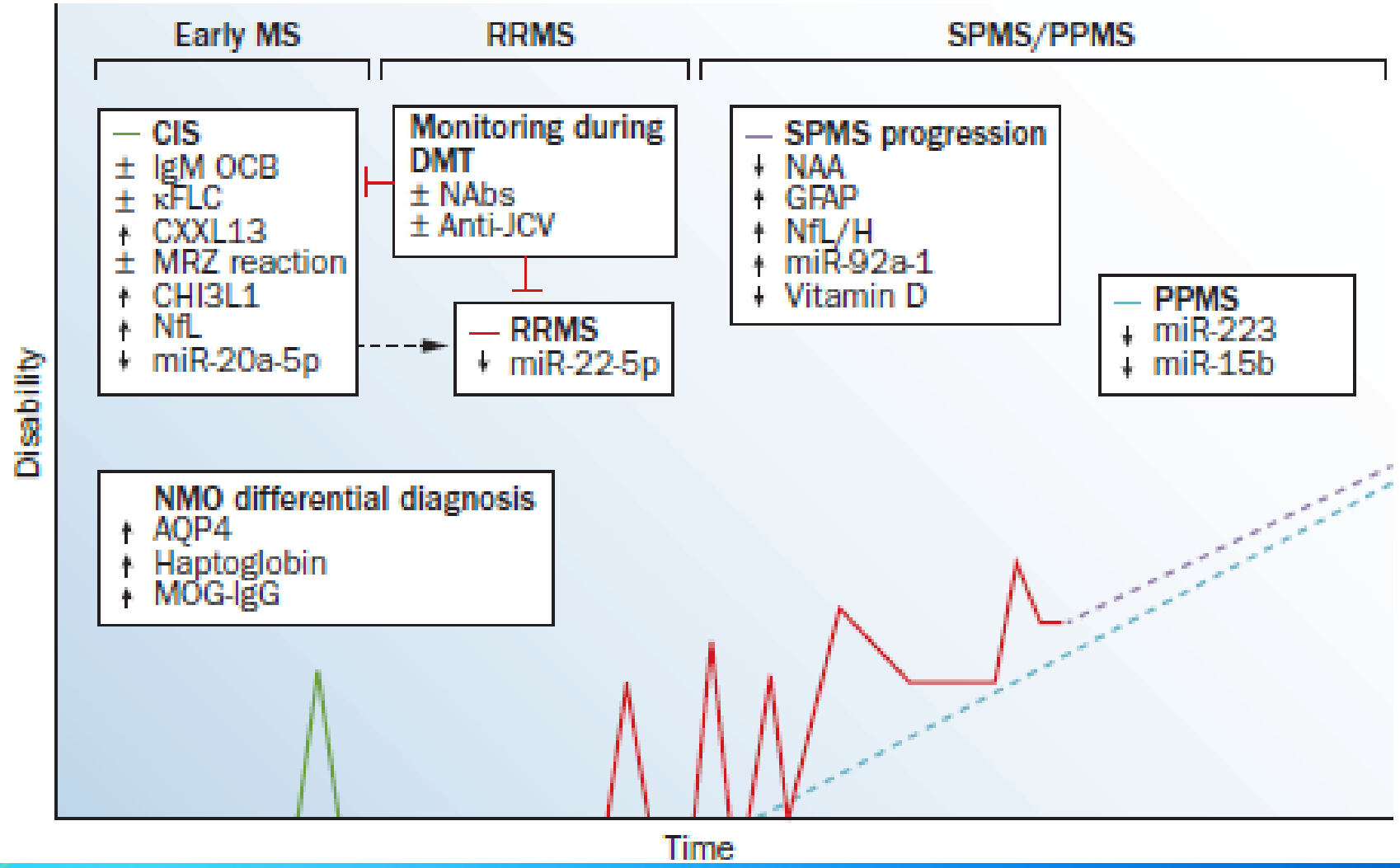
- Relapses
- Medical conditions
- Pregnancies

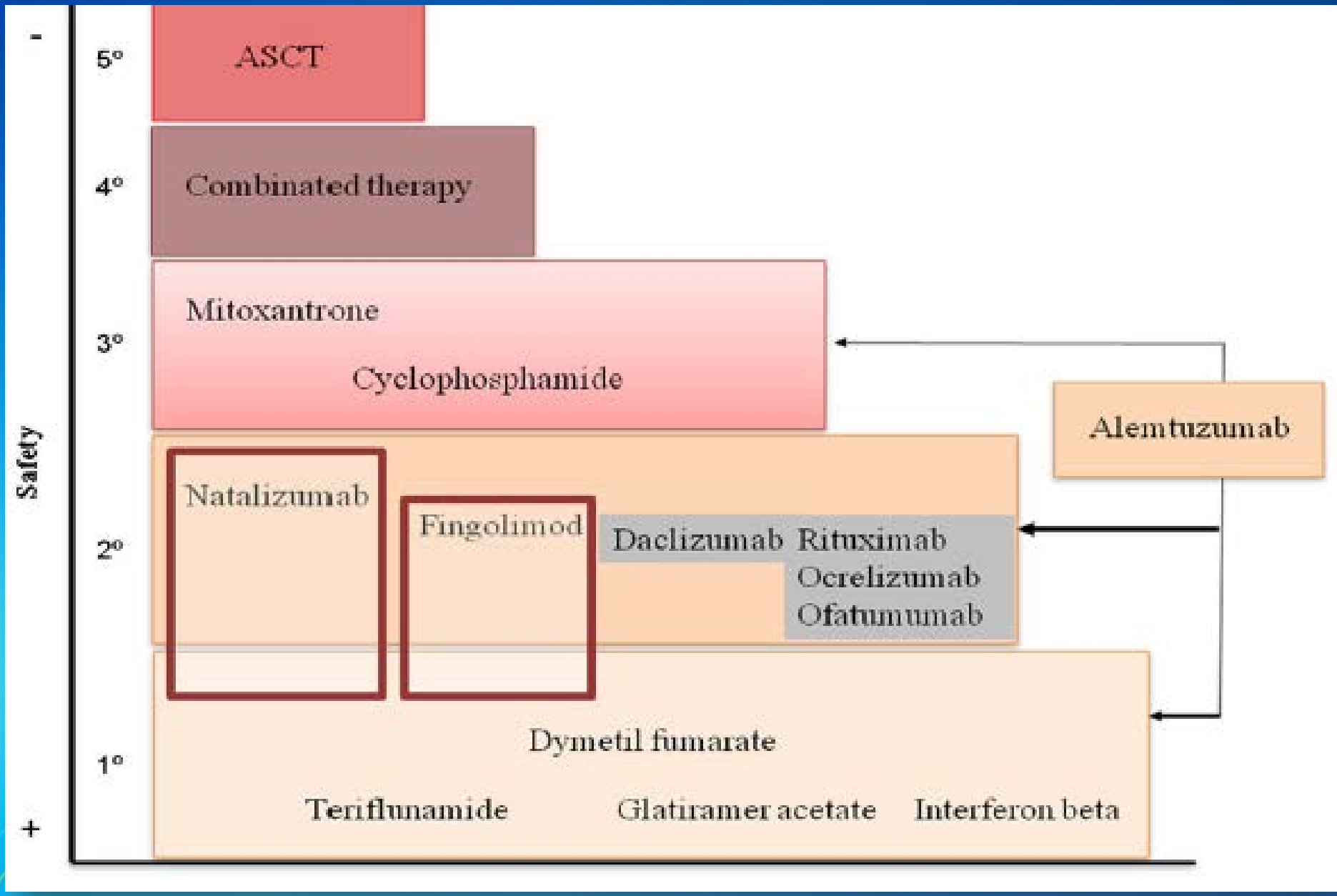
Paraclinical tests

- MRI
- CSF
- Evoked Potentials
- Laboratory tests

- EDSS

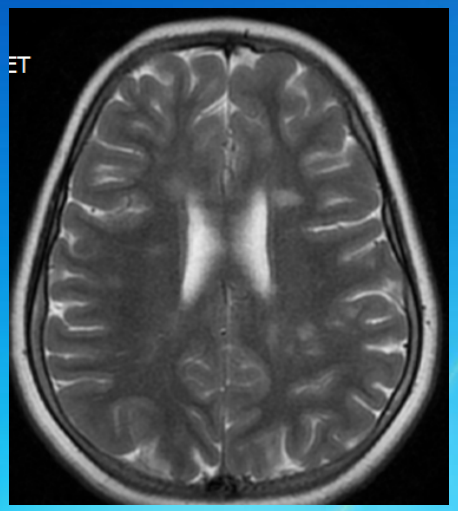
Time Scale
Maximum

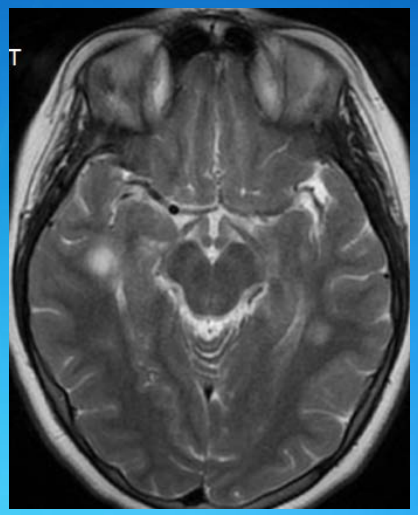

Early MS
RRMS
SPMS/PPMS
— CIS
± IgM OCB
± κFLC
↑ CXXL13
± MRZ reaction
↑ CHI3L1
↑ NfL
↓ miR-20a-5p
Monitoring during DMT
± NAbs
± Anti-JCV
— RRMS
↓ miR-22-5p
— SPMS progression
↓ NAA
↑ GFAP
↑ NfL/H
↑ miR-92a-1
↓ Vitamin D
— PPMS
↓ miR-223
↓ miR-15b
NMO differential diagnosis
↑ AQP4
↑ Haptoglobin
↑ MOG-IgG
Disability
Time

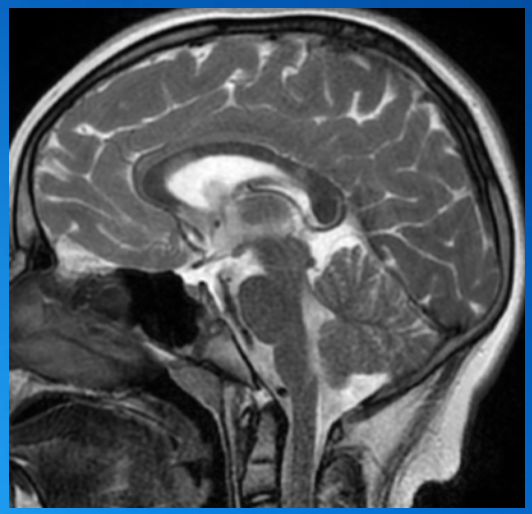


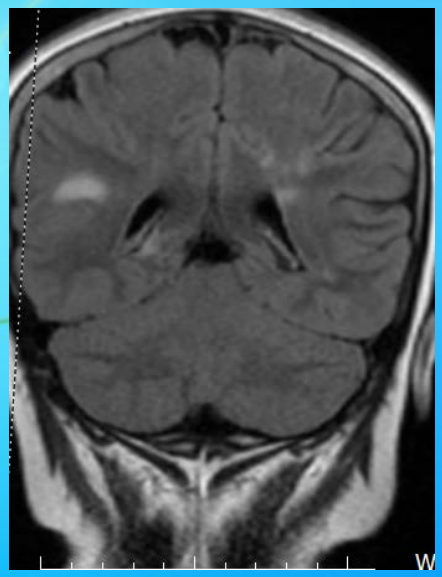
Curr Treat Options Neurol (2015) 17:324

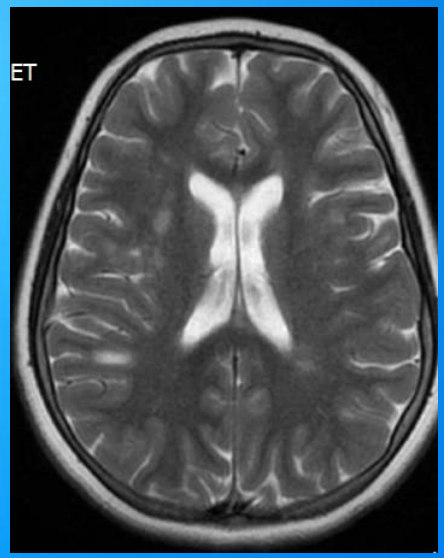
9 y, k, baş ağrısı

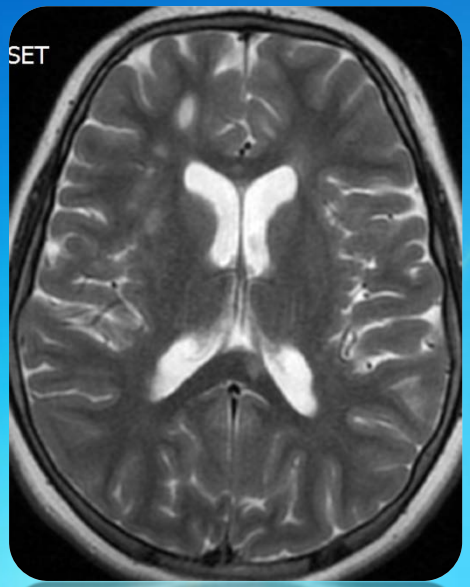


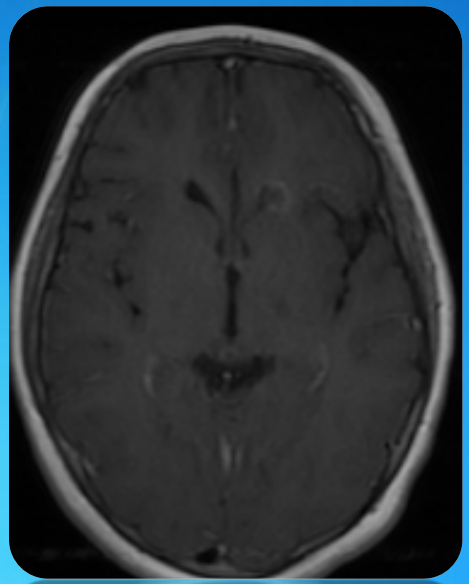


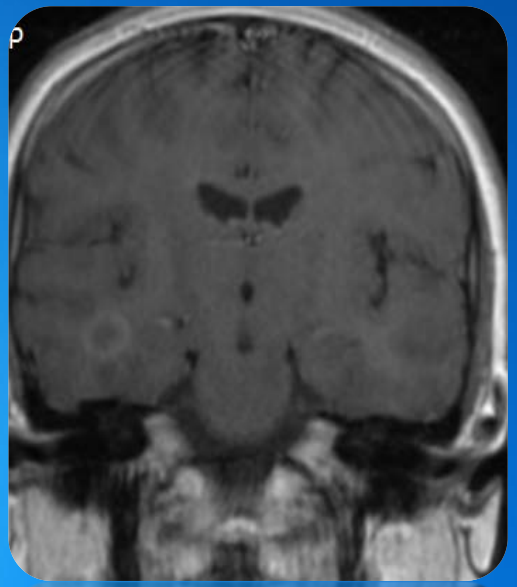




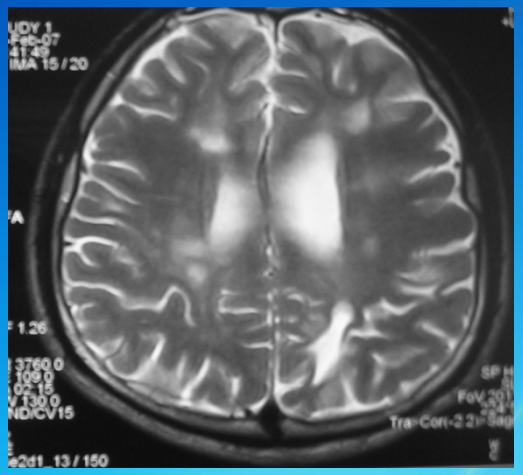


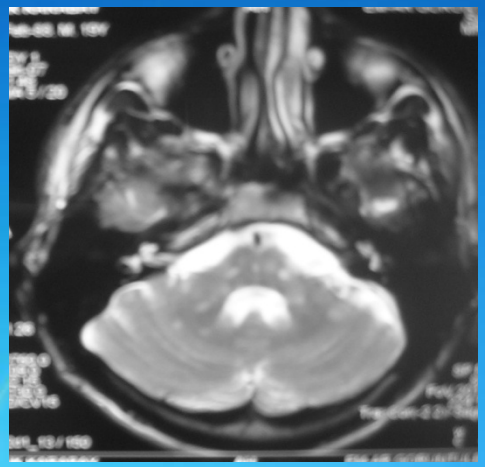

SET

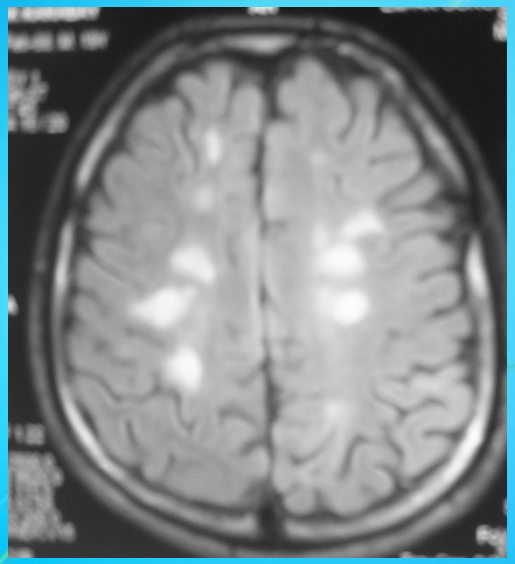


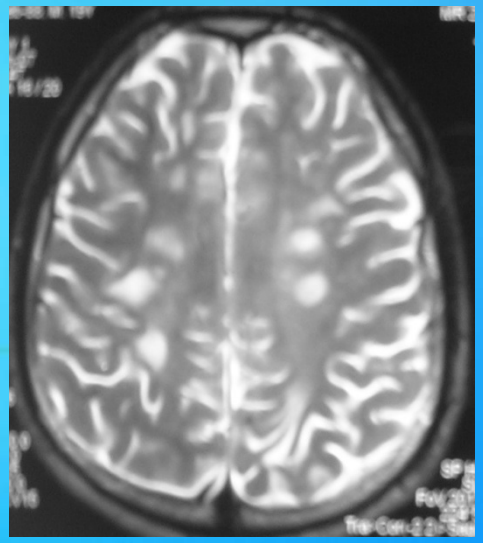


Tipik MRG, klinik normal



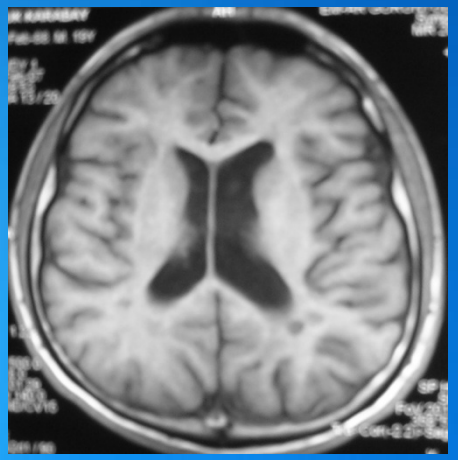


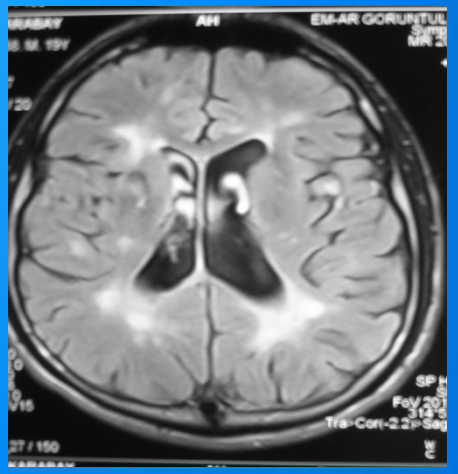


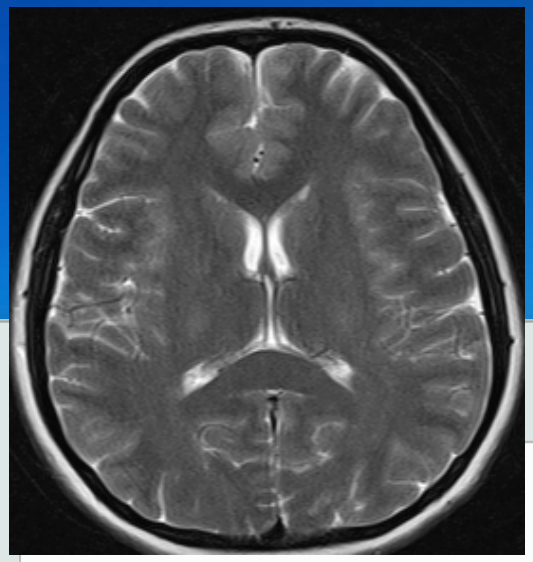


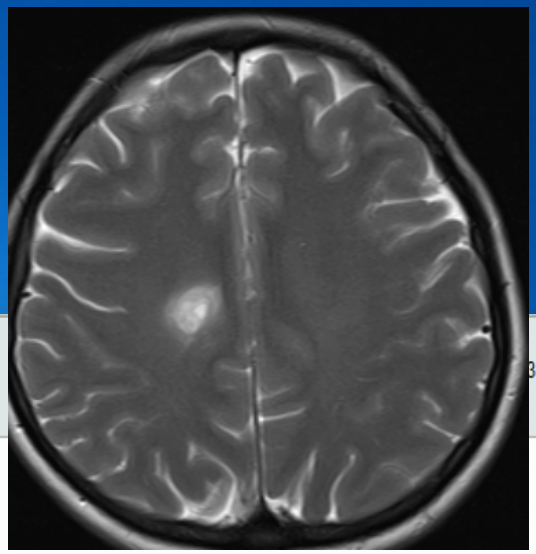
19 y, E

Şubat 2007'de düşme sonrası kafa travması









SALİ DİNAY

Age : 31 Gender : F

3 years

Treatments

- MS specific
- Symptomatic
- Non pharma.

Events

- Relapses
- Medical conditions
- Pregnancies

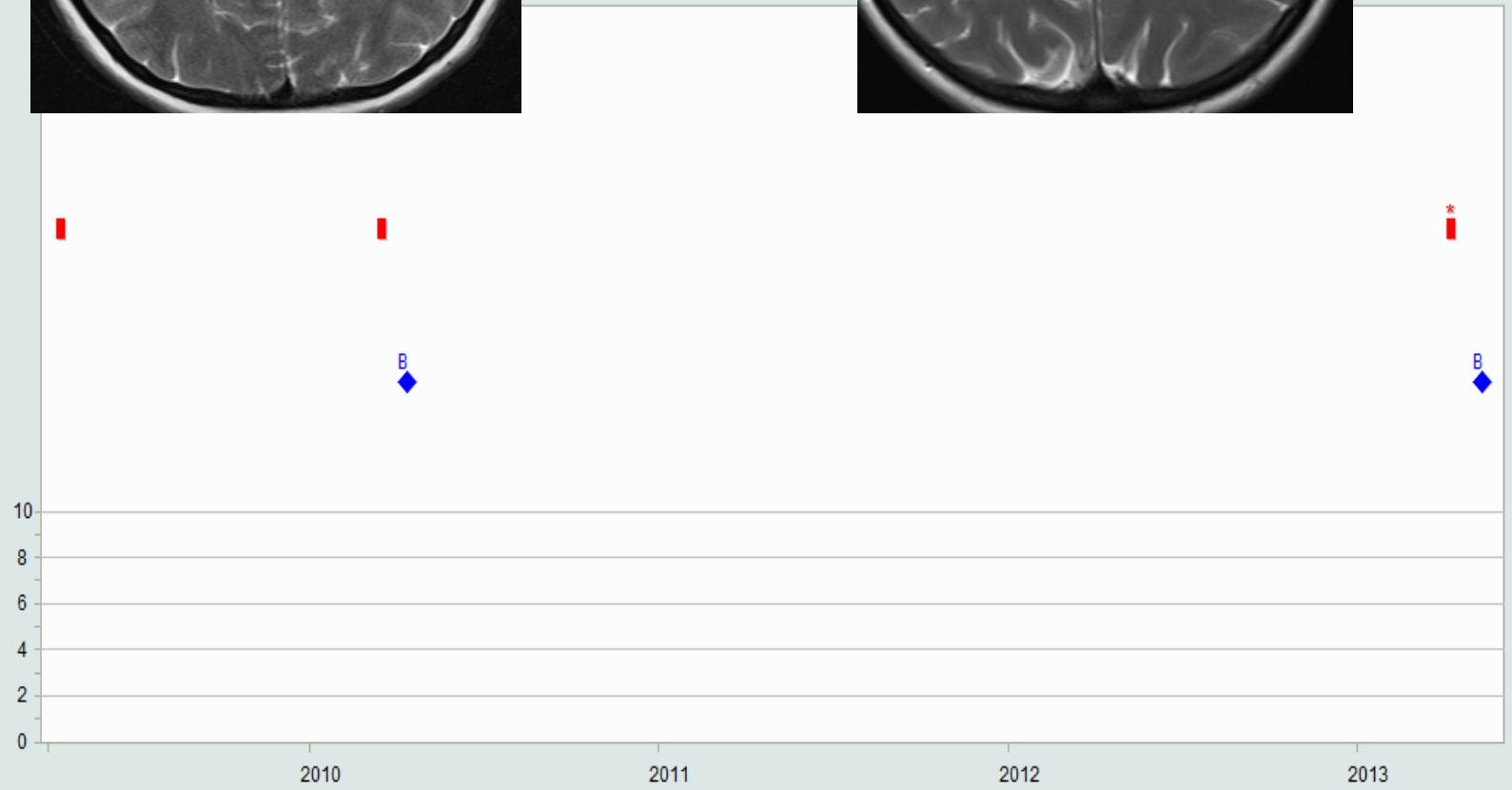
Paraclinical tests

- MRI
- CSF
- Evoked Potentials
- Laboratory tests

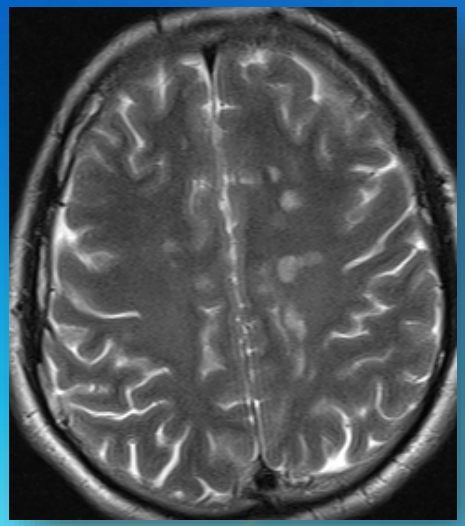
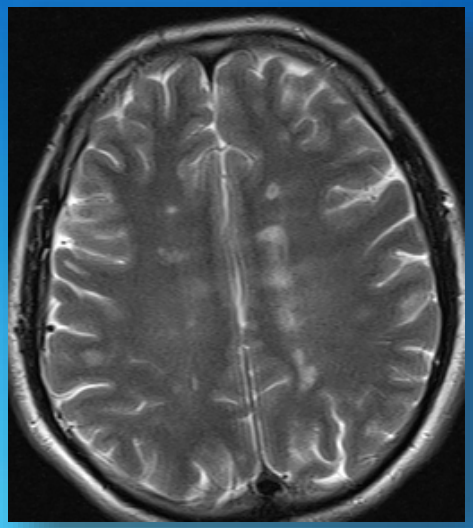
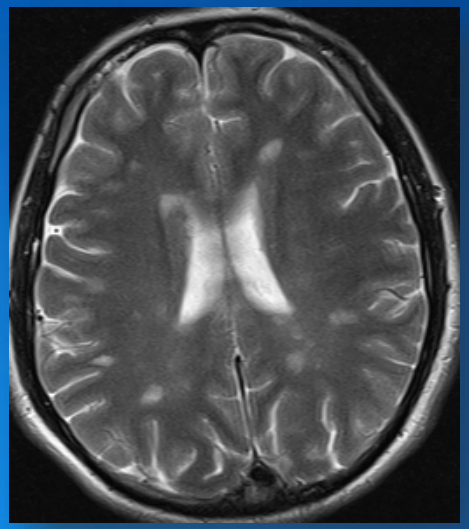
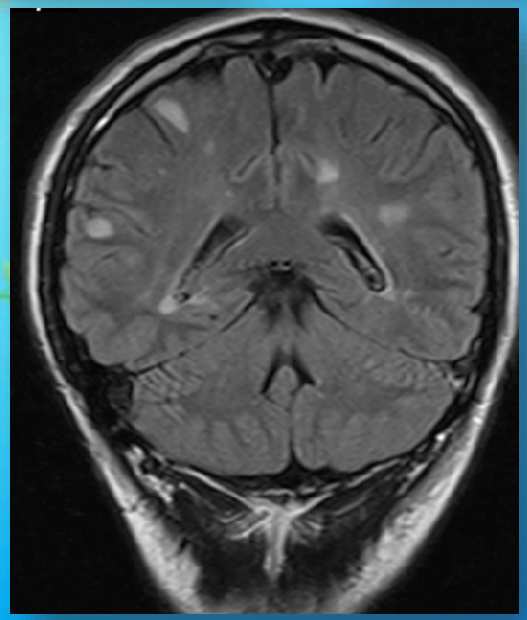
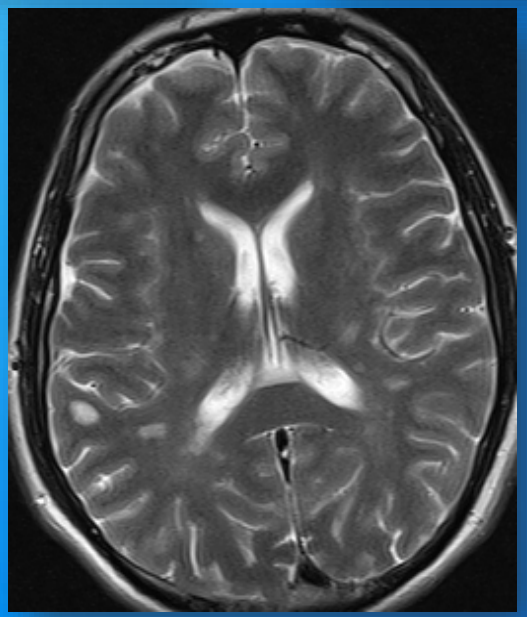
EDSS

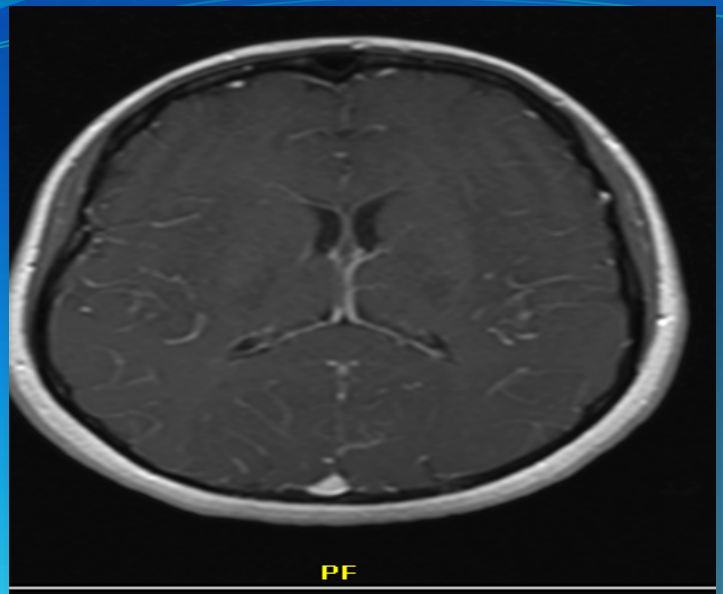
Time Scale :

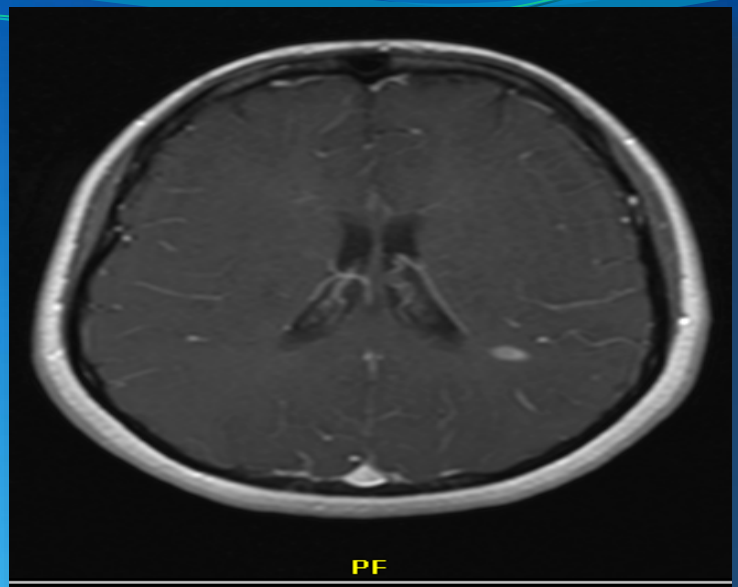
Maximum

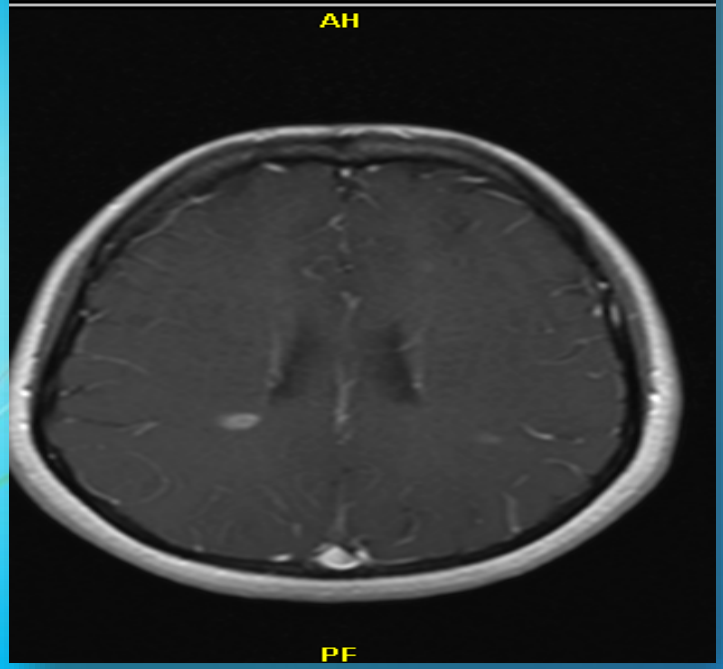


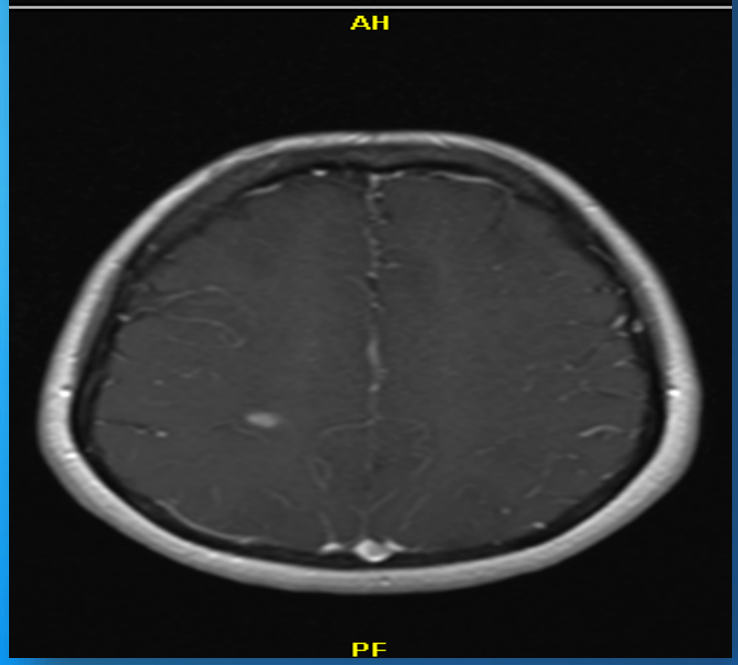
27 y, E,
1 yıldır RRMS ve IMT alıyor


PF

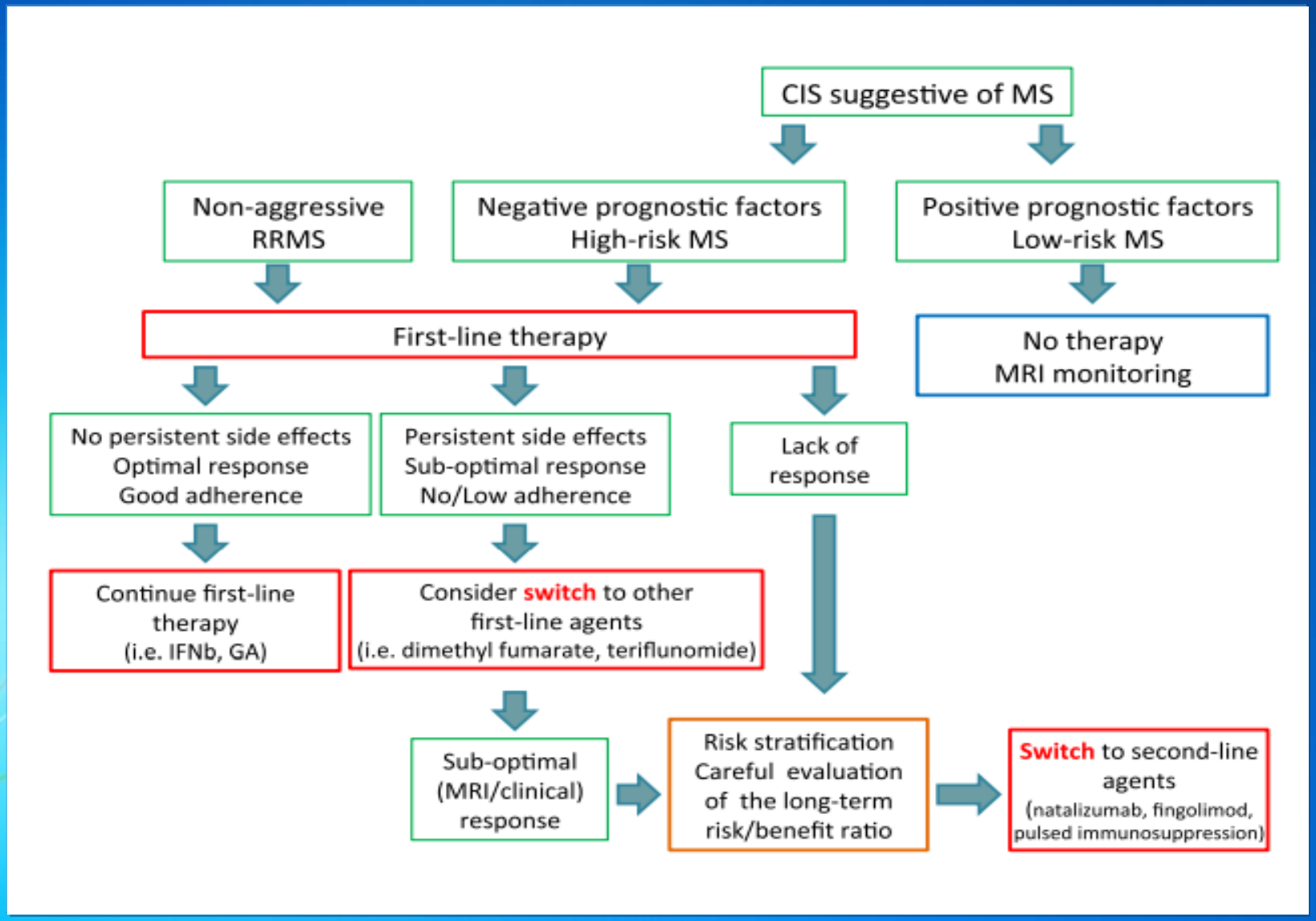

PF


AH
PF


AH
PF

Clinical	Male gender
	Higher age at onset
	Multifocal presentation
	Involvement of pyramidal and cerebellar systems
	Partial recovery from relapses
	High relapse rate during the first 2 years from onset
Magnetic resonance imaging	High T1 lesion load
	Persistence of 'activity' (increased T2 lesion volume, gadolinium enhancement)
	Brain and grey matter atrophy
	Spinal cord lesions
Cerebrospinal fluid markers	Immunoglobulin G oligoclonal bands
	Increased lymphocyte count
	Markers of neurodegeneration (14-3-3, tau, NFL h&l)

European Journal of Neurology 2015, 22 (Suppl. 2): 14–21

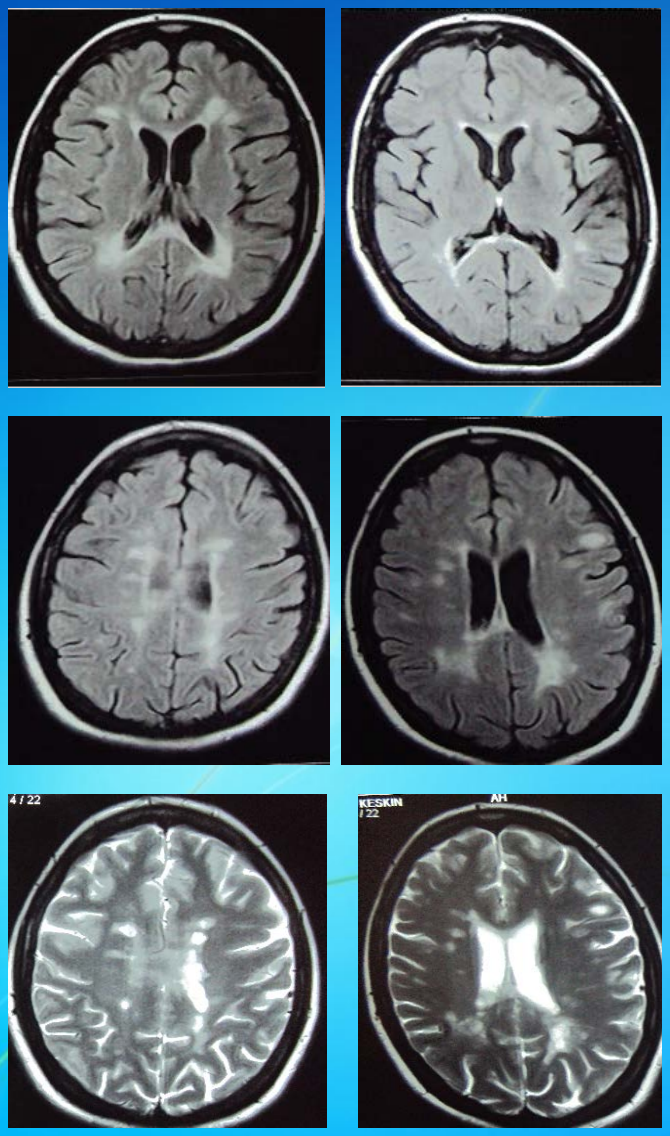


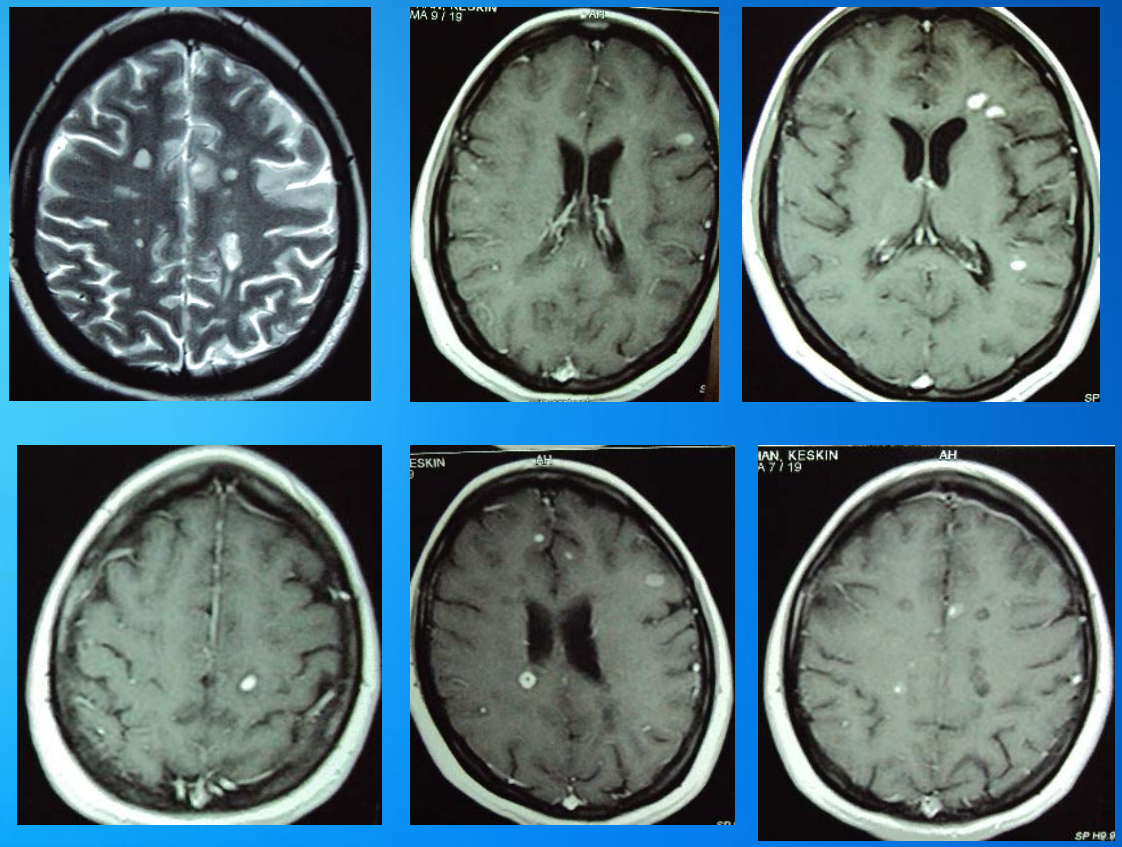
European Journal of Neurology 2015,

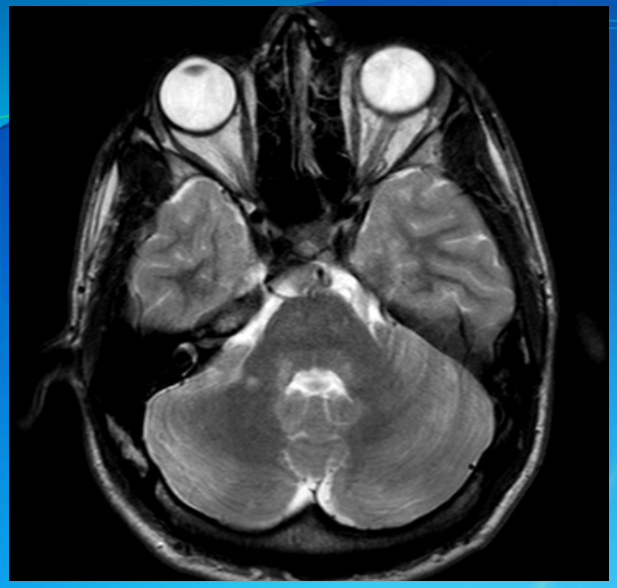
30 Y, K, 2003-2006 yılları arası yılda 2-3 kez piramidal, duyusal ataklar

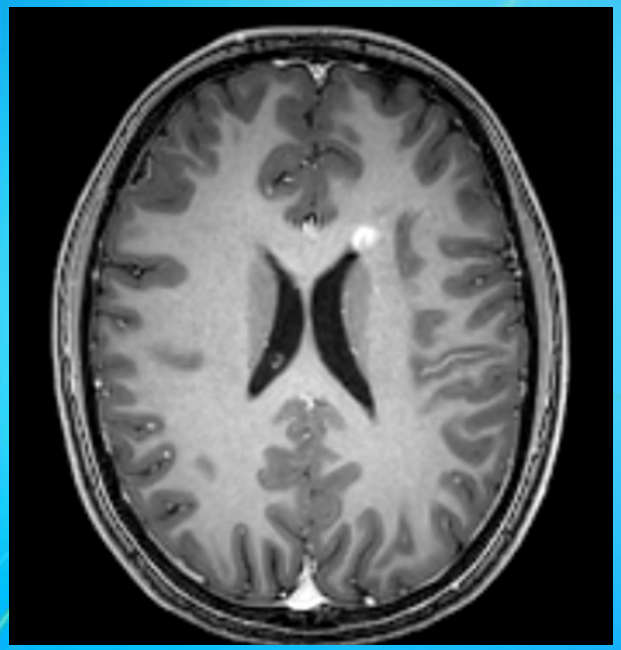
2006'dan sonra var olan yürüme güçlüğü, dengesizlik, otonomik problemler

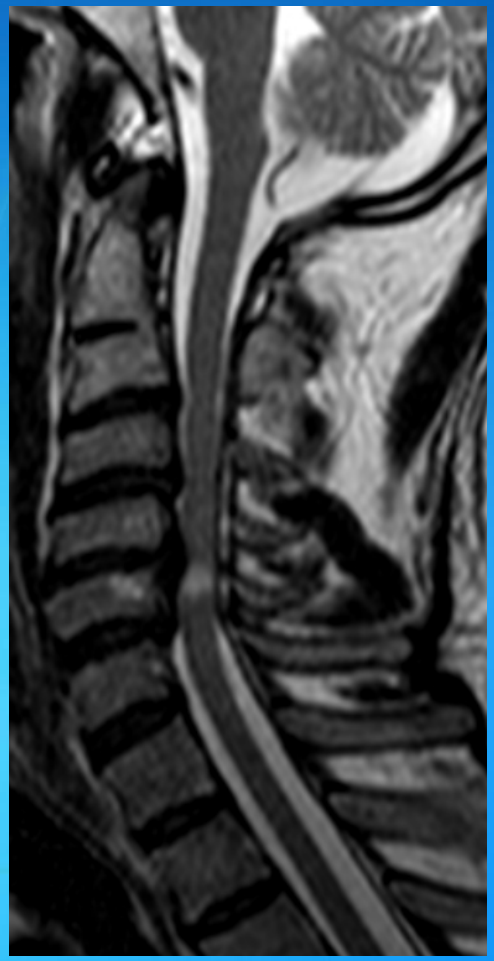
rağmen yılda 2-3 atak (EDSS: 2,5)

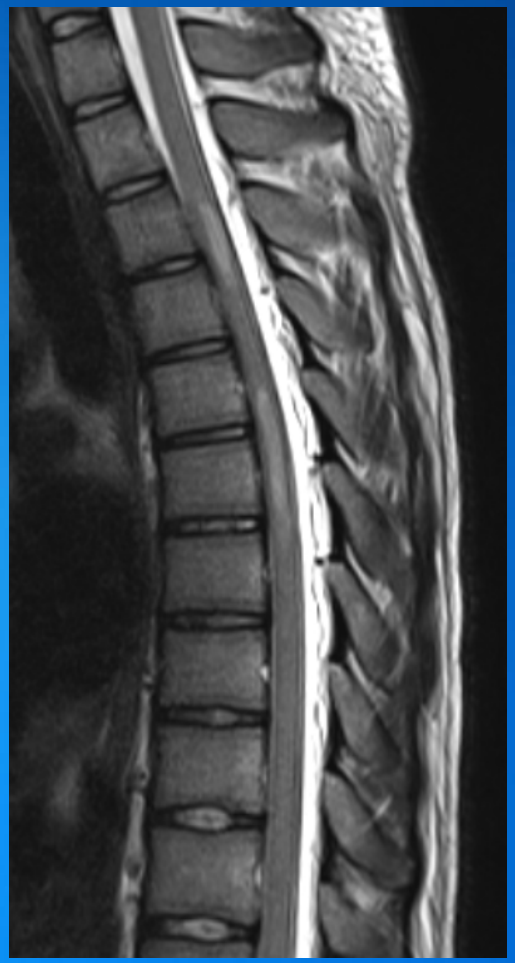


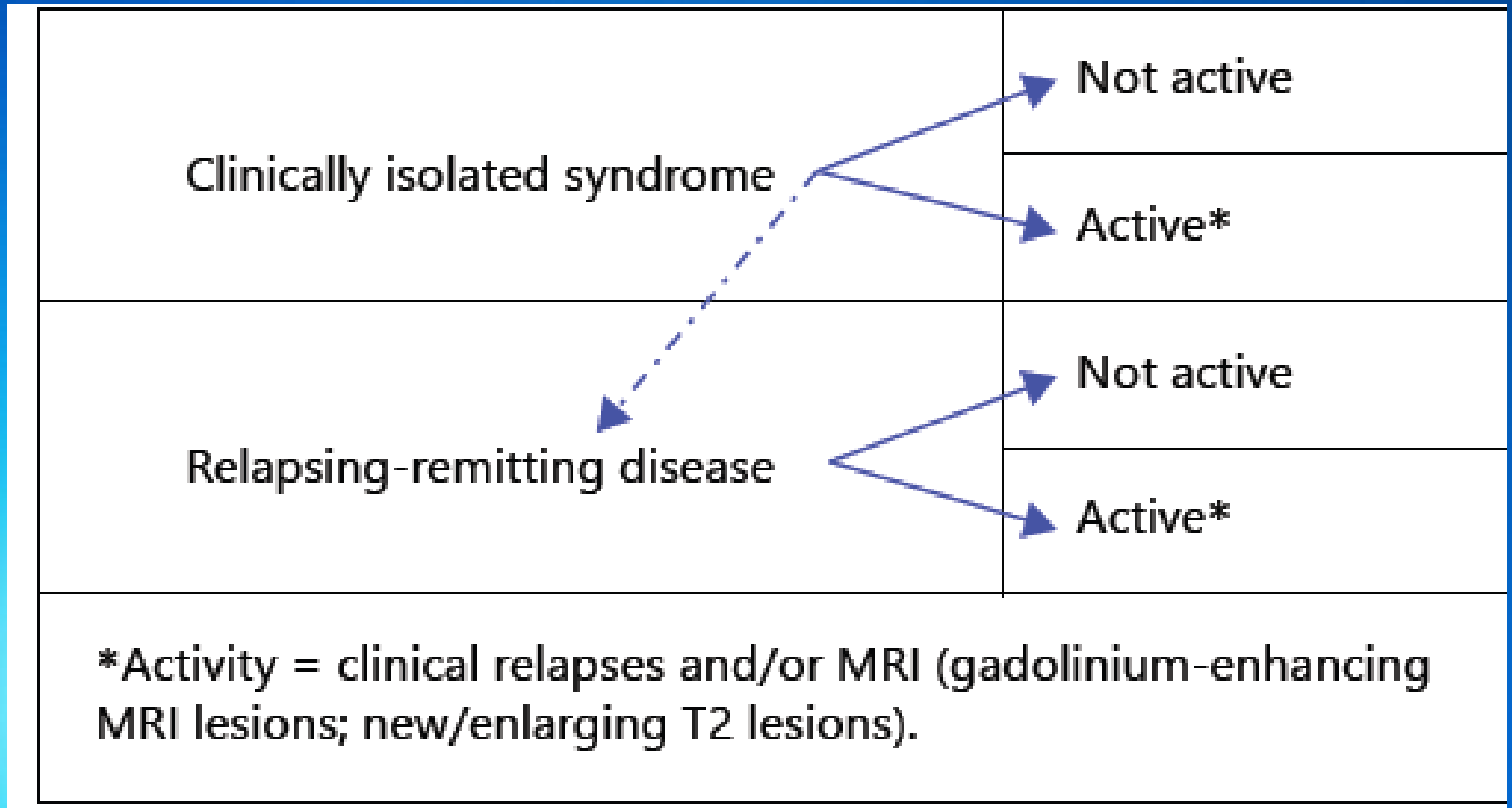


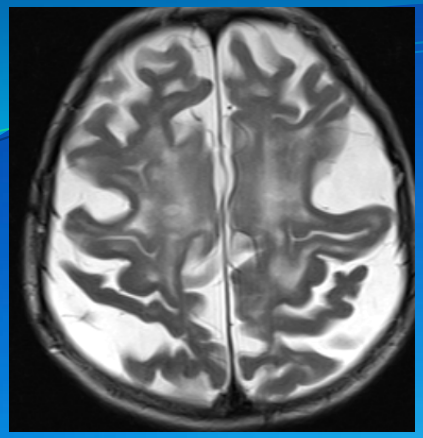
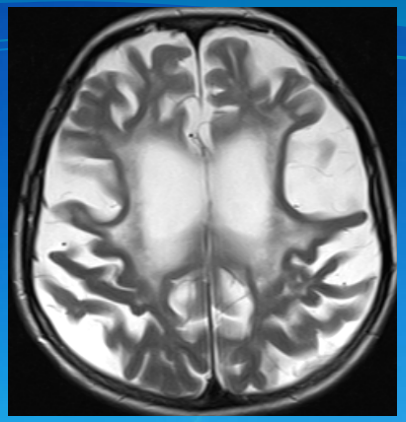






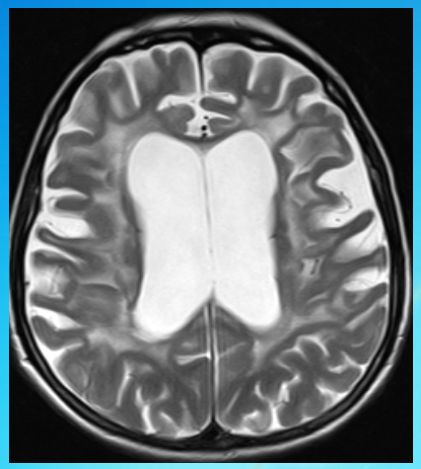
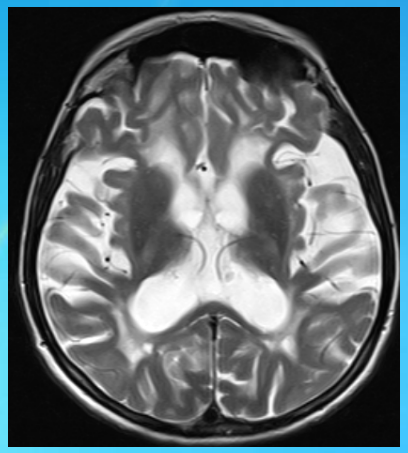
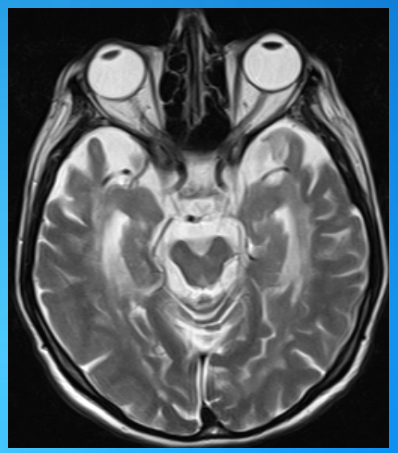
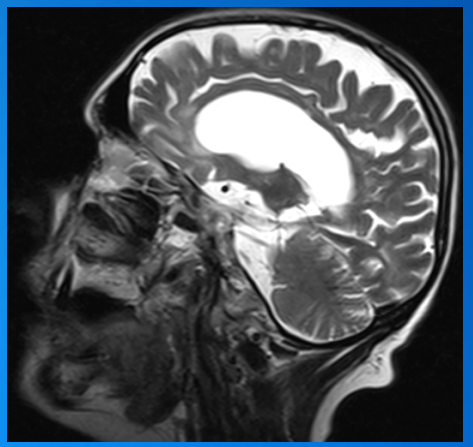
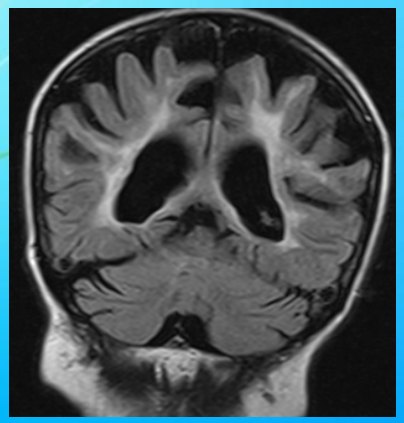
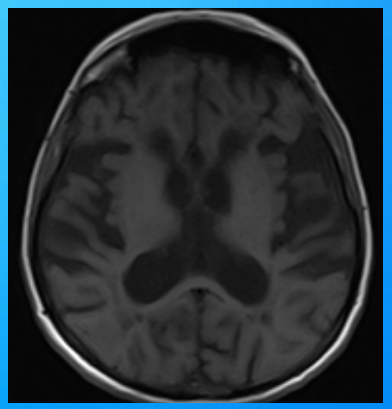
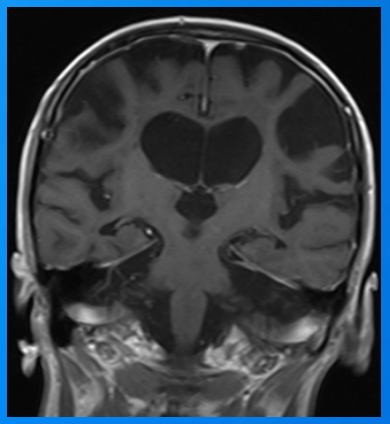



Clinically isolated syndrome
Not active
Active*
Relapsing-remitting disease
Not active
Active*
*Activity = clinical relapses and/or MRI (gadolinium-enhancing MRI lesions; new/enlarging T2 lesions).

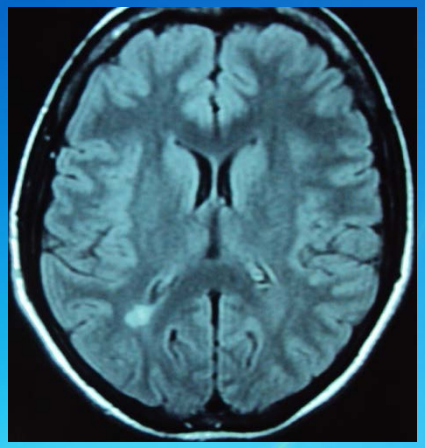
55 Y, K, 1995-2006 yılları arası yılda 1-2 kez piramidal, duyusal ataklar, 2006'dan sonra artan yürüme güçlüğü, dengesizlik, otonomik ve kognitif problemler
EDSS: 6.5

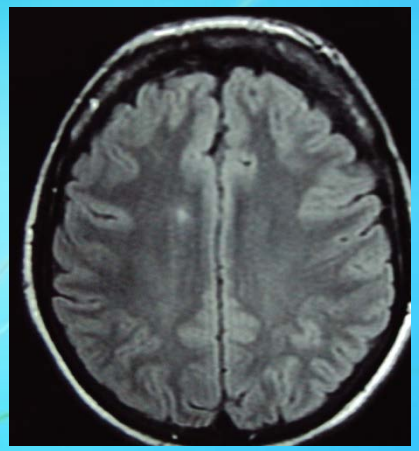
SPMS

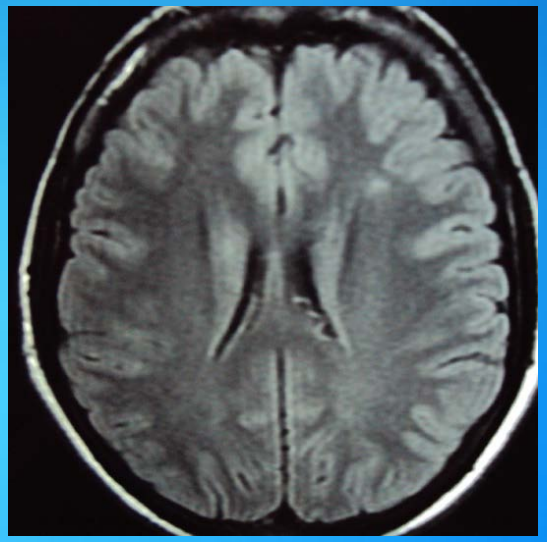








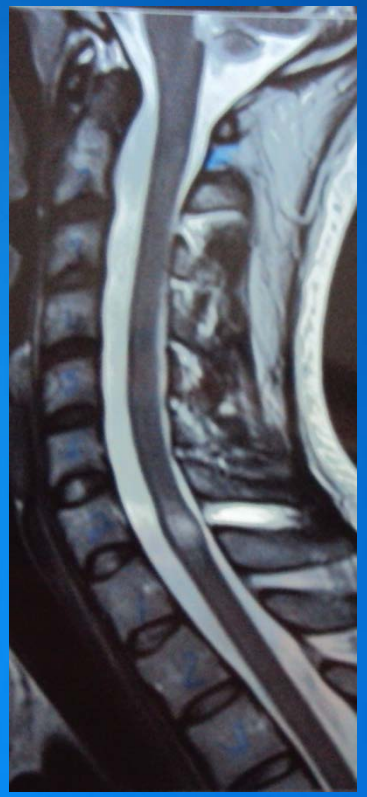
PPMS

42 Y, K, 1.5 yıldır olan ve zamanla artan sağ bacak güçsüzlüğü ve uyuşma





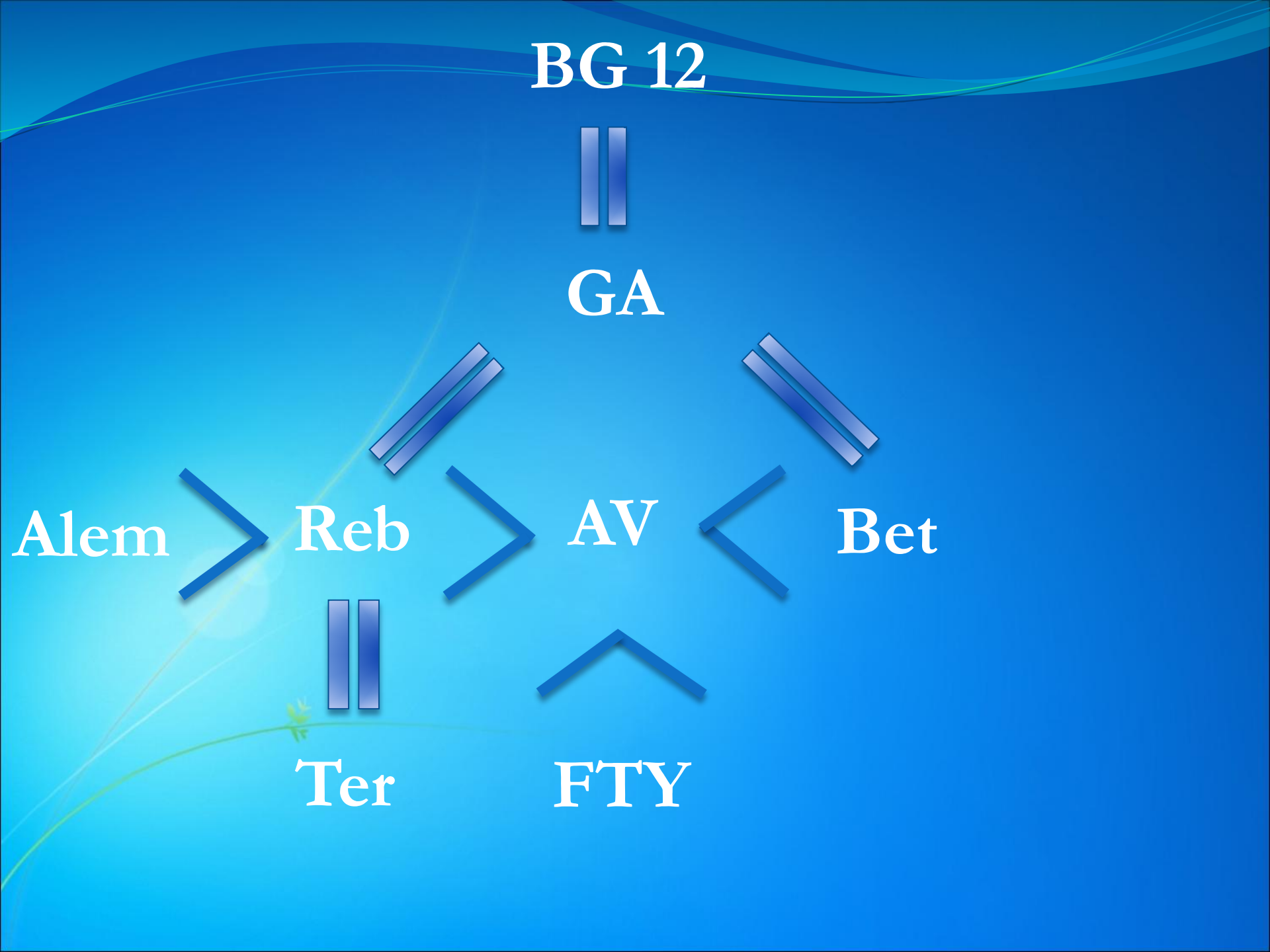


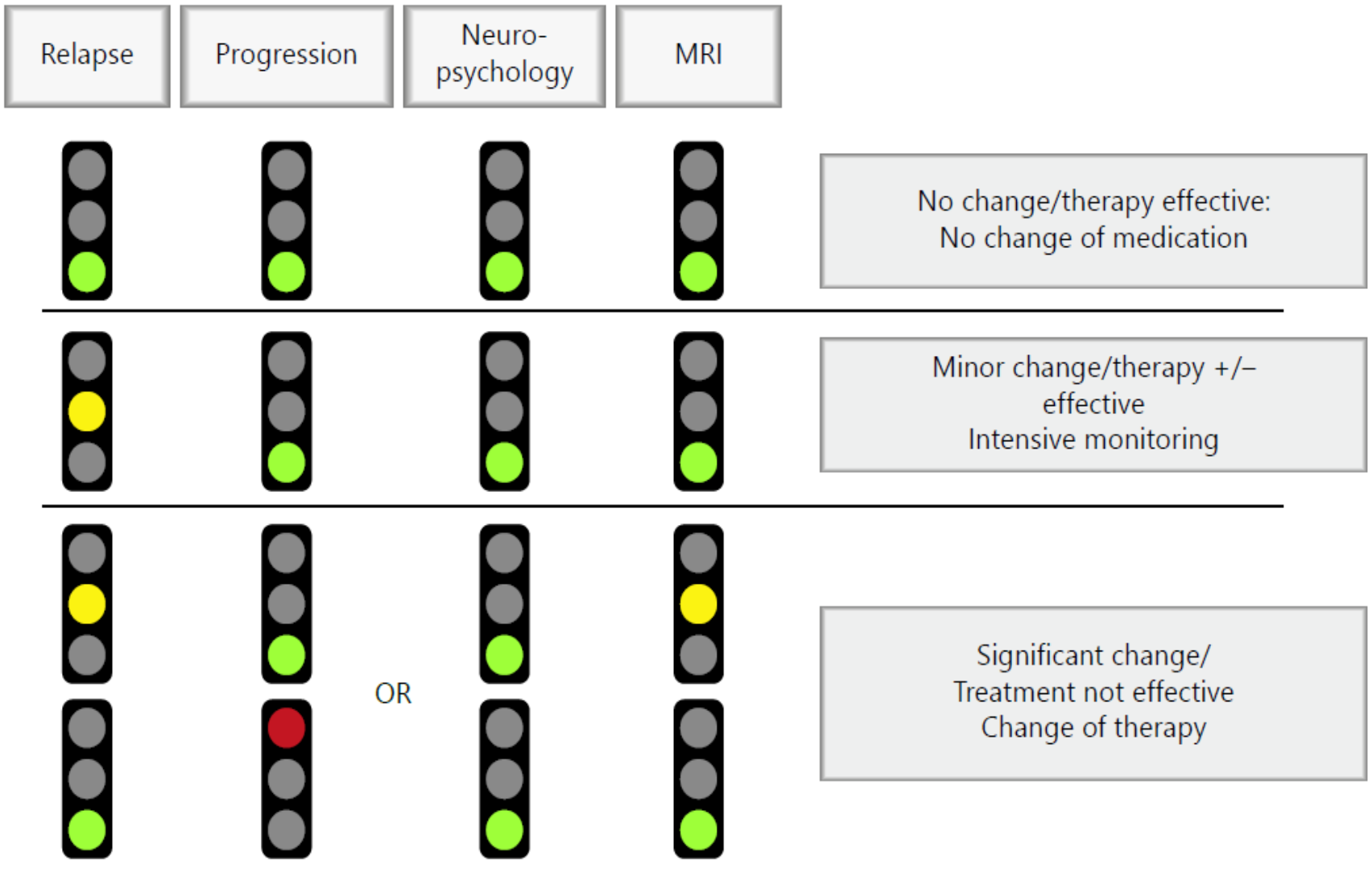


Primary progressive (progressive accumulation of disability from onset)	Active* and with progression#
	Active* but without progression
Progressive disease	Not active but with progression#
Secondary progressive (progressive accumulation of disability after an initial relapsing course)	Not active and without progression (stable disease)

*Activity = clinical relapses and/or MRI (gadolinium-enhancing MRI lesions; new/enlarging T2 lesions).

#Progression measured by clinical evaluation at least once yearly.


BG 12
GA
Alem
Reb
AV
Bet
Ter
FTY

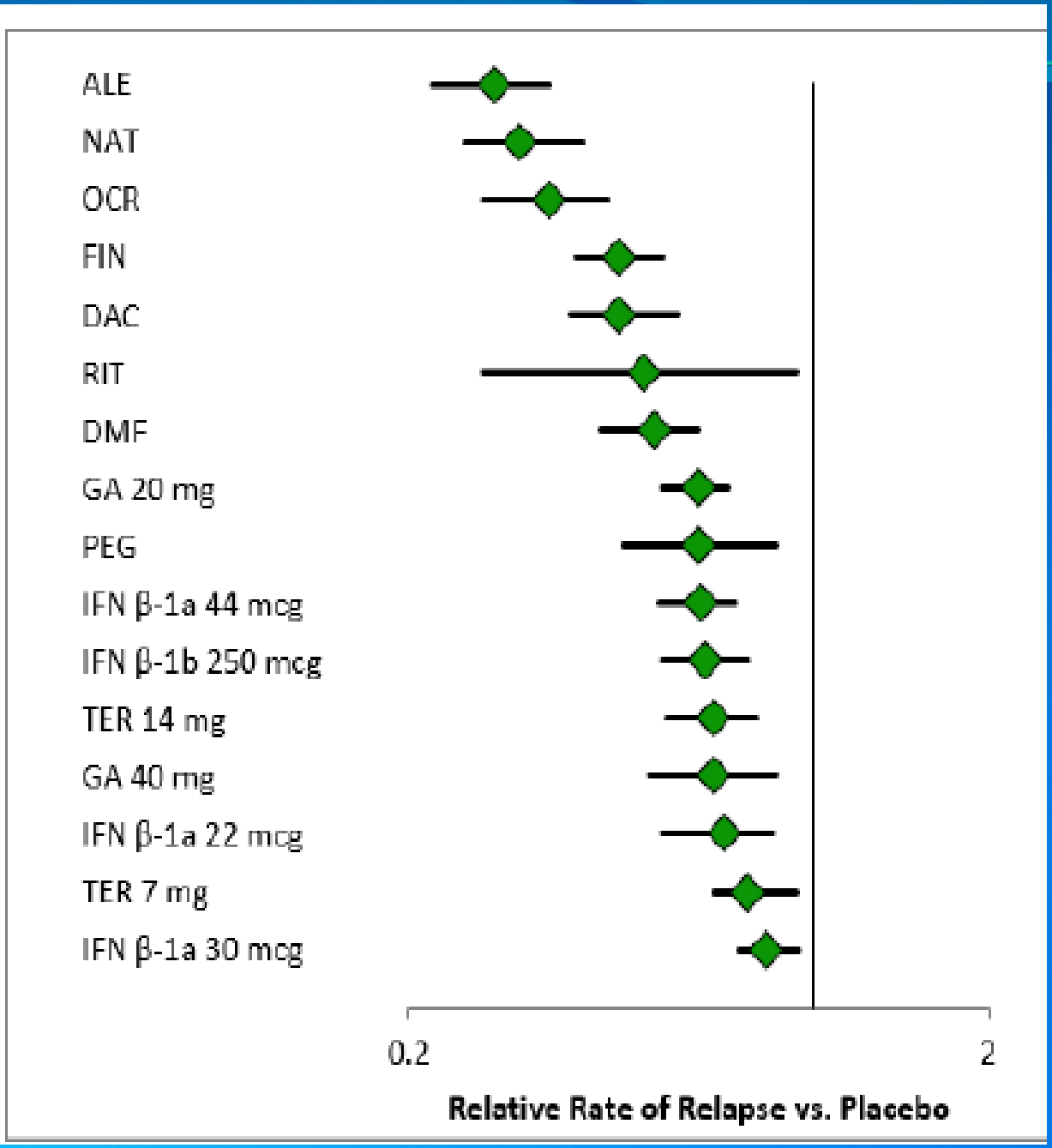


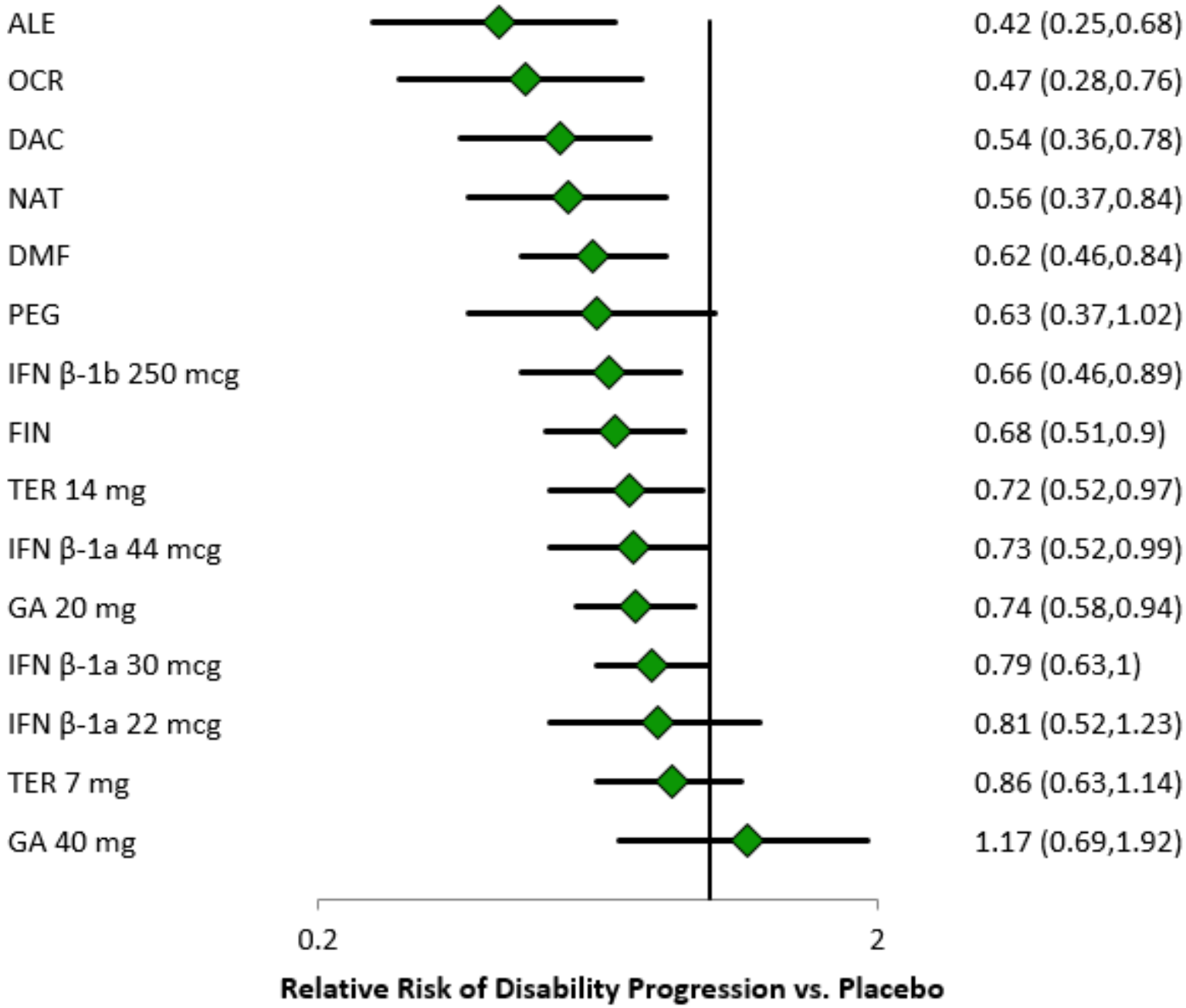
Eur Neurol 2014;72(suppl 1):35–38

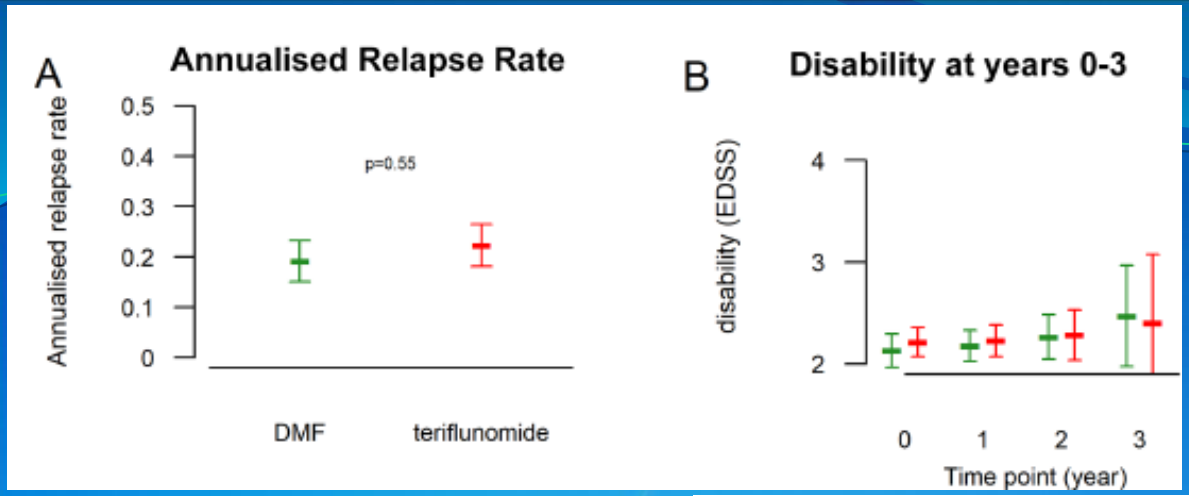
Tedavi Geçişi

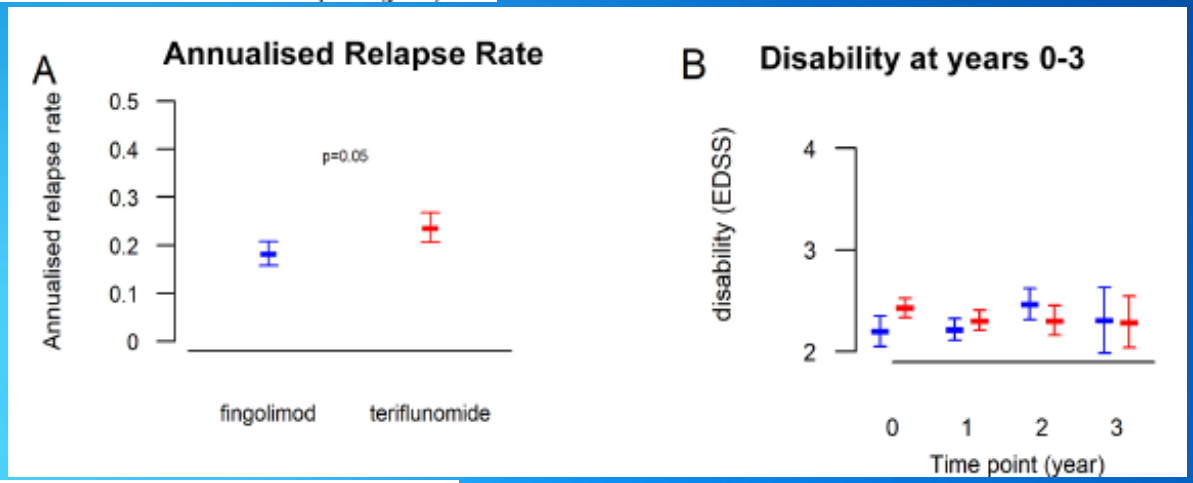
Treatment 1	Treatment 2	Washout
IFN or GA	Any drug	No washout required
Any drug	IFN or GA	No washout required
NTZ	FTY Teriflunomide DMF	< 2 months after discontinuation of NTZ
Teriflunomide	FTY NTZ Alemtuzumab	Accelerated elimination procedure or 3.5 months
FTY	Teriflunomide NTZ Alemtuzumab	When lymphocytes level are returned to normal levels (1 to 2 months)
DMF	Alemtuzumab NTZ FTY	When lymphocytes level are returned to normal levels

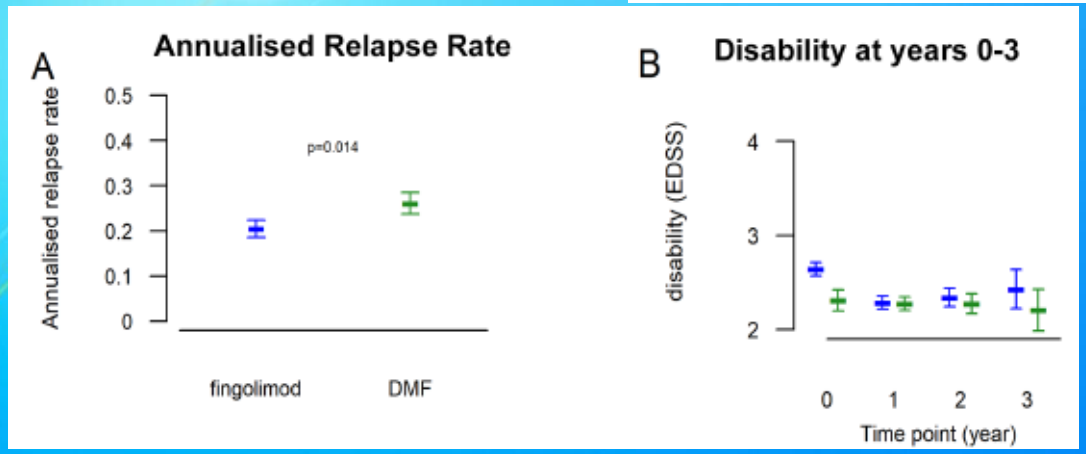
Presse Med. 2015; 44: e137–e151


ALE
NAT
OCR
FIN
DAC
RIT
DMF
GA 20 mg
PEG
IFN β-1a 44 mcg
IFN β-1b 250 mcg
TER 14 mg
GA 40 mg
IFN β-1a 22 mcg
TER 7 mg
IFN β-1a 30 mcg
0.2
2
Relative Rate of Relapse vs. Placebo

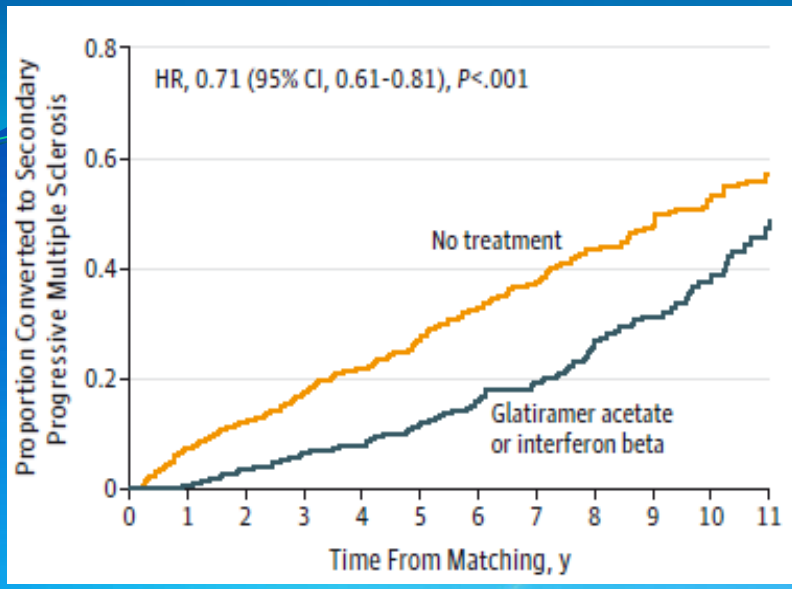

ALE
OCR
DAC
NAT
DMF
PEG
IFN β-1b 250 mcg
FIN
TER 14 mg
IFN β-1a 44 mcg
GA 20 mg
IFN β-1a 30 mcg
IFN β-1a 22 mcg
TER 7 mg
GA 40 mg
0.42 (0.25,0.68)
0.47 (0.28,0.76)
0.54 (0.36,0.78)
0.56 (0.37,0.84)
0.62 (0.46,0.84)
0.63 (0.37,1.02)
0.66 (0.46,0.89)
0.68 (0.51,0.9)
0.72 (0.52,0.97)
0.73 (0.52,0.99)
0.74 (0.58,0.94)
0.79 (0.63,1)
0.81 (0.52,1.23)
0.86 (0.63,1.14)
1.17 (0.69,1.92)
0.2
2
Relative Risk of Disability Progression vs. Placebo

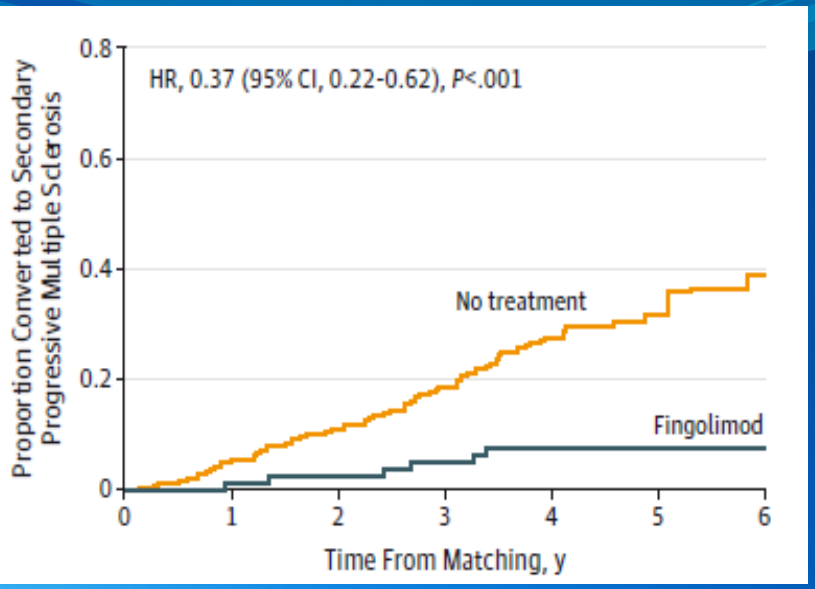


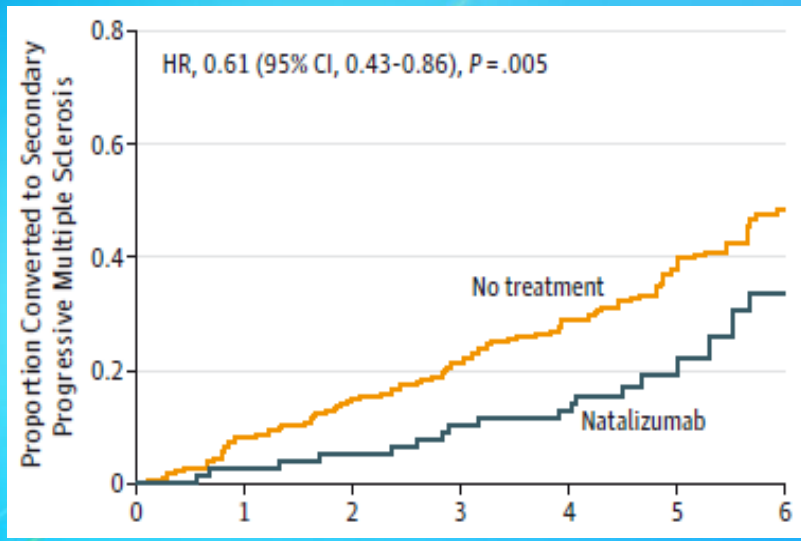


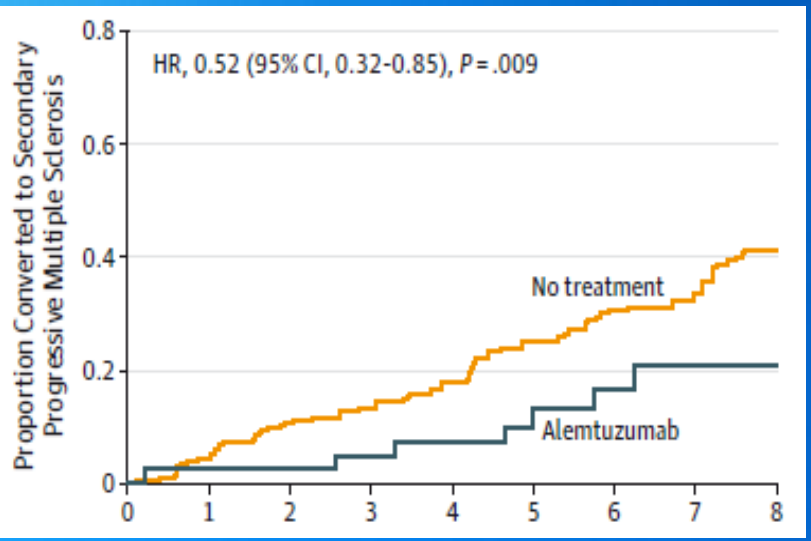


J Neurol Neurosurg Psychiatry
2019;**0**:1–11

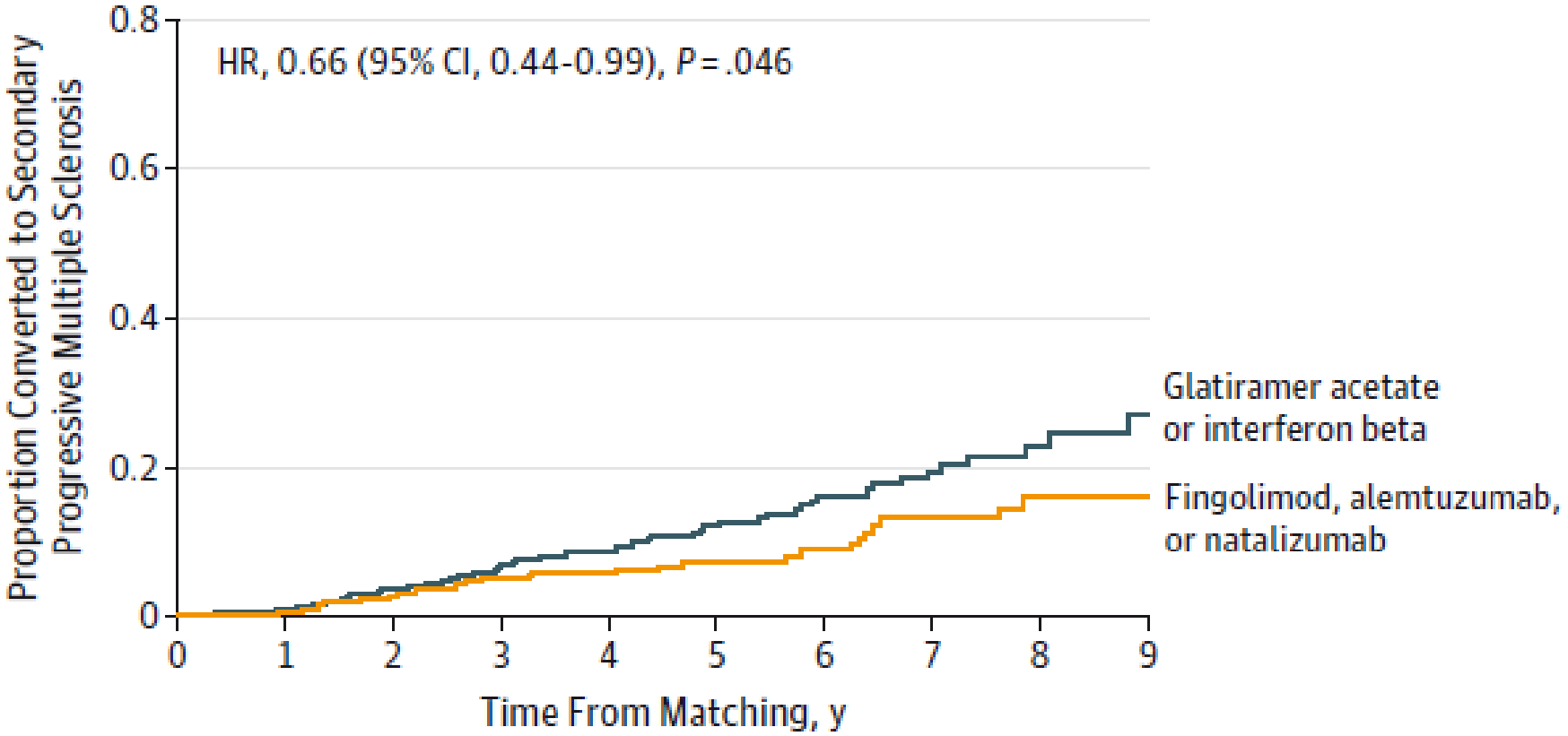




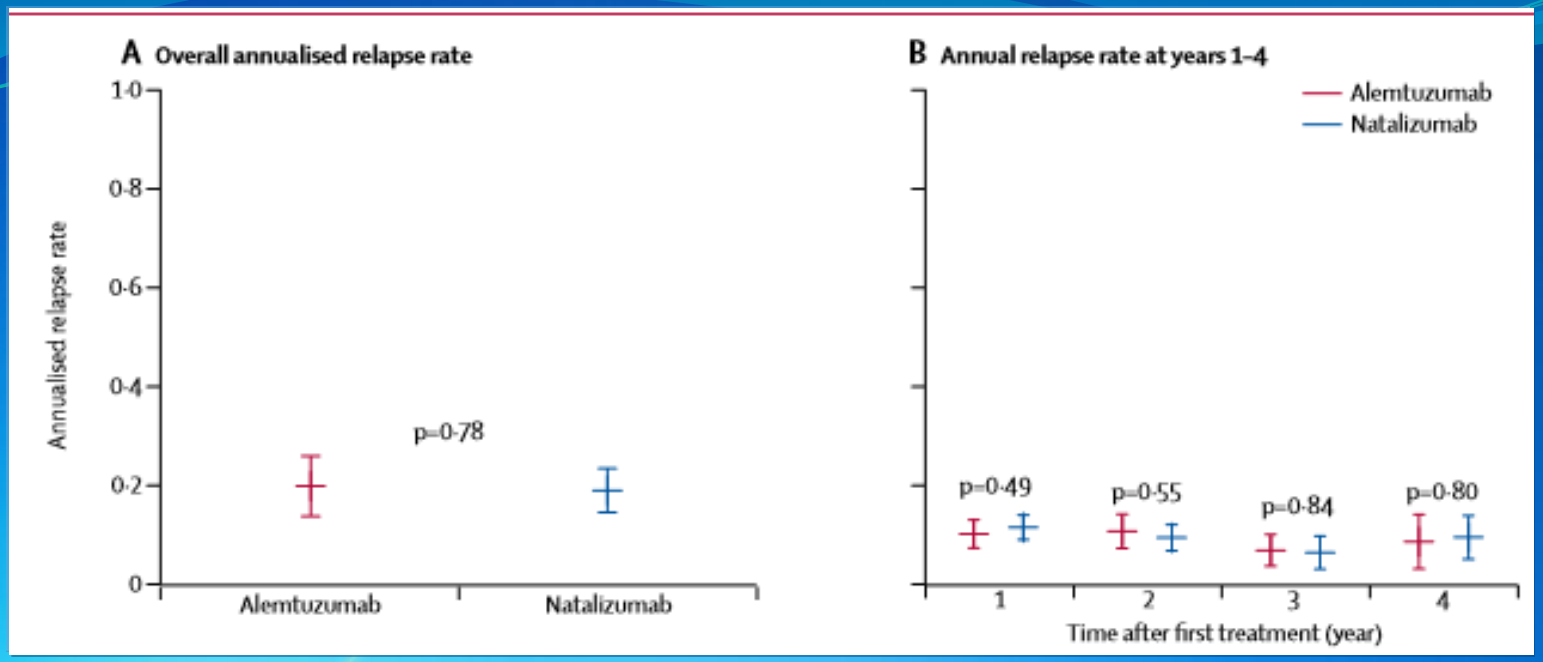


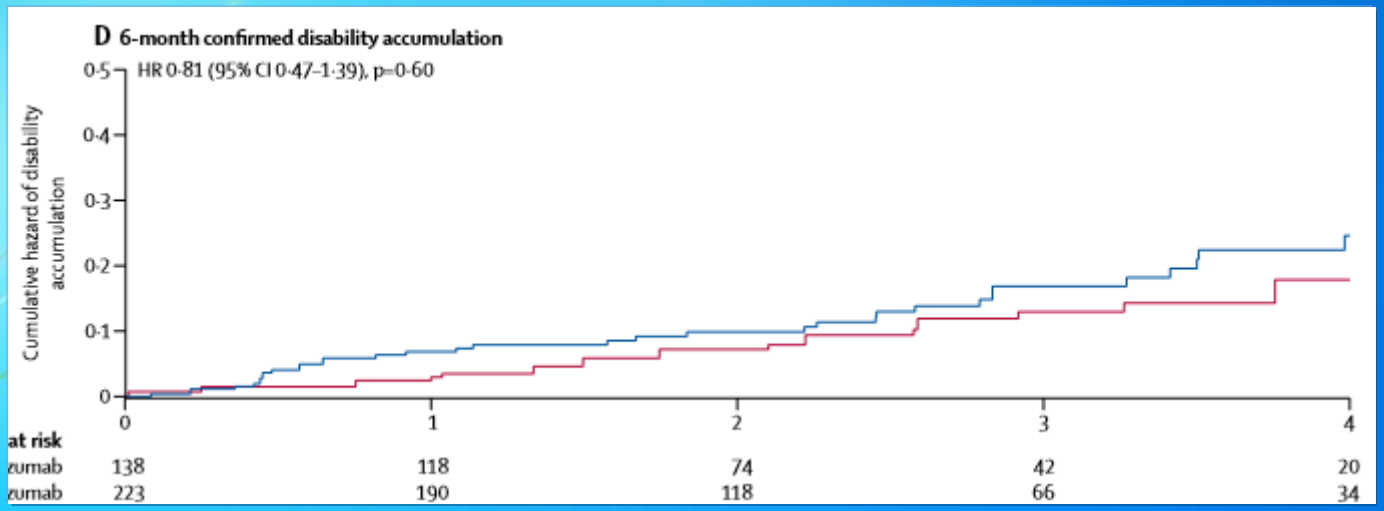


JAMA. 2019;321(2):175-187

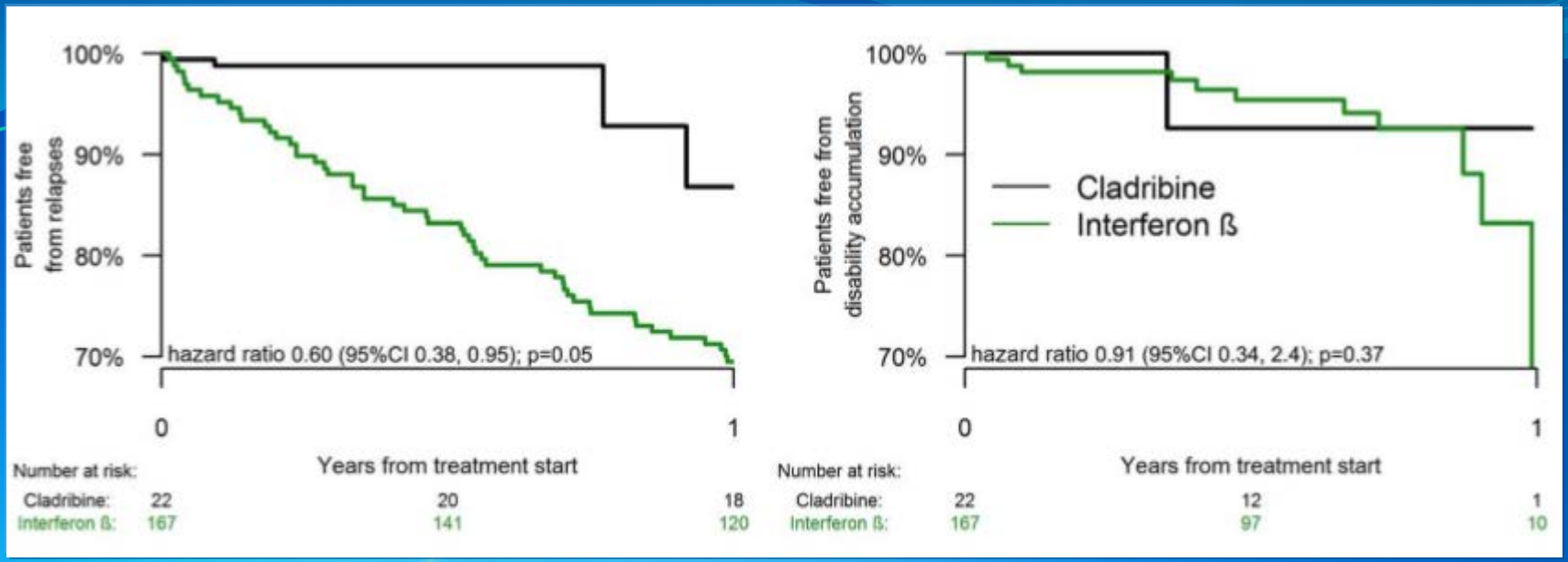


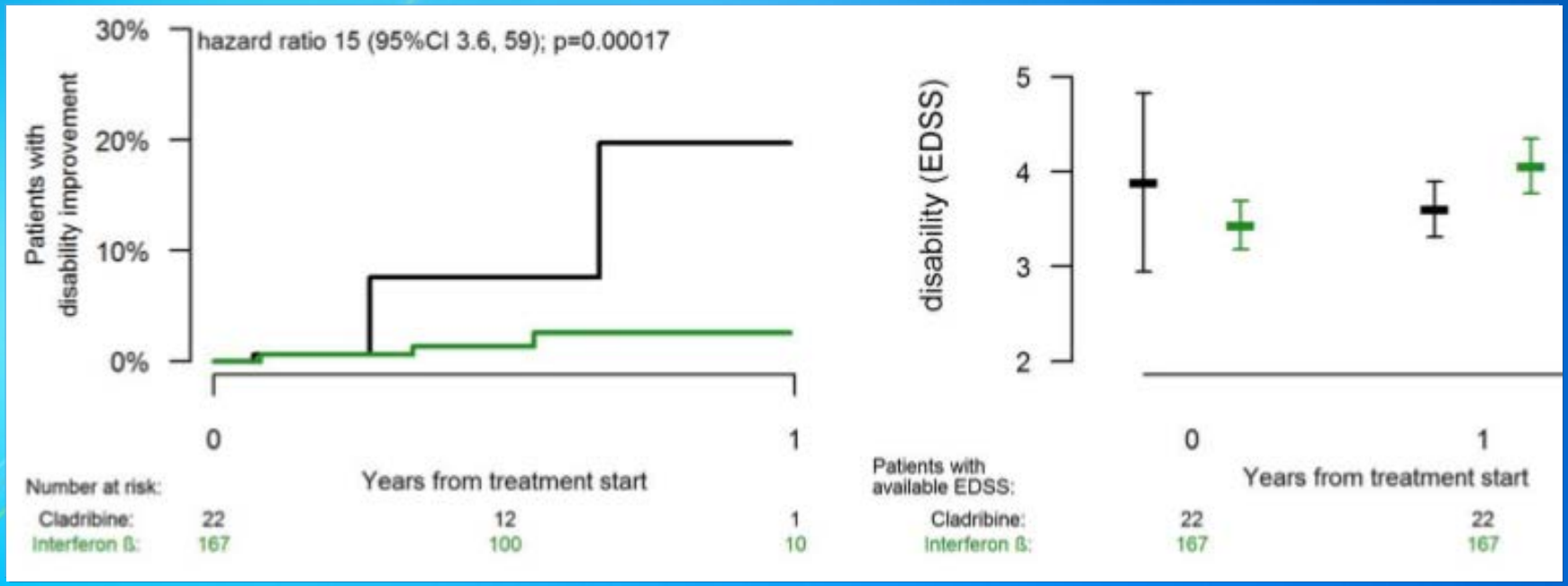
JAMA. 2019;321(2):175-187





Lancet Neurol 2017; 16: 271–81





Annals of Neurology

Monoclonal antibody	Adverse effect
Natalizumab	PML
	PML with IRIS
	Hepatotoxicity
Alemtuzumab	Infections
	Infusion reaction
	Thyroid disorders
	Nephropathy
	Immune thrombocytopenia
Rituximab	Infections
	Infusion reaction
	Hepatitis B reactivation
Daclizumab	Hepatotoxicity
	Encephalitis
	Cutaneous events
	DRESS
Ocrelizumab	Infections
	Infusion reaction
	Hepatitis B reactivation
	Malignancies (breast cancer) (?)
Ofatumumab	Infections
	Infusion reaction
	Hepatitis B reactivation
Opicinumab	Specific adverse effects unknown

BioDrugs
https://doi.org/10.1007/s40259-018-0327-9

Symptom	Intervention	Outcome	Level of evidence[a]
Fatigue	Intensive inpatient rehabilitation [143, 144]	Improving symptom	II
	Extended outpatient rehabilitation [145]	Improving symptom	II
	CBT [138]	Improving symptom	II
	Hydrotherapy [117]	Improving symptom	II
	Gait training [108]	Improving symptom	II
	Cooling devices [146]	Anecdotal evidence in improving symptom	HTA
	Exercise [147, 148]	Inconclusive evidence	I
	Behavior advice [146]	Inconclusive evidence	I
	Complementary and alternative therapies [149]	Inconclusive evidence	I
	Low frequency magnetic field [150]	No beneficial effect	II
Spasticity	Hydrotherapy [117]	Improving symptom	II
	Exercise (stretching/strengthening) [151]	Inconclusive evidence	I
	TENS [5]	No beneficial effect	I
Ataxia/tremor	Neurorehabilitation [37]	Inconclusive evidence	I
Bladder function	MD rehabilitation [50]	Improving symptoms and disability	II
	Exercise-Pelvic floor training [152, 153]	Improving symptoms and QoL	II
	External bladder stimulator (Queen Square Stimulator) [154, 155]	Reduction of resting urinary volume	II
Sexual dysfunction	MD care [156, 157]	Anecdotal evidence in improving symptoms	IV
Pain	TENS [120, 121]	Improving symptoms	II
	Physiotherapy [158]	Anecdotal evidence in improving disability and QoL	Narrative review
	MD rehabilitation [66]	Inconclusive evidence	I
	Complementary and alternative therapies [149]	Inconclusive evidence	I
	Hydrotherapy [117]	Improving symptom	II
Mobility/balance and activity	Exercise [99]	Improving mobility activities and disability	I
	Gait training [108, 109]	Improving mobility parameters Improving QoL	II
	Hippotherapy [112]	Improving balance	I
	OT [123]	Improving ADLs	I
	Mobility assistive device [124]	Inconclusive evidence	I
Psychosocial function	Psychological training [131]	Improving depression, and help adjust and cope	I
	CBT [137]	Improving depression	II

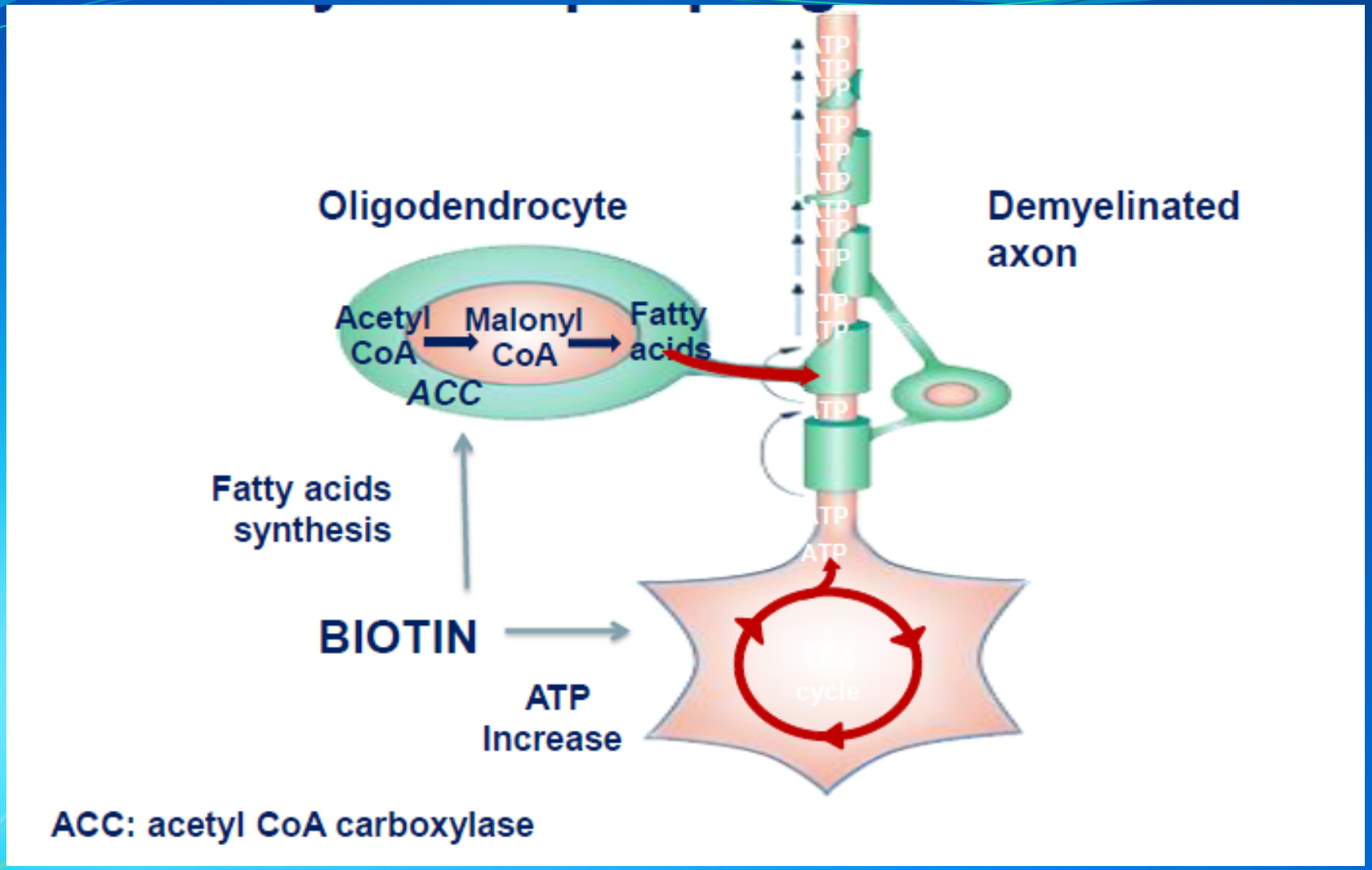
J Neurol (2012) 259:1994–2008

Clinical characteristics	Patient cohort	Pretreatment, mean (SD)	Posttreatment, mean (SD)	p-value	N
Maximal walking distance (m)	Tx	494.5 (337.0)	742.1 (575.7)	.004	34
	Tx*R	496.0 (334.2)	882.8 (631.6)	.003	22
T25FW (s)	Tx	10.3 (6.1)	9.2 (6.1)	.039	34
	Tx*R	9.5 (5.2)	7.8 (3.1)	.024	22
9-HPT, dominant hand (s)	Tx	26.8 (14.7)	26.1 (17.4)	.632	32
	Tx*R	23.9 (6.3)	22.9 (6.4)	.744	22
9-HPT, nondominant hand (s)	Tx	26.7 (11.2)	26.1 (11.5)	.584	33
	Tx*R	26.2 (10.9)	25.0 (9.1)	.194	22
PASAT	Tx	42.9 (13.5)	46.1 (13.3)	.029	33
	Tx*R	42.2 (14.1)	45.8 (13.5)	.651	21
FSS	Tx	49.3 (12.1)	48.1 (13.2)	.680	33
	Tx*R	48.8 (11.7)	45.2 (13.5)	.001	21
BDI	Tx	10.4 (7.0)	9.4 (5.8)	.032	33
	Tx*R	9.7 (7.5)	9.0 (6.0)	.314	22
EQ-5D	Tx	8.0 (1.0)	7.8 (1.3)	.725	33
	Tx*R	7.8 (1.0)	7.4 (1.2)	.086	22
QolVas (%)	Tx	55.2 (17.2)	58.3 (16.4)	.327	32
	Tx*R	56.6 (18.3)	60.0 (17.2)	.890	22

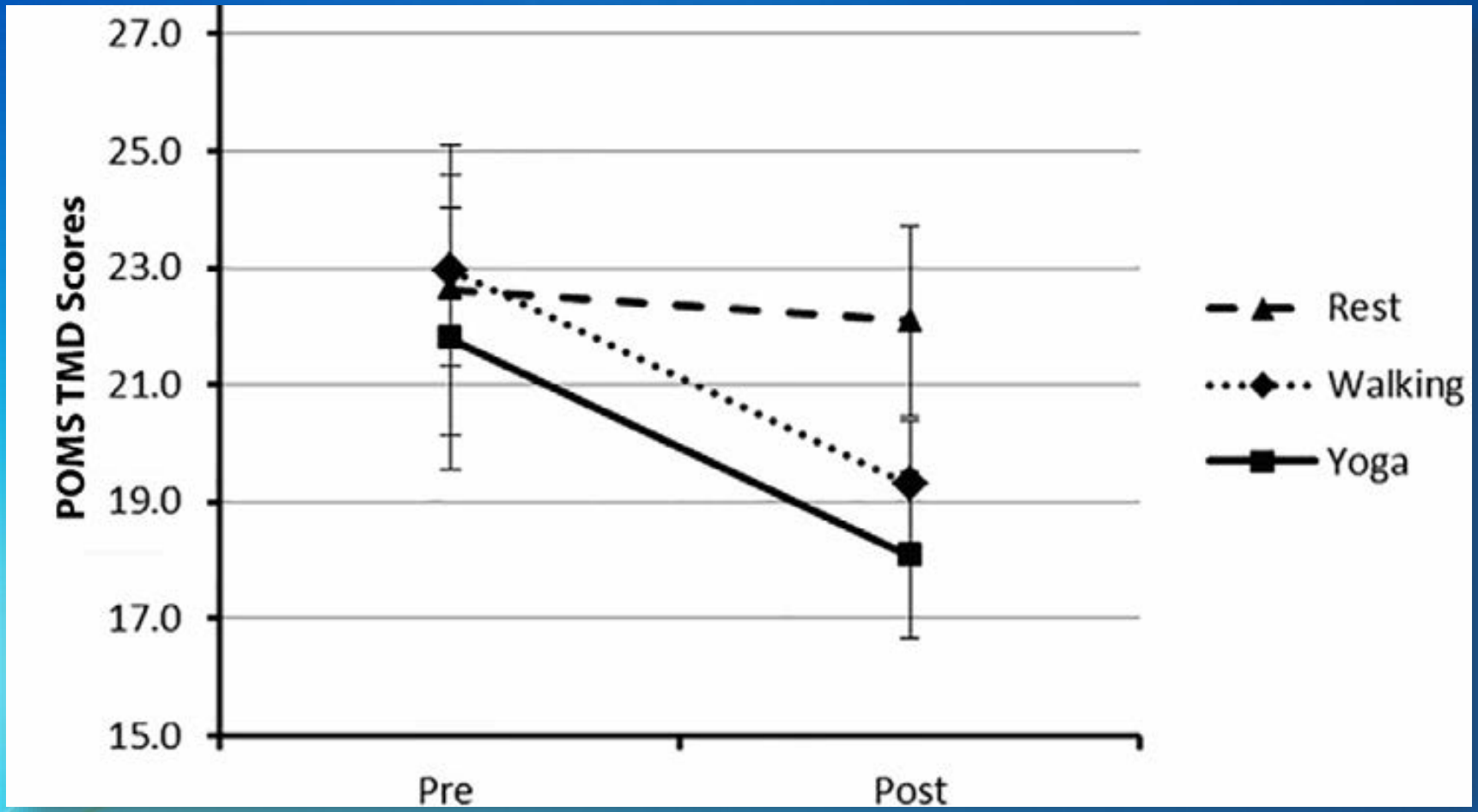
T25FW, timed 25 Foot Walk test; 9-HPT, nine hole peg test; PASAT, paced auditory serial addition test; FSS, fatigue severity scale; BDI, Beck Depression

Fampridine

Journal of Neurology (2018) 265:1016–1025

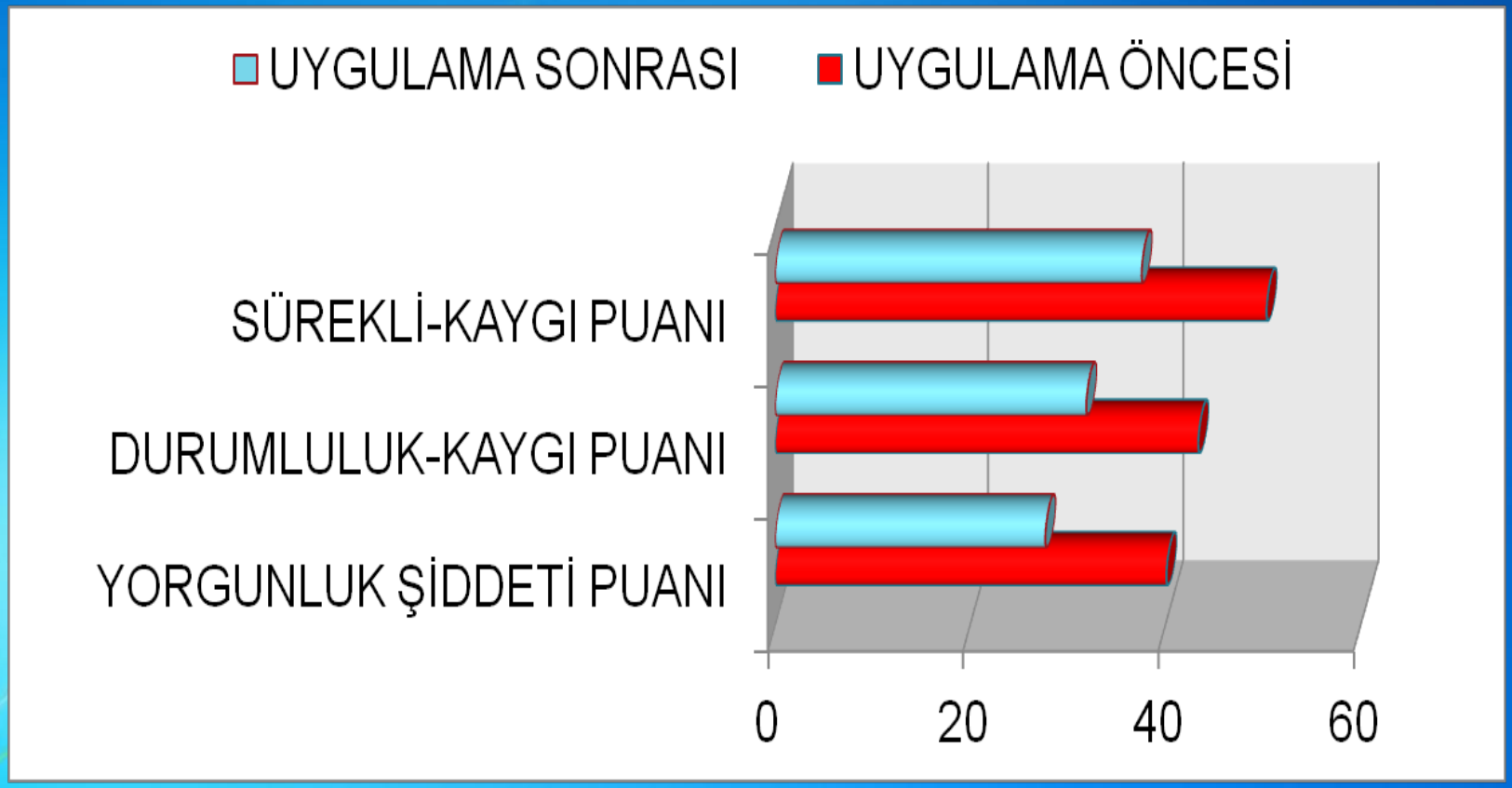


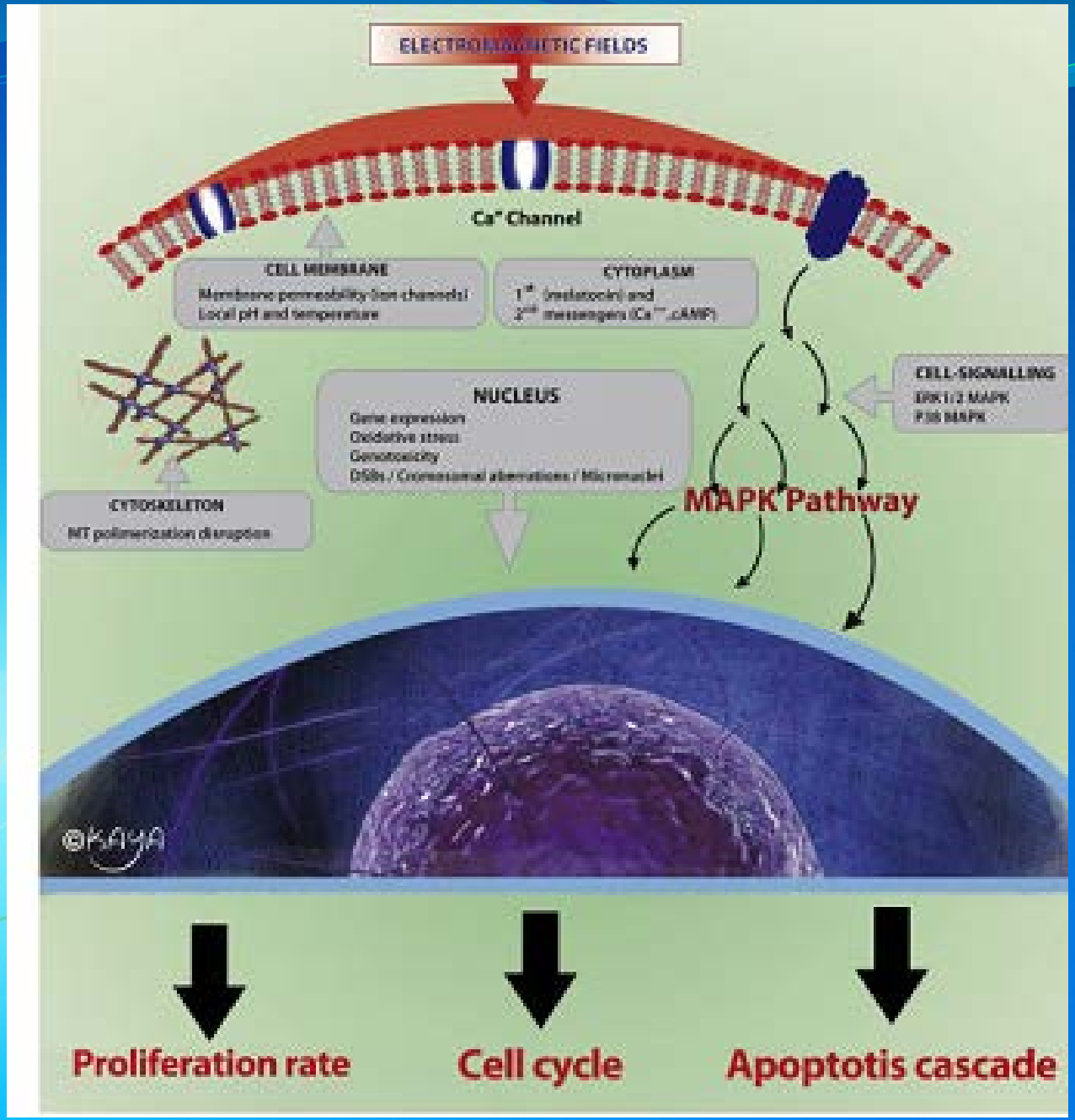
ACC: acetyl CoA carboxylase



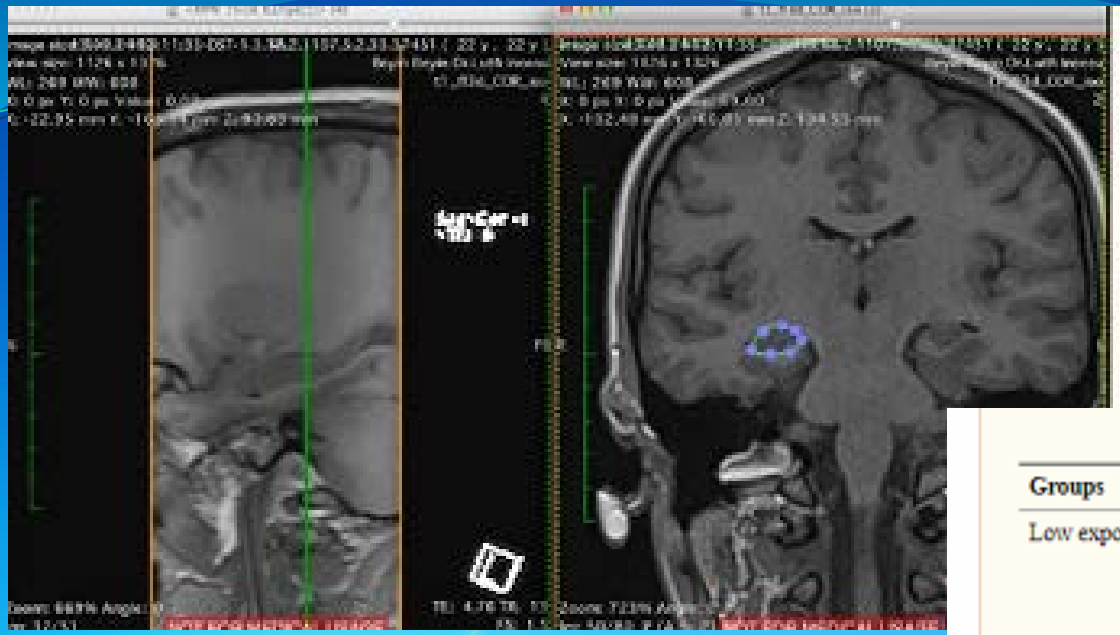
Int J MS Care. 2016;18:1–8.

REFLEKSOLOJİNİN YORGUNLUK ve KAYGI ÜZERİNE ETKİSİ





Journal of Chemical Neuroanatomy 75 (2016) 77–84



Groups	Cognitive tests	Mean ± SD
Low exposure	Hanoi tower test	55.2500 ± 14.64923
	Stroop test	8.7250 ± 1.43485
	Digit symbol test	56.2500 ± 5.72131
	Beck depression test	8.6875 ± 4.20664
	K.A.S. test	42.6250 ± 7.48220
	Line orientation test	53.1875 ± 3.12450
	Digit span test (forward)	5.1250 ± 1.14746
	Digit span test (backward)	4.6250 ± 0.61914
High exposure	Hanoi tower test	54.8667 ± 11.44469
	Stroop test	12.8500 ± 3.39897
	Digit symbol test	55.4667 ± 6.46824
	Beck depression test	6.8667 ± 3.54293
	K.A.S. test	39.7333 ± 14.57722*
	Line orientation test	53.4667 ± 5.81705
	Digit span test (forward)	4.1333 ± 1.06010
	Digit span test (backward)	2.3846 ± 0.96077*

*$p < 0.05$.

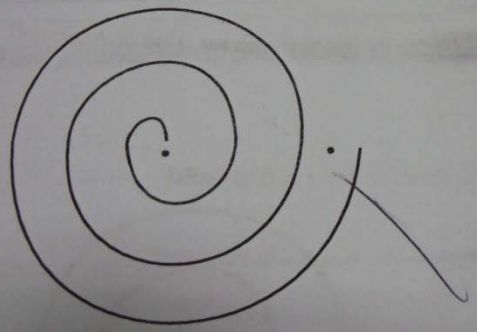
J Microsc Ultrastruct. 2017 Oct-Dec; 5(4): 191–197.

~~Non~~-Dominant Hand

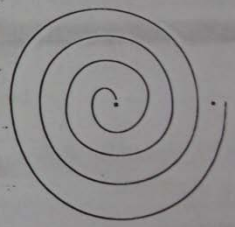
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

DRAWING A



DRAWING B



Bazal

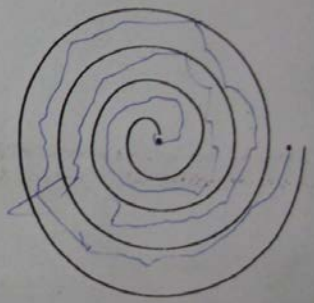
DRAWING C

rawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

DRAWING A

DRAWING B



Sol UIM; 2.4

23.11.2011

DRAWING C

Dominant Hand

Handwriting: This is a sample of my best handwriting

Signature: _____

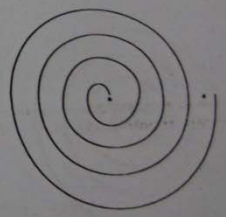
Date: _____

Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

DRAWING A

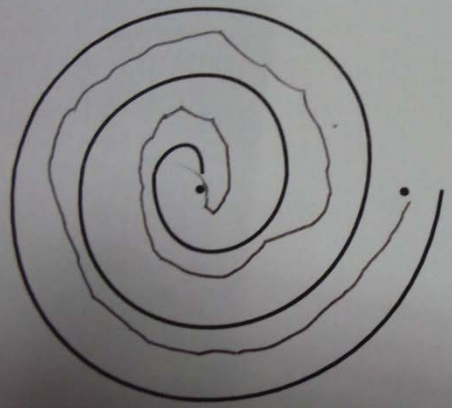
DRAWING B



Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

DRAWING A



DRAWING B

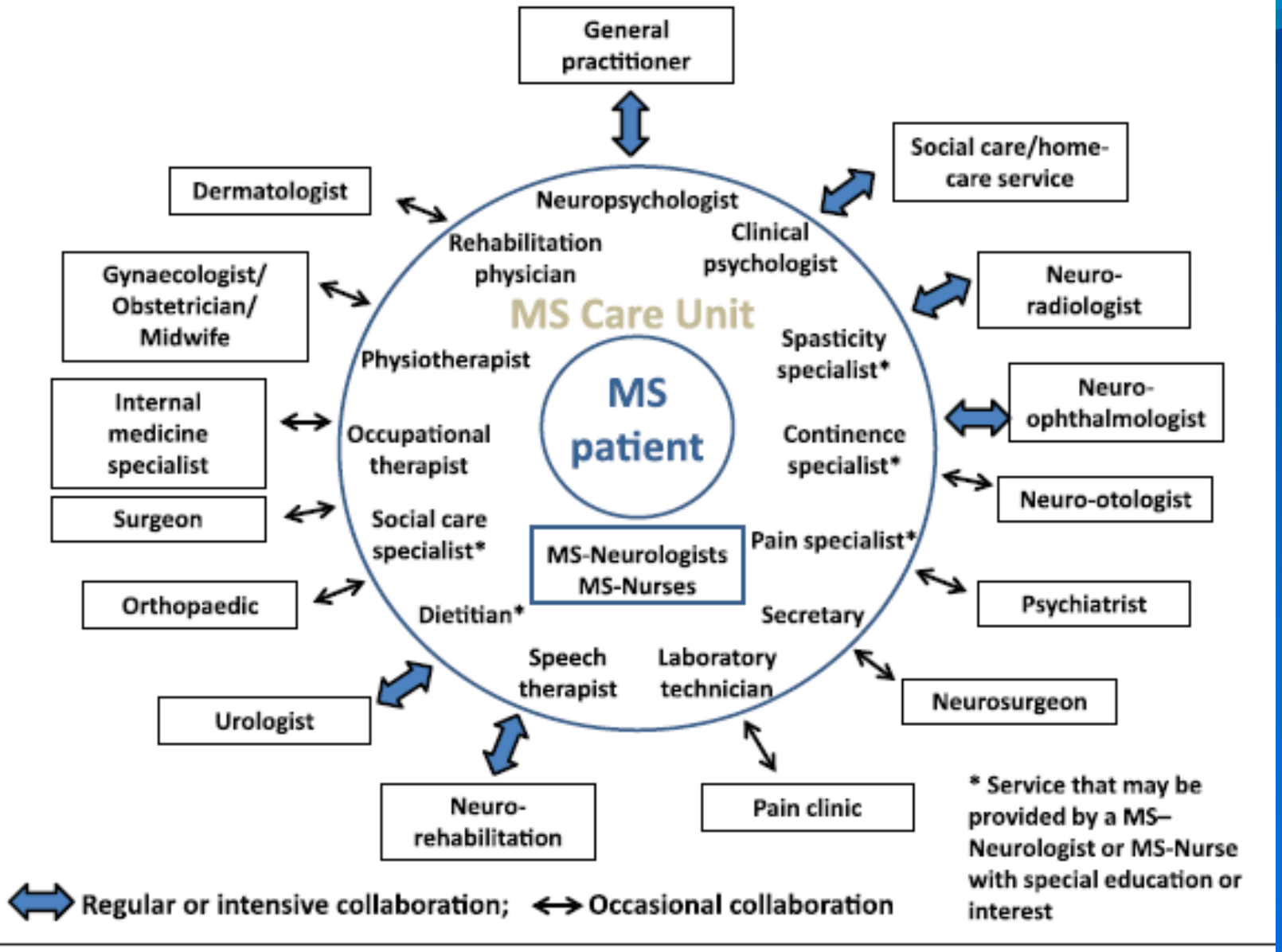
Sq UIM 2.6
01.12.2011

DRAWING C


17
Zambak
16
Kardelen
14
Begonya


Mavi Işıklar
Mavi Işıklar Eğitim, Dinlenme


KATILIM BELGESİ



Multiple Sclerosis Journal 1–10 DOI: 10.1177/


ONDOKUZ MAYIS ÜNİVERSİTESİ
50
YAVAŞ