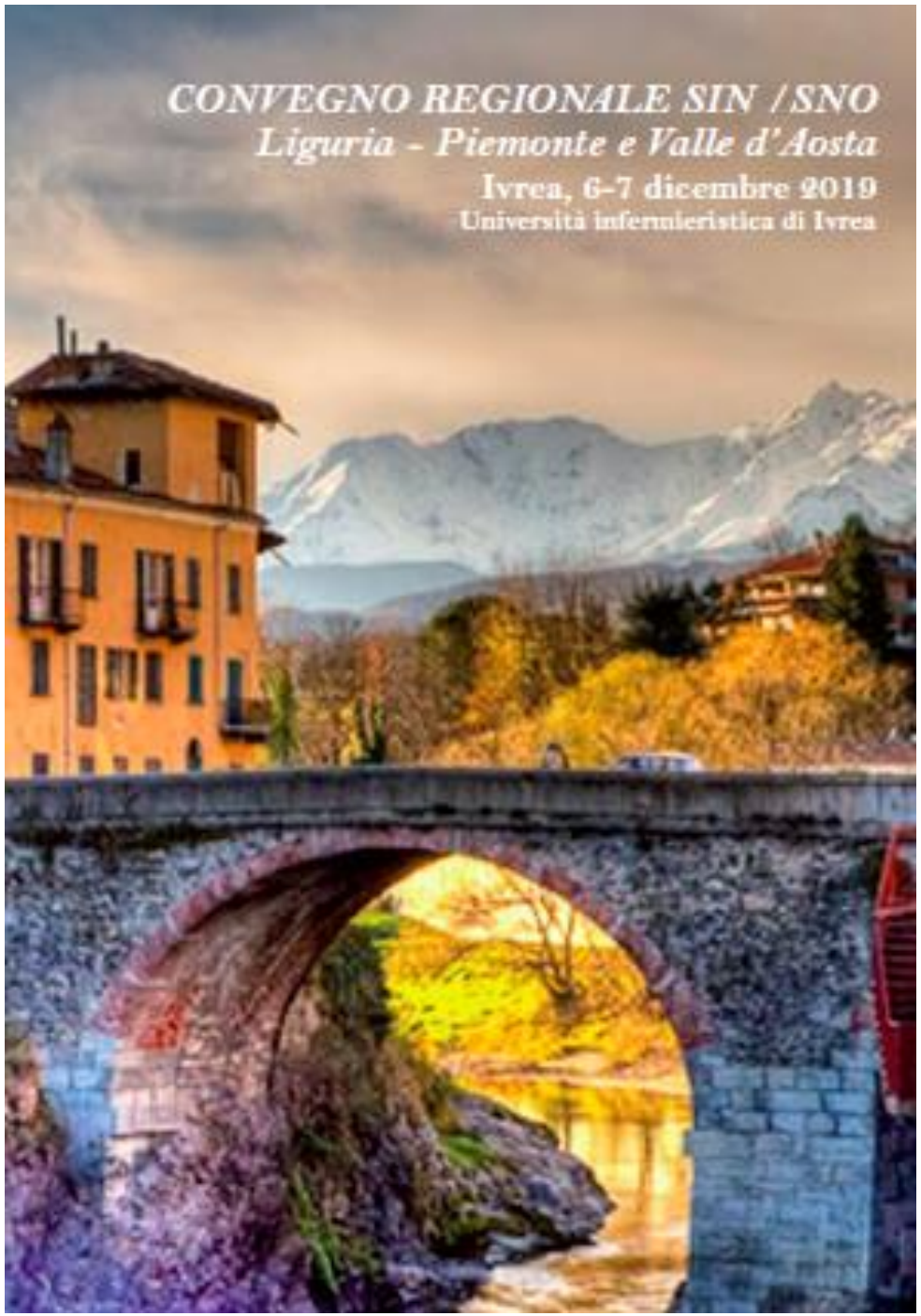


Neuro-news: Innovazioni diagnostiche e terapeutiche in neurologia.

Le novità dell'ultimo anno da non perdere: Sclerosi Multipla

Marco Capobianco

SCDO Neurologia – Centro di Riferimento Regionale Sclerosi Multipla (CReSM)

AOU S. Luigi – Orbassano

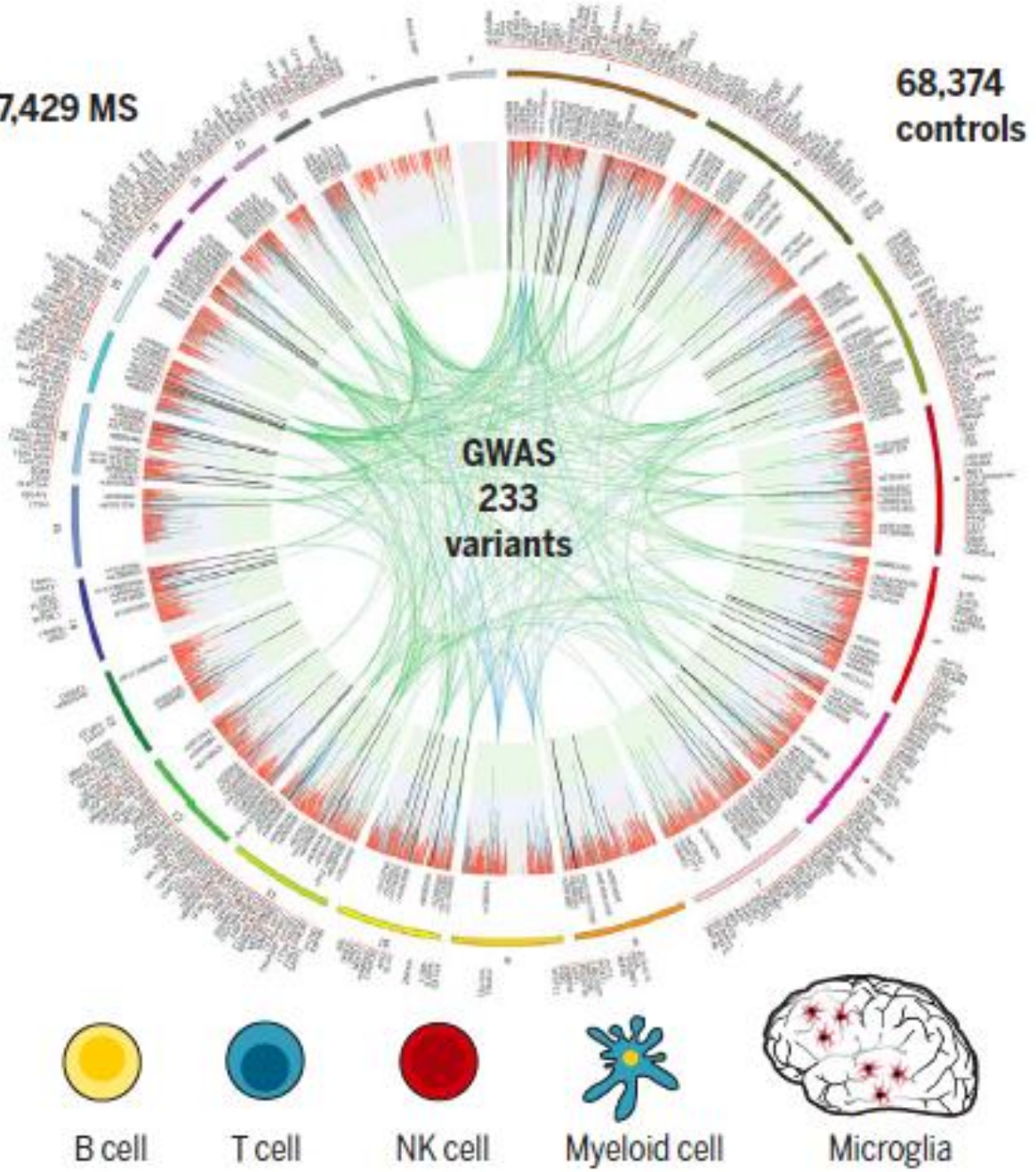
Conflitto di Interesse potenziale:
Advisory Board: Merck Serono, Biogen, Sanofi Genzyme, Roche, Novartis
Corsi ECM: Almirall, Biogen, Novartis, Merck Serono, TEVA, Sanofi Genzyme, Roche
Simposi non ECM: Sanofi Genzyme, Roche

Outline

- Aspetti emergenti di immunopatogenesi
  - Genetica
  - Linfociti B
  - Microglia

- Diagnosi differenziale
  - Central vein sign (SWI)
  - NMOSD/MOGAD

- Novità terapeutiche: raccomandazioni EMA e note AIFA
  - Ocrelizumab, cladribina
  - Sativex
  - IFNs e gravidanza
  - Alemtuzumab
  - Natalizumab
  - Siponimod



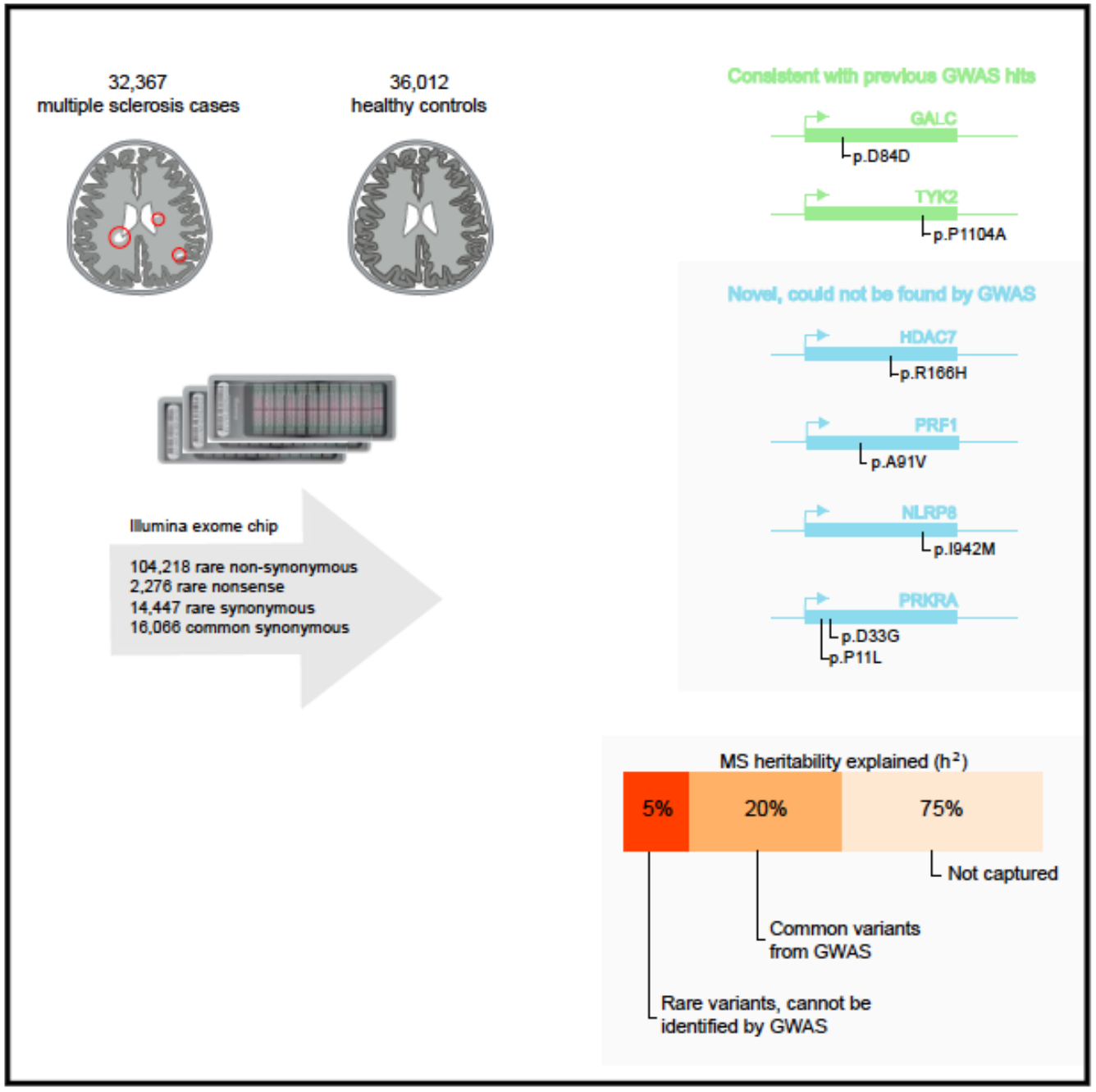
47429 MS cases vs 68374 controls
233 variants
32 on MHC region
1 on X-chromosome (related to M/F disease ratio?)

Large-scale replication effort (3 nonoverlapping cohorts): 200 non-MHC non-coding region

Gene expression data:

- enrichment in many adaptive immune cells
- enrichment for MS genes is seen in human microglia, but not in astrocytes or neurons

Patsopoulos and International Multiple Sclerosis Genetics Consortium, Science 2019

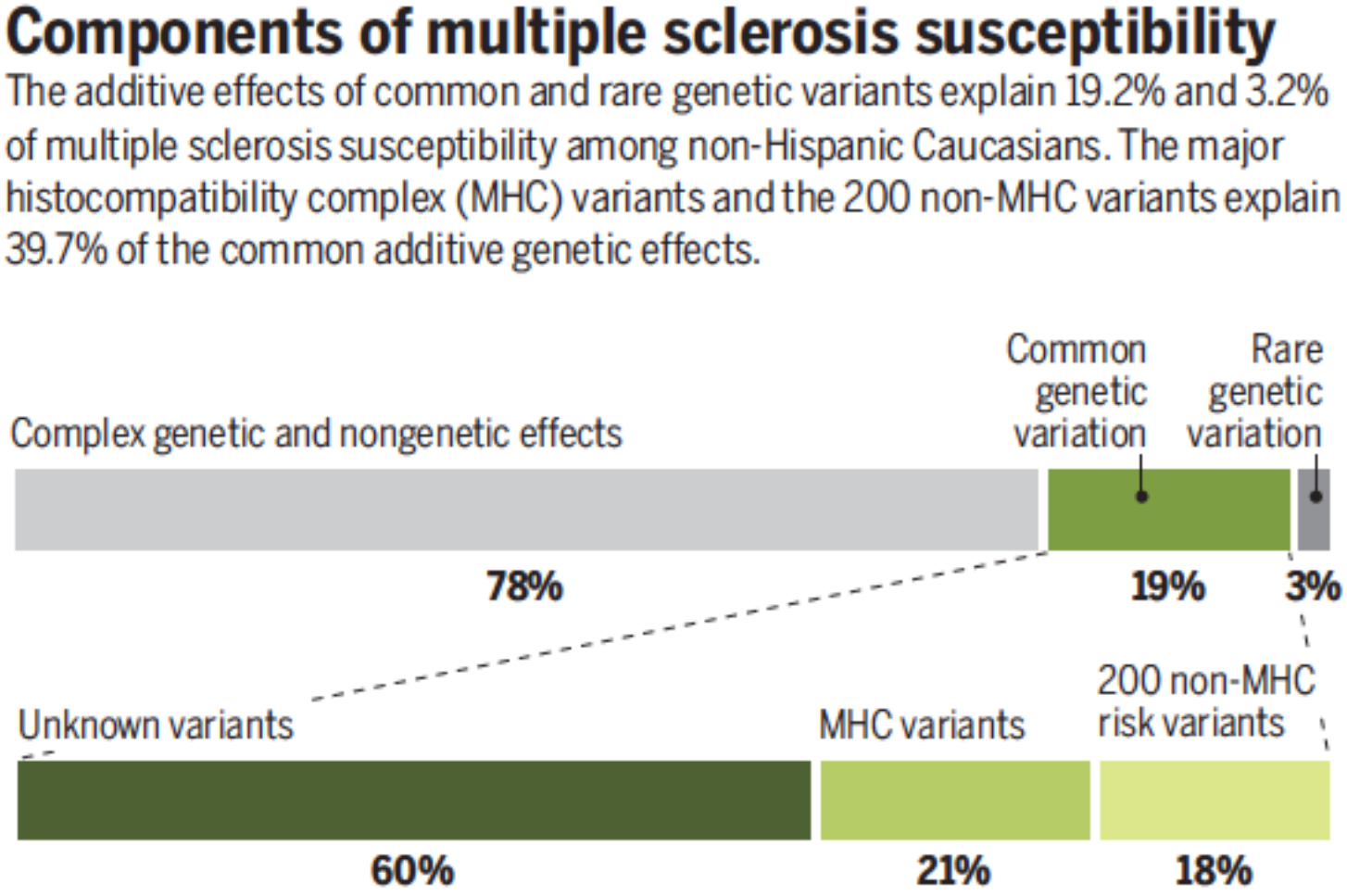


Meta-analysis of 121,000 rare- to low-frequency variants (<1% minor allele frequency) within gene-coding regions from 32,367 MS cases and 36,012 unaffected controls

- Almost 20% of MS risk heritability can be attributed to common genetic variants
- Nearly 5% of heritability is explained by coding low-frequency variants
- Identification of 4 novel genes driving risk independently of common-variant signals, playing a role in adaptive and innate immunity
- Highlighting key pathogenic roles for regulatory T cell homeostasis and regulation, IFN biology, and NFkB signaling

Cotsapas, Cell 2018; Lohith Madireddy, Nat Comm 2019

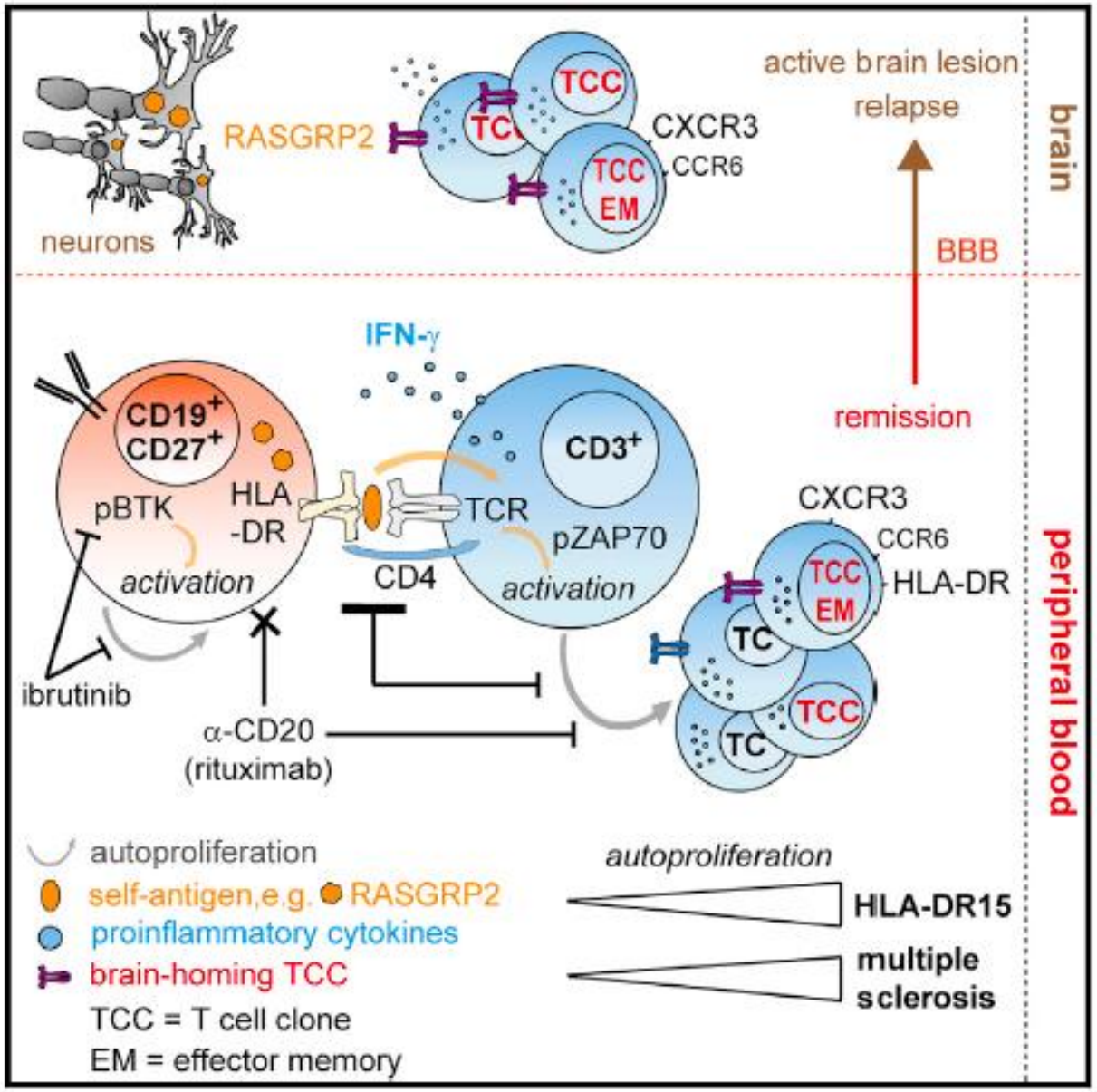
Immunopatogenesi: genetica



Common genetic variation enriched in adaptive immune cells (B and T cells)

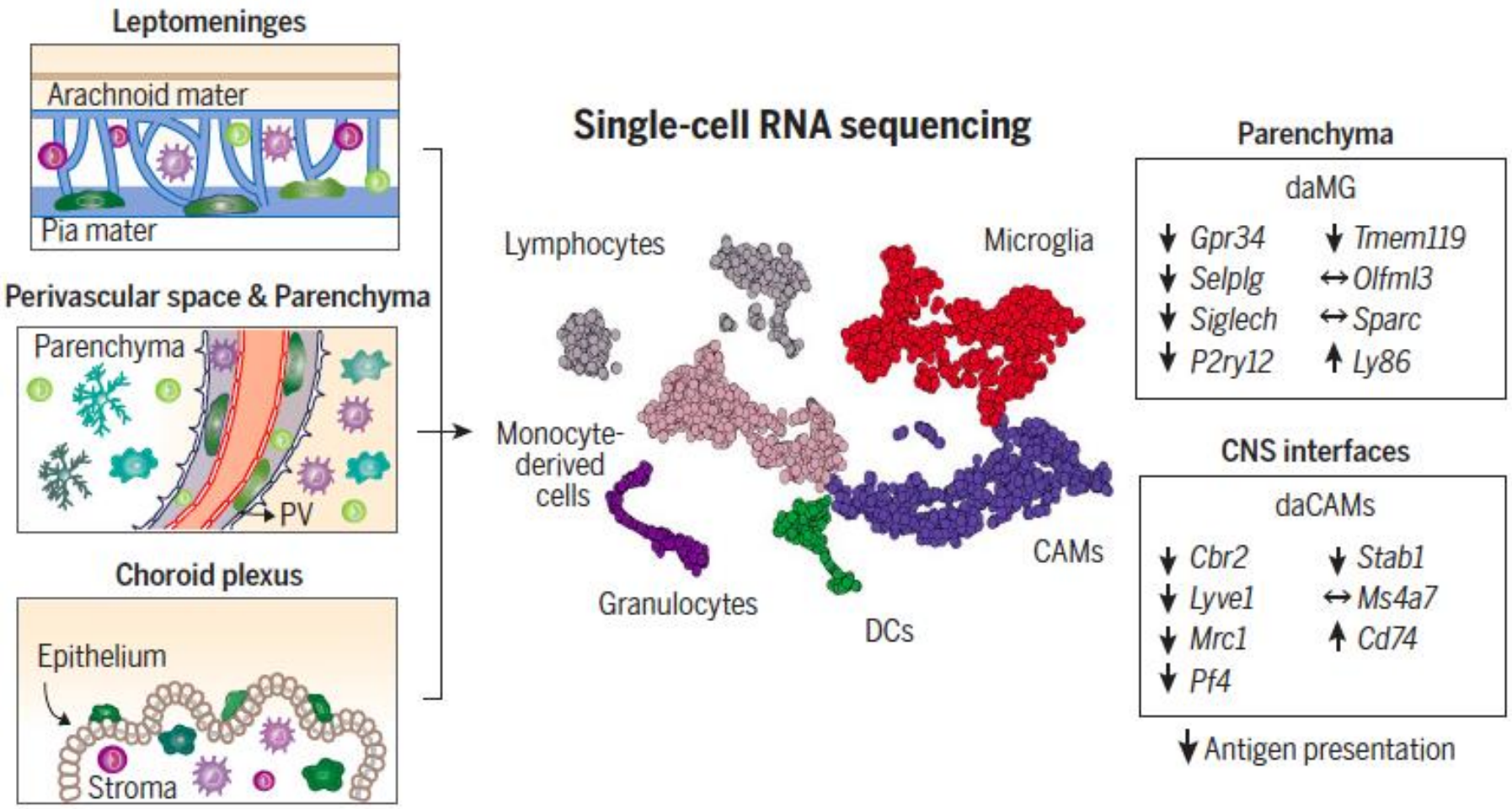
Rare variants expressed by adaptive and innate immune cells, in particular microglia

Farren Briggs, 2019 Science



- Autoproliferation of CD4+ T cells and B cells is involved in MS
- The main genetic factor of MS, HLA-DR15, plays a central role in autoproliferation
- Memory B cells drive autoproliferation of Th1 brain-homing CD4+ T cells
- Autoproliferating T cells recognize antigens expressed in B cells and brain lesions
- RASGRP2 as target autoantigen that is expressed in the brain and B cells

Jelcic, Cell 2018



CNS inflammation in EAE:

- Microglia clonally expand and drastically change transcriptomic profile
- Diverse DC and monocyte subsets symultaneously populate the CNS and show high antigen-presentation capacity

DCs dendritic cells; CAMs CNS-associated macrophages

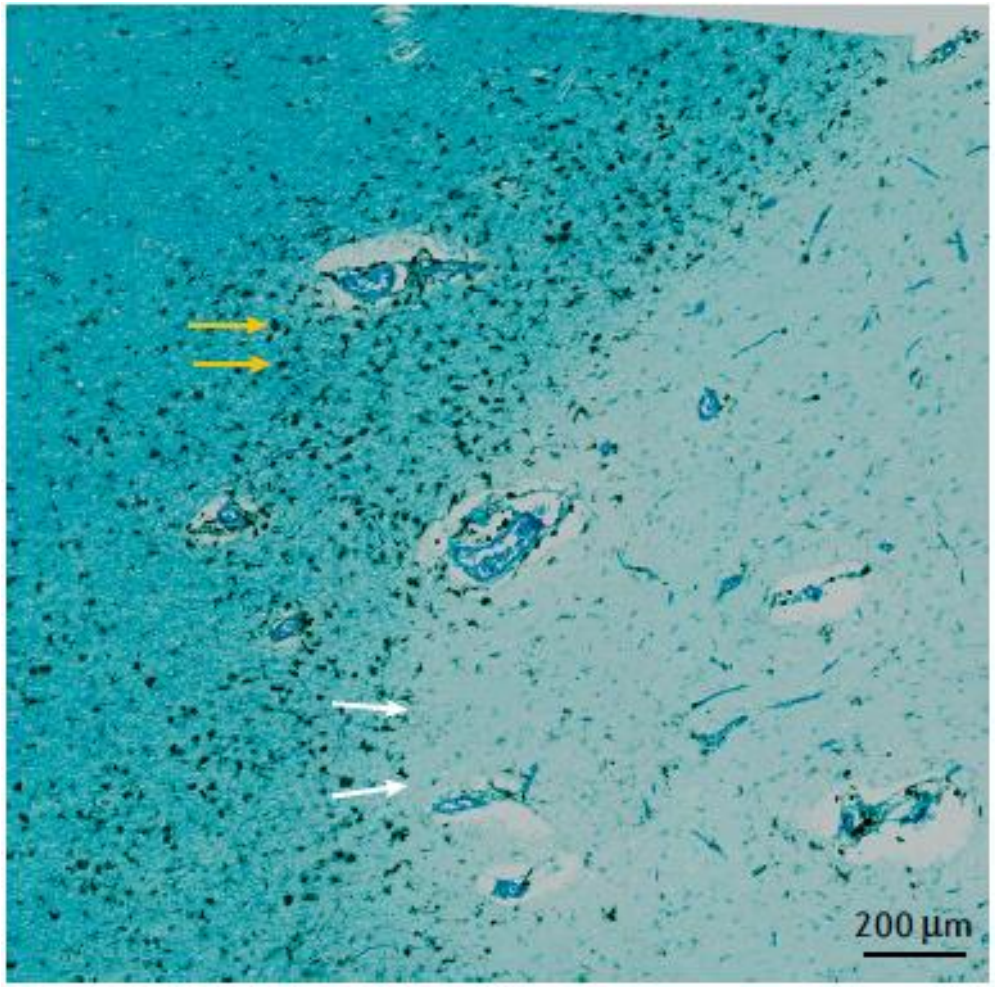
Jordao, Science 2019

Table 1 Sites of microglia activation on MS lesions (Peterson et al. 2001; Kutzelnigg and Lassmann 2014; Calabrese et al. 2015; Kuhlmann et al. 2017) and corresponding potential application of neuroinflammation TSPO-PET tracers

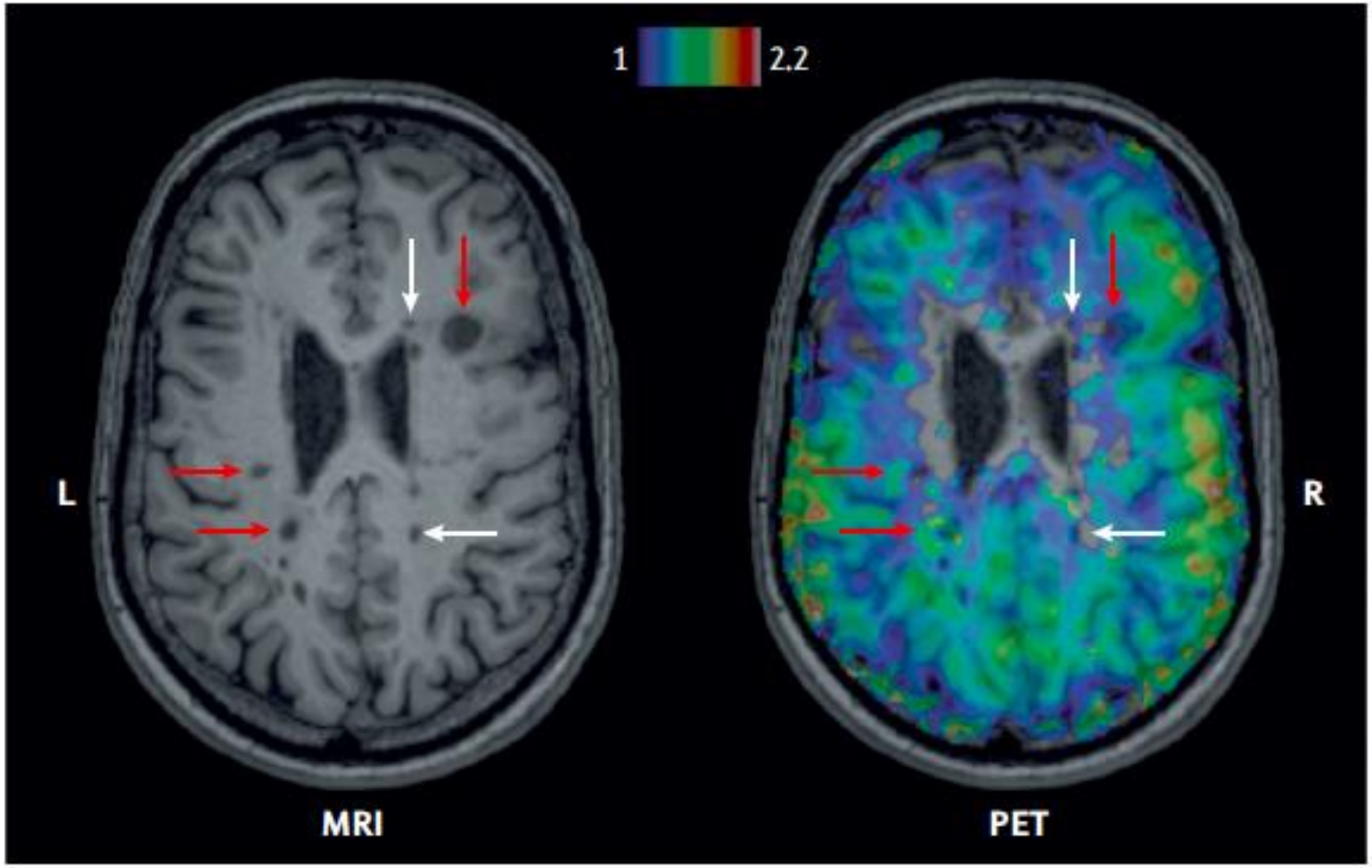
Site	Histopathological features	Corresponding TSPO-PET findings in humans
WM lesions	Active lesions: activated macrophages or microglia throughout the lesions with synchronous myelin destruction. Inactive lesions: lack of microglia or macrophages within the MS lesion Mixed active/inactive lesions: hypocellular core and activated microglia or macrophages at the lesion border. The so-called "smoldering/slowly expanding lesions" are considered a subtype of mixed lesions and are typical in patients affected by progressive forms of MS. (P) reactive lesions: microglial activation prior to the formation of the WM lesions (preactive) or in response to remyelination of older WM lesions (reactive).	Heterogeneous PK11195 uptake pattern within the WM lesions has been described (core versus periphery and lesional vs perilesional (Kaunzner et al. 2019; Datta et al. 2017b; Colasanti et al. 2014)). Lesional and perilesional binding of vinpocetine has been shown to be higher than PK11195 but with small overlap in areas of high uptake between ligands (Park et al. 2015). PK11195, PBR28 and PBR111 uptake pattern has been shown to potentially track disease progression as well response to therapy in RRMS patients (Colasanti et al. 2014; Colasanti et al. 2016; Datta et al. 2017a; Datta et al. 2017b; Datta et al. 2017c; Kaunzner et al. 2017; Kaunzner et al. 2019; Oh et al. 2011; Park et al. 2015).
Non-lesional WM	Activated microglia can be seen in the areas immediately surrounding zones of active demyelination plaques, particularly in progressive forms of MS (periplaque WM, PPWM). This finding is associated with initial myelin loss and apoptosis of oligodendrocytes. In the areas of WM that are distant from plaques, which appear normal on MRI and gross pathology (normal appearing WM, NAWM), diffuse microglial activation and occasionally small microglial nodules has been described.	Increased PK11195 and PBR28 binding has been described in NAWM (Datta et al. 2017b; Rissanen et al. 2014), preceding gadolinium enhancement by 4 weeks (Oh et al. 2011). Enlarging T2 lesion volumes at 1-year MRI follow-up correlated with higher NAWM PBR28 uptake at baseline in RRMS (Datta et al. 2017a).
Lesionals and non-lesionals GM	GM lesions are fewer and usually characterized by lower density of T lymphocytes and microglia or macrophages with respect to WM lesions. However, apoptotic cells are increased, and microglia/macrophages retain an activated morphology irrespective of lesion stage or location of these cells (lesion center versus periphery). These peculiar features of GM lesions might at least partially justify the disproportionately selective GM versus WM atrophy.	Increased non-uniform PK11195 (Politis et al. 2012) and 11C-PBR28 (Herranz et al. 2016) GM binding has been described in MS suggesting the occurrence of neuroinflammation in the cortex. This finding is closely linked to poor clinical outcome and, to a lesser extent, to 7neurodegeneration (Politis et al. 2012; Herranz et al. 2016).

Bauckneht, EJNNMI Radiopharmacy and Chemistry 2019

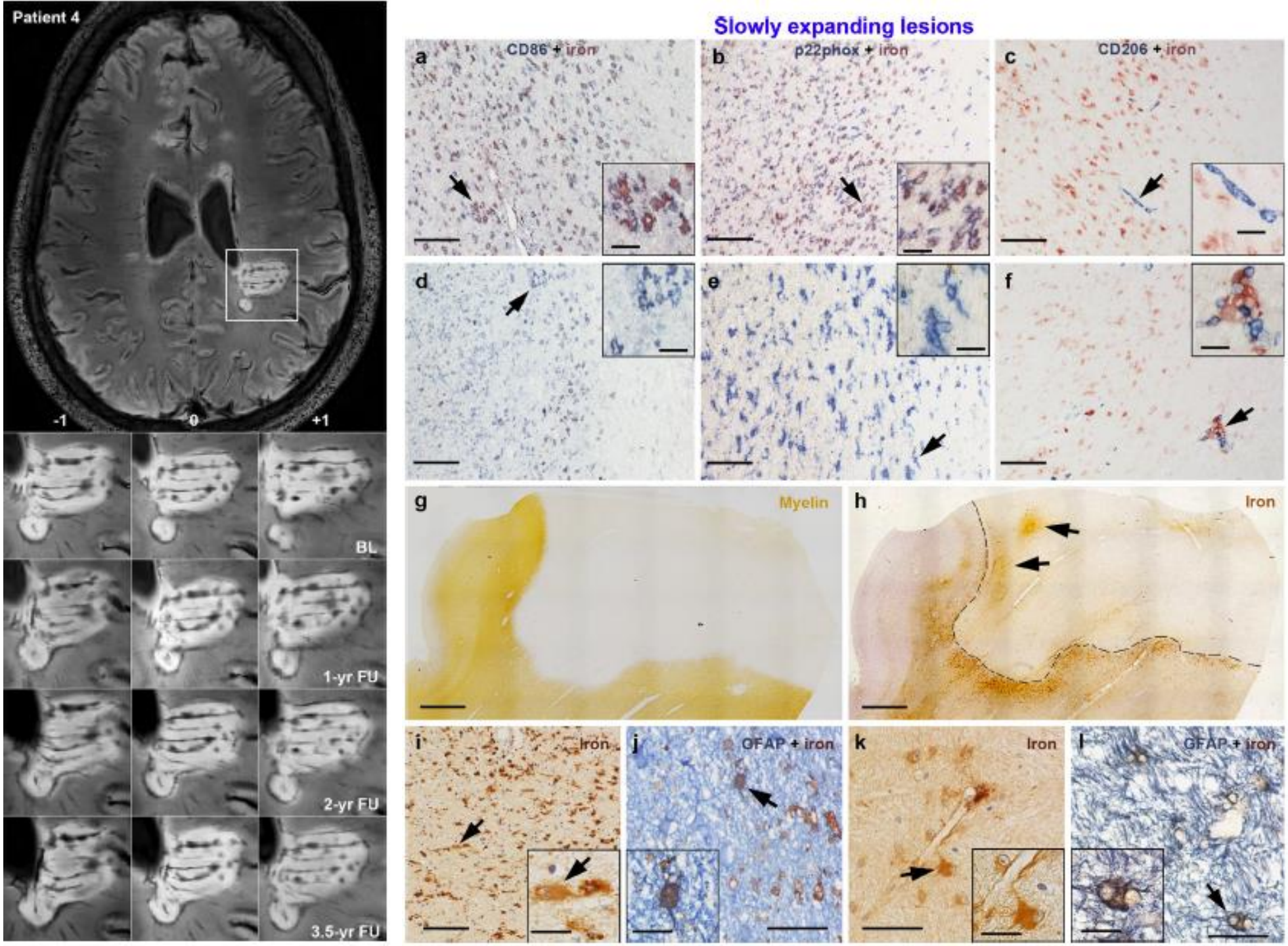
Microglia activation in SPMS



A dense rim of highly activated major histocompatibility complex class II positive microglia (yellow arrows) can be seen around a central demyelinated core (white arrows)



Red arrows indicate chronic lesions with increased microglial activation and higher 11C- PK11195 binding at the lesion edge (mixed active–inactive lesions), and white arrows indicate chronic lesions without notable microglial activation at the lesion edge (chronic inactive lesions)



Dal Bianco, Acta Neuropathol 2017

209 MS patients
107 at least 1 RIM-lesion
>4 RIM-lesions → earlier accrual of cognitive and motor disability

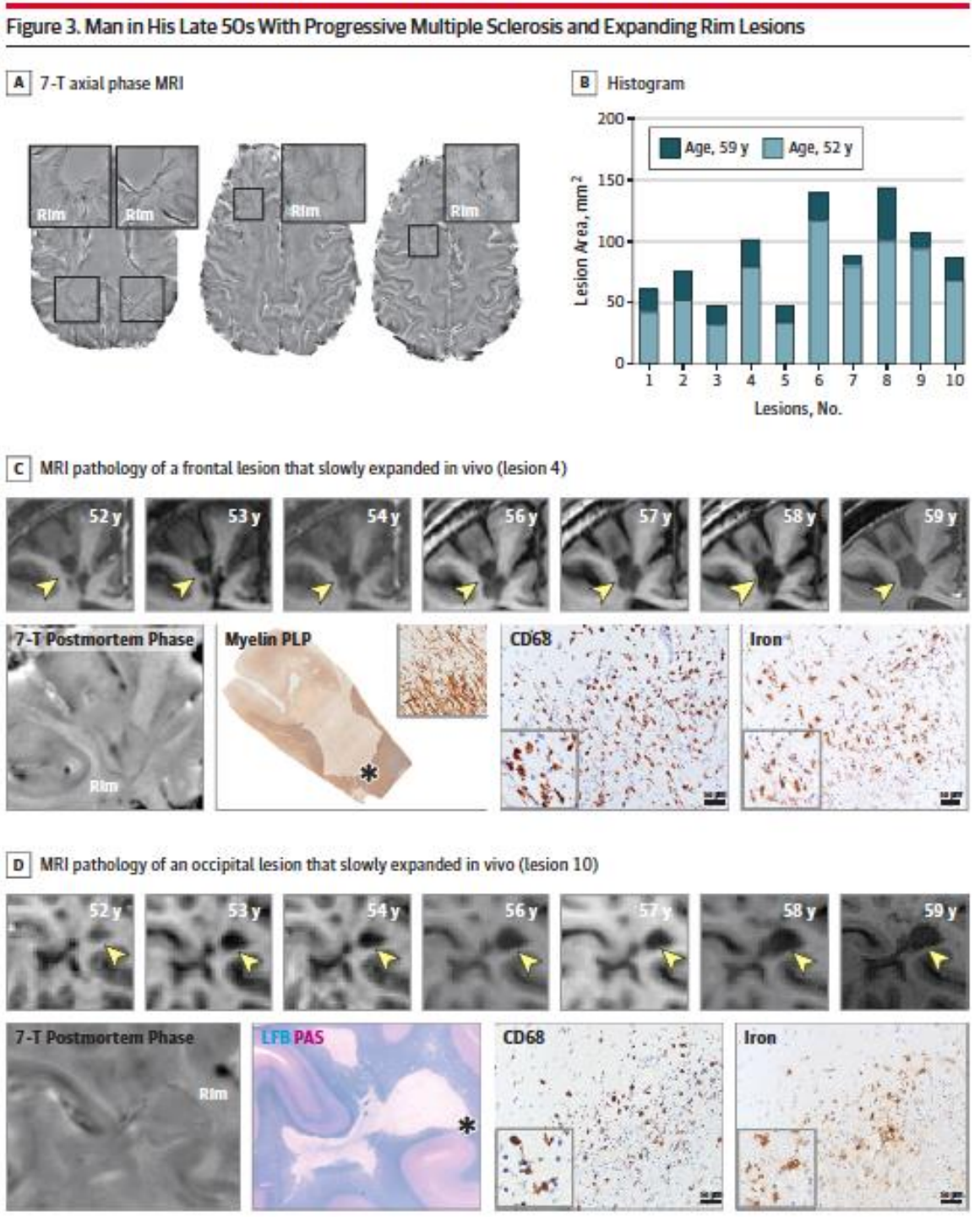
Key Points

Question Are chronic active multiple sclerosis (MS) lesions linked to patient disability and poor long-term lesion outcomes?

Findings In this in vivo cohort study, the association was shown of chronic active/slowly expanding/smoldering MS lesions, which are detectable on high-field susceptibility-based magnetic resonance imaging (MRI) by their characteristic paramagnetic rims, with aggressive disease course and poor clinical outcomes despite approved disease-modifying therapy. Over time, rim lesions do not shrink slowly as other lesions do, but typically remain stable or even enlarge due to ongoing demyelination (confirmed pathologically in one of the patients who later came to autopsy).

Meaning These data provide in vivo evidence that inflammation in chronic active plaques is a prominent feature of MS that is linked to disability accumulation, suggesting a path forward for new susceptibility-based MRI clinical trials to test new types of treatment to ameliorate this process.

Absinta, JAMA Neurol 2019



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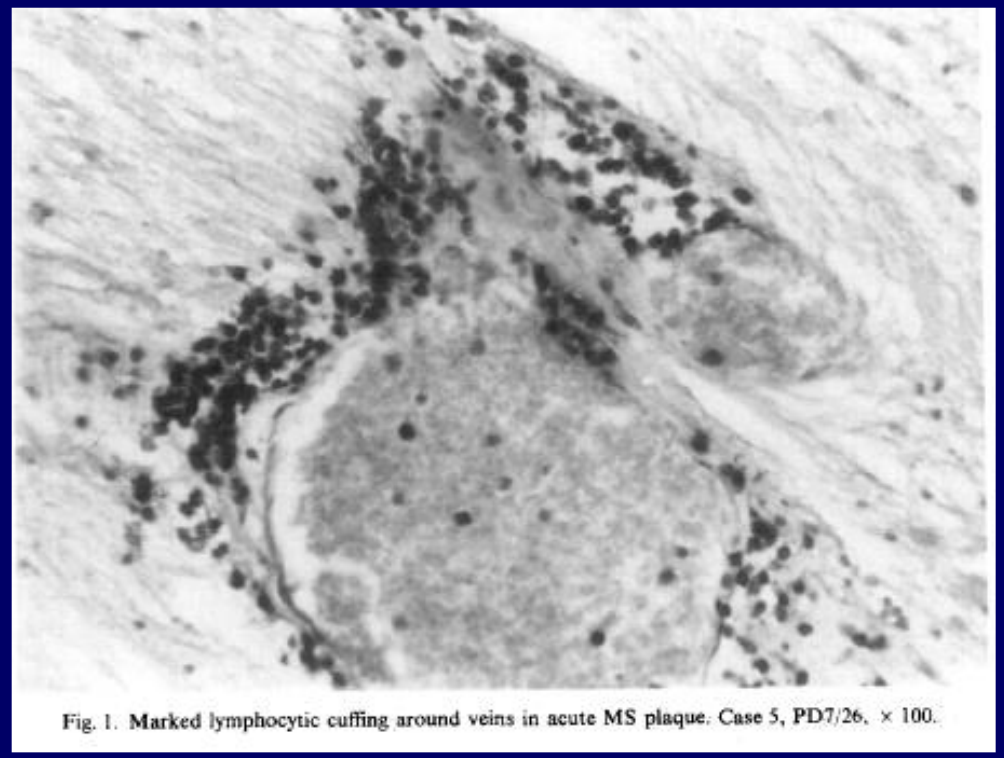


Fig. 1. Marked lymphocytic cuffing around veins in acute MS plaque. Case 5, PD7/26. × 100.

The improved definition of the relation between demyelinating lesions and the intraparenchymal venous system, obtained by use of T2*-weighted magnitude and phase imaging, confirms results of pathological studies showing that many MS plaques form around the microvasculature

Adams CWM J Neurol Sciences 1989

Central Vein Sign Differentiates Multiple Sclerosis from Central Nervous System Inflammatory Vasculopathies

Pietro Maggi, MD, PhD,[1,2,3]* Martina Absinta, MD, PhD,[4,5,6]* Matteo Grammatico, MD,[7] Luisa Vuolo, MD, PhD,[7] Giacomo Emmi, MD, PhD,[8] Giovanna Carlucci, MD, PhD,[9] Gregorio Spagni, MD,[7] Alessandro Barilaro, MD, PhD,[9] Anna Maria Repice, MD,[9] Lorenzo Emmi, MD,[10] Domenico Prisco, MD,[10] Vittorio Martinelli, MD,[5] Roberta Scotti, MD,[11] Niloufar Sadeghi, MD, PhD,[12] Gaetano Perrotta, MD,[1] Pascal Sati, PhD,[4] Bernard Dachy, MD,[2] Daniel S. Reich, MD, PhD,[4] Massimo Filippi, MD,[5,6] and Luca Massacesi, MD[7,9]

A central vessel could be identified in 88% (range: 58-100%) of MS patients and 14% (range:0-50%) of patients with inflammatory vasculopathies (*p* 0.0001)

The separation between the 2 groups based on perivenular lesion frequency was complete (>50% perivenular lesions threshold)

Maggi, Ann Neurol 2018

JAMA Neurology | Original Investigation

Evaluation of the Central Vein Sign as a Diagnostic Imaging Biomarker in Multiple Sclerosis

Tim Sinnecker, MD; Margareta A. Clarke; Dominik Meier, PhD; Christian Enzinger, MD; Massimiliano Calabrese, MD; Nicola De Stefano, MD; Alain Pitiot, PhD; Antonio Giorgio, MD; Menno M. Schoonheim, MD, PhD; Friedemann Paul, MD; Mikolaj A. Pawlak, MD, PhD; Reinhold Schmidt, MD; Ludwig Kappos, MD; Xavier Montalban, MD, PhD; Àlex Rovira, MD; Nikos Evangelou, MD, PhD; Jens Wuerfel, MD; for the MAGNIMS Study Group

Question Is the central vein sign on clinical 3T magnetic resonance imaging a useful biomarker for the diagnosis of multiple sclerosis?

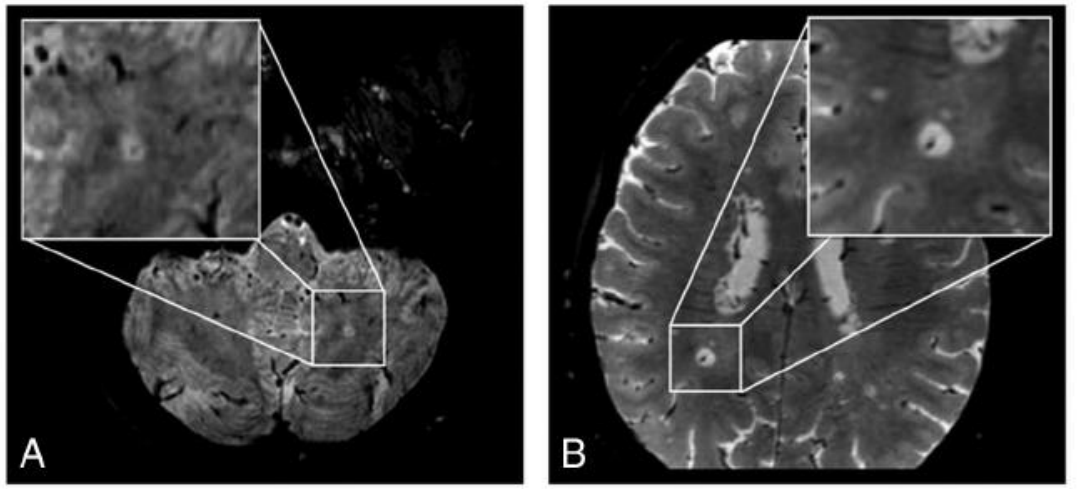
Findings In this multicenter cross-sectional study of 4447 lesions in 606 participants, use of a 35% central vein sign proportion threshold yielded a sensitivity of 68.1% and a specificity of 82.9% for distinguishing multiple sclerosis from non–multiple sclerosis. The criteria of 3 or more central vein sign lesions had a sensitivity of 61.9% and a specificity of 89.0%.

Meaning The 3T central vein sign–based criteria showed a high specificity in the differentiation between multiple sclerosis and non–multiple sclerosis; future studies may be needed to confirm the applicability of this finding to support the diagnosis of multiple sclerosis in clinical practice.

The Central Vein Sign in Radiologically Isolated Syndrome

S. Suthiphosuwan, P. Sati, M. Guenette, X. Montalban, D.S. Reich, A. Bharatha, and J. Oh

MS Diagnostic Criteria Using the CVS	No. of RIS Participants	
	Positive for CVS	Negative for CVS
40% rule	18 (90%)	2 (10%)
Rule of 6	19 (95%)	1 (5%)



CVS may have prognostic value in distinguishing patients with RIS at risk of developing clinical MS from those with white matter lesions of other etiologies

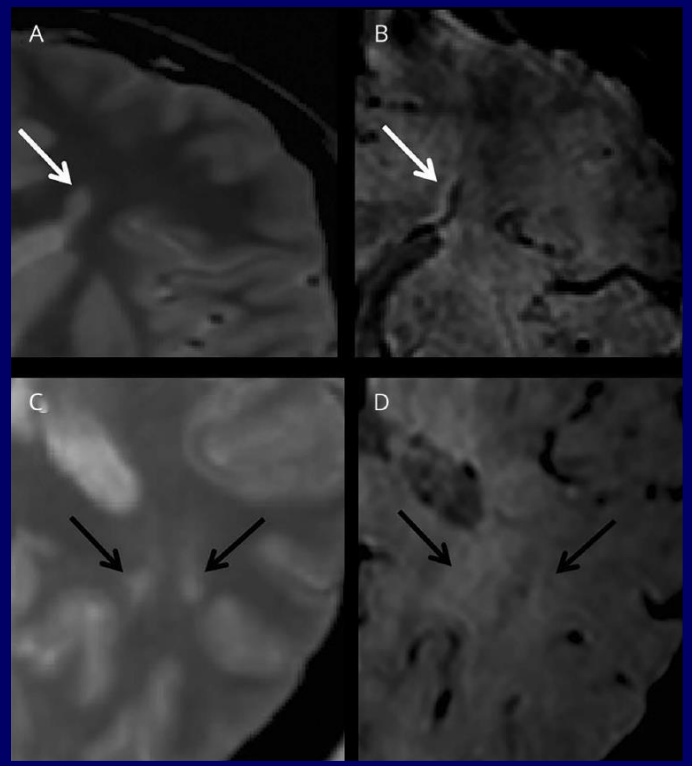
Value of the central vein sign at 3T to differentiate MS from seropositive NMOSD

Rosa Cortese, MD, Lise Magnollay, PhD, Carmen Tur, MD, PhD, Khaled Abdel-Aziz, MRCP, PhD, Anu Jacob, MD, Floriana De Angelis, MD, Marios C. Yiannakas, PhD, Ferran Prados, PhD, Sebastien Ourselin, PhD, Tarek A. Yousry, FRCR, Frederik Barkhof, MD, PhD, and Olga Ciccarelli, FRCP, PhD

Correspondence
Dr. Cortese
r.cortese@ucl.ac.uk

Neurology® 2018;90:e1183-e1190. doi:10.1212/WNL.0000000000005256

18 MS, 18 NMO, 18 HC



Patients with larger number of lesions (>11)

54% cutoff

Sensitivity 94% specificity 100% accuracy 94%

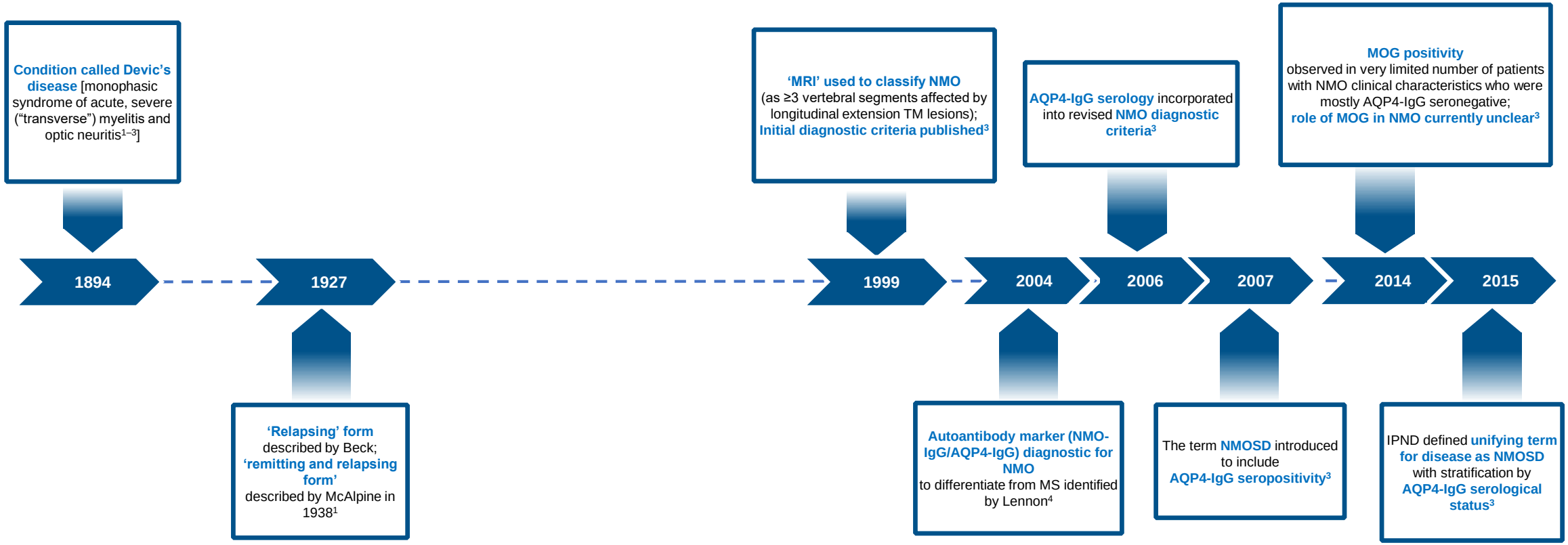
Patients with few lesions (less than 11)

80% cutoff

Sensitivity 50% specificity 93% accuracy 88%

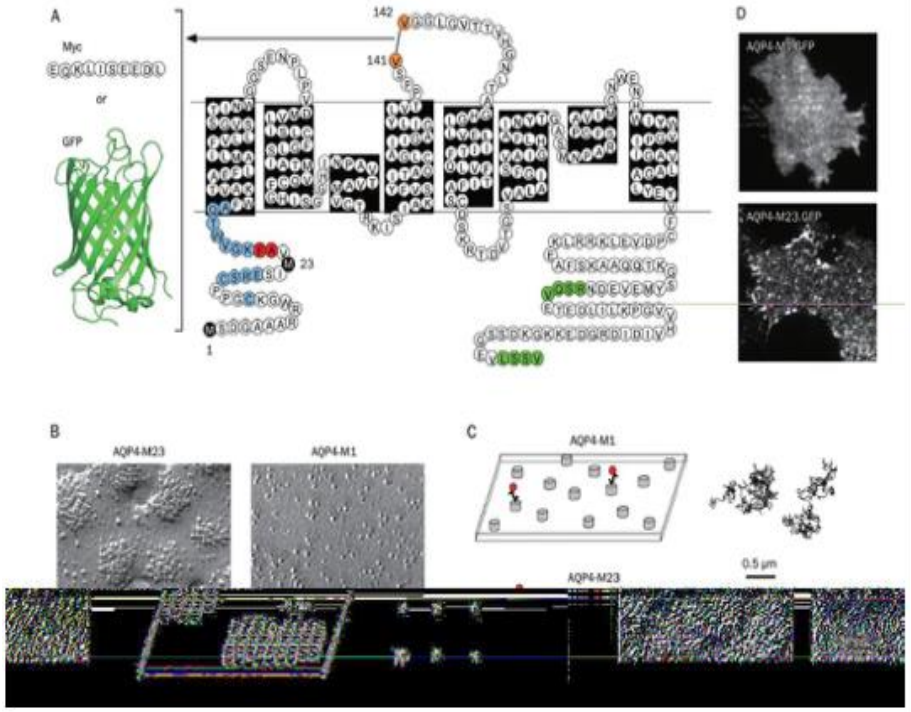
Pick 6 and Pick 3 algorithms were not superior to the 54% cutoff

Sclerosi Multipla: diagnosi differenziale



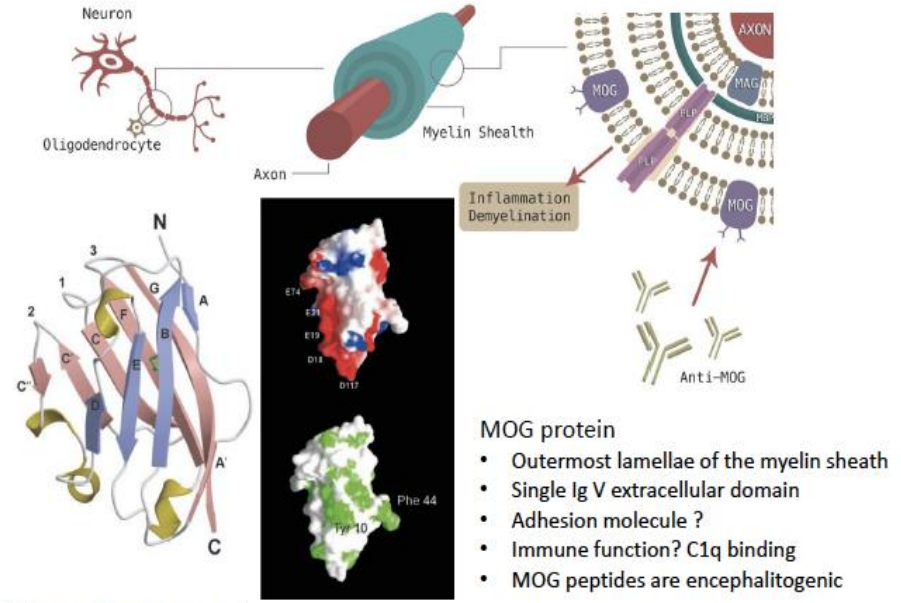
Ag-target and Pathology

AQP-4



Verkman et al. Acta Pharmacol Sin 2011; 32(6):702-710

MOG: Molecule & Localization



MOG protein
- Outermost lamellae of the myelin sheath
- Single Ig V extracellular domain
- Adhesion molecule ?
- Immune function? C1q binding
- MOG peptides are encephalitogenic

(Clements, **PNAS** 2003)

24

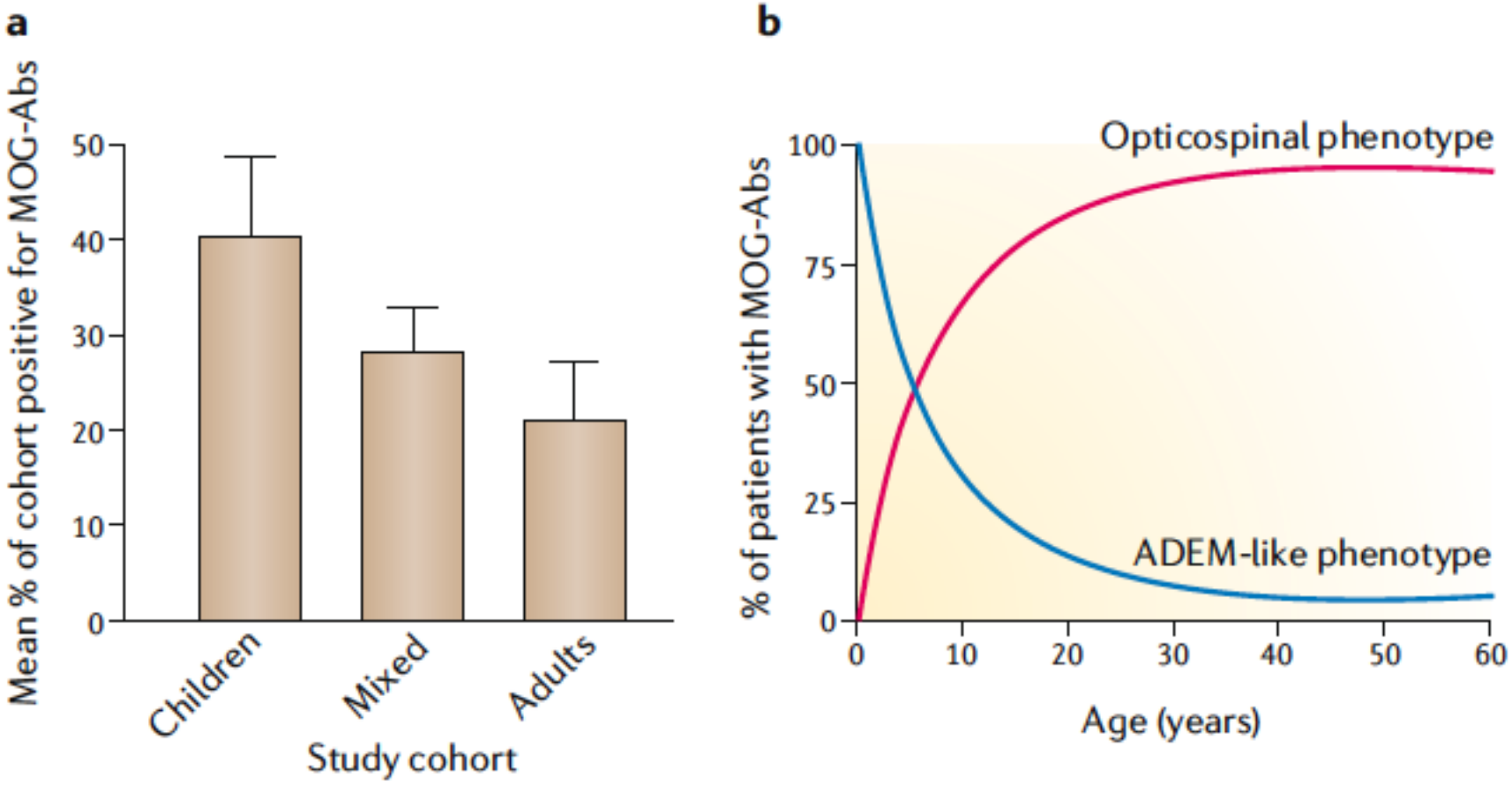
Severe astrocytic damage in AQP4-NMOSD

- Pathogenicity of AQP4 Abs in vitro and in vivo
- Astrocyte pathology in the lesions
- Remarkable high CSF-GFAP during relapse

Severe demyelination in MOG-NMOSD

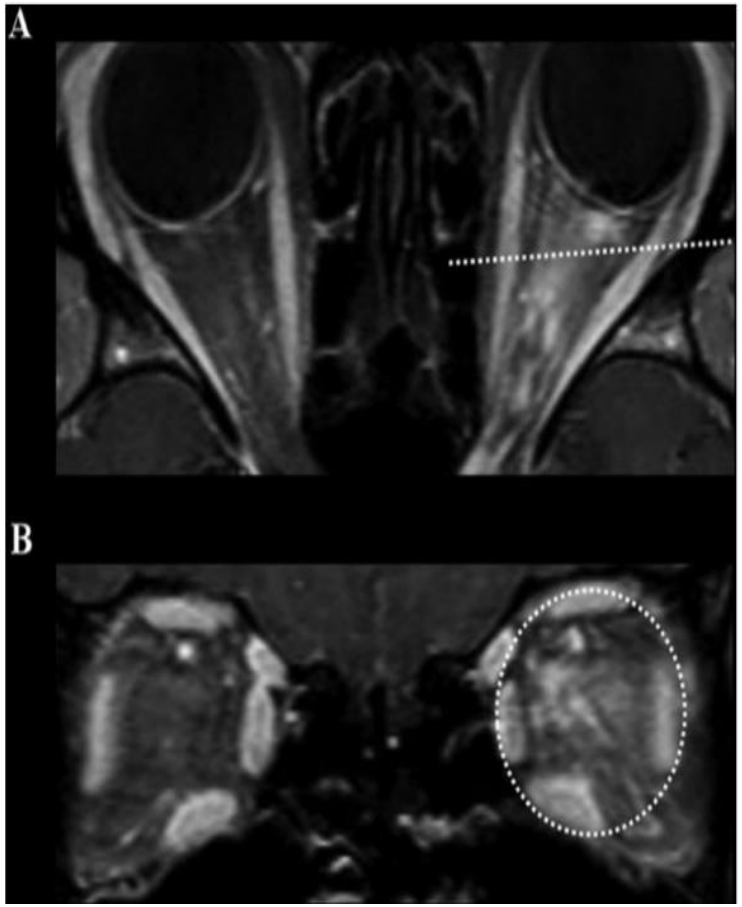
- High CSF-MBP but normal CSF-GFAP during relapse
- Severe demyelinating lesions (MS Type-II)

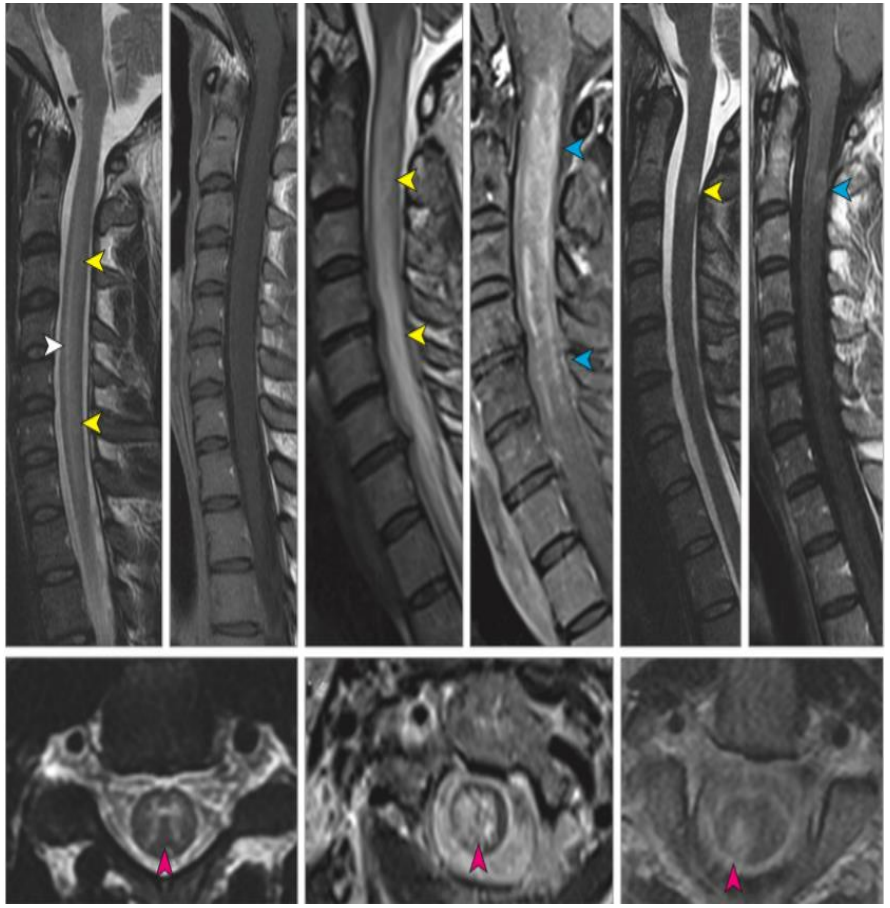
Seroprevalence and clinical presentation associated with anti-MOG Abs



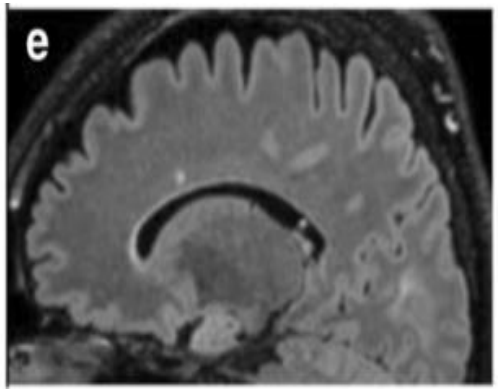
Reindl and Waters, 2019 Nat Rev Neurol

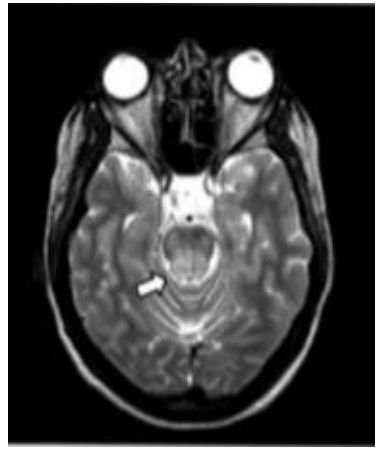
MOGAD, MRI features

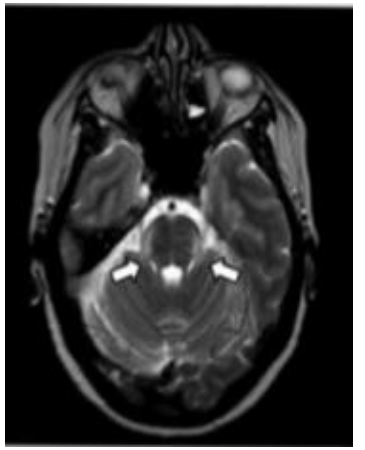


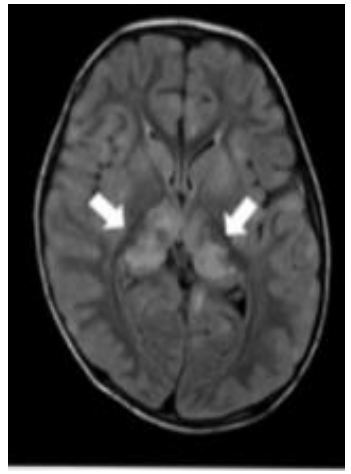


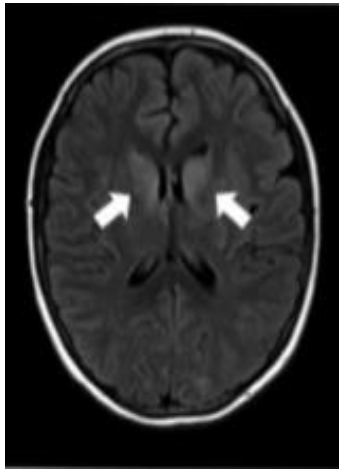
MOG AQP4 MS



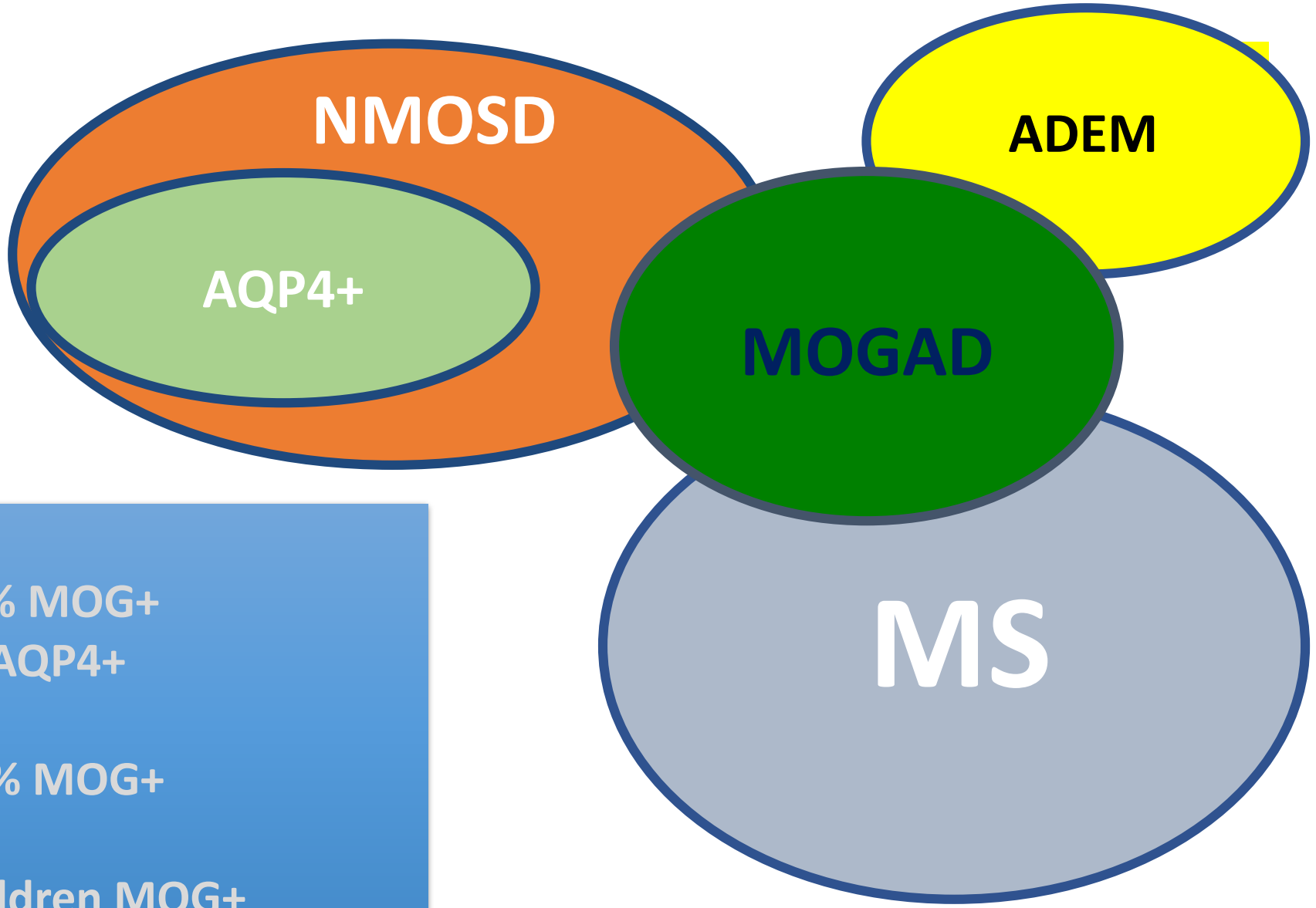








Demyelinating autoimmune diseases, evolving concept



NMOSD:
7-12% MOG+
70% AQP4+

MS-like: 1-2% MOG+

ADEM: > Children MOG+

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  - IFNs e gravidanza
  - Alemtuzumab
  - Natalizumab
  - Siponimod

Nuove autorizzazioni AIFA

Ocrelizumab

- G.U. n.204 del 03-09-2018
- RMS 2ª linea
- PPMS

Cladribina

- G.U. n.65 del 18-03-2019
- RMS 2ª linea, limitatamente ai pazienti che presentino una controindicazione ad almeno uno dei seguenti farmaci: fingolimod, natalizumab e alemtuzumab

Registro AIFA: Sativex

G.U. n 283 del 3-12-2019

- Abolizione Registro
- Istituzione Piano Terapeutico cartaceo (semestrale)

Modifica AIFA RCP: Interferon-β

Gravidanza

Un ampio numero di dati (più di 1.000 gravidanze esposte) derivati da registri e dall'esperienza post-marketing non ha evidenziato un aumento di rischio delle maggiori anomalie congenite a seguito dell' esposizione all 'interferone beta prima del concepimento o durante il primo trimestre di gravidanza. Tuttavia, la durata dell'esposizione durante il primo trimestre è incerta, in quanto i dati sono stati raccolti quando l'uso dell'interferone beta era controindicato durante la gravidanza e il trattamento probabilmente interrotto al rilevamento e/o alla conferma della gravidanza. L'esperienza relativa all' esposizione durante il secondo e terzo trimestre è molto limitata. Sulla base dei dati provenienti da studi condotti sugli animali (vedere paragrafo 5.3), esiste un possibile aumento del rischio di aborto spontaneo. Il rischio di aborto spontaneo nelle donne in gravidanza esposte all'interferone beta non può essere valutato adeguatamente sulla base dei dati attualmente disponibili, ma i dati non suggeriscono finora un aumento del rischio.

Se clinicamente necessario, è possibile considerare l'uso di IFN durante la gravidanza.

Allattamento

Le limitate informazioni disponibili sul passaggio dell'interferone beta-1a nel latte materno, assieme alle caratteristiche chimiche/fisiologiche dell'interferone beta, suggeriscono che i livelli di interferone beta-1a escreti nel latte materno sono trascurabili. Non si prevedono effetti nocivi su neonati/lattanti allattati con latte materno.

IFN può essere utilizzato durante l'allattamento.

Modifica AIFA RCP: Fingolimod

- Nota 2/sett/2019
- A causa del rischio di malformazioni congenite in feti esposti a fingolimod (Gilenya), fingolimod è ora controindicato nelle:
- donne in gravidanza
- donne in età fertile che non usano misure contraccettive efficaci
- I dati post-marketing suggeriscono che neonati nati da madri che erano state esposte a fingolimod durante la gravidanza presentano un aumento del rischio di malformazioni congenite di 2 volte rispetto al tasso osservato nella popolazione generale (2-3 %; EUROCAT).

Note EMA – AIFA: Alemtuzumab

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

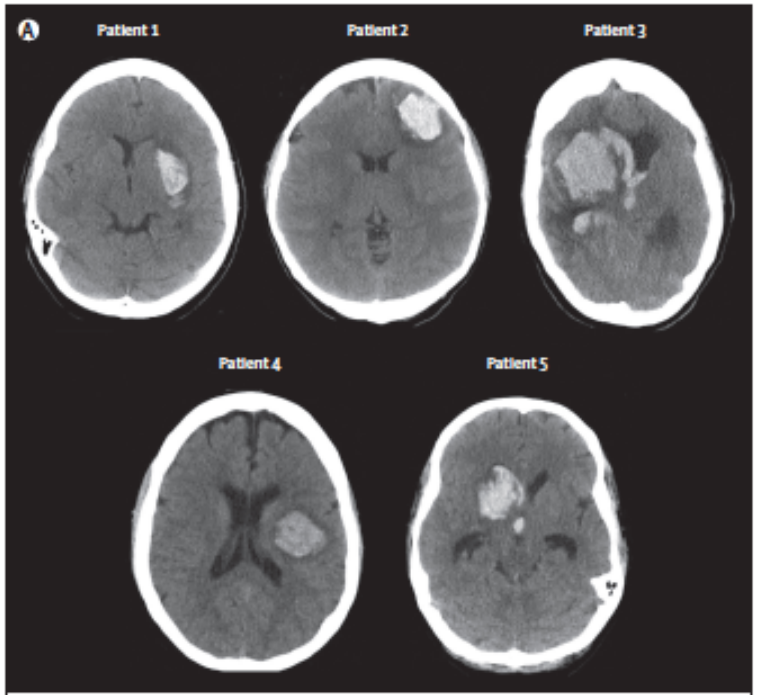
12 April 2019
EMA/220110/2019

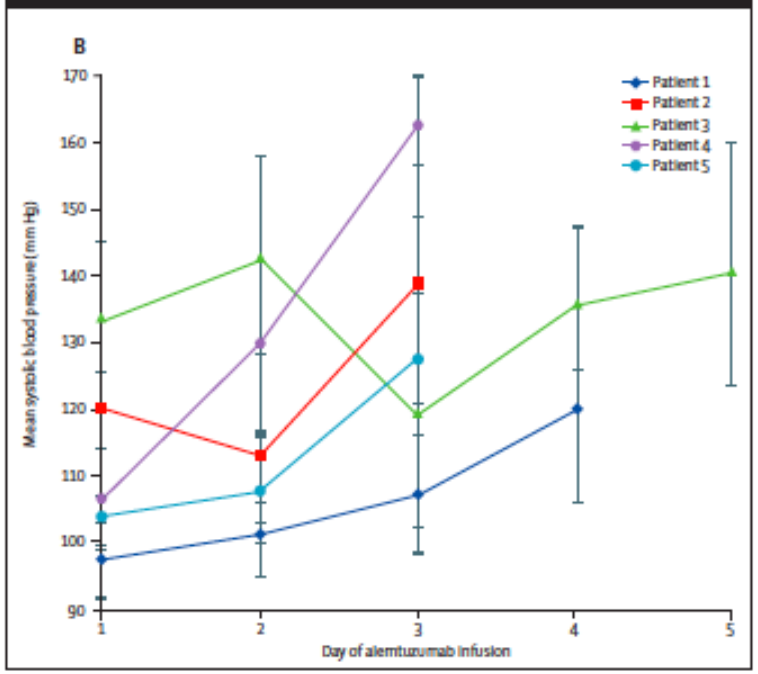
L'uso del medicinale per la sclerosi multipla Lemtrada è stato limitato mentre è in corso una revisione EMA

La revisione da parte del PRAC di alemtuzumab è stata avviata su richiesta della Commissione Europea, ai sensi dell'articolo 20 del regolamento (CE) n. 726/2004.

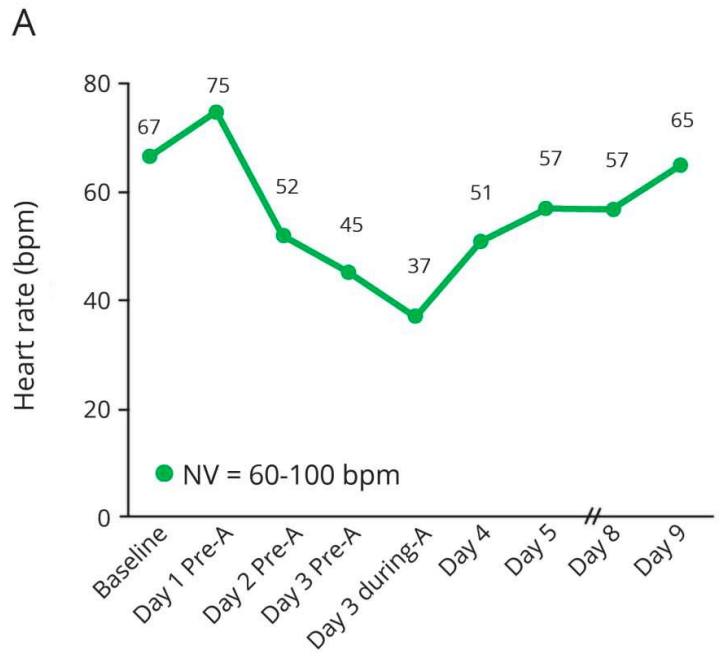
- il trattamento con Lemtrada deve essere avviato solo negli adulti con sclerosi multipla recidivante-remittente altamente attiva nonostante il trattamento con almeno due terapie modificanti la malattia (un tipo di medicinali per la sclerosi multipla) o dove altre terapie modificanti la malattia non possono essere usate

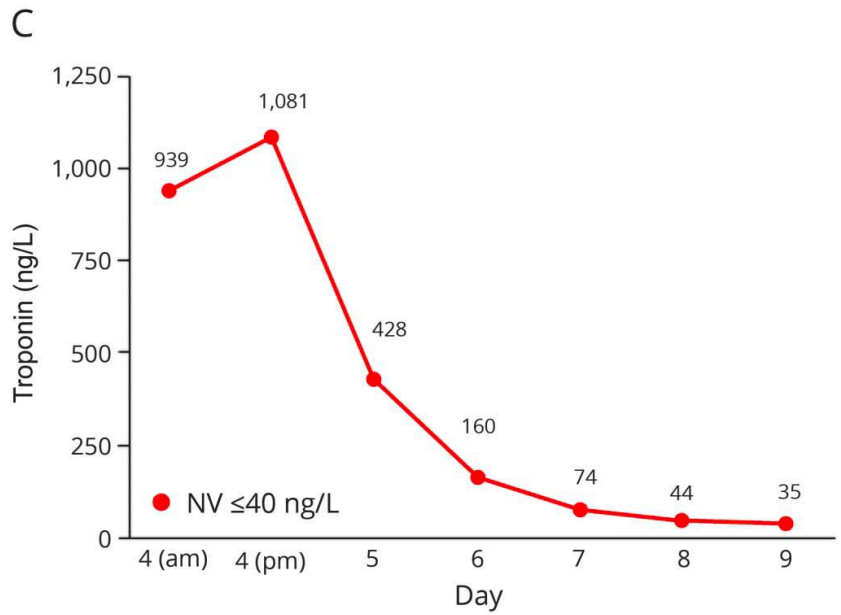
- Malattie autoimmuni: epatite
- Linfoistiocitosi emofagocitica
- IMA, ictus
- Dissecazione TSA
- Alveolite emorragica
- Neutropenia





Azevedo, Lancet Neurol 2019





Ferraro, Neurology 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2019
EMA/609015/2019

Misure per minimizzare il rischio di gravi effetti collaterali per il medicinale della sclerosi multipla Lemtrada

Alemtuzumab: restrizioni d'uso

Lemtrada ora deve essere usato come terapia singola modificante la malattia negli adulti con sclerosi multipla recidivante remittente con:

- malattia altamente attiva nonostante un ciclo completo e adeguato di trattamento con almeno una terapia modificante la malattia o
- malattia grave in rapida evoluzione definita da 2 o più recidive disabilitanti in un anno e con 1 o più lesioni captanti il gadolinio alla Risonanza Magnetica cerebrale o un aumento significativo del carico lesionale in T2 rispetto a una recente Risonanza Magnetica.

Oltre alle attuali controindicazioni, Lemtrada è ora controindicato anche in:

- infezioni attive gravi fino alla completa risoluzione
- ipertensione incontrollata
- storia di angina pectoris, infarto del miocardio, ictus o dissezione delle arterie cervicocefaliche
- coagulopatia, su terapia antipiastrinica o anti-coagulante
- malattie autoimmuni concomitanti diverse dalla sclerosi multipla

Modifica AIFA RCP: Natalizumab

RCP Paragrafo 4.4

- Nei pazienti positivi per gli anticorpi anti-JCV, è stato suggerito che l'estensione dell'intervallo fra le dosi di TYSABRI (intervallo di somministrazione medio di circa 6 settimane) comporta una riduzione del rischio di PML rispetto alla posologia approvata.
- Se si utilizza l'estensione dell'intervallo fra le dosi, è necessaria cautela perché l'efficacia dell'estensione dell'intervallo fra le dosi non è stata stabilita e il rapporto beneficio-rischio associato è attualmente sconosciuto.

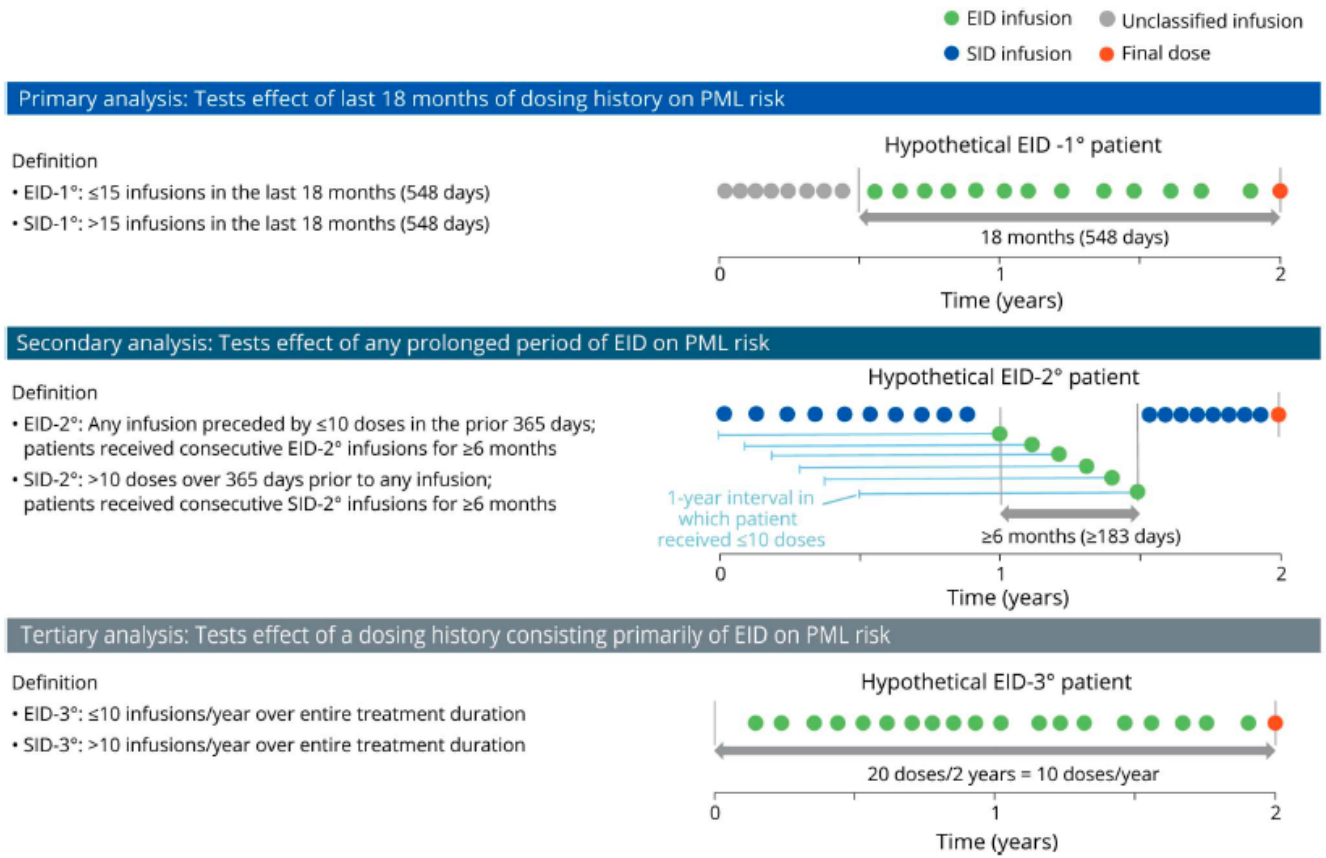
RCP Paragrafo 5.1

- In un'analisi pre-specificata, retrospettiva, di pazienti statunitensi trattati con TYSABRI e positivi per gli anticorpi anti-JCV (registro TOUCH), è stato confrontato il rischio di PML tra pazienti trattati con la posologia approvata e pazienti trattati con l'estensione dell'intervallo fra le dosi (EID, intervalli di trattamento medi di circa 6 settimane), identificati negli ultimi 18 mesi di esposizione. La maggioranza (85%) dei pazienti trattati con EID aveva ricevuto la posologia approvata per ≥1 anno prima del passaggio a EID. L'analisi ad interim ha mostrato un più basso rischio di PML in pazienti trattati con EID (hazard ratio = 0,06 95% CI dell'hazard ratio = 0,01-0,22). L'efficacia della somministrazione di TYSABRI con EID non è stata stabilita e quindi il rapporto beneficio-rischio dell'EID non è noto (vedere paragrafo 4.4).
- È stato costruito un modello per valutare l'efficacia nei pazienti che passano a somministrazioni estese dopo ≥1 anno di trattamento con la posologia approvata di TYSABRI e che non hanno presentato recidive nell'anno precedente al passaggio. Gli attuali modelli statistici e la simulazione di farmacocinetica/farmacodinamica indicano che per i pazienti che passano all'estensione dell'intervallo fra le dosi il rischio di attività di malattia della SM può essere maggiore in quelli con peso corporeo >80 kg o con intervalli di trattamento ≥7 settimane. Non sono stati completati studi clinici prospettici per convalidare questi dati.

Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing.

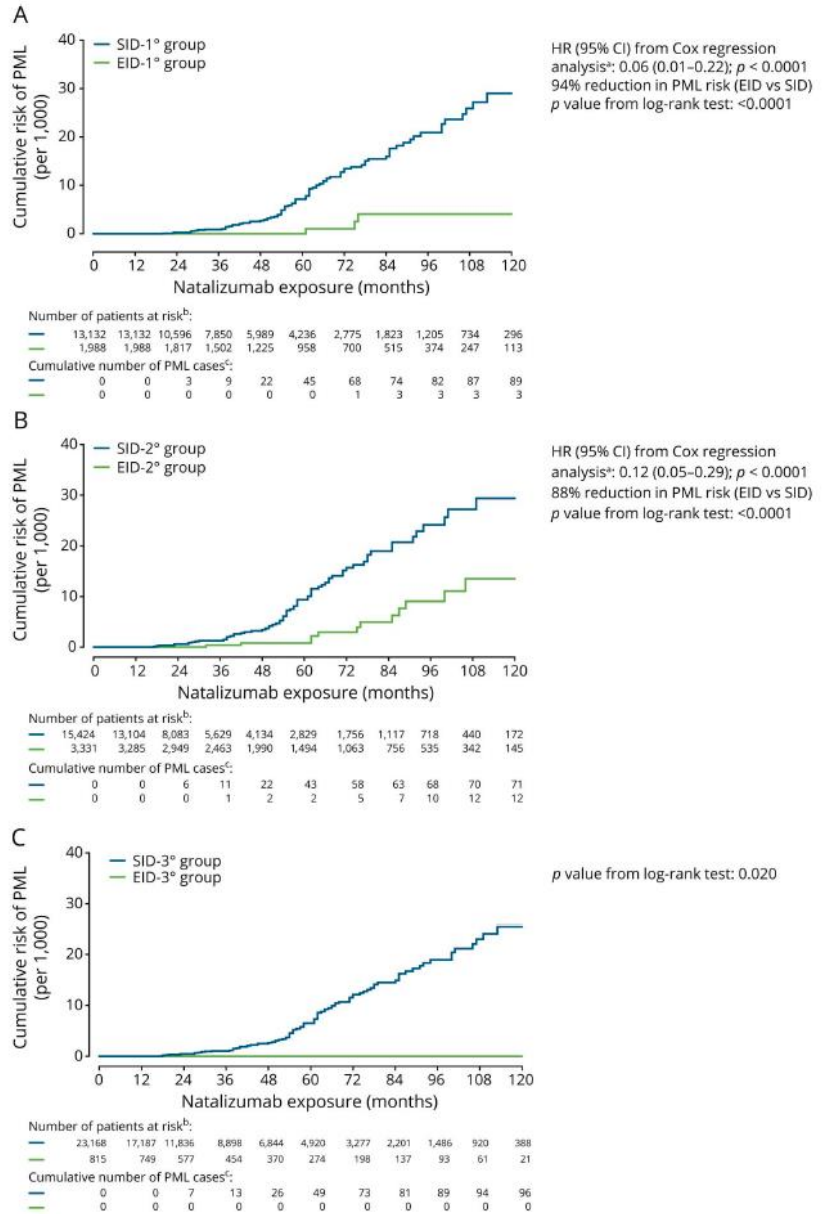
Ryerson et al, Neurology 2019

Figure 1 Descriptions of the 3 planned analyses of PML risk and the definitions of EID and SID used in this study



Each hypothetical patient dosing diagram depicts 2 years of infusion history. EID = extended interval dosing; PML = progressive multifocal leukoencephalopathy; SID = standard interval dosing.

Figure 3 Kaplan-Meier estimates of the cumulative probability of PML in EID vs SID groups in the (A) primary, (B) secondary, and (C) tertiary analyses



CI = confidence interval; EID = extended interval dosing; HR = hazard ratio; PML = progressive multifocal leukoencephalopathy; SID = standard interval dosing. [a]EID vs SID. Model includes age, sex, prior use of immunosuppressants, EID/SID group, and calendar year at the start of natalizumab treatment as covariates. The Cox regression analysis could not be performed for the tertiary analysis because no cases of PML occurred in the EID-3° group. [b]Number of patients who were still in the study and did not have PML at the end of the specified time. [c]Cumulative number of cases of PML at the end of the specified time.

The NOVA trial (phase IIIb)

RW data indicate that EID is not inferior to SID in terms of efficacy

Grimaldi, MSJ 2012
Clerico, Neurotherapeutics 2019
Patti, SIN 2018
Ruggieri, ECTRIMS 2019
Butzkueven, ECTRIMS 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 November 2019
EMA/CHMP/596356/2019
Committee for Medicinal Products for Human Use (CHMP)

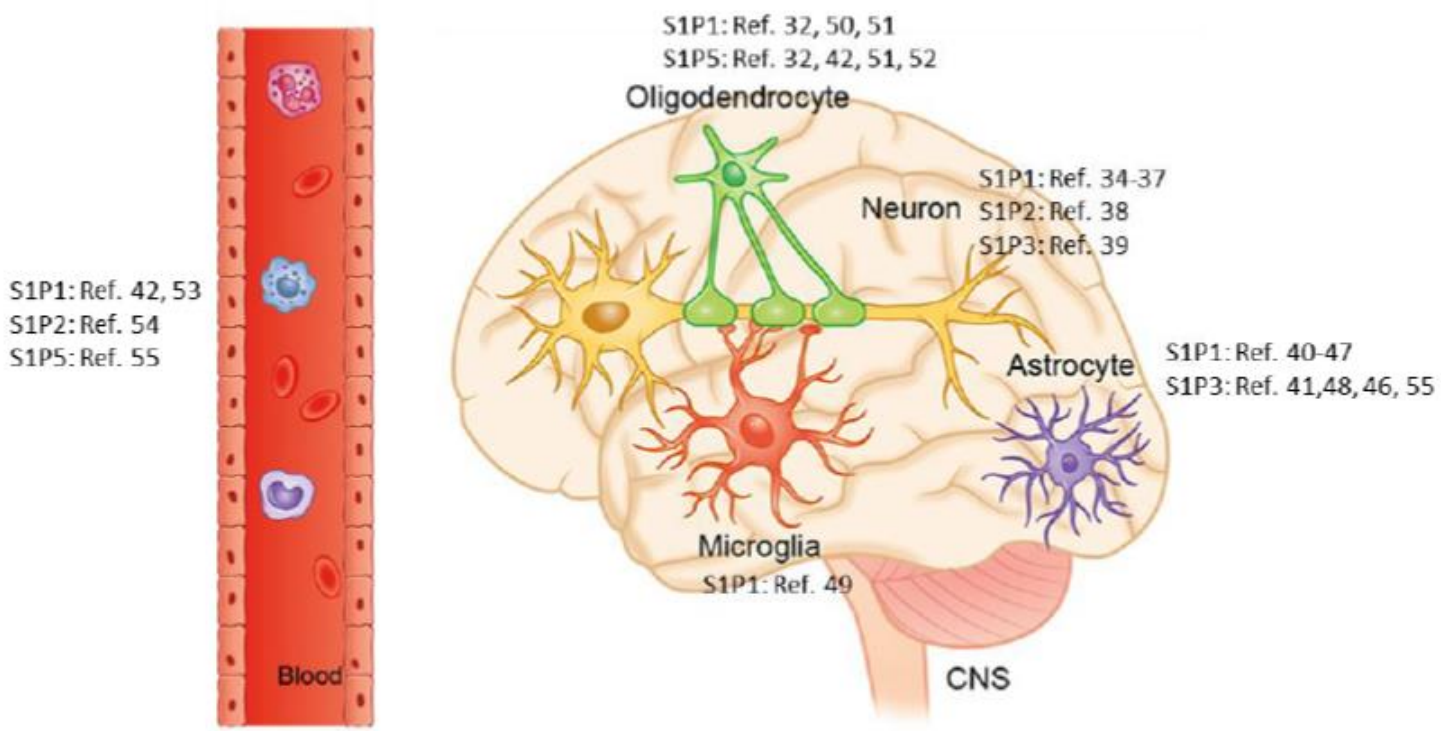
Summary of opinion[1] (initial authorisation)

Mayzent

siponimod

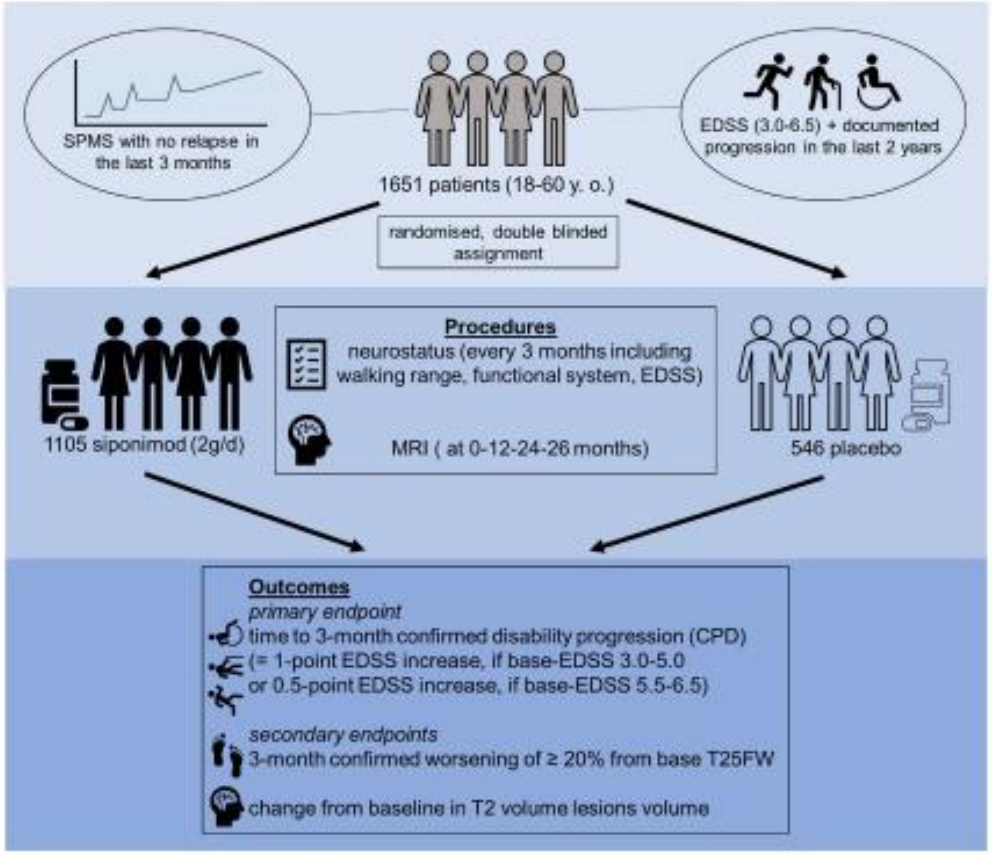
On 14 November 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Mayzent, intended for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease. The applicant for this medicinal product is Novartis Europharm Limited.

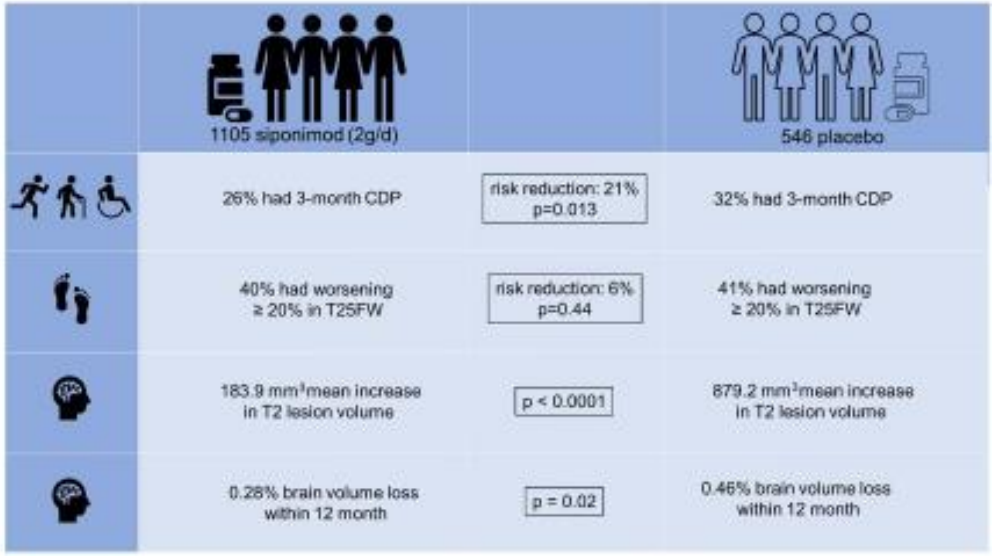
Siponimod (S1P1 and S1P5 functional antagonism): possible «central» MoA and the EXPAND trial



Continuous intracerebroventricular infusion in EAE:

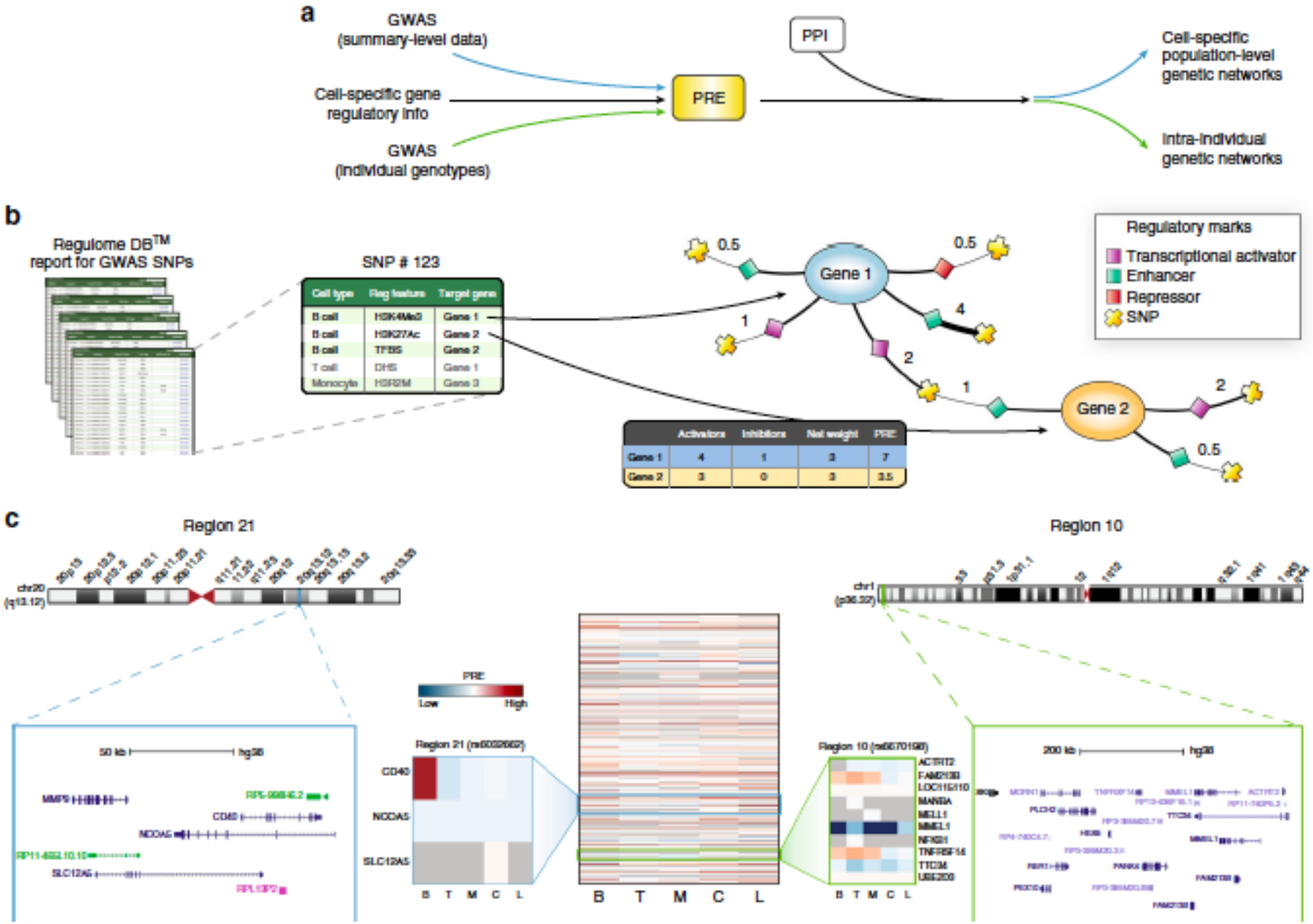
1. astrocytosis and microgliosis as well as neuronal loss were less severe
2. IL6 secretion was ameliorated in cultured microglia
3. decreases oligodendrocyte loss and demyelination in the cuprizone model





Conclusioni

- Patogenesi: dalla periferia al centro e viceversa
- Nuove metodiche RM implementabili nella clinica
- Allargamento dello spettro delle malattie demielinizzanti
- Importanza del post-marketing
- Inizio di una nuova era: terapia per le forme progressive



Lohith Madireddy, International Multiple Sclerosis Genetic Consortium, 2019 Nat Comm

Neurological Sciences
https://doi.org/10.1007/s10072-019-03959-4

ORIGINAL ARTICLE

Four cases of natalizumab-related PML: a less severe course in extended interval dosing?

Cristina Scarpazza[1,2] · Nicola De Rossi[1] · Giulietta Tabiadon[3] · Maria Vittoria Turrini[1] · Simonetta Gerevini[4] · Ruggero Capra[1]

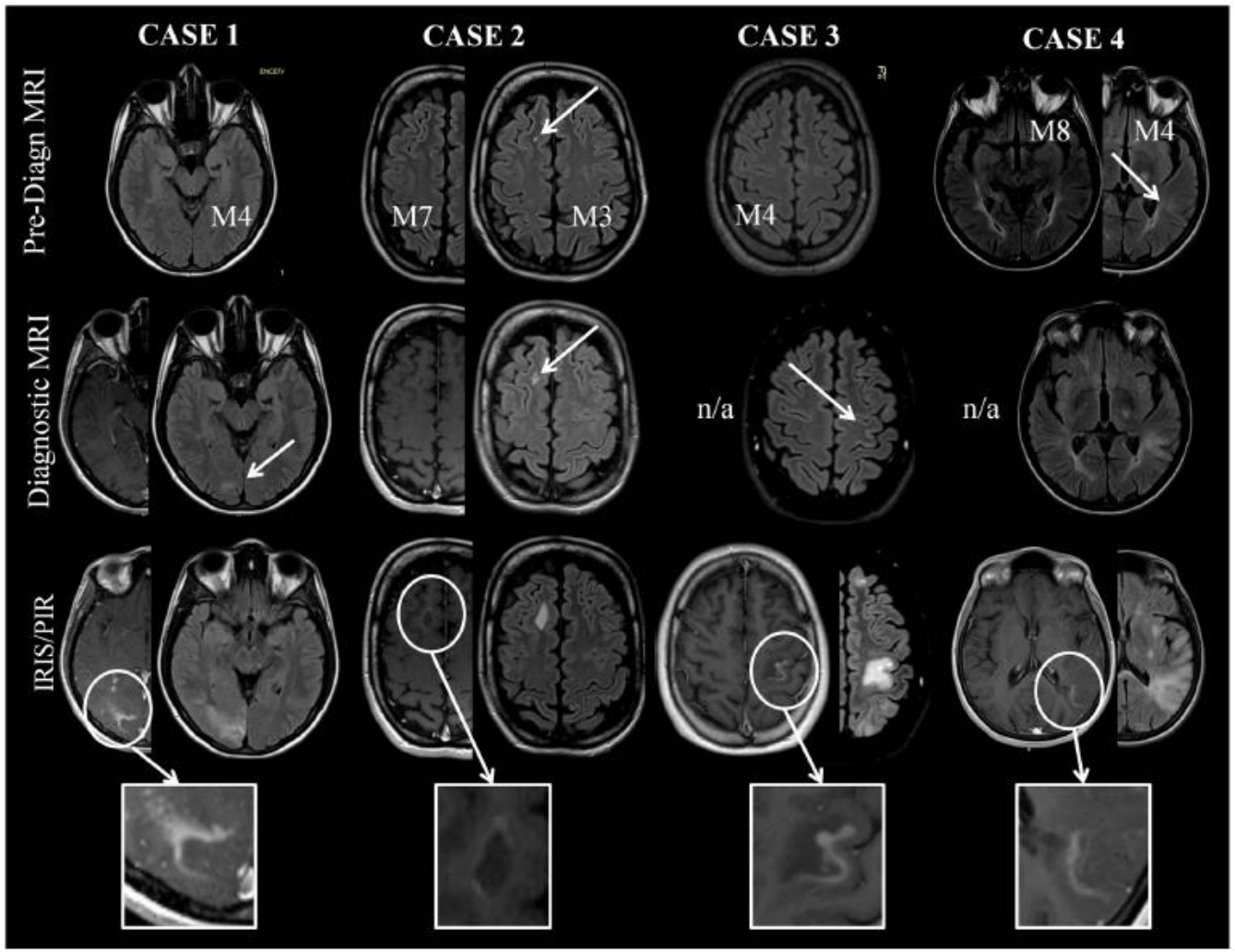


Table 1 Demographic and clinical data of the four Italian cases and the cases described in literature

	Case 1	Case 2	Case 3	Case 4	Hervas [7]	Baldassari [9]
Age at PML onset	29	48	33	46	51	53
Gender	♀	♀	♂	♀	♂	♂
Diagnostic delay (months)	0	3	0	4	3	12
Number of NTZ total infusions	74	50	47	38	55**	77**
Number of NTZ infusions in extended dose	22	9	26	22	9**	17**
Extended dose interval (weeks)	7	6	5.5	6	6	6
Prior immune suppression	No	No	No	No	No	n/a
Prior DMT	Interferon fingolimod	Interferon fingolimod	Glatiramer acetate	Interferon fingolimod	Drug-naïve	n/a
Reason for therapy switching to NTZ	Inefficacy	Inefficacy	Inefficacy	Inefficacy	n/a	n/a
JCv index prior to PML onset	3	3.18	2.3	3.13	3.19	2.8
MRI lesion at PML onset	Occipital	Frontal	Frontal (rolandic)	Temporoparietal	Frontal (Broca area)	Frontoparietal
Lesion volume (mm3)	975	554	309	4781	n/a	n/a
JCv DNA copies at PML onset/ml	0	0	0	37	20	10
Symptoms at PML onset	No	No	Motor impairment of the right hand	Very mild anomia*	Aphasia	Paresthesia, aphasia
Anatomo-clinical correlation	n/a	n/a	Yes	Yes	Yes	Yes
EDSS at NTZ beginning	2	3	4	6	3	n/a
EDSS at PML onset	1.5	3	4	6	3**	n/a
Therapies after PML diagnosis	None	None	None	None	Plasma exchange, cidofovir, mirtazapine, mefloquine, proST	Plasma exchange, maraviroc, mirtazapine
Full-blown PML-IRIS	Yes	No	Yes	Yes	Yes	Yes
Symptoms of IRIS	Phosphenes*	n/a	Worsening of the movement of the right hand + hemianopia	Clear aphasia (both production and comprehension)	"Condition deteriorated"	Aphasia worsened
Time from last NTZ and IRIS onset (days)	110	n/a (118)	90	77	30**	30**
Time from PML onset to last follow-up (months)	12	12	12	7	9	n/a
EDSS at last follow-up	2	3	5	6	6	3.0
ΔEDSS	0.5	0	1	0	3**	n/a
Functional outcome	Occasional phosphenes	No impairment	Impaired writing abilities	Mild anomia	n/a	n/a
Post-PML therapy	Glatiramer acetate (GA) for 1 year. Then, rituximab	Glatiramer acetate from 2 years	Glatiramer acetate from 2 years	None so far	n/a	n/a
Number of relapses with the new therapy	1 during GA	2	2	n/a	n/a	n/a

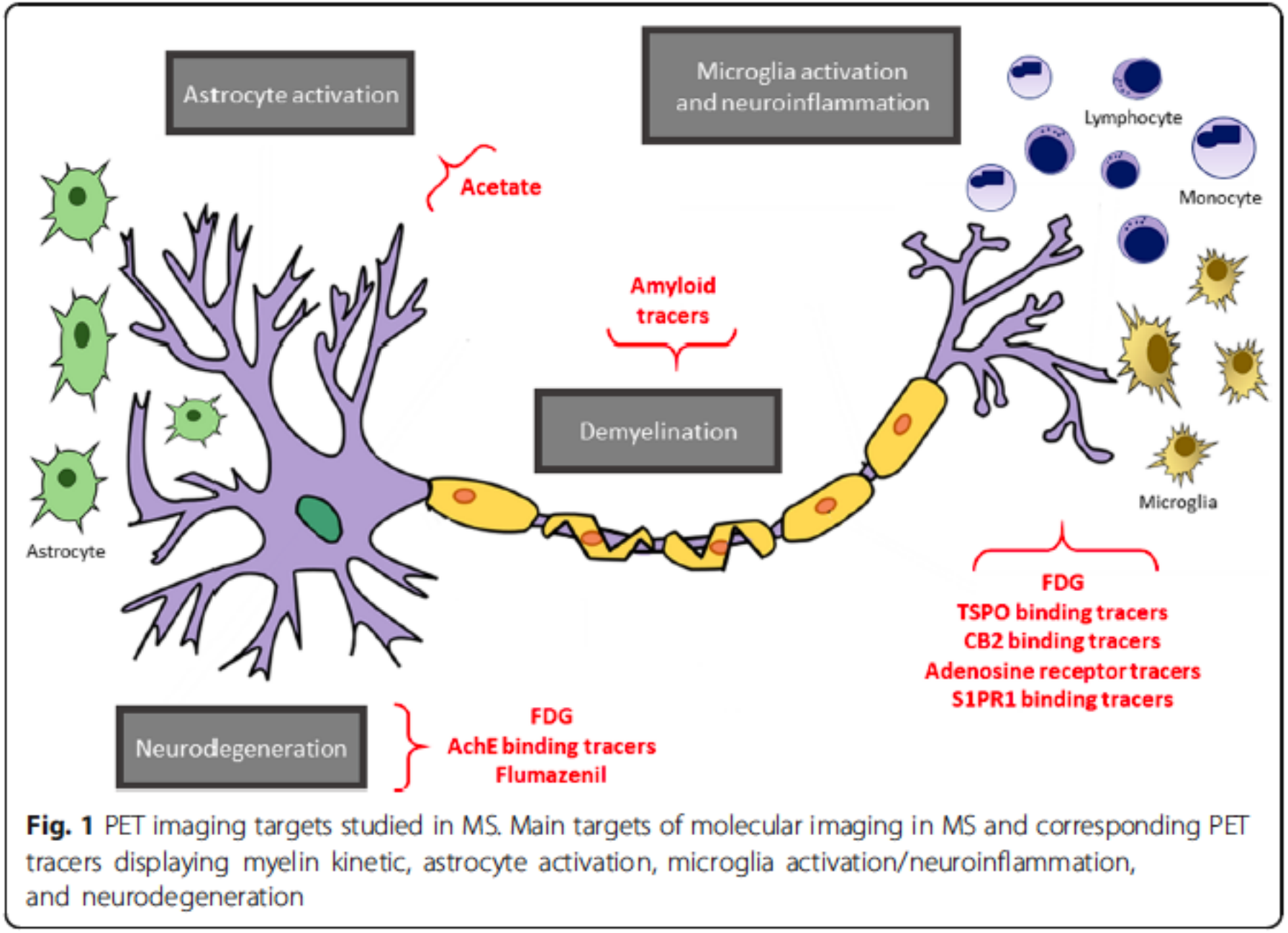


Fig. 1 PET imaging targets studied in MS. Main targets of molecular imaging in MS and corresponding PET tracers displaying myelin kinetic, astrocyte activation, microglia activation/neuroinflammation, and neurodegeneration

Baucknecht, EJNNMI Radiopharmacy and Chemistry 2019

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 November 2019
EMA/CHMP/596356/2019
Committee for Medicinal Products for Human Use (CHMP)

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siponimod

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Mayzent will be available as 0.25 mg and 2 mg film-coated tablets. The active substance of Mayzent is siponimod, a selective immunosuppressant (ATC code: L04AA42) acting as a sphingosine 1-phosphate (S1P) receptor modulator. Siponimod binds selectively to two out of five receptors for S1P, namely S1P1 and S1P5. By acting as a functional antagonist on S1P1 receptors on lymphocytes, siponimod prevents the egression from lymph nodes, reducing the recirculation of T-cells into the central nervous system and limiting central inflammation.

The benefits with Mayzent are its ability to reduce disability progression in active SPMS patients. The most common side effects are headache, hypertension and increased liver enzyme levels.

The full indication is: "treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity (see section 5.1)". It is proposed that Mayzent be prescribed by physicians experienced in the treatment of multiple sclerosis.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

[1] Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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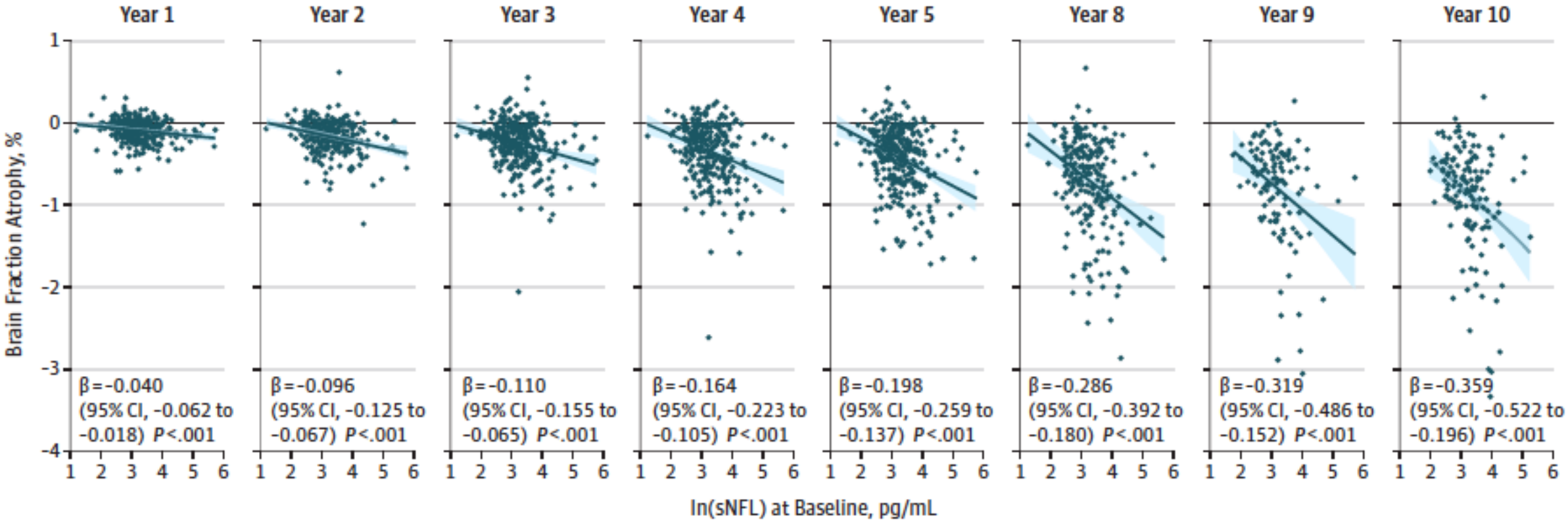
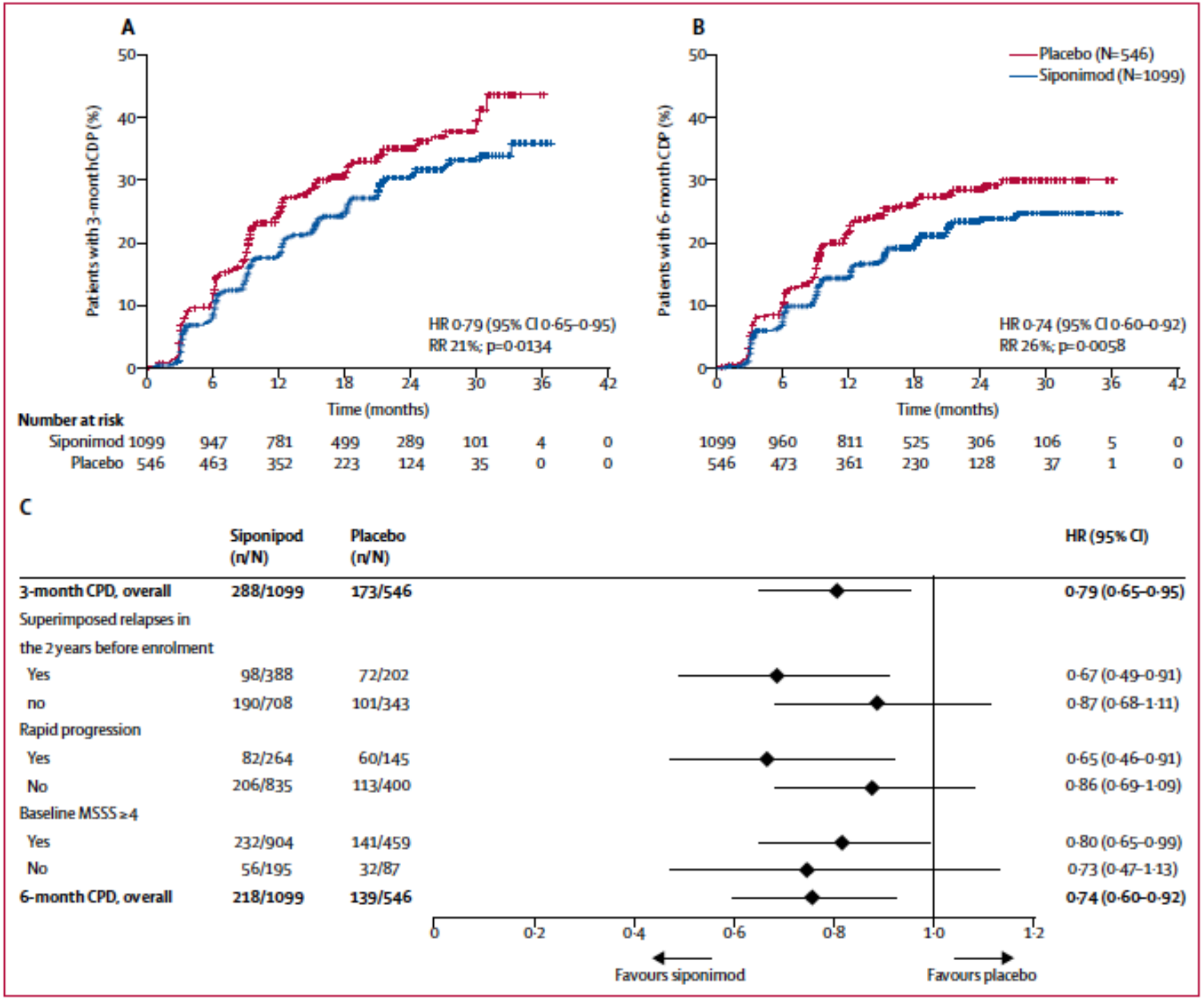
Figure 2. Association of Serum Neurofilament Light Chain (sNFL) Level at Baseline With Percentage of Brain Fraction Change Over Time



In a multivariable model including age, disease duration, and sex, baseline sNFL levels were significantly associated with the percentage of brain fraction change across time.

Canto', JAMA Neurol 2019



Kappos, Lancet 2019

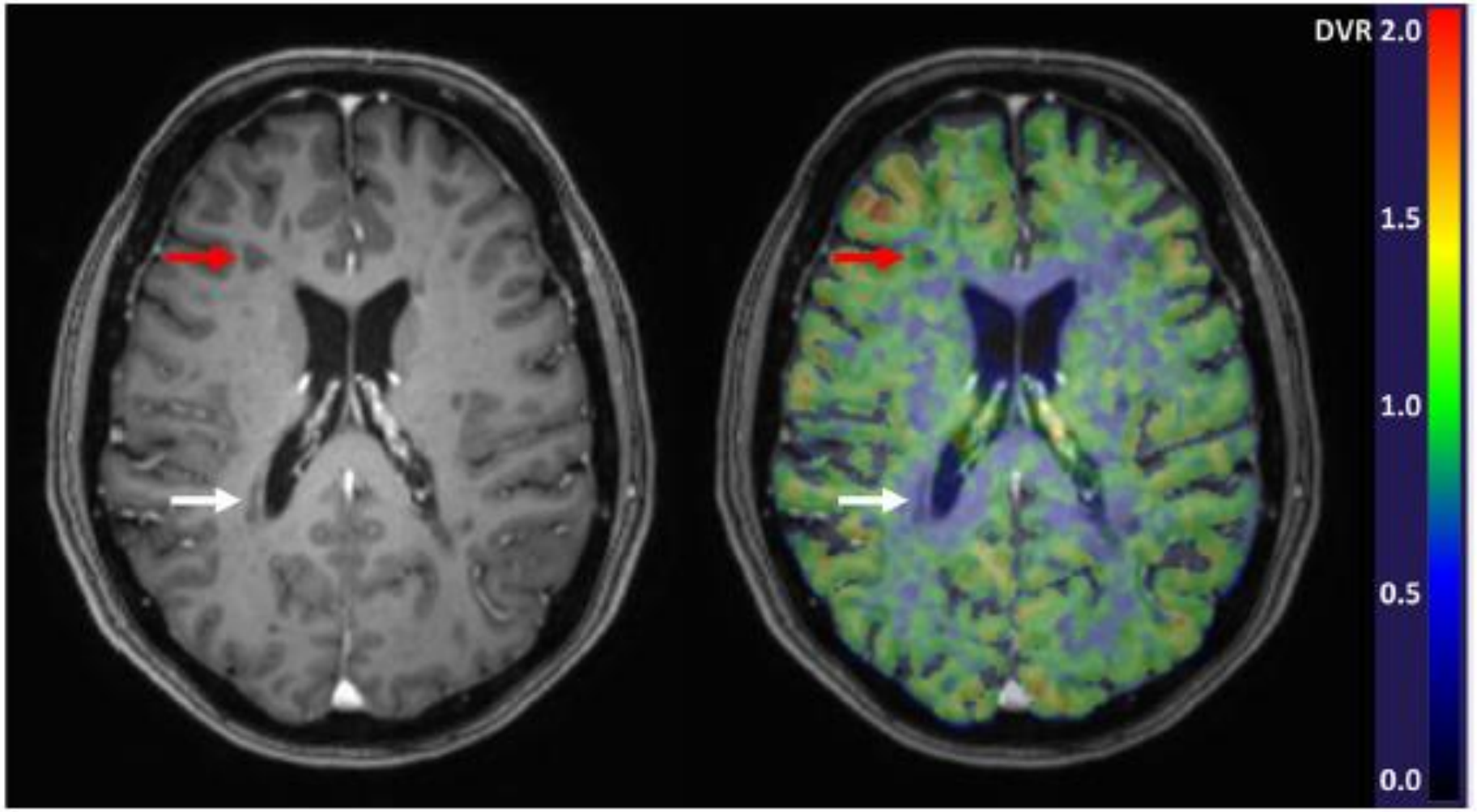
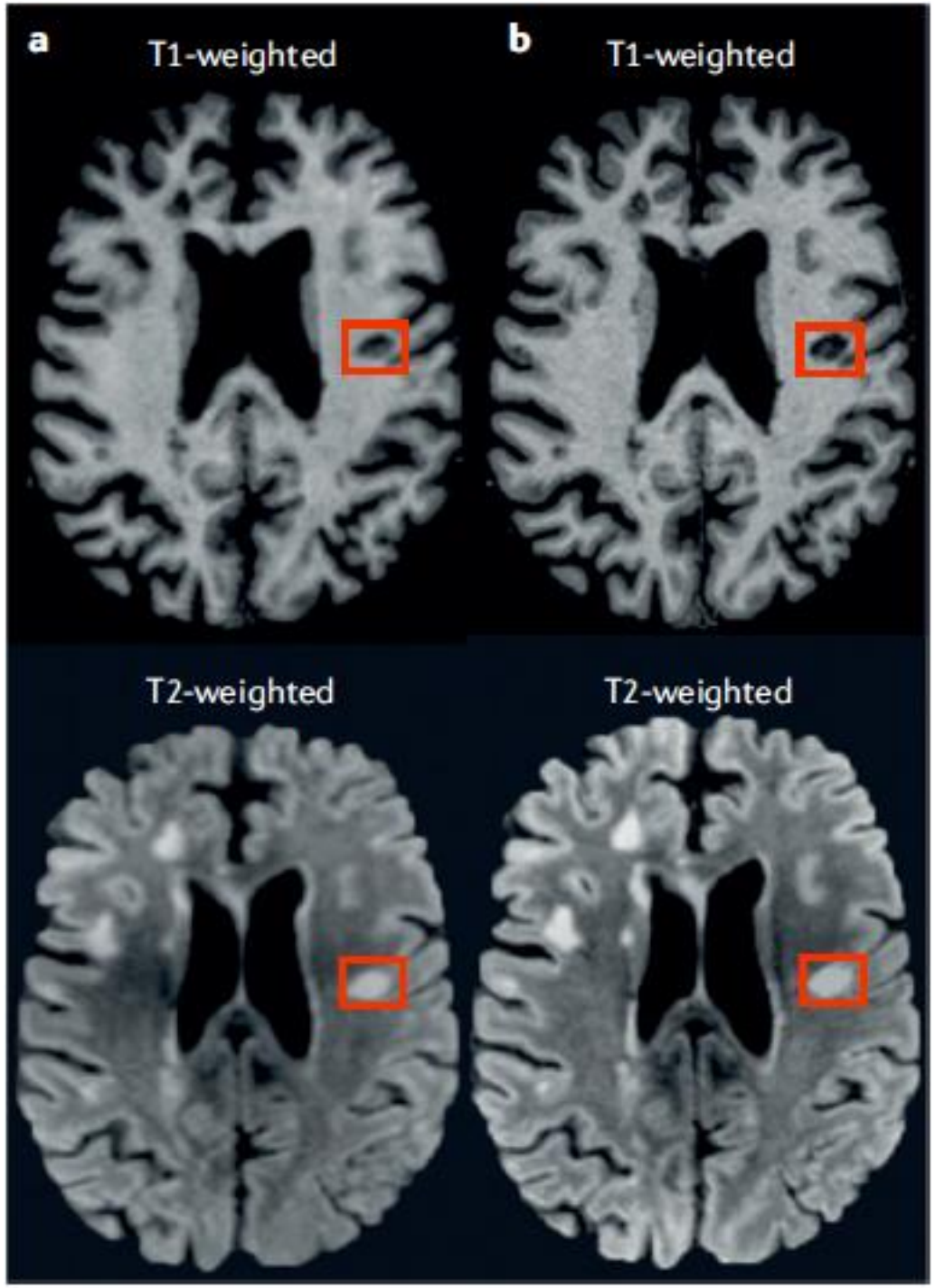


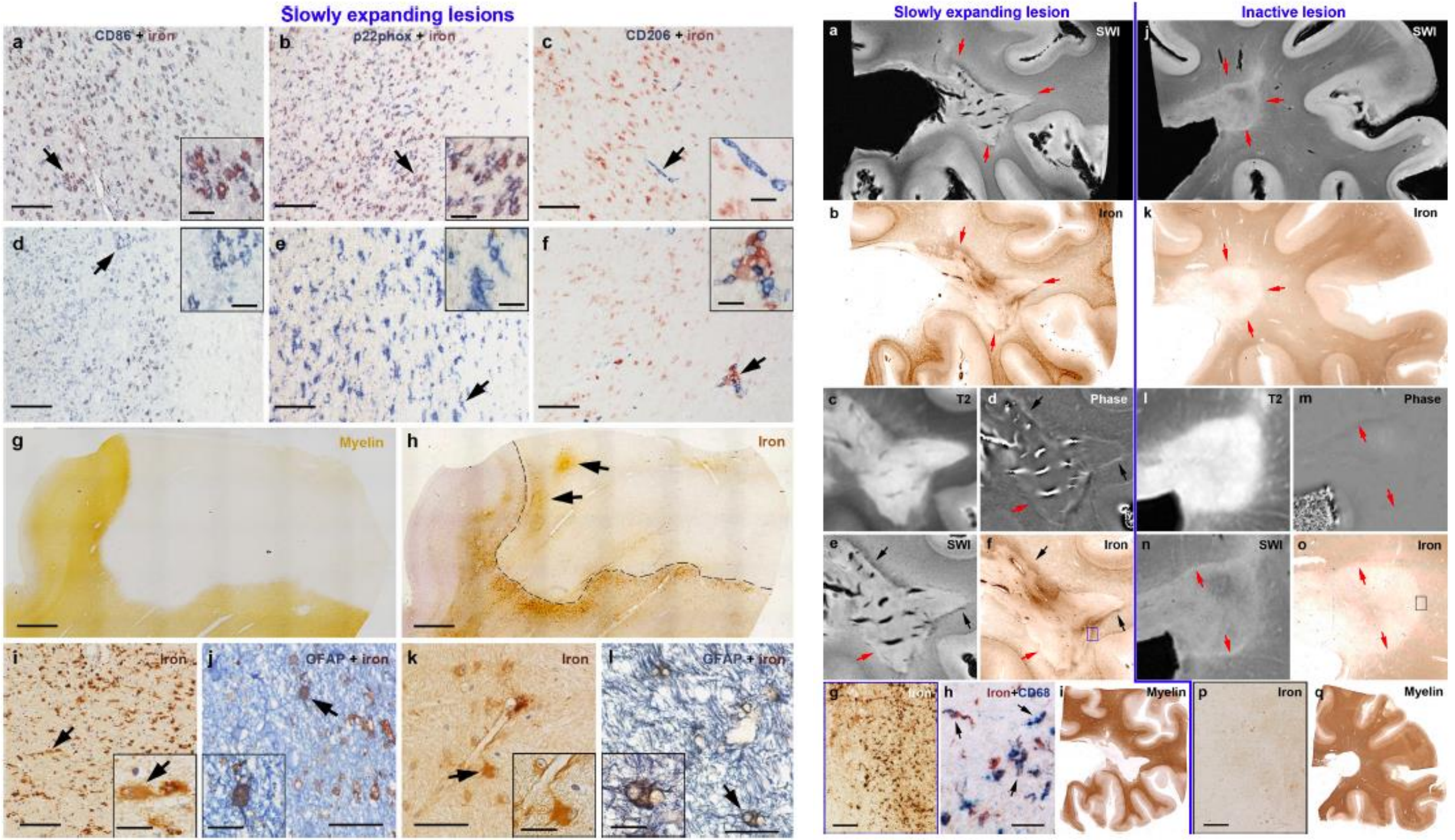
FIGURE 1 | Gadolinium enhanced 3DT1 MRI image (left) and parametric [^{11}C]PK11195-PET image overlayed with the 3DT1 image (right). Red arrows point to a chronic active T1-hypointense lesion with increased perilesional [^{11}C]PK11195 binding demonstrative of microglial activation, and white arrows point to a chronic inactive lesion with negligible radioligand binding. In the parametric PET image, the color of each voxel represents the intensity of specific radioligand binding measured as distribution volume ratio (DVR) and denoted by the scaled color bar.

Airas, Front Neurol 2018

Key points

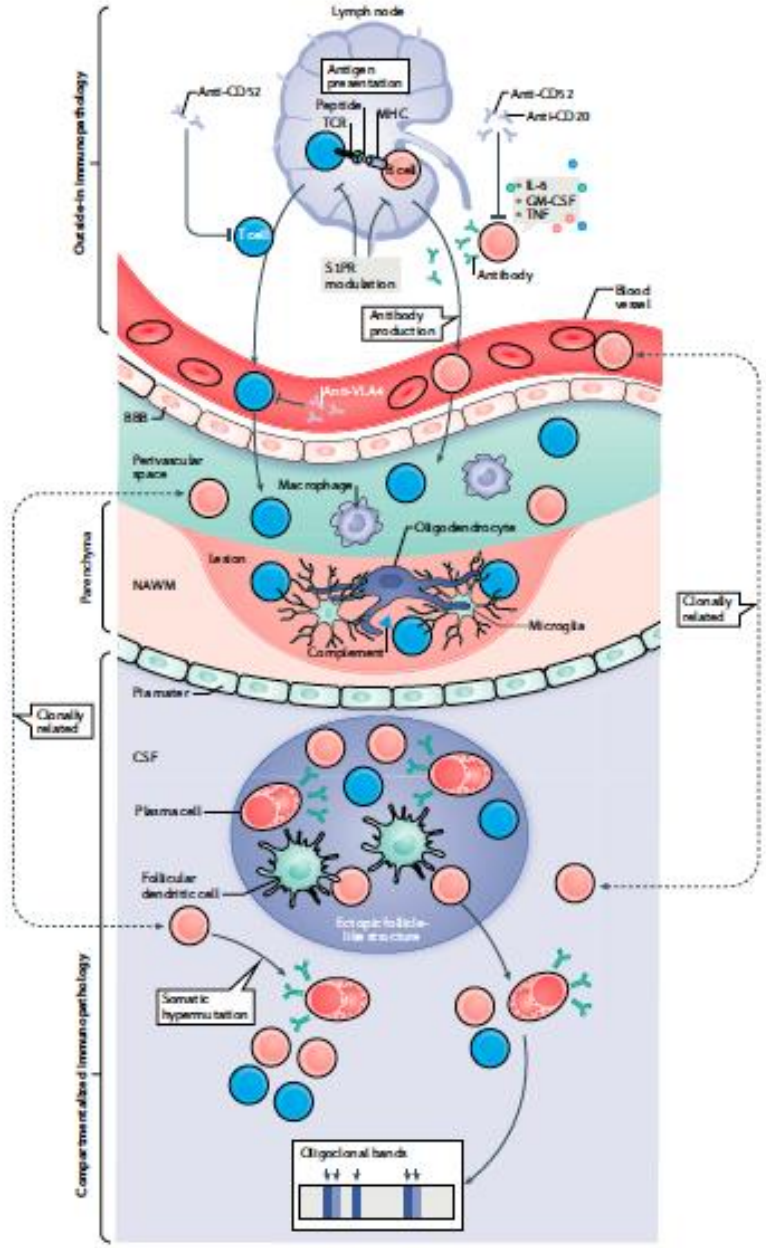
- Advanced MRI and PET methods enable visualization of features related to chronic inflammation in progressive and relapsing–remitting forms of multiple sclerosis (MS).
- Quantitative analysis of uptake of gadolinium contrast agent and ultra-small paramagnetic particles provide in vivo evidence of chronic, low-grade inflammation in people with progressive or relapsing–remitting MS (RRMS).
- Lesions associated with activated macrophages/microglia (slowly expanding T2 hyperintense lesions and lesions with high susceptibility-weighted MRI signals at their rims) are more common in progressive MS than in RRMS.
- Persistent focal leptomeningeal inflammation, detectable with gadolinium contrast-enhanced T2 fluid attenuation inversion recovery MRI in many people with MS (particularly progressive MS), is associated with cortical lesions and accelerated cortical atrophy.
- Translocator protein PET can detect increased innate immune activation in brains of people with MS; typically, activation is greater in secondary progressive MS than in RRMS.
- Indirect evidence suggests that magnetic resonance spectroscopy measures of *myo*-inositol and some recently introduced PET measures can reflect contributions of astrocyte activation to brain innate immune responses.





Dal Bianco, Acta Neuropathol 2017

B-cells


Lymph node
Antigen presentation
Peptide
MHC
TCR
B cell
T cell
Anti-CD52
Anti-CD52
Anti-CD20
IL-6
GM-CSF
TNF
Antibody
S1PR modulation
Antibody production
Blood vessel
Anti-VLA4
BBB
Perivascular space
Macrophage
Oligodendrocyte
Lesion
NAWM
Microglia
Complement
Pia mater
CSF
Plasma cell
Follicular dendritic cell
Ectopic follicle-like structure
Somatic hypermutation
Oligoclonal bands
Clonally related
Clonally related
Outside-in immunopathology
Parenchyma
Compartmentalized immunopathology

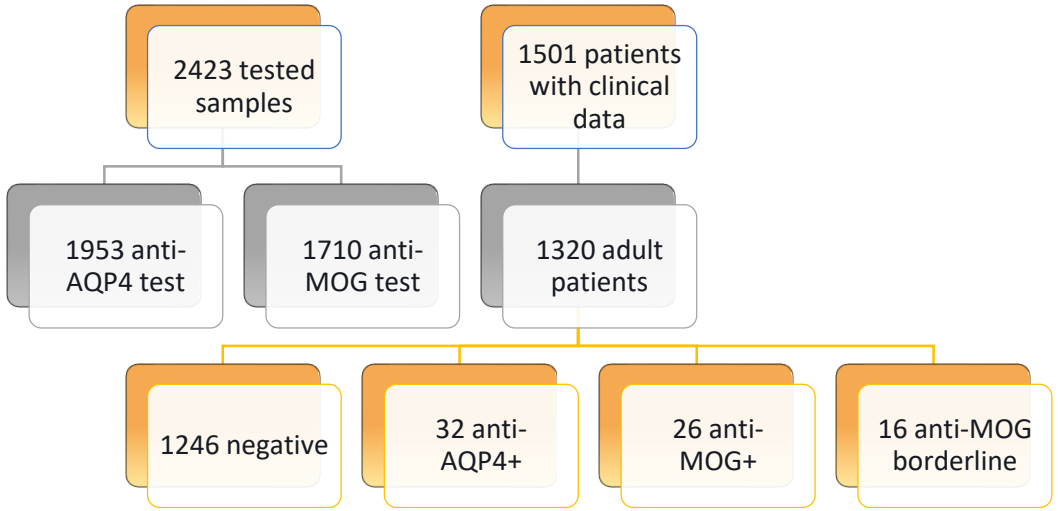
2019 NMOSD trials – Summary

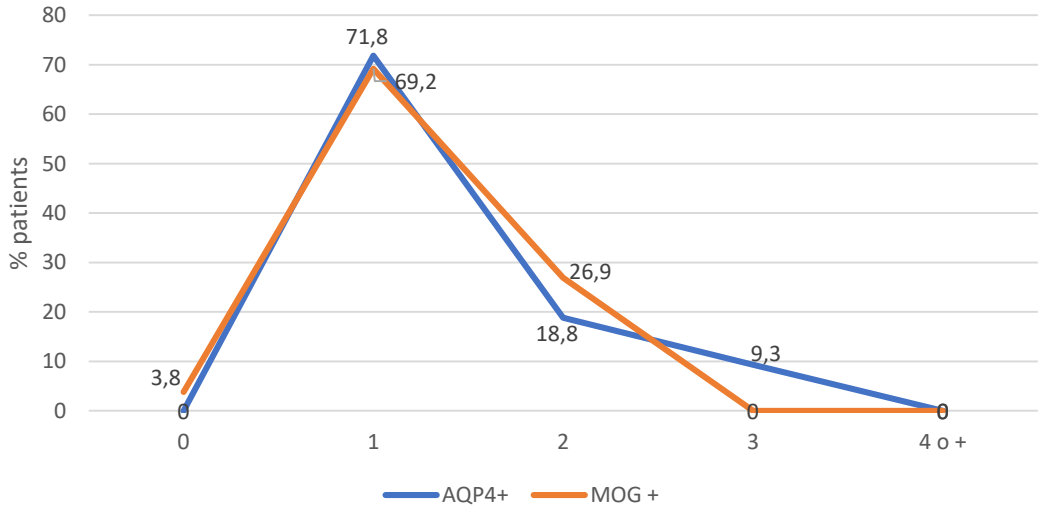
	PREVENT Eculizumab Anti-C5	N-Momentum Inebilizumab Anti-CD19	SAkuraSky Satralizumab Anti-IL6R	SAkuraStar Satralizumab Anti-IL6R
Subjects (n)	AQP4+ only N=143	AQP4+/- N=212 + 18 = 230	AQP4+/- N=55 + 28 = 83	AQP4+ only N=64 + 31 = 95
Placebo arm	Background IST allowed	Placebo only	Background IST allowed	Placebo only
Relapse reduction	94.2%	73% overall AQP4+ 77.3%	62% overall AQP4+ 79% AQP4- 34% (NS)	55% overall AQP4+ 74% AQP4- 34% (NS)
Relapse-free, 28 wks	NR	AQP4+ 87.6% PBO 56.6% AQP4- NR	NR	NR
Relapse-free, 48 wks	97.9% vs PBO 63.2%	NR	AQP4+ 91.5% vs PBO 59.9% AQP4- 84.4% vs PBO 75.5%	AQP4+ 82.9% vs PBO 55.4% AQP4- 63.3% vs PBO 77.8%
Relapse-free, 96 wks	96.4% vs PBO 51.9%	NR	AQP4+ 91.5% vs PBO 53.3% AQP4- 56.3% vs PBO 67.1%	AQP4+ 76.5% vs PBO 41.1% AQP4- 63.3% vs PBO 77.8%
Disability	NS	OR 0.371 P=0.007	NR	NR

Weinshenker et al. ECTRIMS 2019;

2015 REVISED DIAGNOSTIC CRITERIA FOR NMOSD APPLIED TO ANTI-AQP4+ AND ANTI-MOG+ ANTIBODIES PATIENTS: A PROSPECTIVE INCIDENTAL STUDY IN A LARGE ITALIAN POPULATION

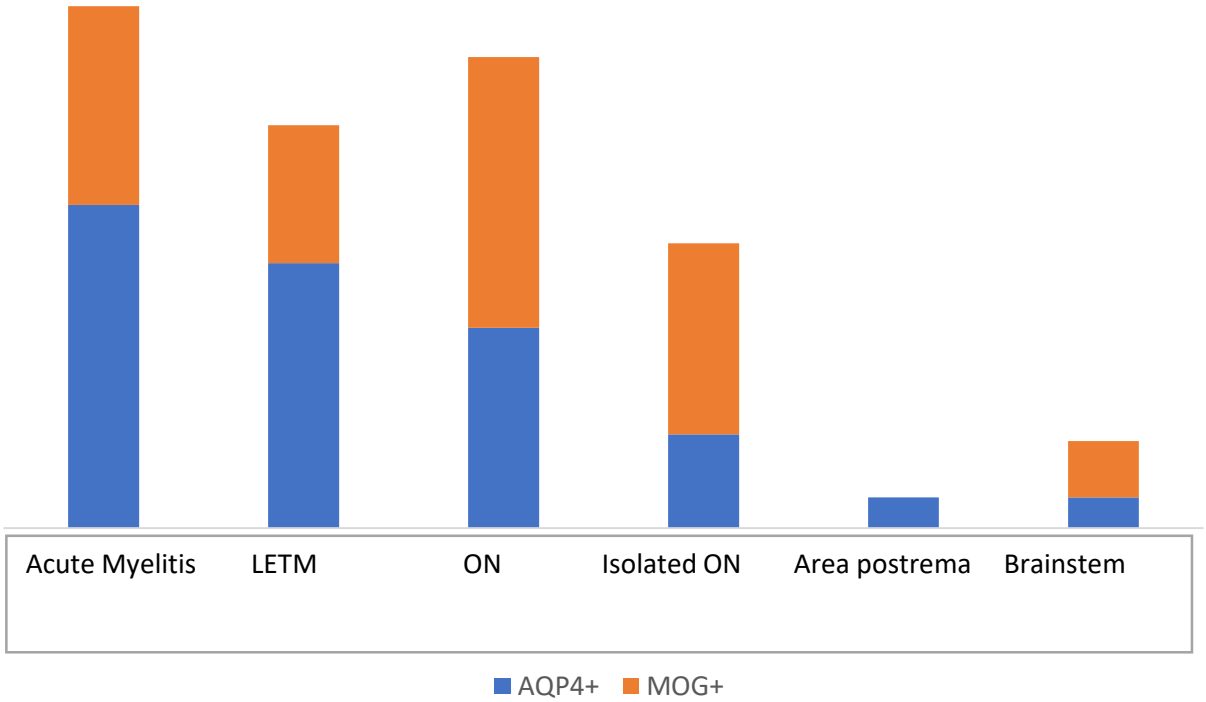
Semistructured questionnaire based on 2015 revised NMOSD diagnostic criteria[1]





N of NMOSD core criteria fullfilled

Clinical characteristics of MOG+ VS AQP4+



Capobianco et al, SIN Bologna 2019

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Matthews, Nat Rev Neurol 2019