Actualités dans la sclérose en plaques

Caroline Pot
Unité de neuroimmunologie et sclérose en plaques
Service de Neurologie
Département des Neurosciences cliniques

Delémont/ 10 mars 2022

Quels sont les points communs entre ces deux musiciennes?

Jacqueline du Pré

Alice Sara Ott

Quels sont les points communs entre ces deux musiciennes?

- Musiciennes et brillantes interprètes
- Femmes
- Agées d’une vingtaine d’années
- Atteintes de sclérose en plaques

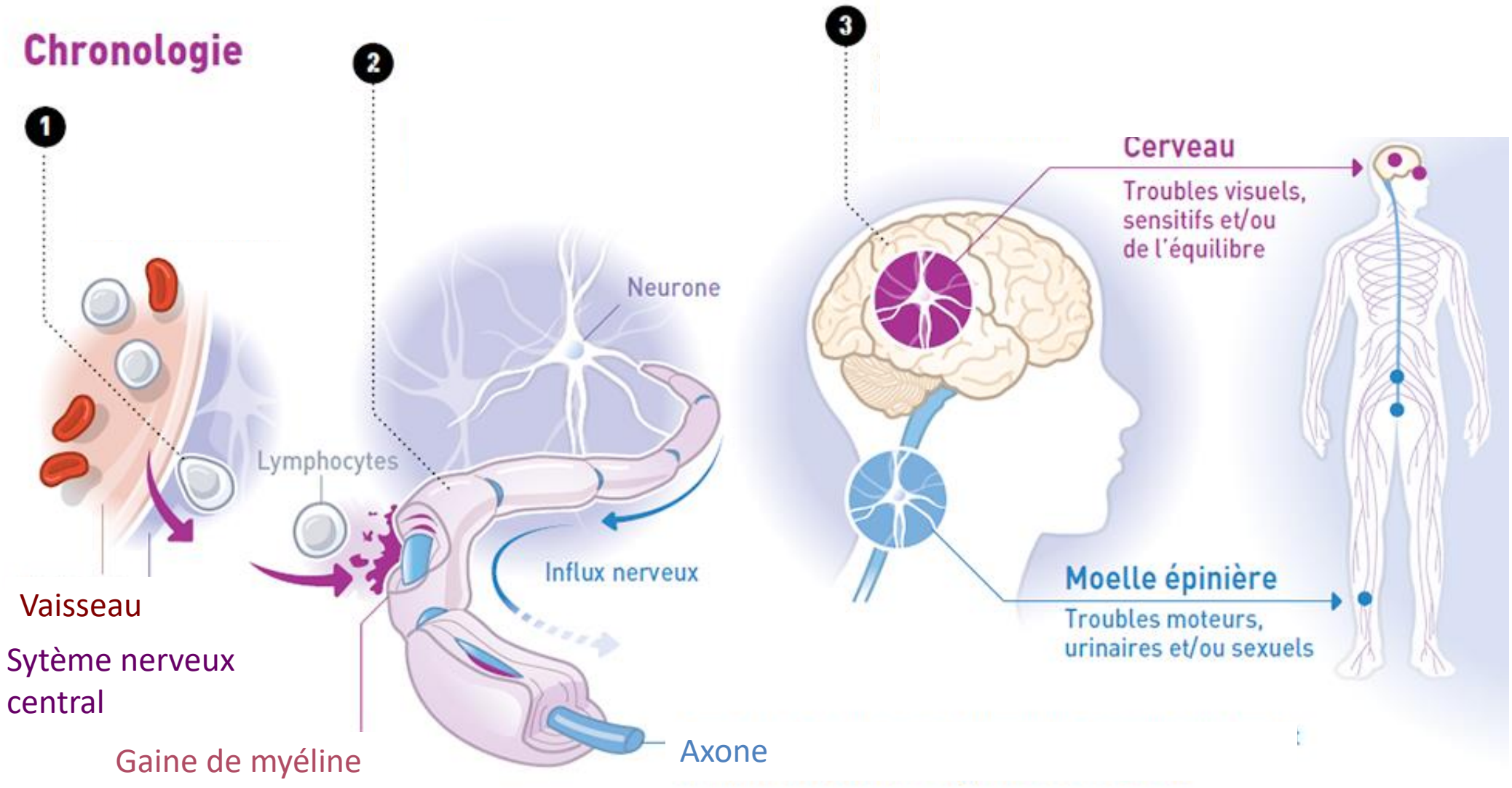
Sclérose en plaques: introduction

- Maladie «auto-immune »
- Affection chronique du système nerveux central (SNC)

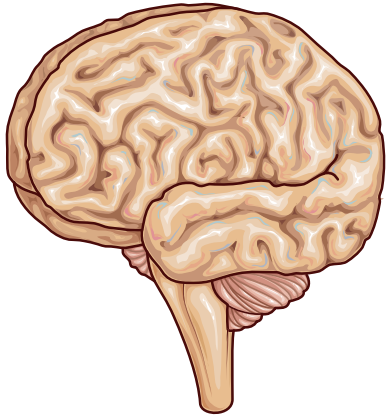
- Facteurs démographiques:

- 1ère manifestation généralement entre 20 et 40 ans
- Incidence (pays occidentaux): 3-7/100.000
- Prévalence: 50-200/100.000
- Suisse: env. 10.000 personnes atteintes
- Ratio femmes/hommes 2:1 (formes progressive: 1:1)

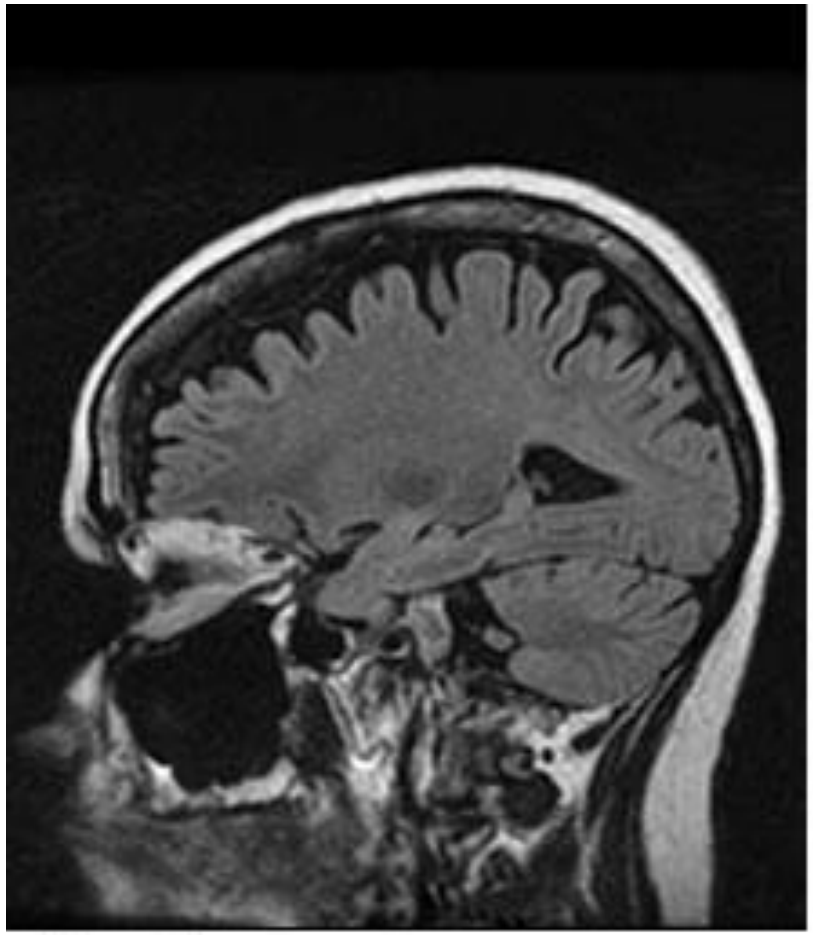
La sclérose en plaques : un système immunitaire qui se trompe



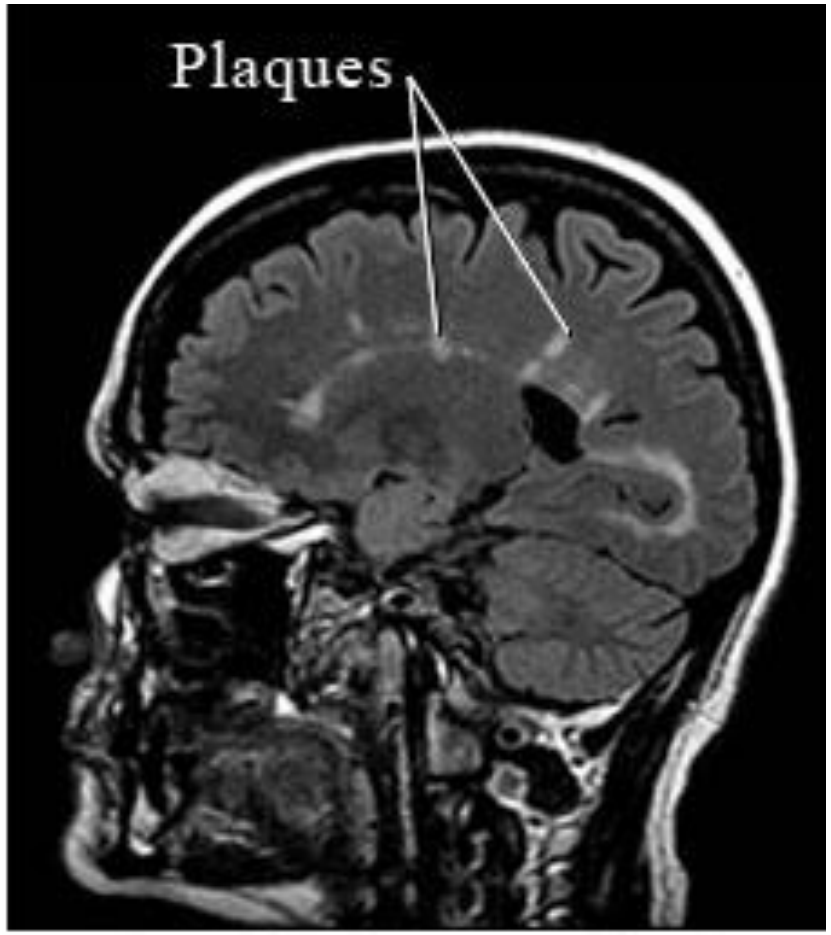
La sclérose en plaques (SEP)



Cerveau sans SEP

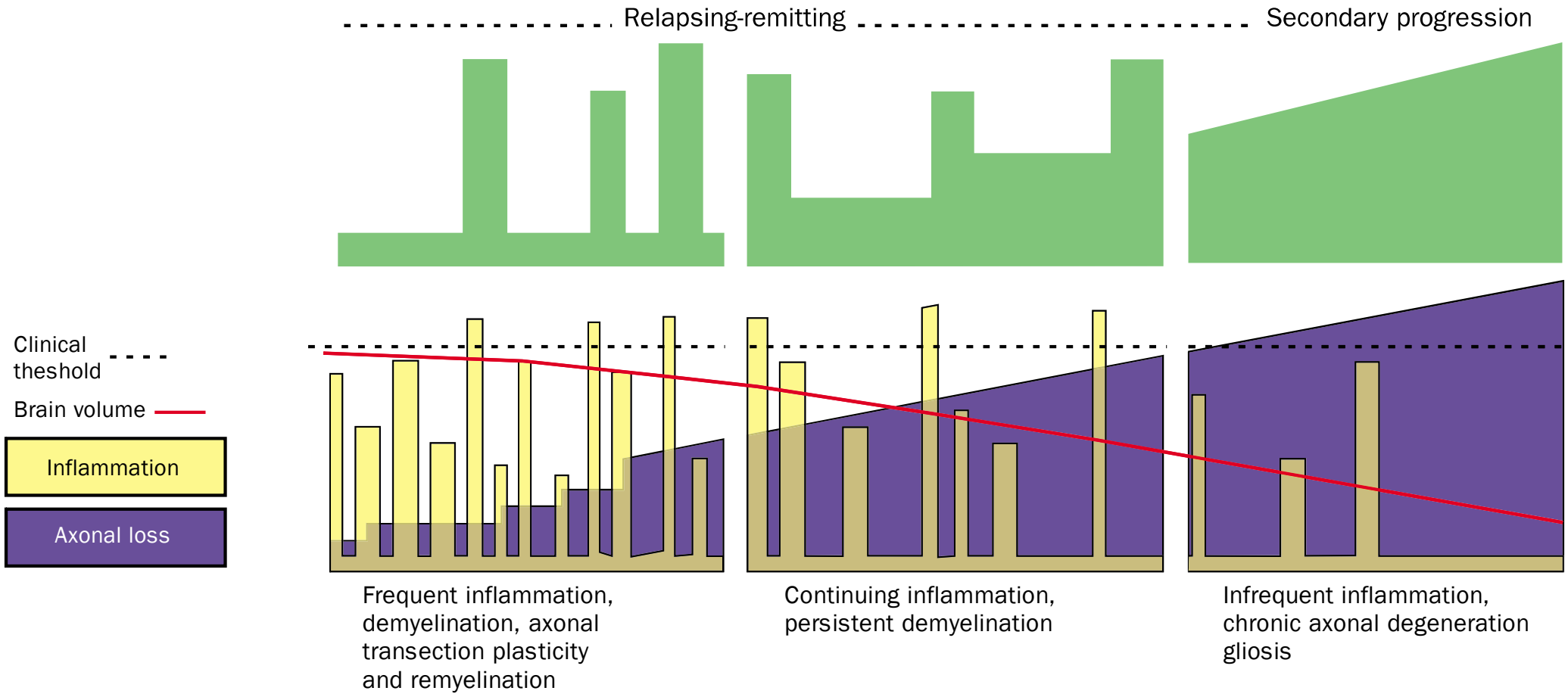


Cerveau avec SEP



Courtesy of Intermountain Medical Imaging, Boise, Idaho.

Sclérose en plaques: lésions précoces



Compston A and Coles A, Multiple sclerosis, Lancet 2002; 359- 1221-1231

Le temps compte dans la SEP

- Les traitements de fond doivent être débutés rapidement avec le but de réduire le handicap clinique à long terme

Diagnostiquer rapidement: critères McDonald 2017

Diagnostic criteria for multiple sclerosis (MS) include clinical and paraclinical laboratory assessments[1,2] emphasizing the need to demonstrate dissemination of lesions in space (DIS) and time (DIT) and to exclude alternative diagnoses.

Diagnostiquer rapidement: critères McDonald 2017

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5. ¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

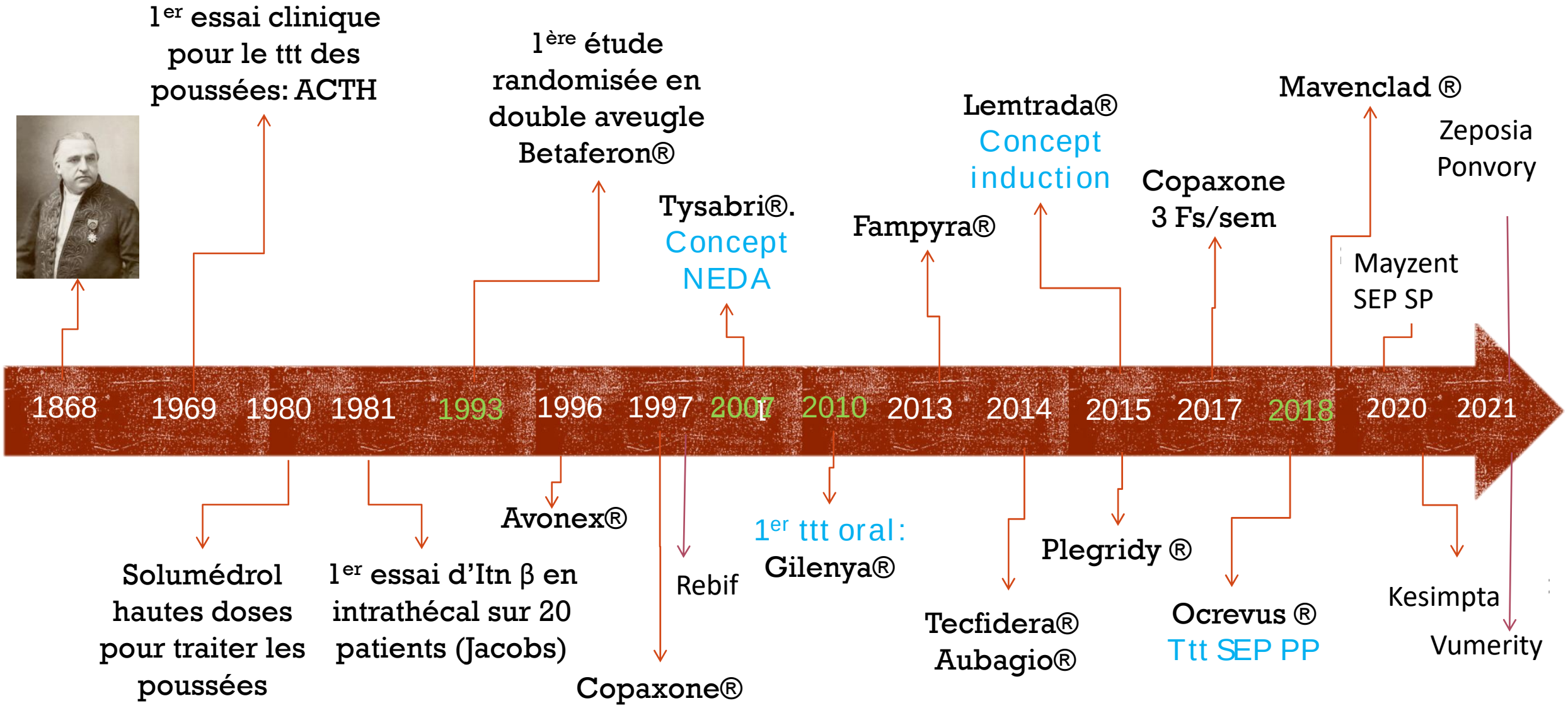
Table: **The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset**

Quelle est la différence entre ces deux musiciennes?

Jacqueline du Pré
Diagnostic de sclérose en plaques ***en 1973***

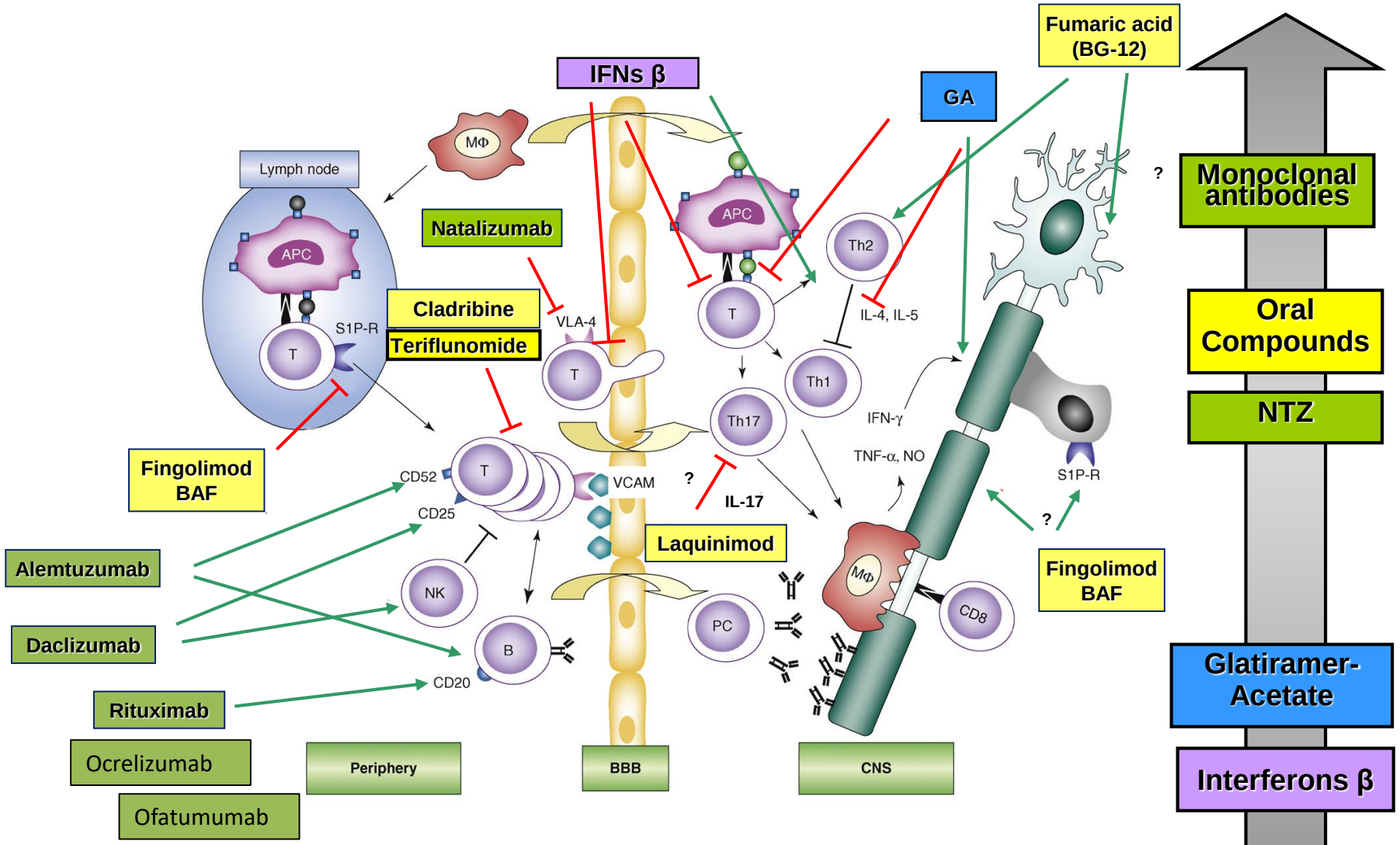
Alice Sara Ott
Diagnostic de la sclérose en plaques ***en 2019***

Traiter rapidement : « *disease-modifying treatments : DMT*»



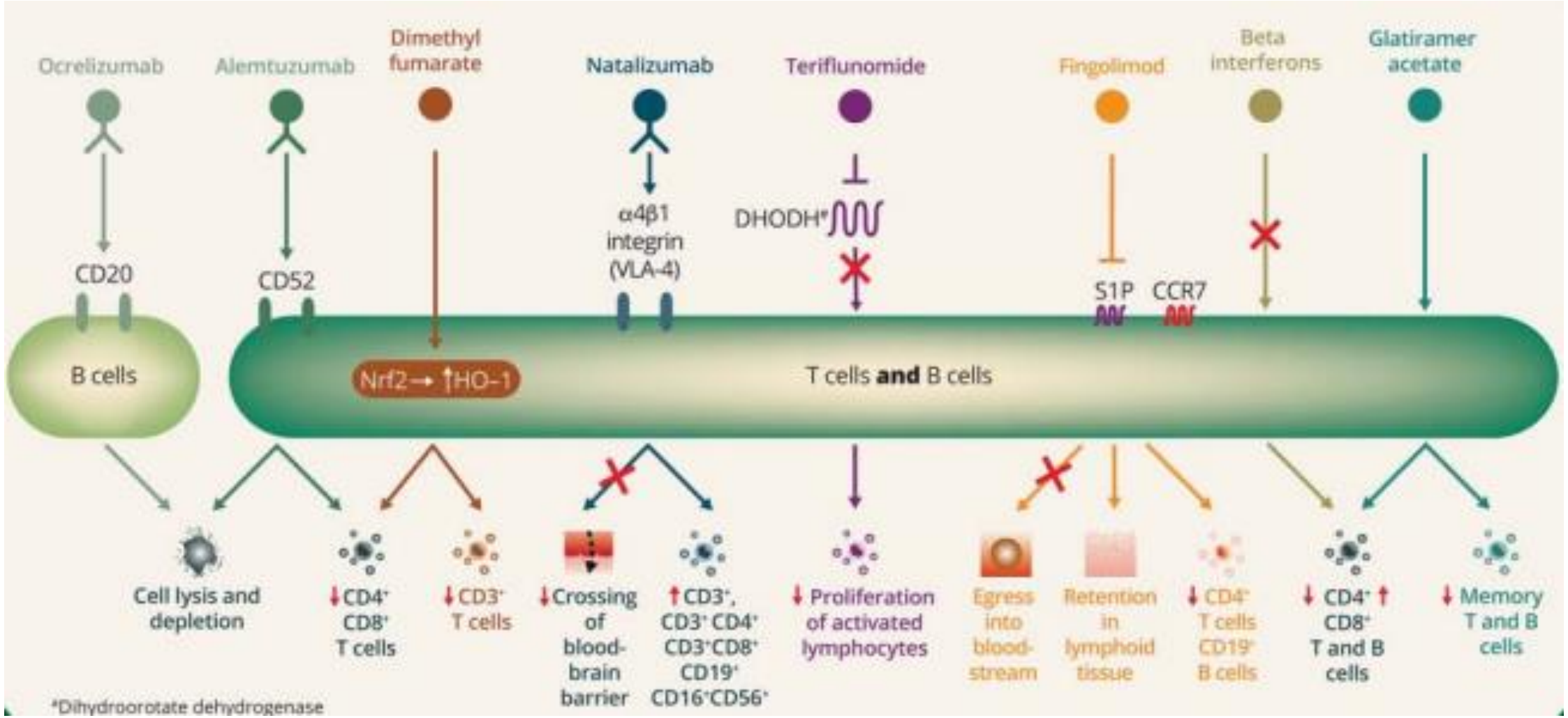
Molécule	Indication	Mode d'action
Interférons-beta	Forme poussées-rémission. 1ère ligne	Immunomodulateur, agit sur les récepteurs de l'interféron gamma. Augmente l'activité suppressive des cellules sanguines mononucléées du sang périphérique.
Acétate de glatiramère	Forme poussées-rémission. 1ère ligne	Immunomodulateur, sel d'un polypeptide synthétique composé de 4 acides aminés naturels, qui module la réponse immunitaire
Fingolimod, Ozanimod, Ponesimod	Forme poussées-rémission. 1ère ligne	Modulateur des récepteurs à la sphingosine 1-phosphate (S1P), bloquent l'égression des lymphocytes actifs hors des organes lymphoides secondaires.
Siponimod*	Forme secondaire progressive*	
Diméthylfumarate Diroximel fumarate	Forme poussées-rémission. 1ère ligne	active la voie transcriptionnelle du Nrf2 qui représente le système de défense cellulaire
tériflunomide	Forme poussées-rémission. 1ère ligne	inhibe la dihydroorotate déhydrogénase (DHO-DH), enzyme mitochondriale nécessaire à la synthèse de novo de pyrimidine, bloque la prolifération des lymphocytes activés.
Natalizumab	Forme poussées-rémission. 2ème ligne ou 1ère ligne pour forme aggressive	Anticorps monoclonal contre la sous-unité alpha-4 des intégrines beta1 et 7, bloque la migration des leucocytes activés dans le SNC
Ocrelizumab* Ofatumumab	Forme poussées Forme primaire progressive* 1ère ligne	Anticorps monoclonal anti-CD20, détruit les lymphocytes B qui présentent les antigènes
Cladribine	Forme poussées-rémission. 2ème ligne ou forme agressive	Traitement inducteur, Analogue des purines, cytotoxique pour les cellules à prolifération rapide et pour les cellules au repos.
Alemtuzumab	Forme poussées-rémission. 3ème ligne	Traitement inducteur anticorps monoclonal anti-CD52 induisant une déplétion des lymphocytes T et B puis un reset du système immunitaire
Mitoxantrone	Forme secondaire progressive	Traitement inducteur. Antitumoral cytostatique appartenant à la famille des anthracène-diones de synthèse

Mode de fonctionnement des traitements de fond

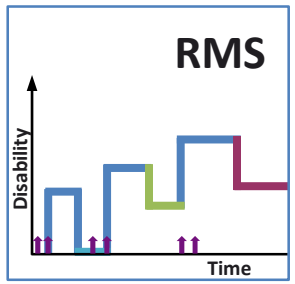


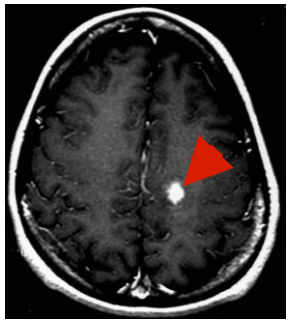
Hartung et al, J Neurol, 2004
Linker et al, Trends Pharmacol Science, 2008

DMT: traitements qui modulent le système immunitaire



But du traitement: atteindre le “ no evidence of disease activity “





No relapses

No evidence of clinical disease

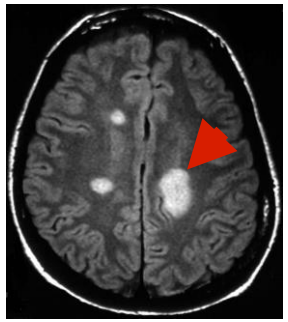
No confirmed disability progression

NEDA

No T1 Gd⁺ lesions

No evidence of MRI disease

No new/enlarging T2 lesions



- NEDA: score composite pour évaluer l’absence de progression clinique et radiologique
- **NEDA à 2 ans: haute valeur prédictive pour l’absence de progression de la maladie à 7 ans**

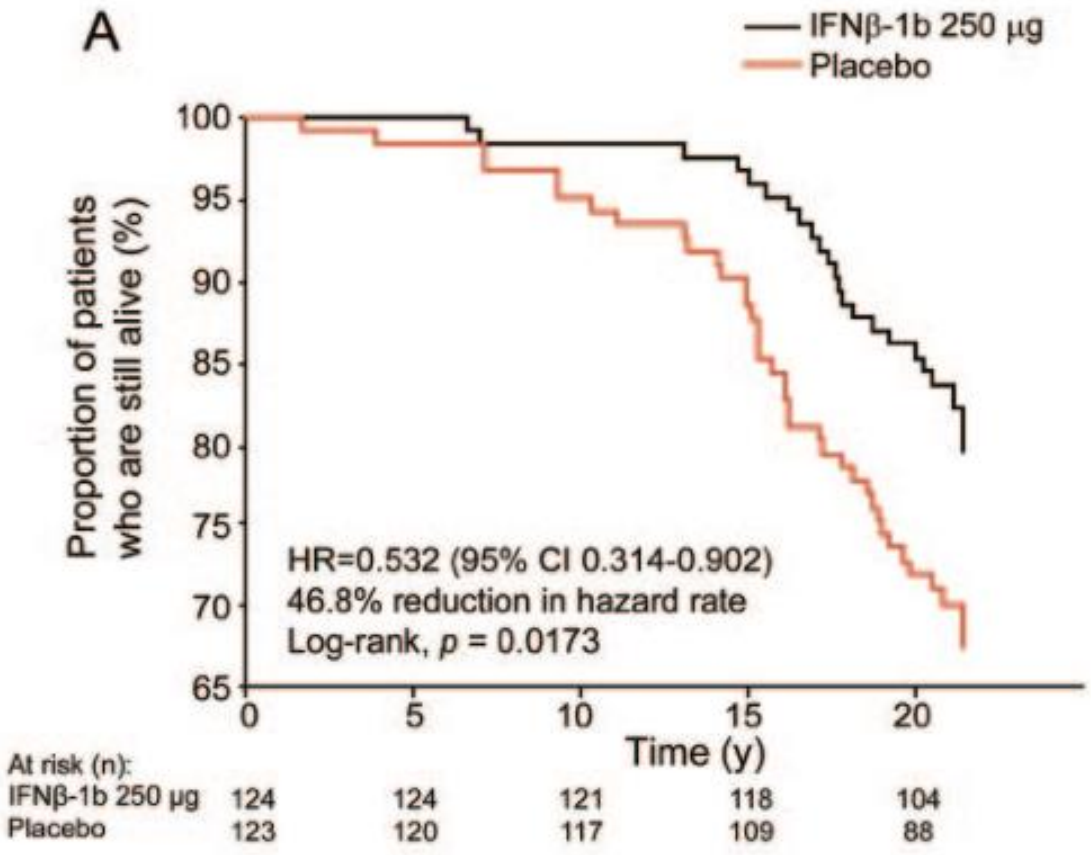
NEDA in MS Phase III clinical studies

Clinical study	Patients with NEDA, %			
	Drug	Comparator	Study duration	p value
AFFIRM[1]	Natalizumab **37%**	Placebo **7%**	2 yrs	**<0.0001**
FREEDOMS[2]	Fingolimod **33%**	Placebo **13%**	2 yrs	**<0.001**
CARE MS I[3]	Alemtuzumab **39%**	SC IFN beta-1a **27%**	2 yrs	**0.006**
CARE MS II[4]	Alemtuzumab **32%**	SC IFN beta-1a **13%**	2 yrs	**<0.0001**
OPERA I	Ocrelizumab **48%**	SC IFN β-1a **29%**	2 yrs	**<0.0001**
OPERA II	Ocrelizumab **48%**	SC IFN β-1a **25%**	2 yrs	**<0.0001**

Le temps compte dans la SEP

- Les traitements de fond doivent être débutés rapidement avec le but de réduire le handicap clinique à long terme

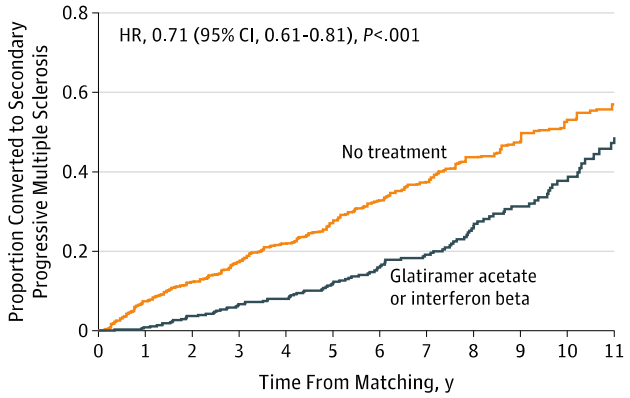
Interferon et efficacité à long-terme sur la mortalité (>20 ans)



D.S. Goodin et al. Neurology 2012;78:1315-1322

Efficacité à long-terme sur le passage en forme progressive

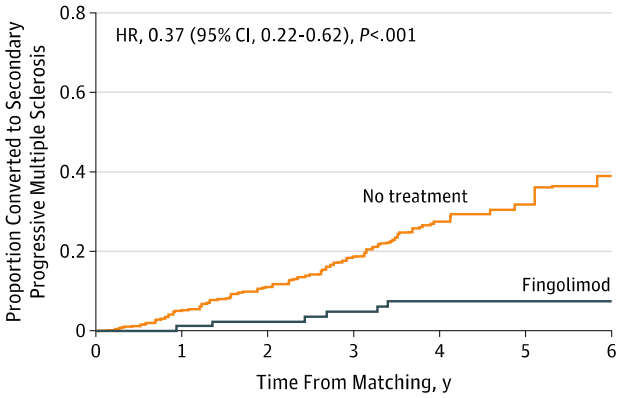
A Glatiramer acetate or interferon beta vs no treatment



No. with follow-up data

No treatment	213	213	213	213	213	180	153	126	96	74	51	33
Glatiramer acetate or interferon beta	407	407	407	407	407	355	300	251	191	142	98	62

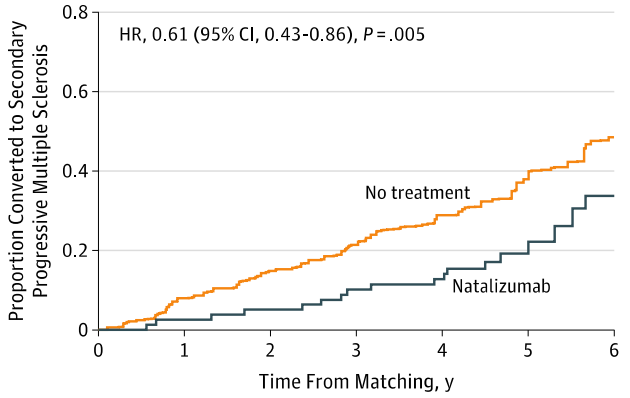
B Fingolimod vs no treatment



No. with follow-up data

No treatment	174	174	174	174	174	39	20
Fingolimod	85	85	85	85	85	21	11

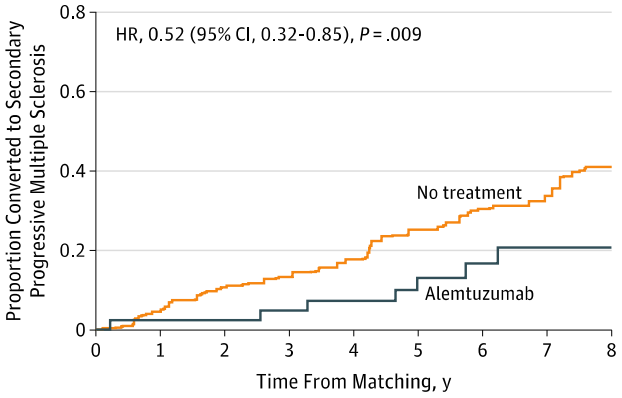
C Natalizumab vs no treatment



No. with follow-up data

No treatment	164	164	164	164	164	77	35
Natalizumab	82	82	82	82	82	36	17

D Alemtuzumab vs no treatment

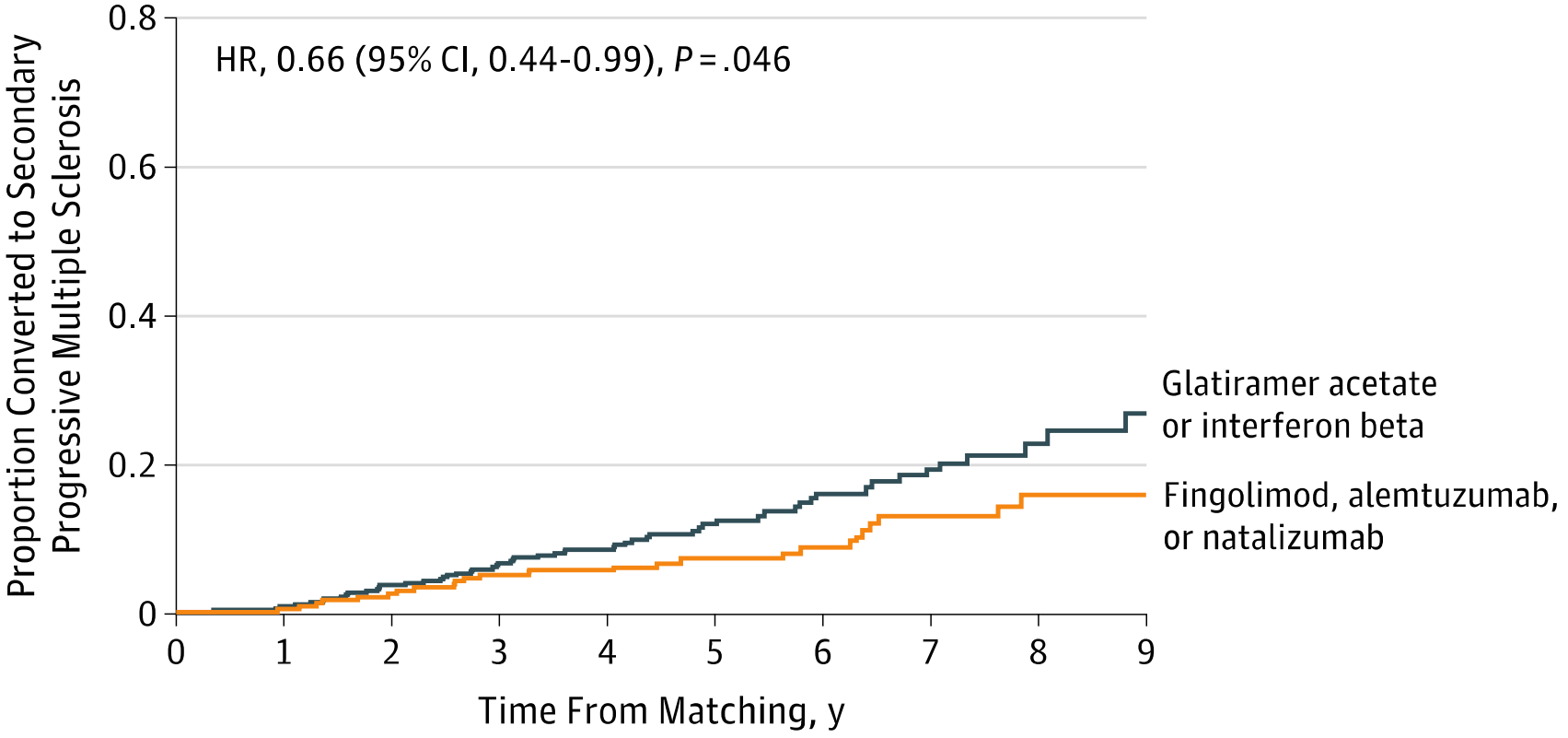


No. with follow-up data

No treatment	92	92	92	92	92	77	68	50	36
Alemtuzumab	44	44	44	44	44	37	34	24	17

JAMA January 15, 2019 Volume 321, Number 2

Limiter le passage en forme progressive: traiter vite et fort

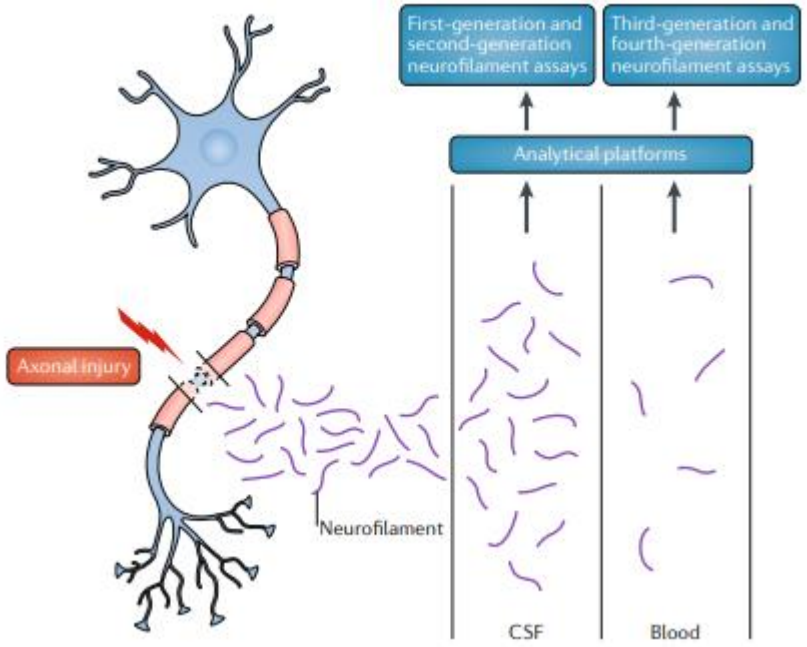


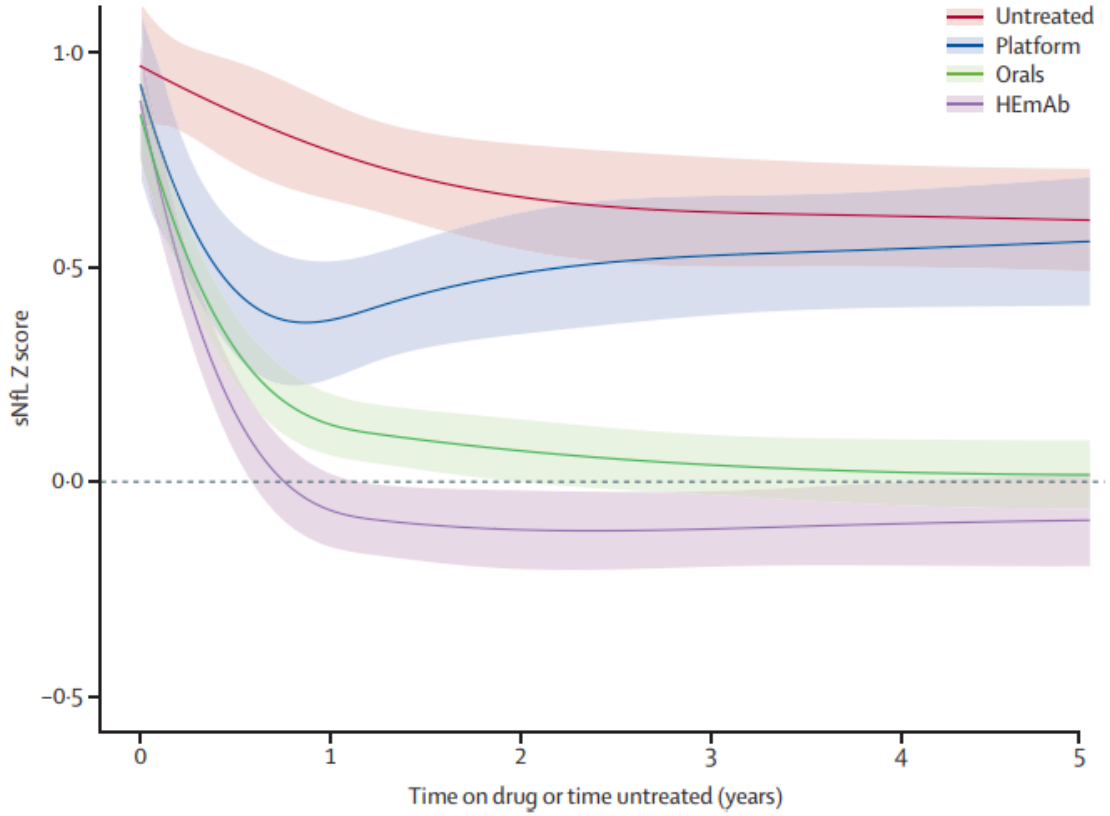
No. with follow-up data										
Initial treatment										
Glatiramer acetate or interferon beta	380	380	380	380	380	252	182	142	93	44
Fingolimod, alemtuzumab, or natalizumab	235	235	235	235	235	148	103	80	54	30

JAMA January 15, 2019 Volume 321, Number 2

Moins de souffrance axonale si traitement rapide et fort

NfL

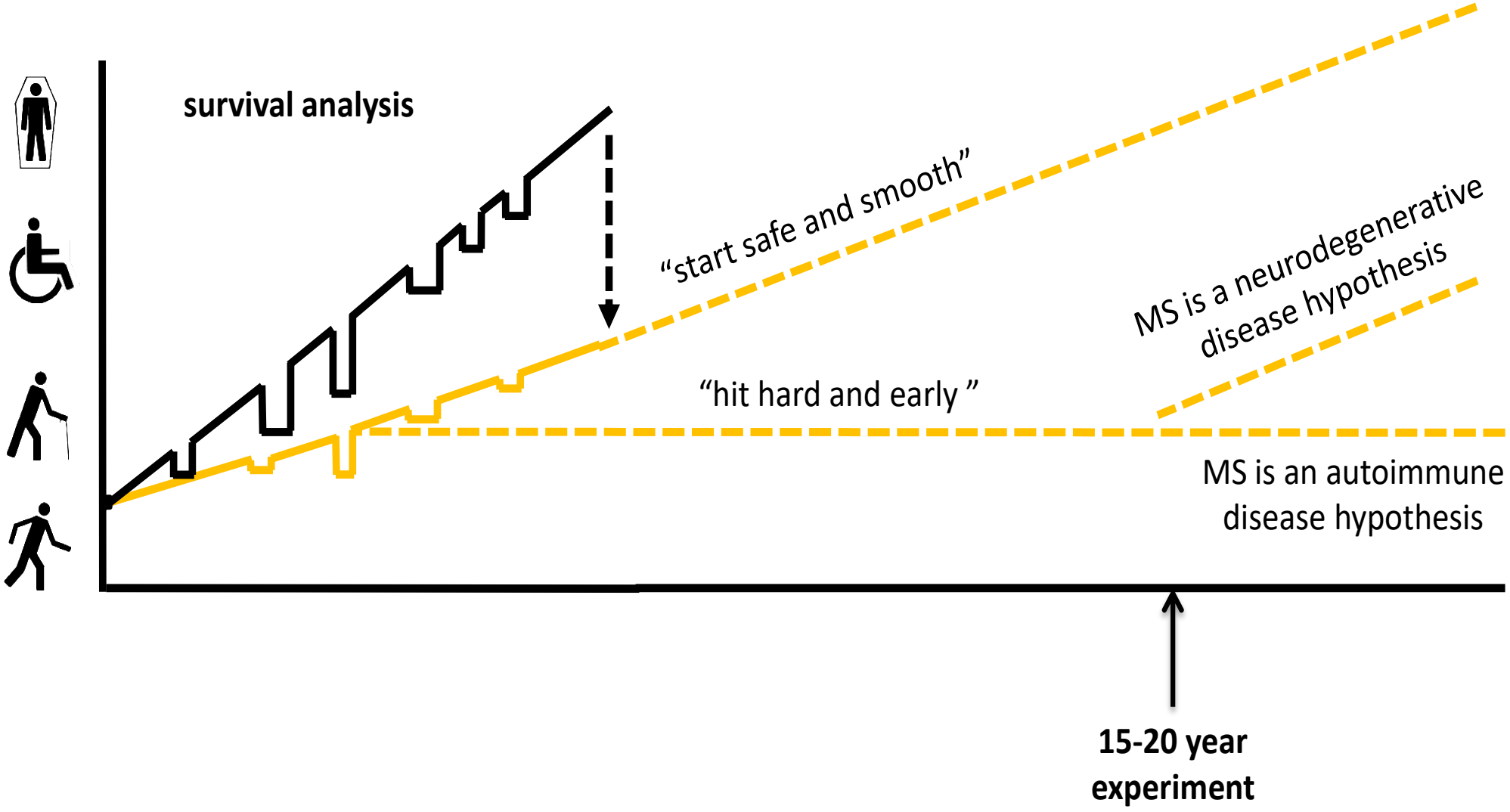




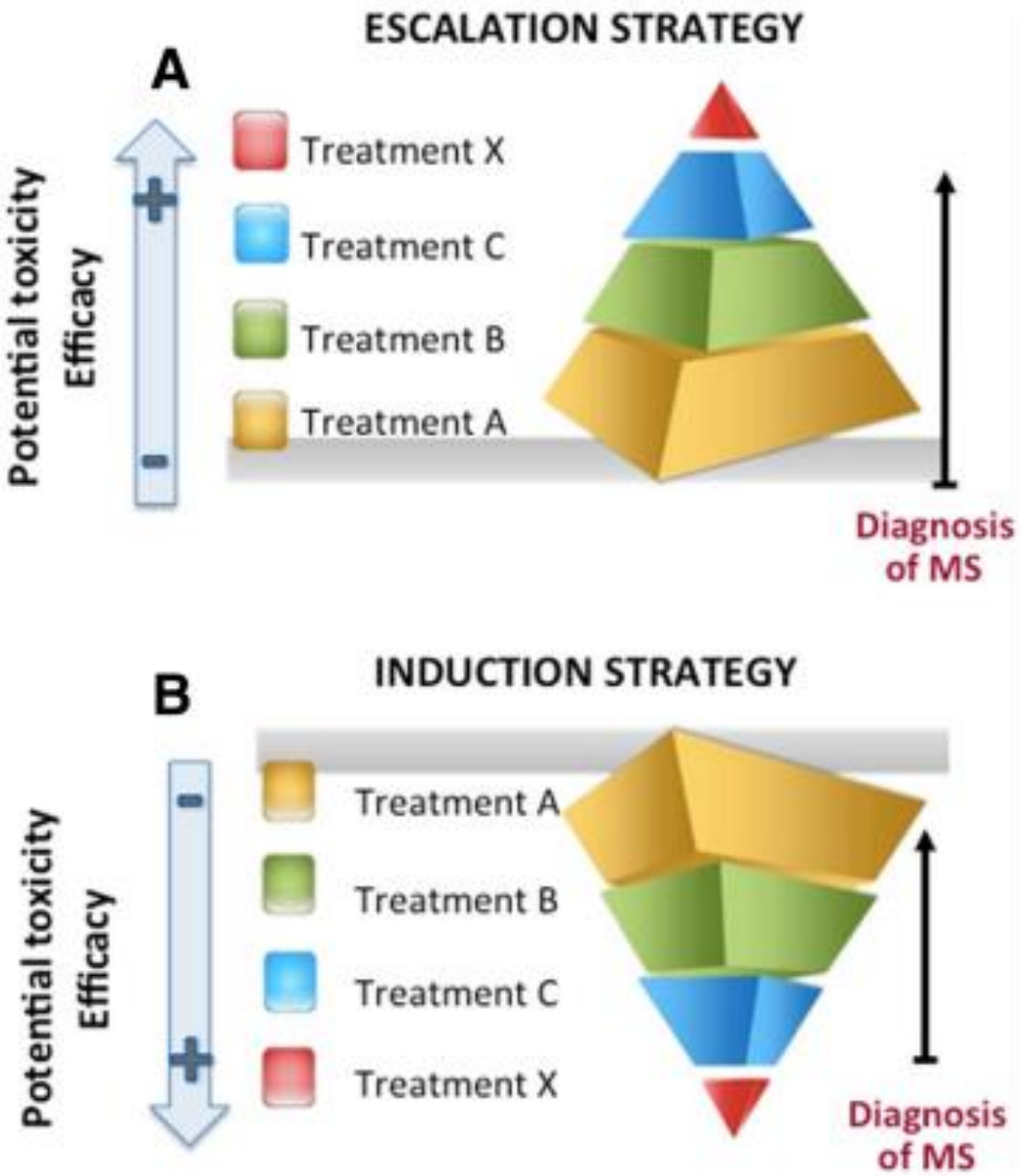
Number of samples					
Untreated	375	163	101	76	66
Platform	170	115	92	57	48
Orals	804	785	611	490	358
HEmAb	561	422	292	161	153

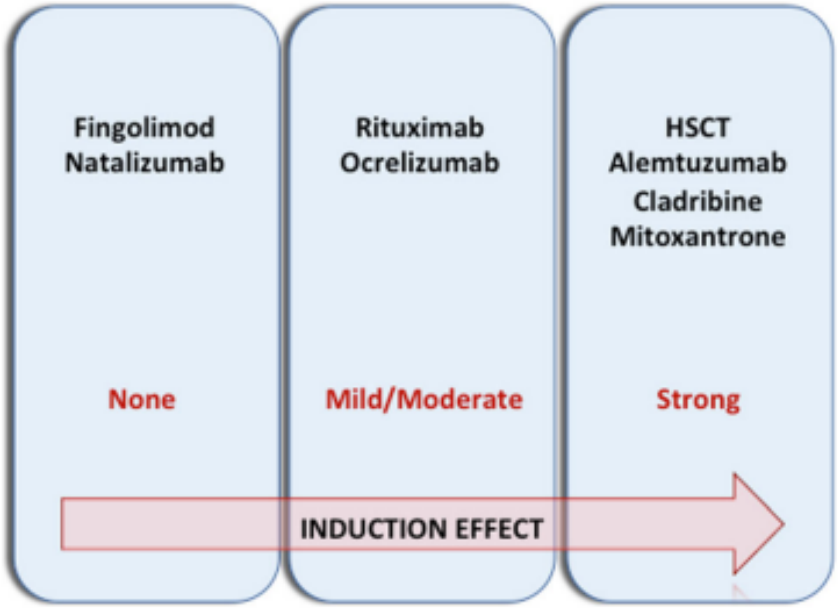
Benkert P et al. Swiss Multiple Sclerosis Cohort Study Group. Lancet Neurol. 2022 Mar;21(3):246-257.

Options thérapeutiques: traitement tôt et efficace



Quelle stratégie pour débuter un traitement?



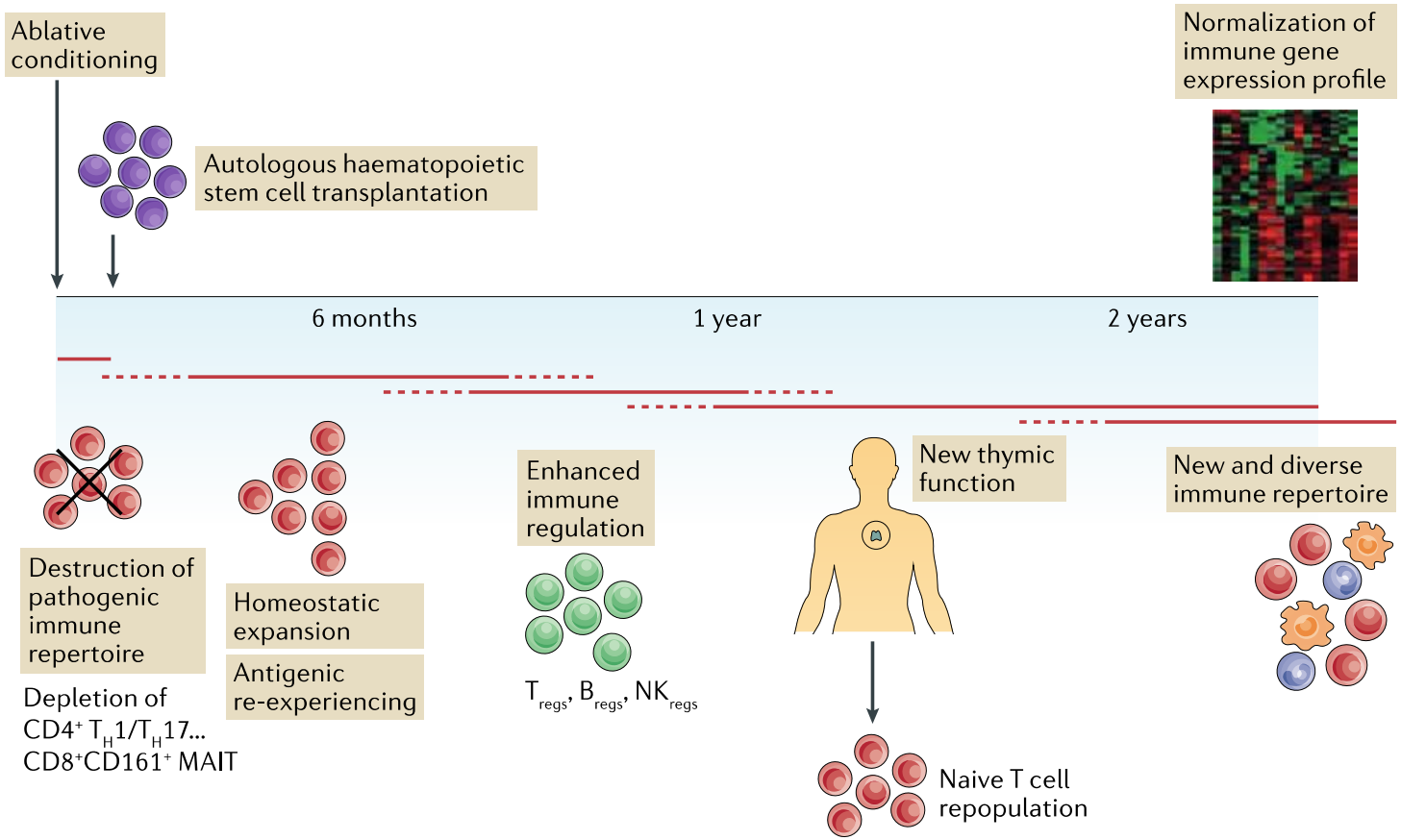


Ruggieri, S., Pontecorvo, S., Tortorella, C. *et al.* Induction treatment strategy in multiple sclerosis: a review of past experiences and future perspectives. *Mult Scler Demyelinating Disord* **3,** 5 (2018).

Treatment options: maintenance-escalation versus induction

Maintenance therapies	Induction therapies
Continuous treatment	Short-courses or pulsed therapy
First line injectables, oral tt, NTZ,	Alemtuzumab, Mitoxantrone?, cladribine?, anti-CD20(?), BMT
Low to very high efficacy	High efficacy
Reversible	Irreversible
“lower risk”	“higher risk”
Rebound activity: Highly likely	Rebound activity: Less likely
Pregnancy: some tt contra-indicated	Good strategy
No potential for cure	Potentially curative??

Autologous hematopoietic stem cell transplantation (aHSCT) in highly active multiple sclerosis (MS)



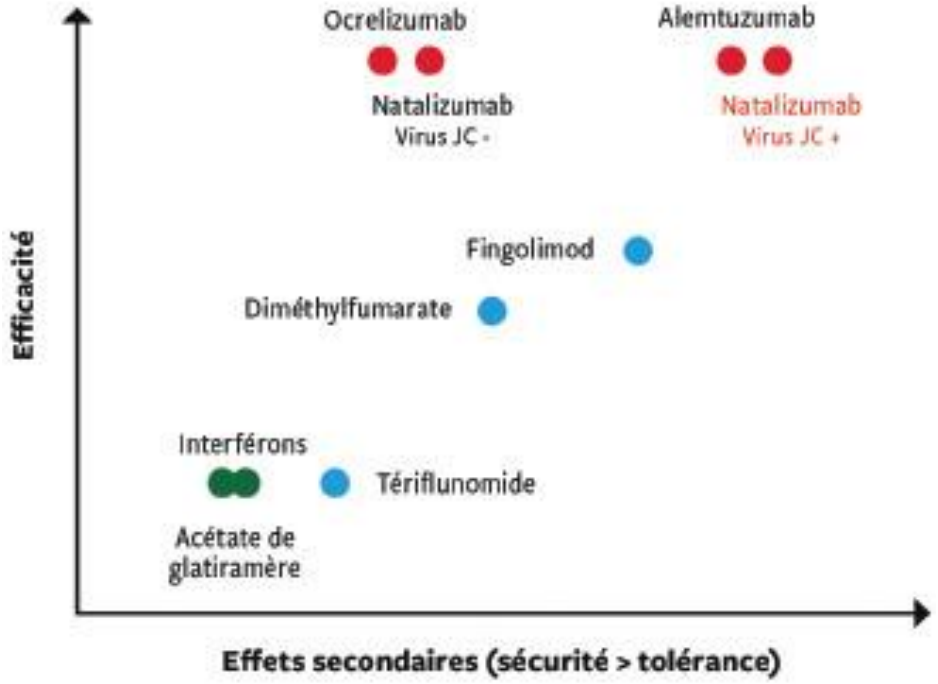
Eligible patients

- SINCE JULY 1ST 2018

- Active/aggressive relapsing-remitting multiple sclerosis (1 or more relapses/year prior to aHSCT; last two years are most important)
- Failed at least one highly active therapy, e.g. natalizumab, rituximab, ocrelizumab,...
- ≤ 50 years
- Several new T2/new or contrast-enhancing lesions
- 10 years or less after diagnosis
- EDDS < 6.5
- Clear disease activity (clinical and/or MRI) in patients with chronic progressive disease

Sécurité

Sécurité des traitements de fond



Risques infectieux:

- Infections opportunistes

Risques d'auto-immunité

- Traitements inducteurs

Update sur les infections opportunistes: cryptocoques

ELSEVIER

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Neuroradiology

Cryptococcal meningitis in a multiple sclerosis patient treated with Fingolimod: a case report and review of imaging findings

Insun Chong*, Kevin Yuqi Wang, Christie M. Lincoln

Department of Radiology, Baylor College of Medicine, One Baylor Plaza, BCM 360, Houston, TX 77030, United States

46 cas rapportés d'infection aux cryptocoques sous Fingolimod

Attention aux céphalées fébriles sous S1P inhibiteurs (fingolimod, siponimod, ozanimod, ponesimod…)

Sécurité à long terme: risques infectieux LEMP

LEMP signalés chez des personnes atteintes de SEP traitées par

Natalizumab (Tysabri)
Fingolimod (Gilenya)
Diméthylfumarate (Tecfidera)

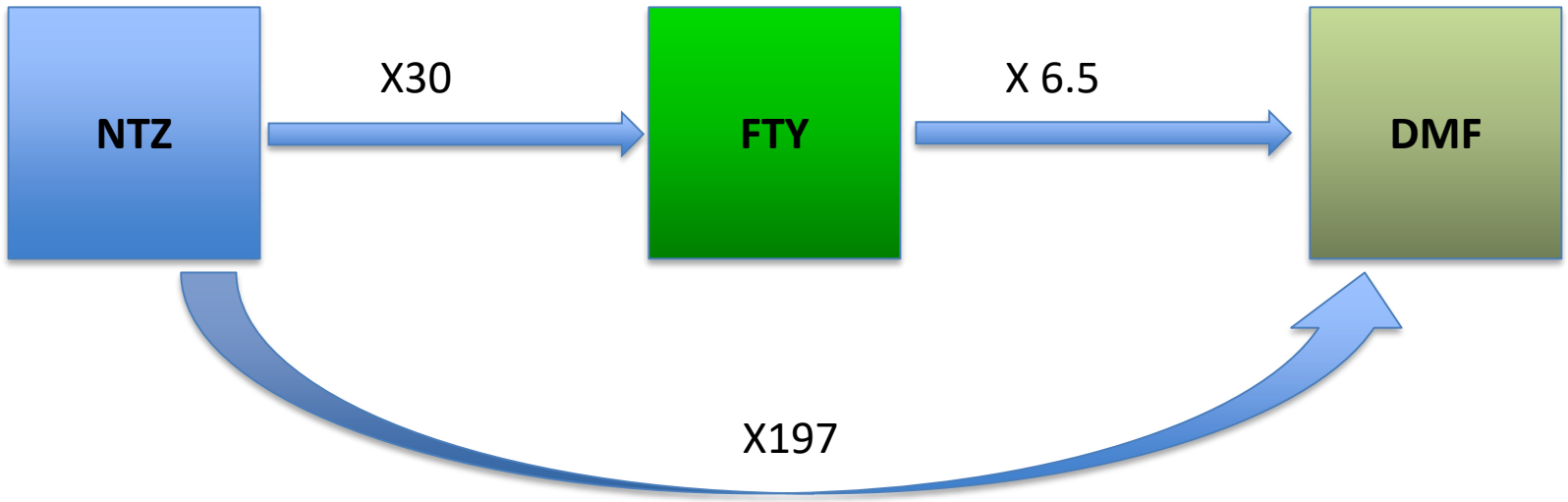
Peut se manifester un peu comme une poussée de SEP:

· troubles de la coordination, maladresse;
· altération du langage (aphasie);
· pertes de mémoire;
· troubles de la vision;
· faiblesse des bras et des jambes qui va en s'aggravant.

leucoencéphalopathie multifocale progressive (LEMP)

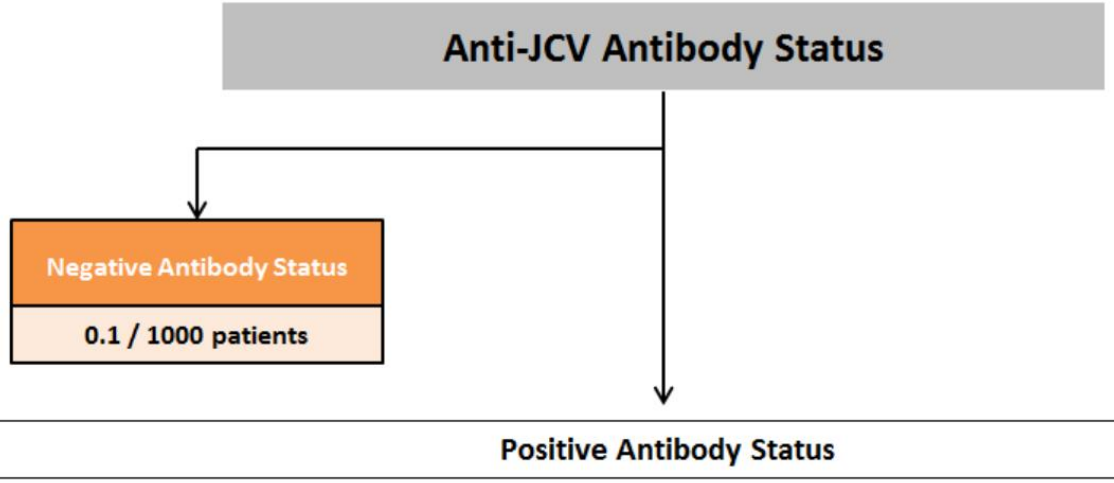
MS Disease-modifying treatments and PML risk

- NTZ: 839 PML; incidence: 39.4/10’000 pts
- FTY: 40 PML; incidence: 1.3/10’000 pts
- DMF: 11 PML; incidence: 0.2/10’000 pts



Courtesy slide of Prof. Du Pasquier
Adapted from communication from Biogen and Novartis, Jan. 2021

PML: risk stratification for Natalizumab



Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Natalizumab and PML risk factors in real-life in 2020

- 36 University Hospitals in Europe.
- 1,307 multiple sclerosis patients (70.8% JCV positive antibodies) treated with natalizumab for a median time of 3.28 years.
- 35 PML cases

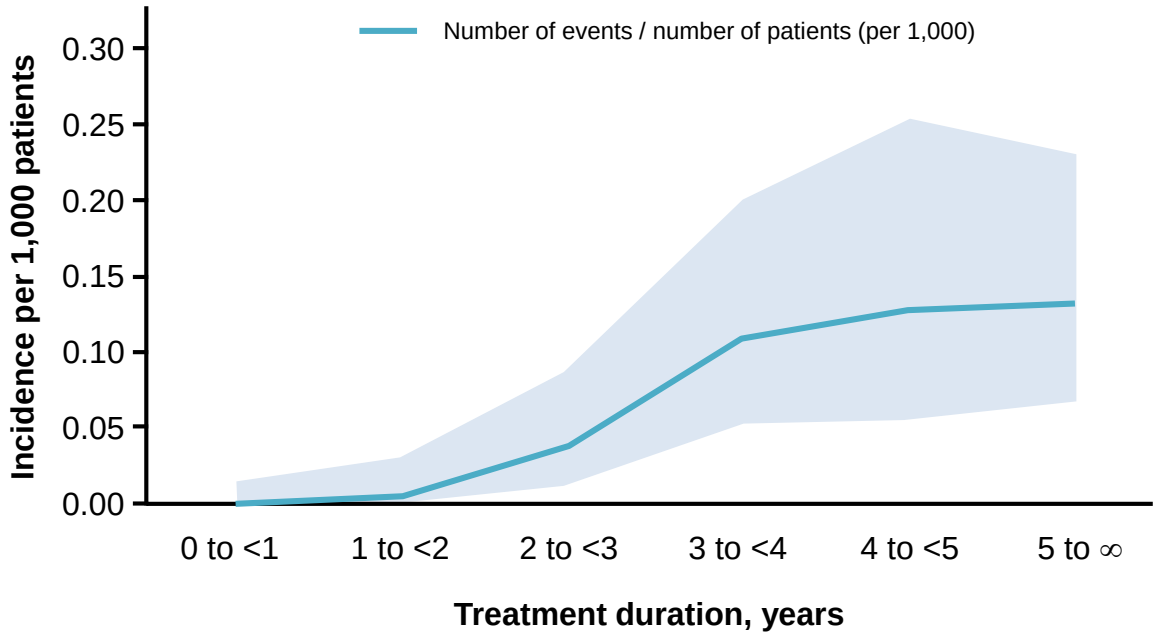
Significant risks of PML

- Age older than 45 years at natalizumab onset
- JCV Stratify Index >0.9
- Annualized relapse rate <0.5

Toboso et al, New Algorithms Improving PML Risk Stratification in MS Patients Treated With Natalizumab
Front. Neurol., 17 December 2020

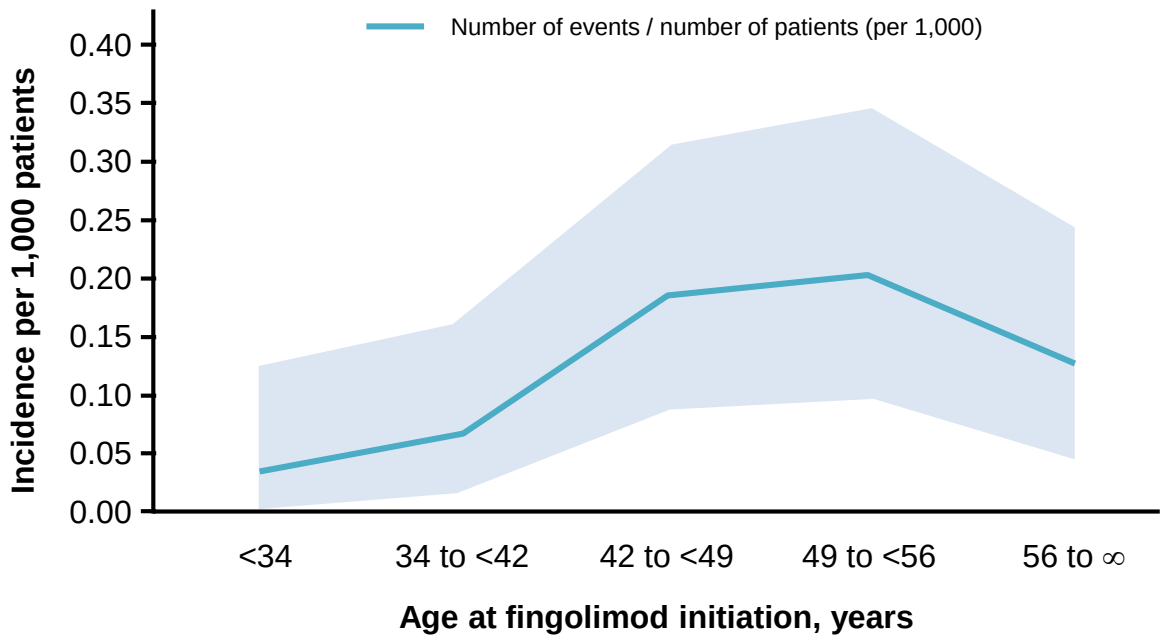
Incidence of PML in Fingolimod-treated patients according to treatment duration and age

Incidence of PML per 1,000 patients by treatment duration



Shaded area represents 95% confidence intervals

Incidence of PML per 1,000 patients by age at fingolimod initiation



Shaded area represents 95% confidence intervals

Courtesy slide of Prof. Du Pasquier
Adapted from Fox et al, Oral presentation FC02.02 at ECTRIMS/ACTRIMS 2020

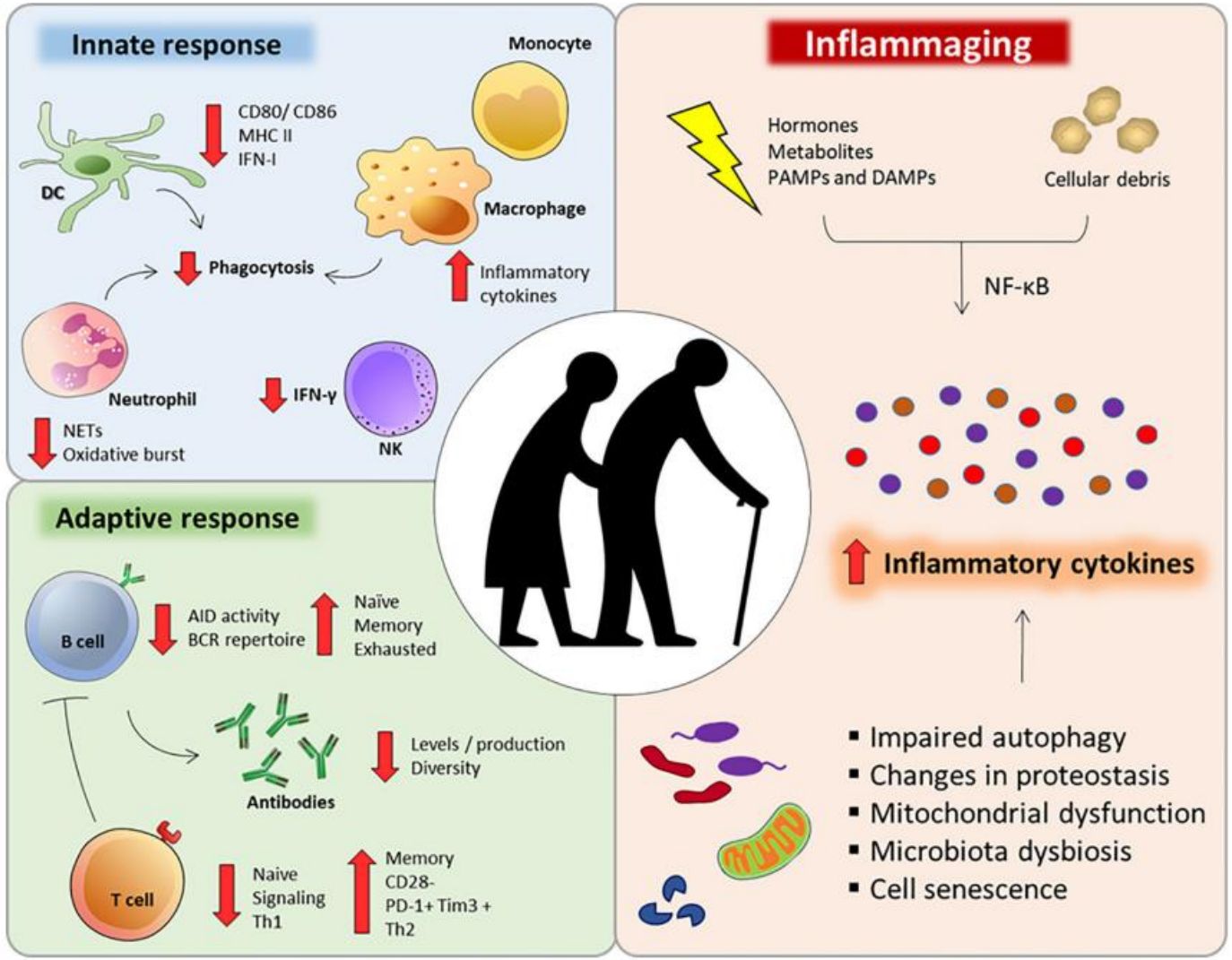
Table 3. Selected adverse events of DMTs and correlation with age

Drug	Most important adverse events	(Potentially) increased risk with age	References
Natalizumab	Occurrence of PML		Dong-Si *et al.*, 2015 [37] Blankenbach *et al.*, 2019 [38] Bachelet *et al.*, 2016 [39]
	Fatal cases of PML	(↑)	
	HSV1/VZV reactivation	↑	
	Neutralizing antibodies	(↑)	
Fingolimod	Bradycardia	↑	Lebrun *et al.*, 2018 [6▪] Berger *et al.*, 2018 [40▪] Ritter *et al.*, 2017 [41]
	Arterial hypertension	↑	
	HSV1/VZV reactivation	↑	
	PML	(↑)	
	Skin malignancies (BCC)	↑	
	HPV infection		
Alemtuzumab	HSV1/VZV reactivation	↑	Huhn *et al.*, 2018 [42] Pfeuffer *et al.*, 2019 [43]
	Listeriosis, candidiasis, nocardiosis		
	Secondary autoimmune diseases		
Cladribine	HSV1/VZV reactivation	↑	EMA, Mavenclad EPAR 2017 [44]
	Tuberculosis		
	Solid malignancies	↑	
Ocrelizumab	HSV1/VZV reactivation	↑	EMA, Ocrevus EPAR 2018 [45]
	HBV		
	Hypogammaglobulinemia	(↑)[a]	
	Breast cancer	↑	
	PML (carry over)	(↑)	

Schweitzer F et al. Age and the risks of high-efficacy disease modifying drugs in multiple sclerosis Current Opinion in Neurology: June 2019 - Volume 32 - Issue 3 - p 305-312

Système immunitaire et âge: immunosénescense

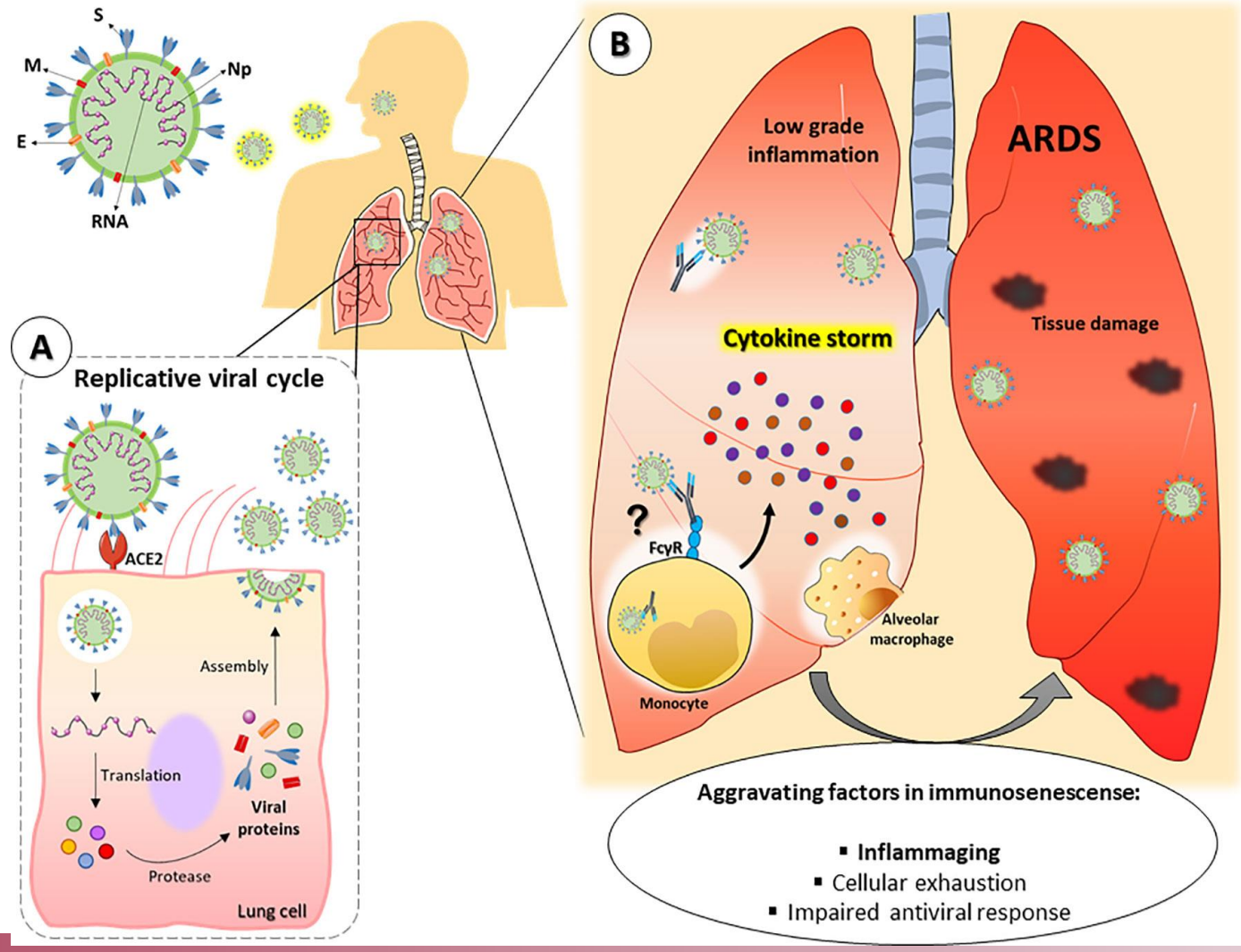
Affaiblissement du système immunitaire avec l'âge.



Pietrobon AJ, Teixeira FME and Sato MN (2020) Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Front. Immunol. 11:579220. doi: 10.3389/fimmu.2020.579220

Immunosénescense: COVID

Covid-19

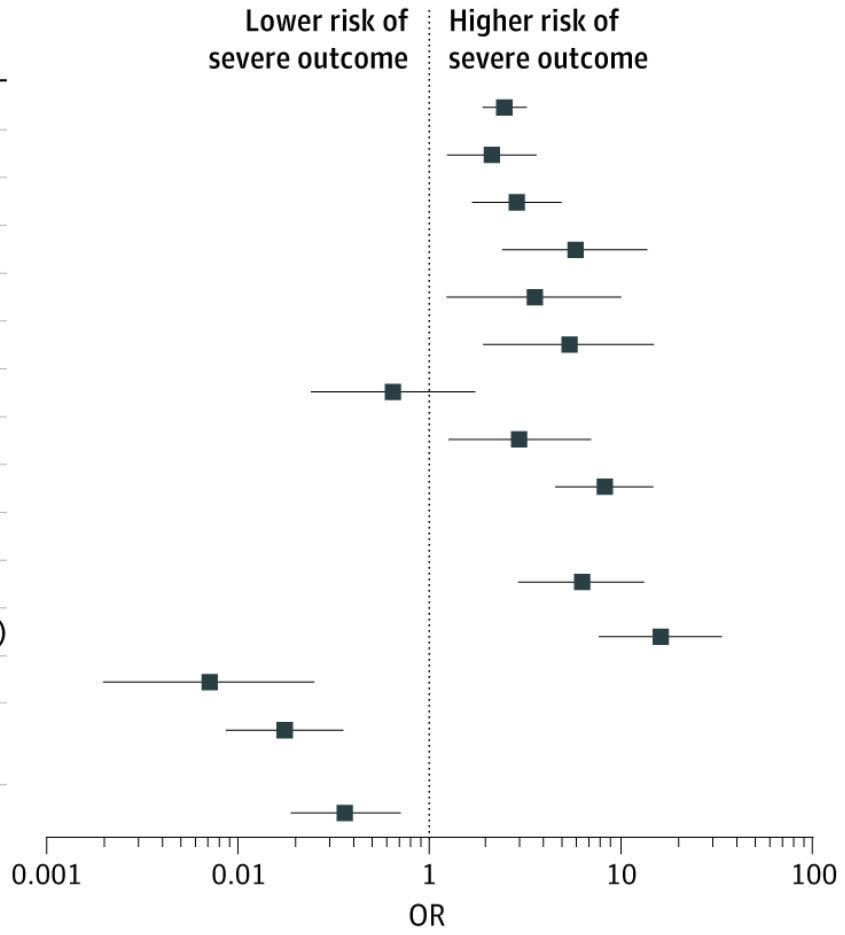


Pietrobon AJ, Teixeira FME and Sato MN (2020) Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Front. Immunol. 11:579220. doi: 10.3389/fimmu.2020.579220

COVID et SEP

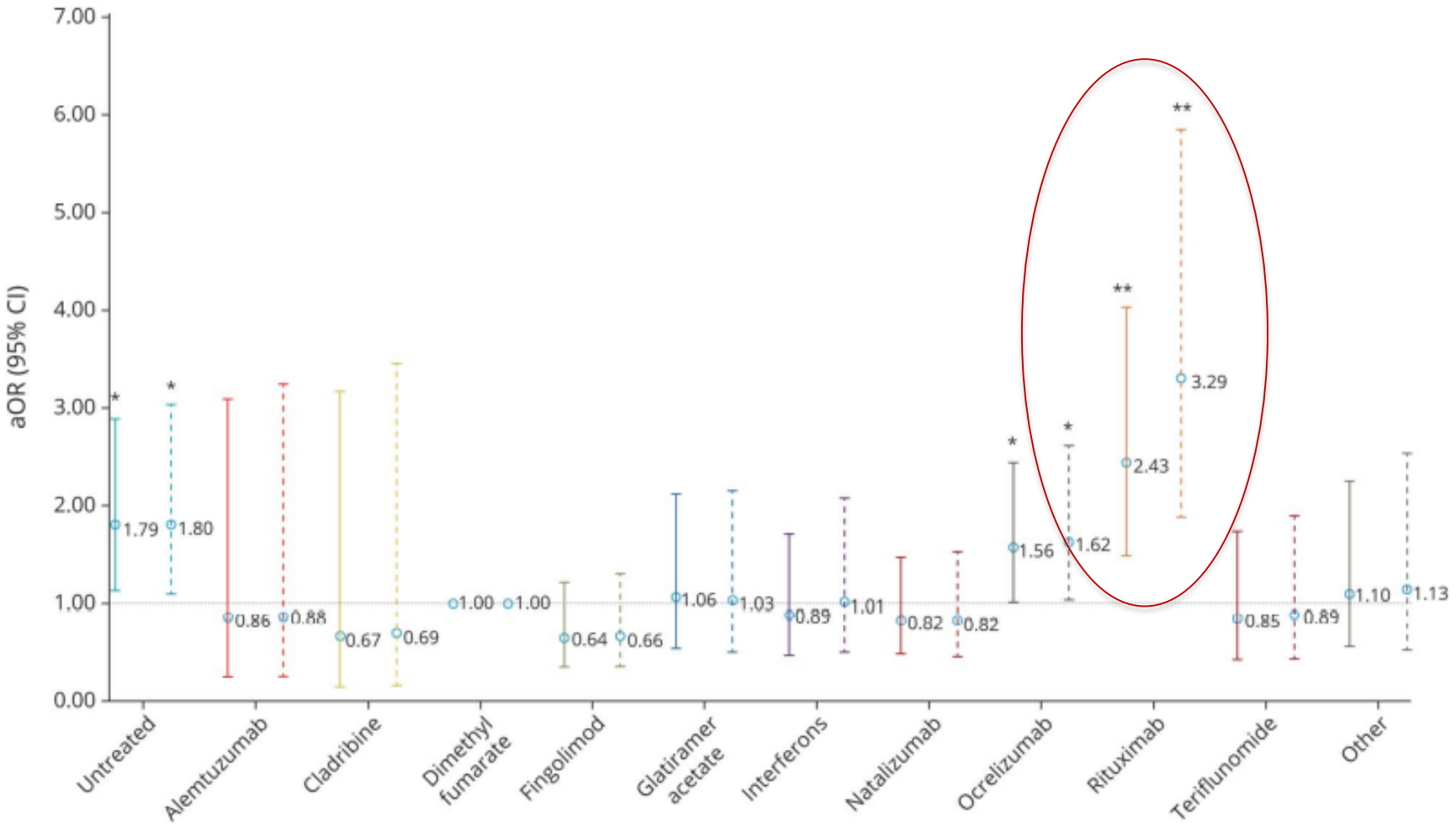
A Univariate analysis

Group	OR (95% CI)
Age per 10 y	2.49 (1.92-3.22)
Male	2.11 (1.23-3.63)
≥1 Comorbidity	2.93 (1.73-4.99)
Cardiac comorbidity	5.72 (2.39-13.66)
Pulmonary comorbidity	3.53 (1.23-10.07)
Diabetes	5.36 (1.93-14.95)
Smoking	0.65 (0.24-1.74)
Obesity	2.95 (1.25-6.94)
Progressive course	8.22 (4.52-14.96)
EDSS <3	NA
EDSS 3-5.5	6.28 (2.97-13.26)
EDSS ≥6	16.10 (7.72-33.58)
Interferon or glatiramer acetate	0.07 (0.02-0.25)
Teriflunomide, dimethlyfumarate, natalizumab, or other	0.18 (0.09-0.36)
Alemtuzumab, cladribine, fingolimod, ocrelizumab, or rituximab	0.37 (0.19-0.72)



JAMA Neurol. 2020;77(9):1079-1088.

Figure 2 Risk of Hospitalization by DMT Among Suspected/Confirmed (Solid Line) and Confirmed-Only (Dashed Line) Cases



Simpson-Yap S, De Brouwer E, Kalincik T, et al. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. *Neurology*. 2021;97(19)

Nouveaux traitements et risques infectieux: prévention

Avant de débuter un traitement de fond:

- Remettre le carnet de vaccin à jour et discuter vaccins Prévenar, Hépatite B, VZV, COVID
- Sous certains traitements, la réponse immunitaire est diminuée
- Les vaccins ne sont pas contre-indiqués dans la SEP (caveat fièvre jaune)
- Eviter les vaccins vivants (risque bénéfice)
- Vacciner en période “calme”, à distance d’une poussée (6 semaines)

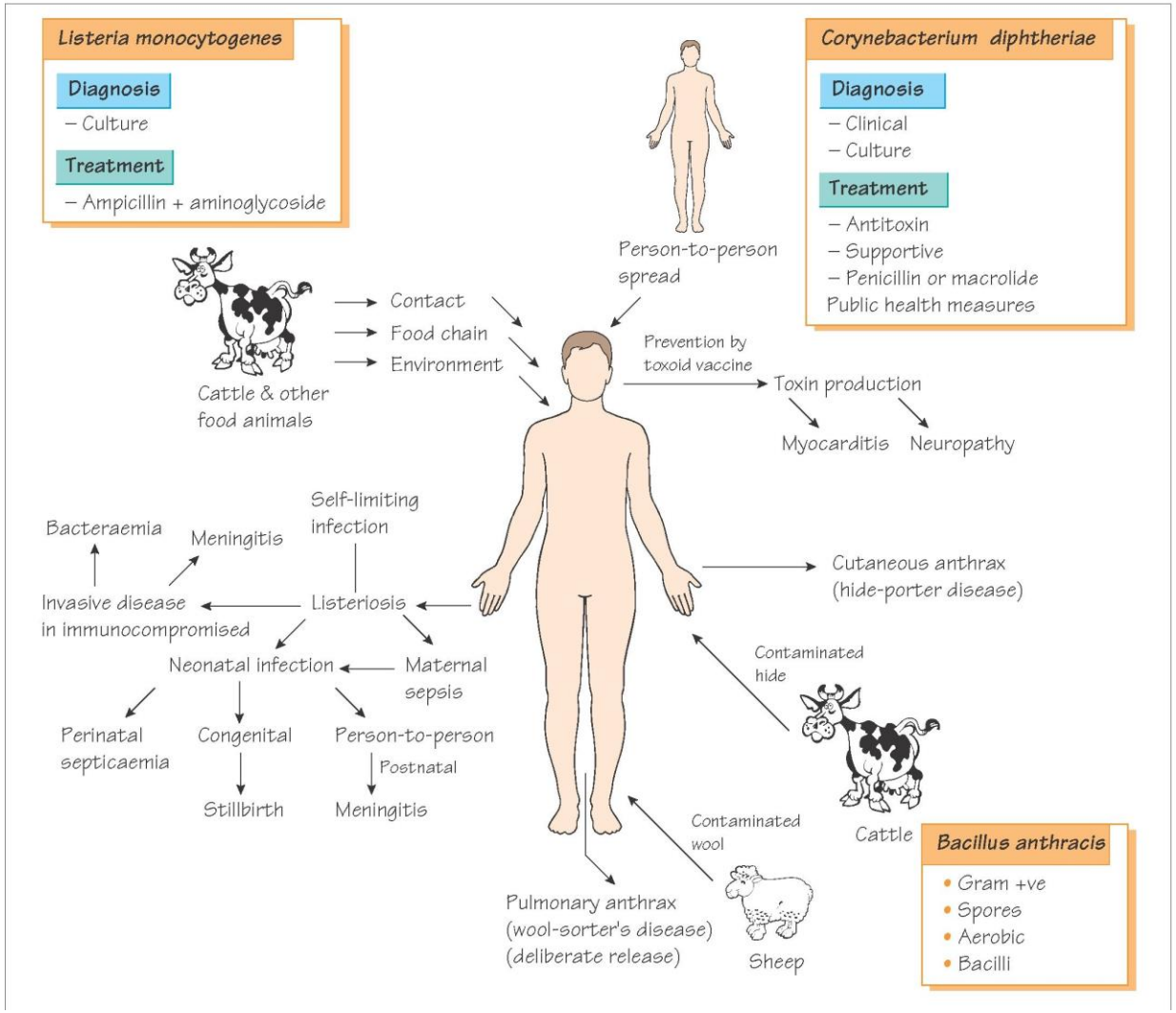
Risque infectieux: prophylaxie anti-infectieuse (exemple Alemtuzumab)

Listeria meningitis 0.26% of listeria meningitis (32 cas)
incubation 1 to 91 days

Recommendation:

Pas de consommation de produit laitier non pasteurisé

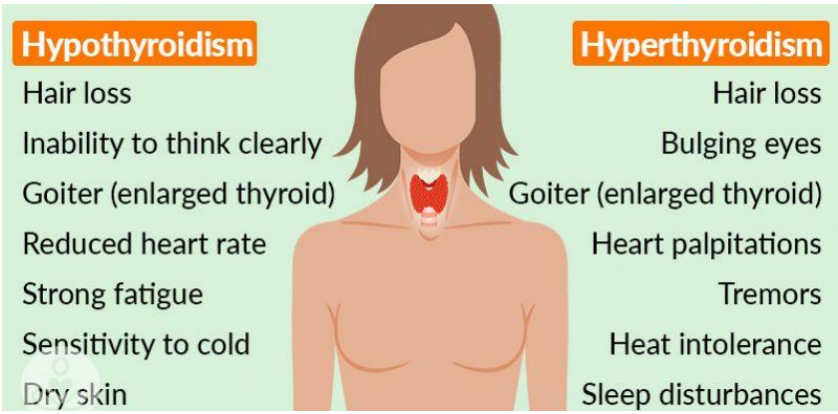
Prophylaxie anti-bactérienne: Bactrim (min. 1 mois)



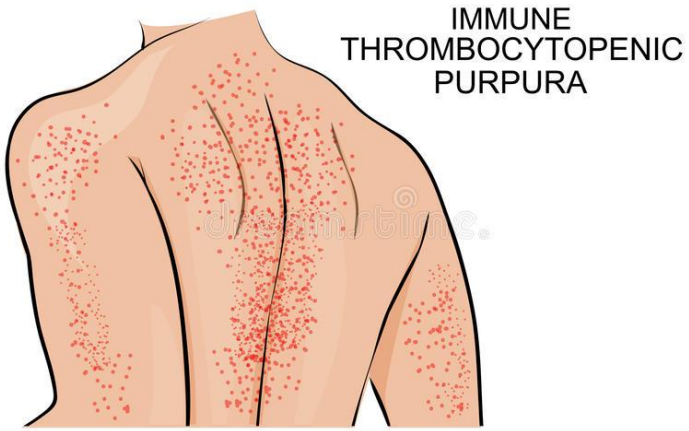
Nouveaux traitements biologiques: risque d'autoimmunité

Exemple: Alemtuzumab

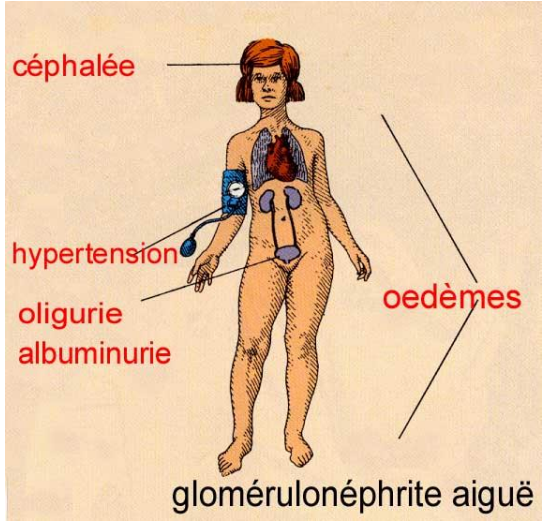
Troubles endocrinologiques



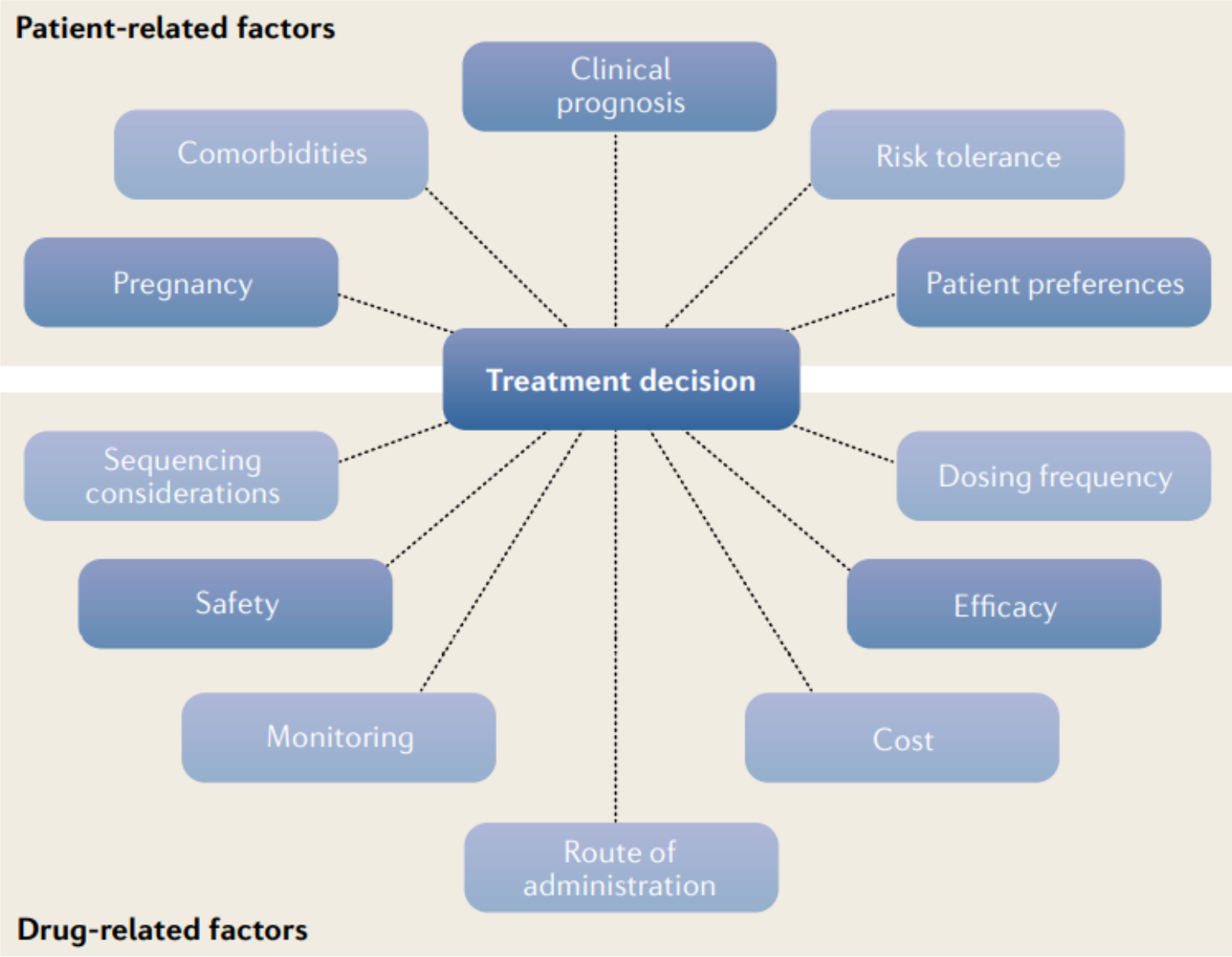
Troubles hématologiques



Troubles néphrologique



Quels traitements pour quels patients?


Patient-related factors
Clinical prognosis
Comorbidities
Risk tolerance
Pregnancy
Patient preferences
Treatment decision
Sequencing considerations
Dosing frequency
Safety
Efficacy
Monitoring
Cost
Route of administration
Drug-related factors

Demographic and environmental factors

- Older age
- Male sex
- Not of European descent
- Low vitamin D levels
- Smoking
- Comorbid conditions

Clinical factors

- Primary progressive disease subtype
- A high relapse rate
- A shorter interval between the first and second relapses
- Brainstem, cerebellar or spinal cord onset
- Poor recovery from the first relapse
- A higher Expanded Disability Status Scale score at diagnosis
- Polysymptomatic onset
- Early cognitive deficits

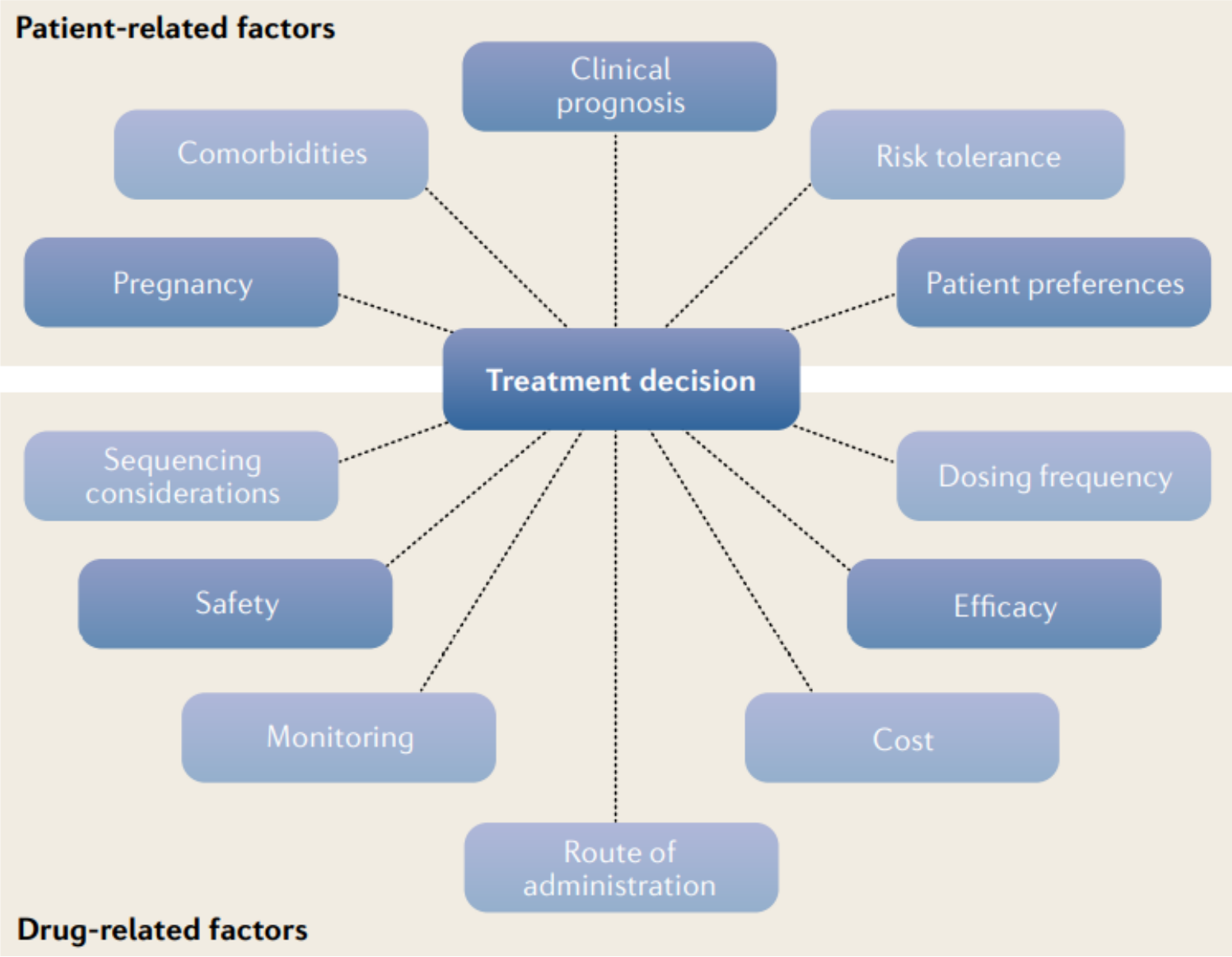
Poor prognosis

MRI observations

- A high number of T2 lesions
- A high T2 lesion volume
- The presence of gadolinium-enhancing lesions
- The presence of infratentorial lesions
- The presence of spinal cord lesions
- Whole brain atrophy
- Grey matter atrophy

Biomarkers

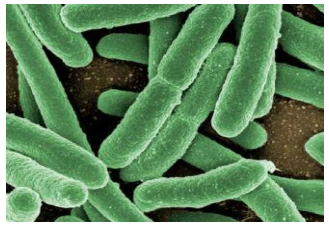
- A high number of T2 lesions
- The presence of IgG and IgM oligoclonal bands in the CSF
- High levels of neurofilament light chain in the CSF and serum
- High levels of chitinase in the CSF
- Retinal nerve fibre layer thinning detected with optical coherence tomography


Patient-related factors
Clinical prognosis
Comorbidities
Risk tolerance
Pregnancy
Patient preferences
Treatment decision
Sequencing considerations
Dosing frequency
Safety
Efficacy
Monitoring
Cost
Route of administration
Drug-related factors


DÉSIR D'ENFANT
ET SEP SONT
COMPATIBLES

Et ne pas oublier…

Importance d’une bonne hygiène de vie



Conclusion

La SEP est une maladie chronique invalidante

Les atteintes neuronales et axonales sont précoces

Diagnostiquer et traiter le plus tôt possible (escalade versus induction)

Multiples nouveaux traitements efficaces

Prévention des complications infectieuses:
les vaccins ne sont pas contre-indiqués dans la SEP

Garder un oeil ouvert: effets secondaires, infections opportunistes

Jacqueline du Pré
Diagnostic de sclérose en plaques ***en 1973***

Alice Sara Ott
Diagnostic de la sclérose en plaques ***en 2019***

Merci pour votre attention

Questions?