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Teaching Course 11

Current treatment in neurology (Level 1)

Multiple Sclerosis: an up-to-date treatment algorithm

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MS: an up-to-date treatment algorithm

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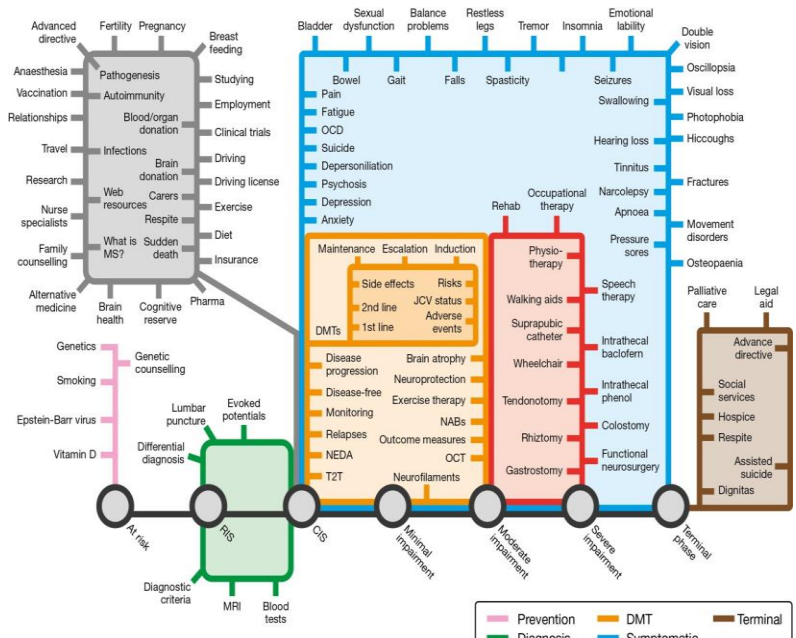
Disclosure of conflict of interest

- Speaker: Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, Teva
- Scientific advisory board: Merck, Novartis, Roche, Sanofi-Genzyme
- Steering committee: Roche

- Introduction
- Impact of the disease. Disability
- Factors to consider for treating
- Treatment:
  - Injectables
  - Orals
  - Monoclonal antibodies
- Escalation vs. induction
- Algorithms of treatment
- Conclusions



Giovanonni, Brainhealth

MS and its treatment has a substantial humanistic and economic burden

Quality of life[1,2]

- Significant reduction in quality of life of the patient
- Impact on family and others close to the patient

Treatment burden[3,4]

- Need for life-long therapy
- Inconvenience of administration and high incidence of side effects associated with many treatment options

Economic burden[1,5]

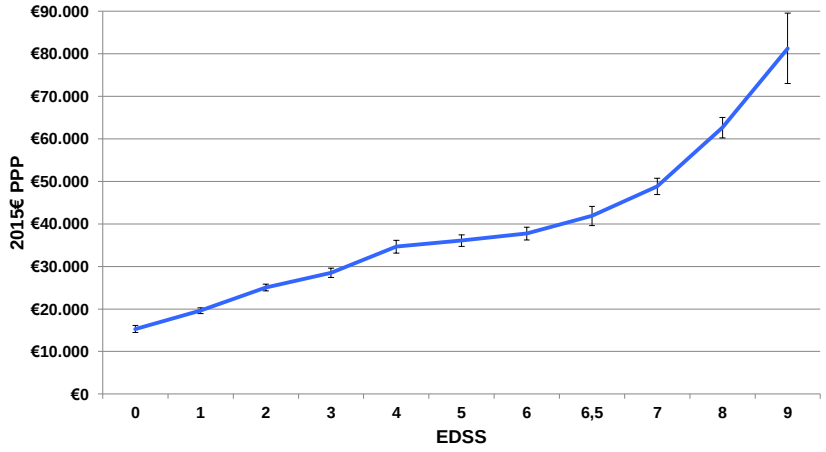
- Early loss of work capacity
- Costs of health services
- Costs of domestic help and accessibility equipment

MS is typically diagnosed in the most active phase of the life of an individual, and thus interferes with important life challenges and responsibilities[1]

1. Fattore G et al. Mult Scler 2012;18(2 Suppl):5–6; 2. Forbes A et al. Clin Rehab 2006;20:67–78; 3. Patti F. Patient Prefer Adherence 2010;4:1–9; 4. Rommer PS et al. Clin Exp Immunol 2014;175:397–407; 5. Whetten-Goldstein K et al. Mult Scler 1998;4:419–25.

Costs related to disability

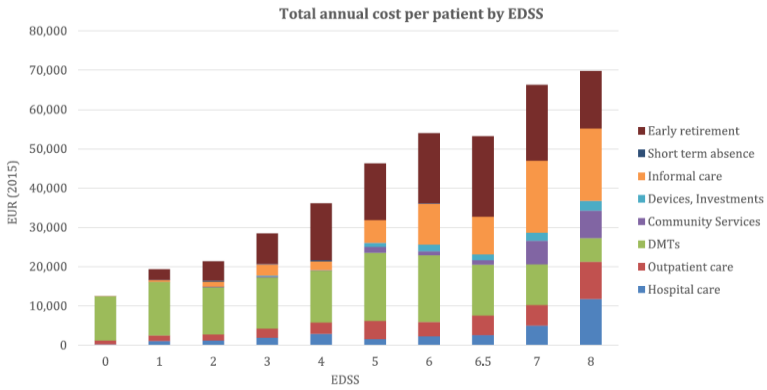
16 countries, N = 16,808, EUR PPP 2015



- Costs are proportional to degree of disability
- The majority of untreated patients develop disability

Source: Kobelt et al, MSJ 23(8) 2017

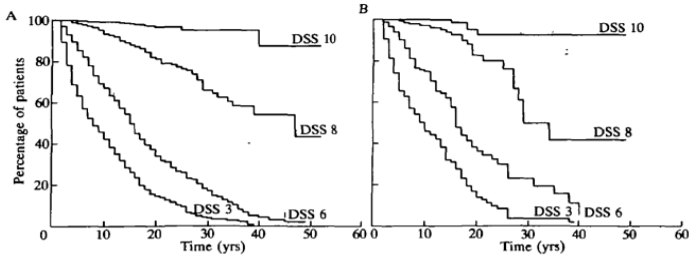
Cost structure (SPAIN)



- The majority of untreated patients develop disability

Oreja-Guevara C, KobeltG, Berg J, CapsaD, Eriksson J; European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: Results for Spain. Mult Scler. 2017 Aug;23(2_suppl):166-178.

Untreated MS Patients Develop Disability



Mean time to DSS 6 (needing a cane) was 15 years; *N* = 1099

At 6–10 years, 30–40% with initial RRMS developed progressive MS

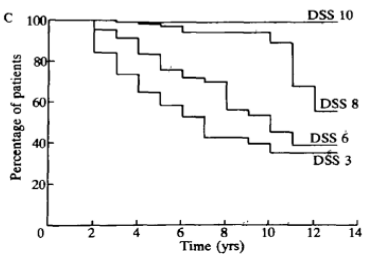
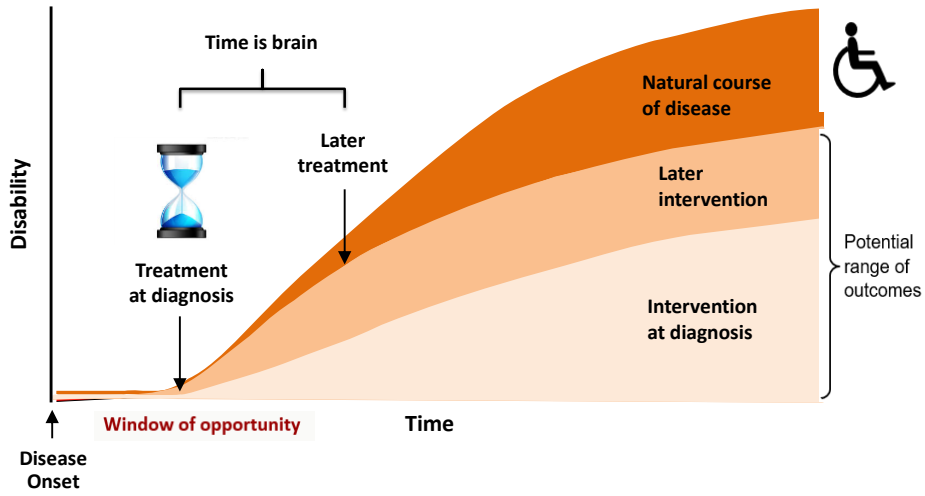


FIG. 1. Actuarial analysis of disability from onset of MS in the (A) total population, (B) Middlesex County subgroup, (C) SO subgroup.

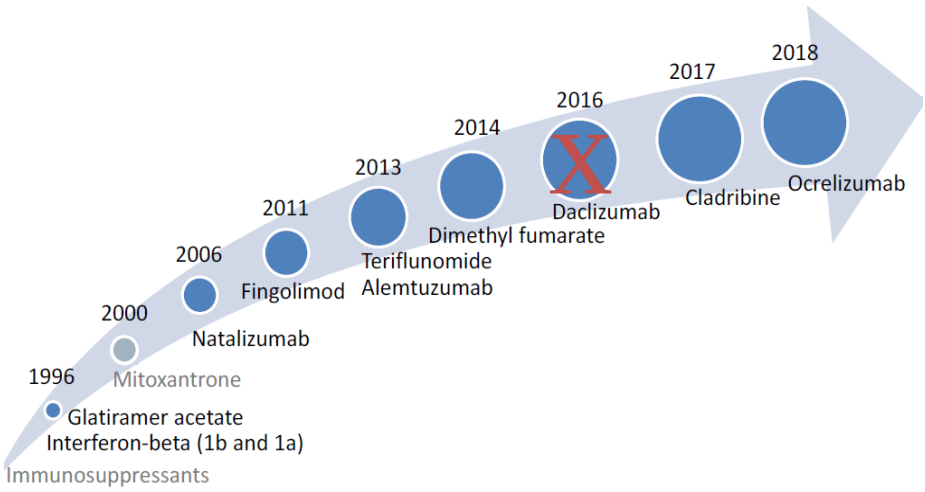
DSS = Disability Status Scale; RRMS = relapse-remitting multiple sclerosis.
Weinshenker et al. Brain. 1989;112(Pt 1):133-146.

Time is brain



Giovannoni et al. Mult Scler Relat Disord. 2016;9(Suppl)1:S5–S48

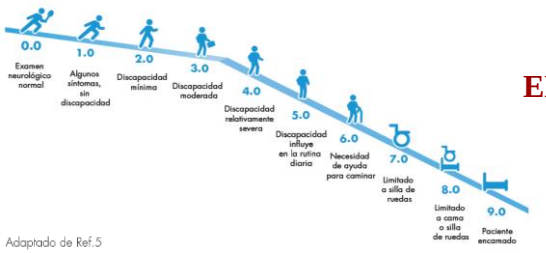
An evolving treatment landscape



1. Betaferon® SmPC, April 2017; 2. Avonex® EU SmPC, July 2017; 3. Rebif® EU SmPC, July 2017; 4. Copaxone® EU SmPC, January 2017; 5. Tysabri® EU SmPC, May 2017; 6. Gilenya® EU SmPC, June 2017; 7. Lemtrada® EU SmPC, July 2016; 8. Aubagio® EU SmPC, June 2017; 9. Tecfidera® EU SmPC, June 2017; 10. Zinbryta® EU SmPC, July 2017; 11. Ocrevus® EU SmPC, January 2018; 12. MAVENCLAD® EU SmPC, September 2017; 13. Plegridy® EU SmPC, August 2017; 14. http://www.tevapharm.com/news/15_european_countries_agree_to_approve_copaxone_08_01.aspx

Therapy of MS

- Treatment of relapses: corticosteroids, plasmapherese
- Symptomatic treatments for pain, fatigue, bladder alterations, tremor…
- Disease modifying treatment (DMTs) : to reduce relapses, progression and radiological activity



Adaptado de Ref.5

EDSS

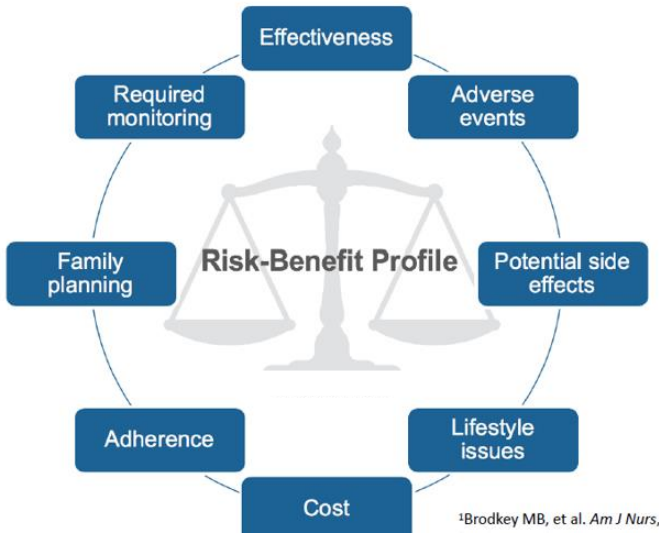
When to start treatment

Disease Modifying Therapies should be started:

- As soon as possible after diagnosis with relapsing disease
- After excluding other conditions in persons with a clinical event and MRIs consistent with MS lesion profiles
- MRI and CSF are recommended to avoid misdiagnosis

CONSENSUS GOAL: Prevent long-term disability

Factors to consider when choosing a therapy



[1]Brodkey MB, et al. *Am J Nurs*, 2011

Factors to consider when choosing a therapy

- **Patient factors** : lifestyle, comorbidities, pregnancy, support system, expectations, risk-taking
- **Disease factors**: clinical/MRI activity, prognostic profile, MS phenotype
- **Drug factors** : efficacy, tolerability, adverse events, safety, route of administration, prior DMT use, required monitoring.

Factors associated with more aggressive MS

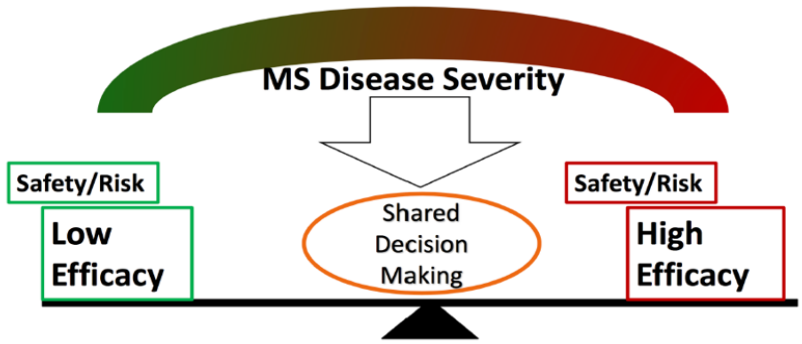
Clinical factors

- Male gender
- Older age at onset
- African American/Hispanic
- Motor/Cerebellar/Sphincter involvement
- Frequent relapses
- Poor recovery from relapses
- Multifocal involvement at onset
- Early cognitive dysfunction

Paraclinical factors

- MRI high lesion burden at presentation
- New T2 lesion(s) in first year of symptom onset
- Brainstem, Cerebellum or Spinal cord lesion(s)
- Brain/spinal cord atrophy early on
- OCT changes early on (RNFL and/or GCIP thinning)
- Oligoclonal Bands present
- Low Vitamin D

Therapy selection: a balancing act



Risk-Benefit information should be communicated to patients ---- shared decision

Disease Modifying Therapies (DMTs)

- Self-injectables: Interferon-beta, Glatiramer acetate
- Oral treatments: teriflunomide, Dimethyl fumarate, cladribine, fingolimod
- Monoclonal antibodies: natalizumab, alemtuzumab, ocrelizumab

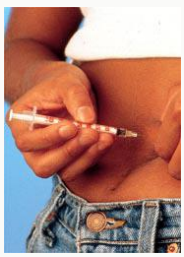
Inyectables treatments

INTERFERONS:

- INTERFERON BETA 1b s.c (BETAFERON®, EXTAVIA®)
- INTERFERON BETA 1a i.m (AVONEX®)
- INTERFERON BETA 1a s.c (REBIF 22®, REBIF 44®)
- INTERFERON BETA 1a PEGILADO s.c (PLEGRIDY®)

GLATIRAMER ACETATE:

- COPAXONE 20® sc
- COPAXONE 40® sc
- Biosimilars



Interferons

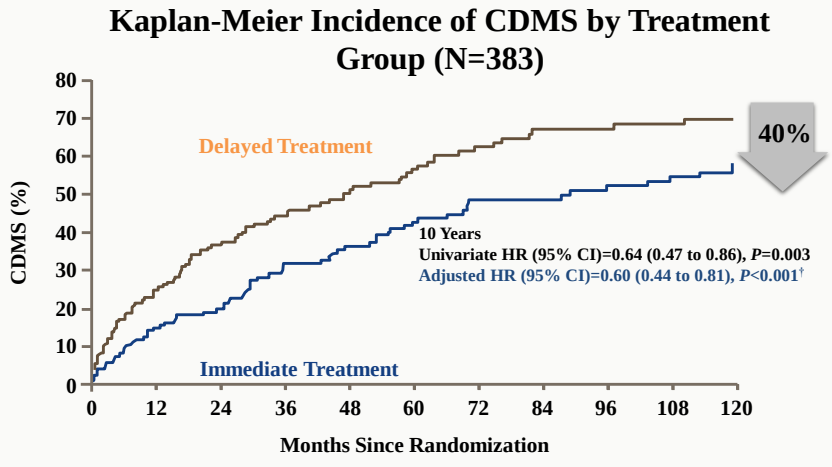
Efficacy in RRMS:

- Injectables: ~30% reduction in annualized relapse rates (ARR)
  - Head-to-head comparisons of injectables have found them more similar than different
  - Pegylated IFNβ-1a appears to have similar efficacy as other IFNβ's

Choice of injectable should be driven primarily by:

- Expected side-effect profile
- Patient preference (IM vs SC; weekly vs. more frequent)

Starting Early Remains Important Even 10 Years Later



*CHAMPIONS study; 10-year, open-label, extension study of patients (N=155) who participated in CHAMPS trial.
†Adjusted for age, qualifying event, baseline MRI T2 lesion volume, and baseline number of Gd+ lesions.
Kinkel R et al. Presented at AAN; April 25–May 2, 2009; Seattle, WA.

Interferons

<u>Safety issues</u>

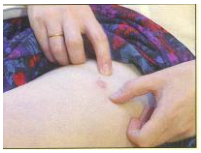
Flu-like syndrom

Local skin reactions

Increase of liver enzymes

Depression

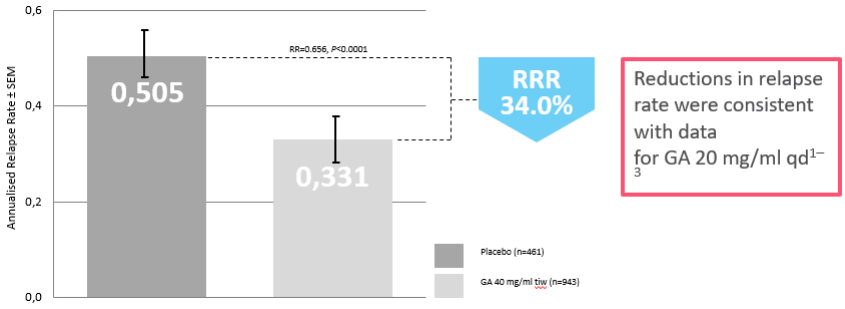
Cytopenias



The majority of Aes observed are usually mild and reversible, and respond well to dose reductions

Glatiramer acetate

- Increases production of anti-inflammatory cytokines (th2) and decreases production of proinflammatory cytokines (th1)
- Significantly greater reduction in ARR for GA 40 mg/ml tiw vs. placebo at 12 months



Glatiramer acetate

Safety issues

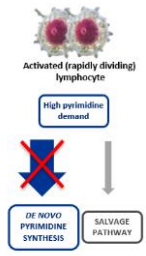
Injection-site reactions

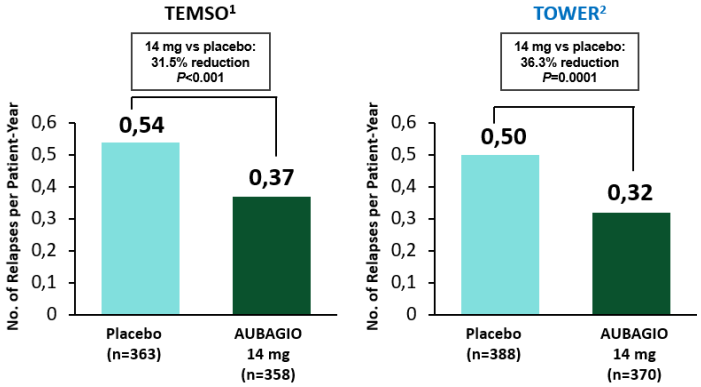
Lipoatrophy

Post-injection systemic reactions

Teriflunomide

Selectively and reversibly inhibits dihydro-orotate dehydrogenase
(DHO-DH), a key enzyme in *de novo* pyrimidine synthesis required by rapidly dividing lymphocytes





Teriflunomide

Safety issues

Hair thinning

Diarrhea

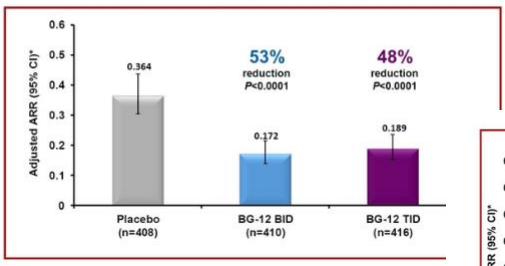
Nausea

ALT increase

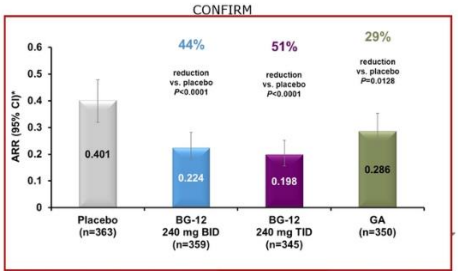
Dimethylfumarate

- Administered orally 240 mgr twice a day
- MoA: Nrf2 pathway

DEFINE



CONFIRM



Dimethylfumarate

Safety issues

Flushing

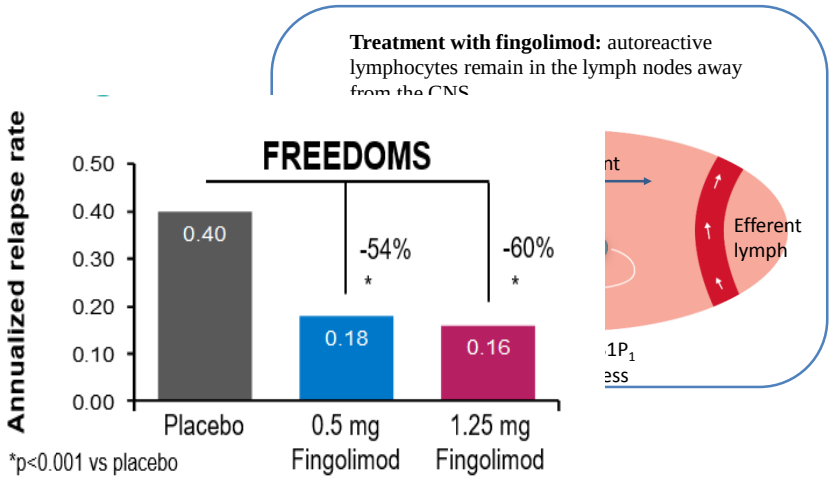
Gastrointestinal effects

Lymphopenia (30% drop at 12 months)

PML (associated with low lymphocyte count)

Fingolimod

- Administered orally 0.5 mg a day



Fingolimod

Safety issues

Bradycardia with first dose

Herpes infections (9%)

Macular edema (0,3-1%)

Liver enzymes abnormalities(14%)

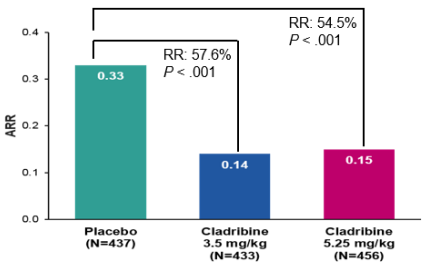
Lymphopenia (very common, usually benign)

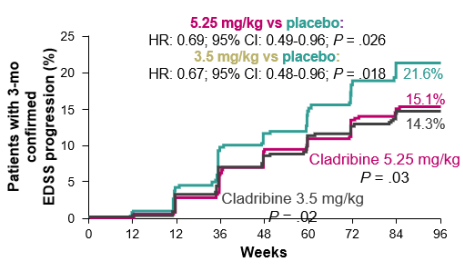
Skin cancer

PML (rare)

Cladribine

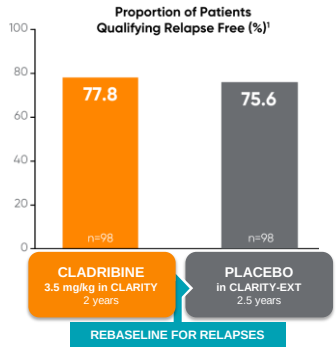
Cladribine a structural analogue of deoxyadenosine with the addition of a chlorine atom

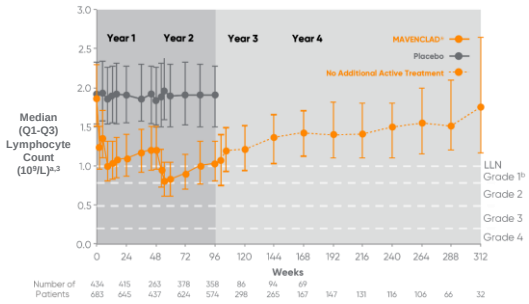




oral cladribine significantly reduced relapse rates and risk of confirmed disability worsening in patients with RRMS

Following CLADRIBINE dosing, efficacy was sustained in years 3 & 4 while lymphocyte counts returned to within normal range[1,2]





Long-lasting efficacy

[a]Pooled data from CLARITY, CLARITY EXT and PREMIERE; figure includes treatment gap. Visits with sample size ≥30 are displayed
[b]Graded according to the Common Terminology Criteria for Adverse Events (CTCAE): 1, <lower limit of normal–800/mm³; 2, <800–500/mm³; 3, <500–200/mm³; 4, <200/mm³. 1. Giovannoni G, et al. Mult Scler J 2017 DOI:10.1177/1352458517727603 p 1-11 2. Giovannoni G, et al. ECTRIMS 2016 Abstract 554, Oral 164 3. Sorensen PS, et al. ACTRIMS 2018 [P084]

Cladribine

Safety issues

Lymphopenia (very common, usually benign)

Fatigue, headache

Herpes infections

A personalized weight-based dosing regimen

Dose of MAVENCLAD® per treatment week by patient weight in each treatment year[1]

Number of tablets (10mg each) per treatment week

WEIGHT RANGE, KG	TREATMENT WEEK 1	TREATMENT WEEK 2
40 to <50	4	4
50 to <60	5	5
60 to <70	6	6
70 to <80	7	7
80 to <90	8	7
90 to <100	9	8
100 to <110	10	9
≥110	10	10

MAVENCLAD® 10mg tablets per week day[1]

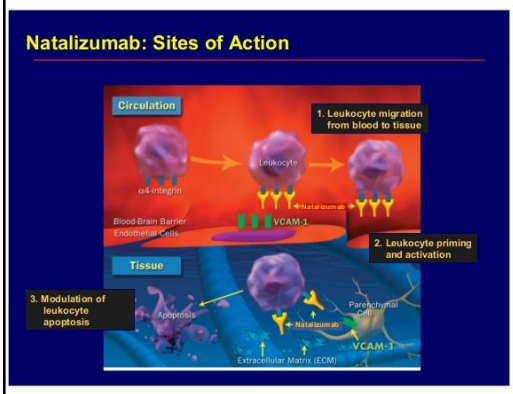
TOTAL NUMBER OF TABLETS PER WEEK	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
4	1	1	1	1	0
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

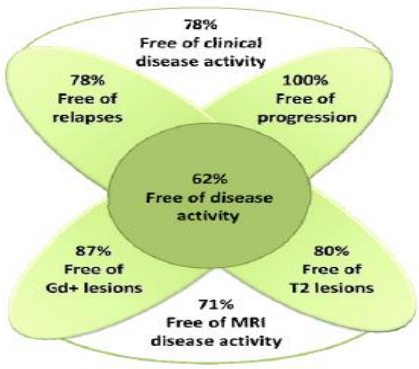
For some weight ranges, the number of tablets may vary from one treatment week to the next. Use of MAVENCLAD® in patients weighing less than 40kg has not been investigated. It is recommended that the daily MAVENCLAD® doses in each treatment week be taken at intervals of 24 hours at approximately the same time each day. If a daily dose consists of 2 tablets, both tablets are taken together as a single dose[1]
*From publicly available information, accurate at date of creation – February 2019. RMS, relapsing MS.

1. MAVENCLAD® EU SmPC, July 2018;
2. Giovannoni G et al. N Engl J Med 2010; 362:416–426.

Natalizumab

Intravenous every 4 weeks





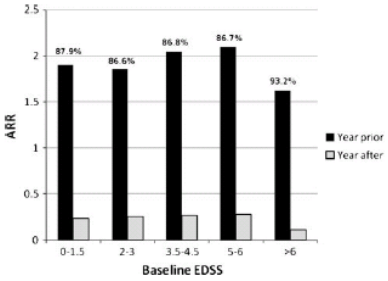
Giovannoni G, Kappos L, Berger J, Cutter G, Fox R, Wiendl H, Chang I, Kasliwal R, Lee L, Licata S, Ho P-R. Incidence of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy and Its Relationship with the Pattern of Natalizumab Exposure over Time. Presented at: 34th Congress of the European Committee for Treatment & Research in Multiple Sclerosis ECTRIMS (2018) Meeting. October 10–12, 2018 I Berlin, Germany. P604.

J Neurol
DOI 10.1007/s00415-012-6414-9

ORIGINAL COMMUNICATION

Natalizumab treatment of multiple sclerosis in Spain: results of an extensive observational study

O. Fernández · C. Oreja-Guevara · R. Arroyo · G. Izquierdo · J. L. Pérez · X. Montalban

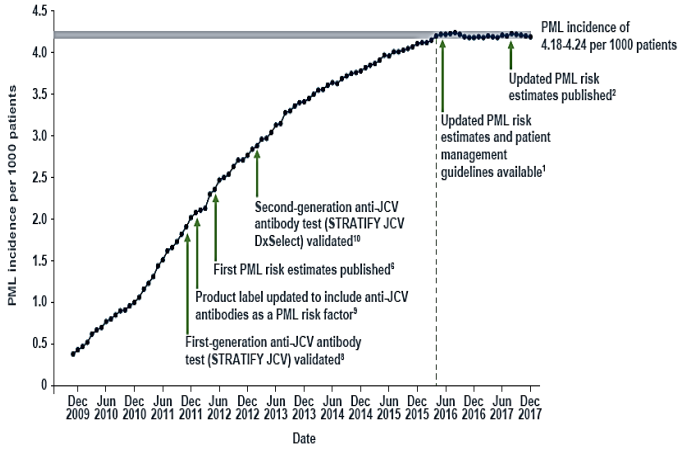


Change in disease status	Time period relative to baseline		
	−12–0 months	0–6 months	6–12 months
Improvement	3.55	17.52	23.77
Stability	68.14	78.68	69.98
Worsening	28.31	3.8	6.25

Natalizumab safety

PML incidence among Natalizumab-treated patients
from November 2009 to December 2017

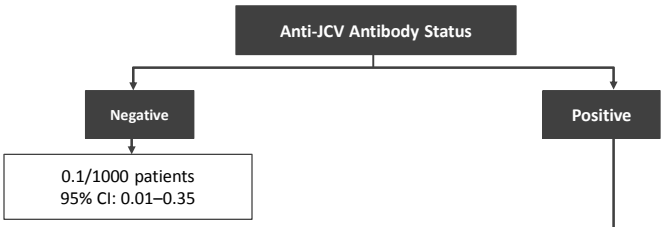
Figure 2. PML incidence among natalizumab-treated patients from November 2009 to December 2017



Green arrows show key milestones in PML risk stratification. The dashed line marks April 2016, when PML incidence appeared to stabilise.

Giovannoni G, Kappos L, Berger J, Cutter G, Fox R, Wiendl H, Chang I, Kasliwal R, Lee L, Licata S, Ho P-R. Incidence of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy and Its Relationship with the Pattern of Natalizumab Exposure over Time. Presented at: 34th Congress of the European Committee for Treatment & Research in Multiple Sclerosis ECTRIMS (2018) Meeting. October 10–12, 2018 I Berlin, Germany. P604.

Updated PML Risk Estimate Algorithm



Natalizumab Exposure, Months*	Patients Without Prior IS Use, per 1000 Patients (95% CI)				Patients with Prior IS Use, per 1000 Patients (95% CI)†
	Index Value Not Available	Index ≤0.9	Index >0.9 to ≤1.5	Index >1.5	
1–12	0.1 (0–0.4)	0.01 (0–0.03)	0.1 (0–0.2)	0.2 (0–0.5)	0.3 (0–1.9)
13–24	0.6 (0.2–1.1)	0.05 (0–0.1)	0.3 (0–0.6)	0.9 (0.3–1.6)	0.4 (0–2.3)
25–36	1.6 (0.9–2.5)	0.2 (0–0.4)	0.8 (0.1–1.5)	2.6 (1.4–3.9)	3.6 (1.4–7.4)
37–48	4.1 (2.8–5.7)	0.4 (0–1.0)	2.0 (0.2–3.8)	6.8 (4.4–9.1)	8.3 (4.3–14.5)
49–60	4.8 (3.2–7.0)	0.5 (0–1.2)	2.4 (0.2–4.5)	7.9 (4.9–10.9)	8.4 (3.7–16.6)
61–72	6.0 (3.7–9.3)	0.6 (0–1.5)	3.0 (0.2–5.8)	10.0 (5.6–14.4)	5.5 (1.1–16.0)‡

Koendgen H et al. Presented at ECTRIMS; September 14–17, 2016; London, UK. P1249.

Extended Interval Dosing Natalizumab: The future?

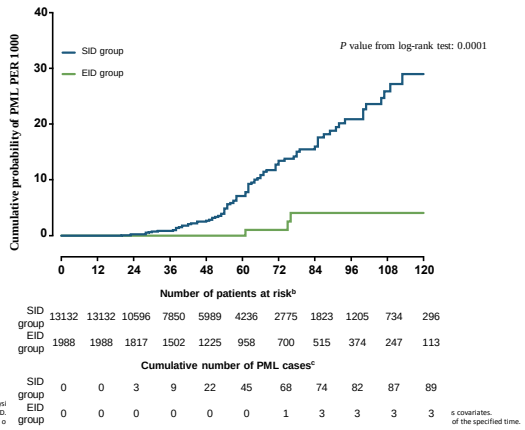
- A retrospective chart review in 9 MS centers was performed in order to identify patients treated with extended interval dosing (EID) of NTZ.
- All patients had SID of NTZ infusions for at least 6 months prior to start of EID
- 1080 patients were on SID and 894 on EID

- The TOUCH® Prescribing Program, a mandatory US risk evaluation and mitigation program, provides the largest data source that could inform on PML risk in patients on EID
- TOUCH Prescribing Program data as of June 1, 2017 were used for this analysis
- This analysis included only patients who were anti–JC virus (anti-JCV) antibody positive
- Hazards of PML in EID and SID cohorts were compared using Cox regression models (adjusted for age, sex, prior immunosuppressant, initiation calendar year, and number of infusions
- The primary definitions of EID and SID use was ≤15 infusions/18 months and >15 infusions/18 months

Table 3 Comparisons of standard interval dosage and extended interval dosage groups on MS activity and NEDA

	SID	Total EID	EED	LED	VED	Within EID
Participants (n)	1080	894	246	269	379	
Percentage with no radiological activity	756/928 81%	558/681 82%	177/195* 91%	114/142 80%	267/344 78%	EED>LED
Percentage of patients with no clinical activity	704/957 74%	464/620 75%	153/203* 75%	121/146 83%	190/271 70%	EED>LED, VED
Percentage of patients with zero combined activity (NEDA)	507/819 62%	373/476 78%	134/192* 70%	89/134 66%	150/254 59%	EED>LED, VED

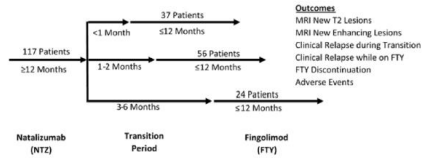
Means and SDs (in parentheses).
(A) Comparisons in columns 2–5 are to SID group. Comparisons between the three EID groups (EED vs LED vs VED) are displayed in column 6.
*Indicates EID group differs from SID group at p<0.05.
Indicates EID group differs from SID group at 0.05<p<0.10.
EED, early extended dosing; EID, extended interval dosing; LED, late extended dosing; MS, multiple sclerosis; NEDA, no evidence of disease activity; SID, standard interval dosing; VED, variable extended dosing.

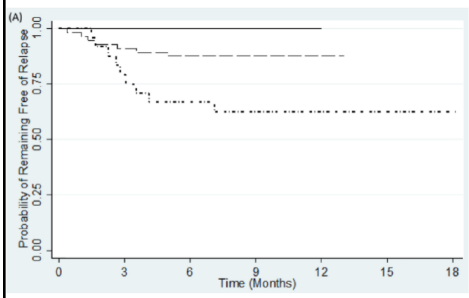


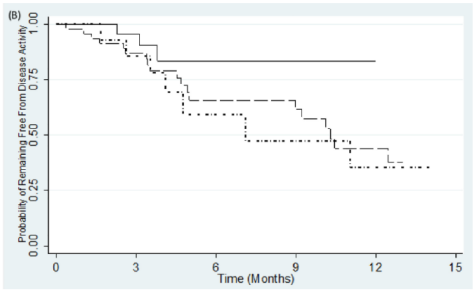
Zhovtis Ryerson et al. JNNP 2016

Zhovtis Ryerson et al ACTRIMS Forum 2018;San Diego, CA

Rebound after natalizumab







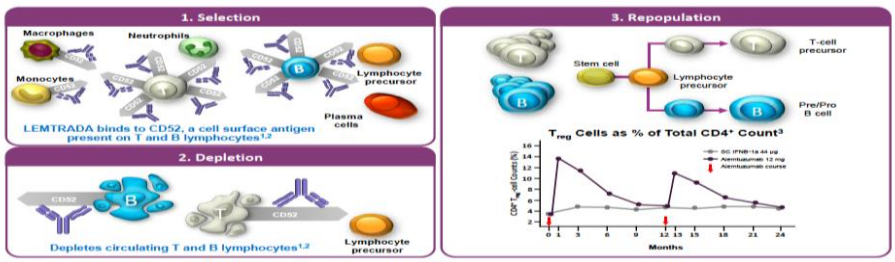
Clinical relapses

Relapses, New T2/Gad lesions

Vollmer, B et al, J Neurol Sci. 2018 Jul 15;390:89-93.

Alemtuzumab

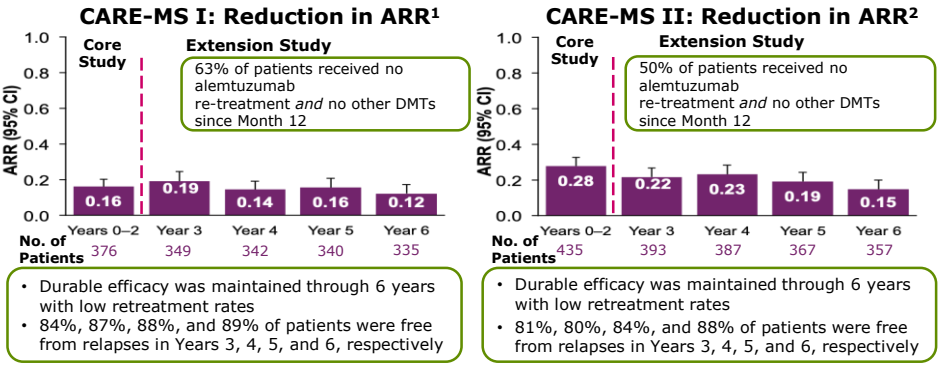
- Non-continuous administration
- Targets the CD52 receptor
- Near complete depletion of lymphocyte populations from the circulation



- Distinctive repopulation pattern, resulting in a relative increase in the proportion of T regulatory and memory lymphocyte subsets and a decrease in cells with a pro-inflammatory signature[4,6]

1. Hu Y, et al. *Immunology*. 2009;128:260-270; 2. Rao SP, et al. *PLoS One*. 2012;7:e39416; 3. Hartung HP et al. ECTRIMS 2012; P935; 4. Cox AL et al. *Eur J Immunol*. 2005;35:3332-3342; 5. Hill-Cawthorne GA et al. *J Neurol Neurosurg Psychiatry*. 2012;83:298-304; 6. Zhang X et al. *J Immunol*. 2013;191:5867-5874.

Alemtuzumab: Annualized Relapse Rate



1. Coles AJ et al. ECTRIMS 2016, Presentation 213; 2. Fox E et al. ECTRIMS 2016, P1150.

Alemtuzumab

Most frequent AEs:

- IARs: rash (53%), headache (52%), pyrexia (29%), and nasopharyngitis (25%)

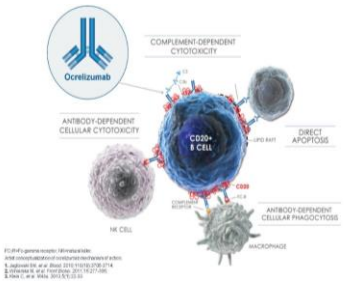
EU label special warnings and precautions for use

- Autoimmunity: Thyroiditis ~30%), ITP (~ 1%), Goodpasture (< 1%)
- Infusion-associated reactions
- Infections: Herpes, Listeria
- Malignancy ?

Ocrelizumab in Relapsing-remitting MS

Non-continuous administration

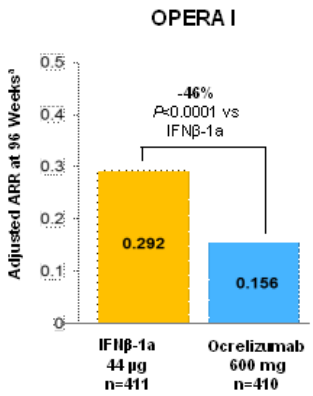
Humanized monoclonal antibody that selectively targets CD20, a cell-surface antigen that is expressed on pre-B cells, mature B cells, and memory B cells but not on lymphoid stem cells and plasma cells

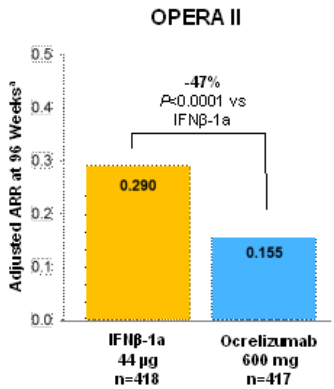


Ocrelizumab exerts its effects by continuous suppression of B cells

- Intravenous every 6 months

Ocrelizumab in Relapsing-remitting MS





Ocrelizumab

Safety issues

Infusion related adverse events (rash, fever, headache)

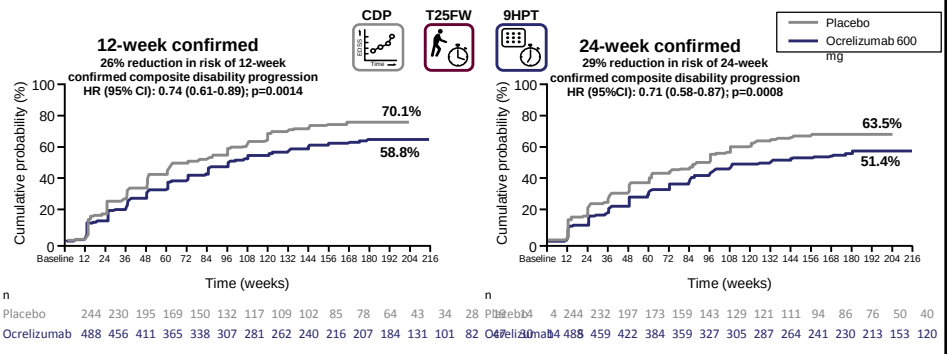
Herpes infections

Upper respiratory and urinary infections

Fatigue

Ocrelizumab in Primary progressive MS

ORATORIO: Time to onset of 12- and 24-week composite confirmed disability progression was delayed with ocrelizumab vs placebo



- Compared with placebo (PBO), OCR significantly reduced the risk of 12-and 24-week confirmed composite disability progression by 26% (p=0.0014) and 29% (p=0.0008), respectively

Giovannoni G. et al. ECTRIMS 2016. Poster 746 and Montalban X, et al. *N Engl J Med* 2017;376:209–220. Suppl. Appendix.

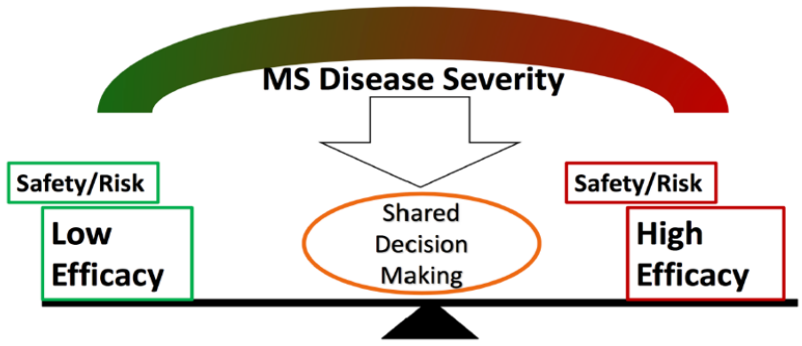
Ocrelizumab in Primary progressive MS

ORATORIO: Summary of efficacy

Endpoint	Risk reduction: OCR vs PBO	P value	Significant?
Time to CDP 12 week	24%	0.0321	●
Time to CDP 24 week	25%	0.0365	●
Progression in T25FWT (baseline to Week 120)	29% reduction	0.0404	●
Percent change in MRI total T2 lesion volume (baseline to Week 120)	PBO: +7.4% OCR: -3.4%	<0.0001	●
MRI total brain volume loss (Week 24 to Week 120)	17.5% reduction	0.0206	●
Change in SF-36 PCS [physical scores] (baseline to Week 120)	PBO: -1.1 OCR: -0.7	0.60	Not significant

CDP, confirmed disability progression; PBO, placebo; OCR, ocrelizumab; SF-36 PCS, SF-36, short form (36); physical component summary; T25FWT, timed 25 foot walk test
Montalban X, et al. *N Engl J Med* 2017;376:209–20; Montalban X, et al. ECTRIMS 2016 (Platform presentation number 228)

Therapy selection: a balancing act

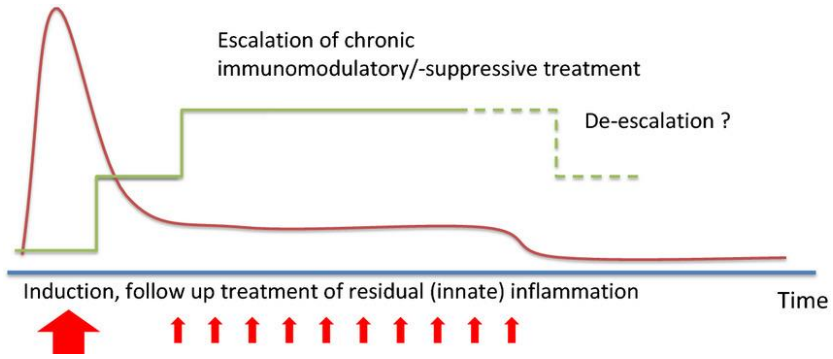


Risk-Benefit information should be communicated to patients ---- shared decision

Treatment paradigms

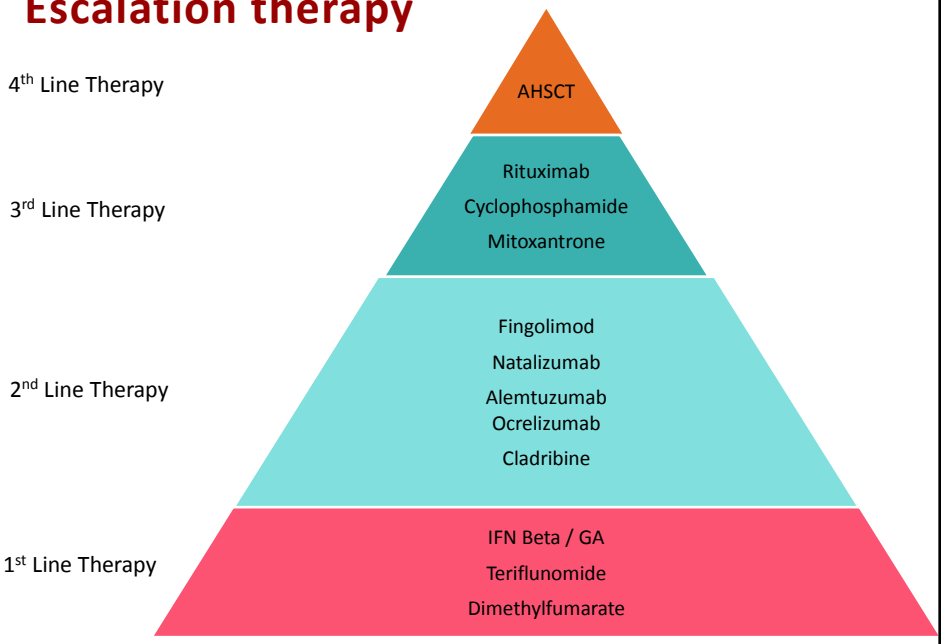
- Immunomodulation versus immunosuppression
- Maintenance versus reconstitution
- Escalation versus induction
- Conventional versus high efficacy

Different approaches to treat



Piehl F. J Intern Med. 2014 Apr;275(4):364-81

Escalation therapy

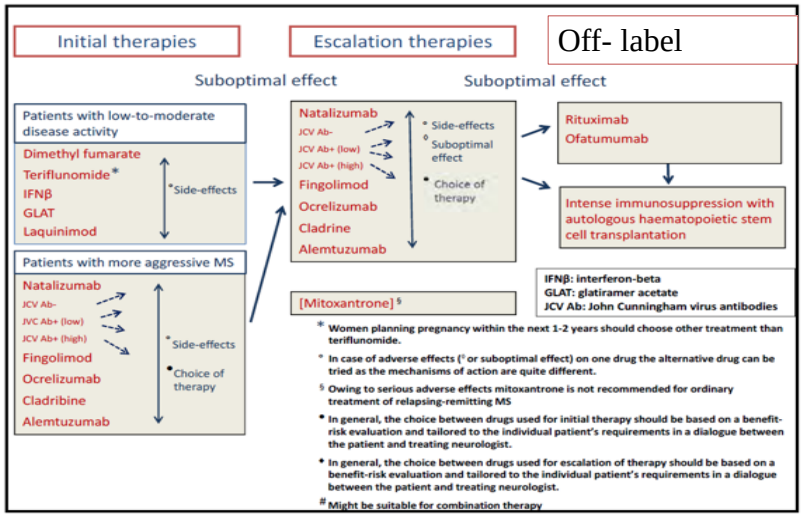


AHSCT: Autologous Hematopoietic Stem Cell Transplantation

ECTRIMS-EAN Guidelines consensus statement

General recommendations	• Adequate infrastructure must be in place for the monitoring, assessment, detection and management of side effects
CIS + abnormal MRI	• IFN and GA should be considered
RRMS	• Early DMD treatment for patients with active RRMS
Monitoring	• MRI and clinical measures to monitor disease • Standardized reference brain MRI within 6 months of initiation[a]
Poor response	• Escalate to a higher efficacy DMD
If higher efficacy DMD is stopped	• Consider another higher efficacy DMD[b]

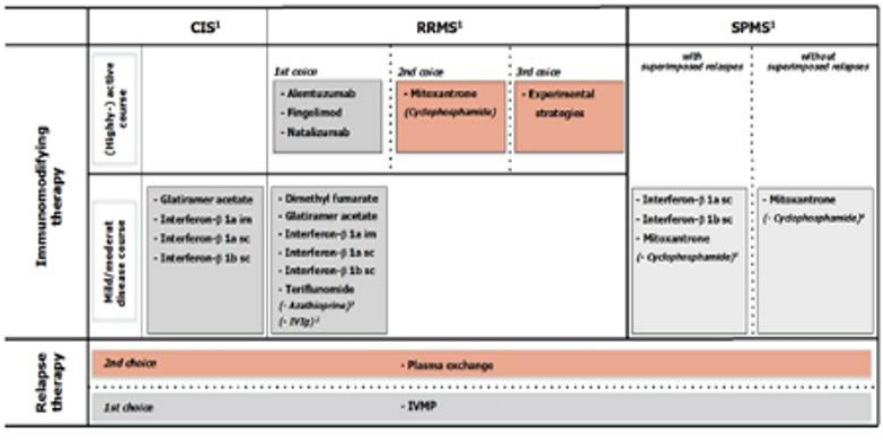
Montalban, X, 2018



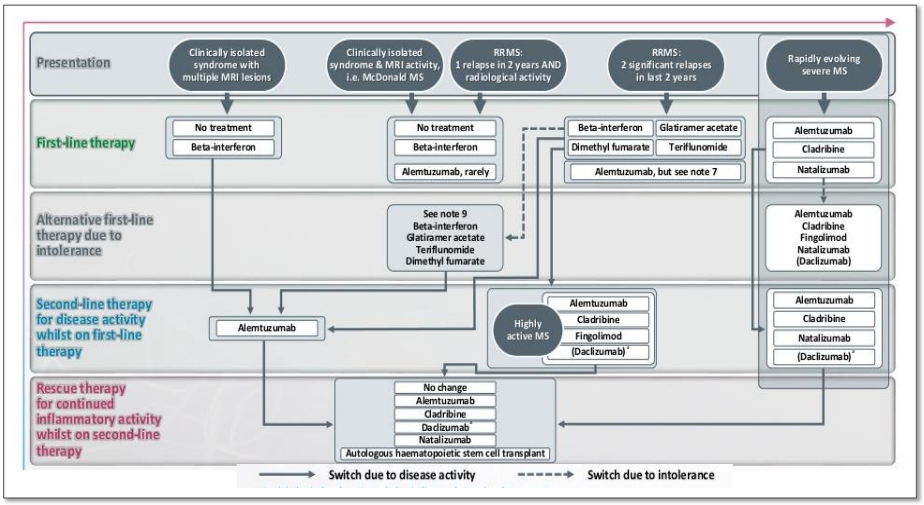
Treatment algorithm for relapsing–remitting multiple sclerosis

Sorensen , 2018

German treatment algorithm



Possible treatment algorithm



*As of March 2, 2018, daclizumab was removed from the market worldwide
Giovannoni G. Sequencing workshop treatment algorithm 2018. Available at: https://www.slideshare.net/gavingiovannoni/sequencing-workshop-treatment-algorithm [Accessed Mar 2018]

Conclusions

- MS is a complex disease
- Untreated patients develop more disability and in a shorter period of time
- Start therapy before disability accumulates
- Balance of benefit/risks of treatment versus risk of disease
- The importance of adherence is related to the success of the treatment
- Goals of treatment: to prevent relapses and long-term progression
- Burden of therapy: tolerability, safety, convenience, monitoring
- DMTs: injectables, orals and monoclonal antibodies for Relapsing-Remitting MS
- Ocrelizumab is the only approved treatment for primary progressive MS
- Take into consideration the associated risks of switching with some treatments: rebound, breakthrough disease, PML
- Escalation vs. induction


Thank you very much