“CONSIDERACIONES DEL CLÍNICO”

Dr. Óscar Fernández :

Presidente – Sociedad Española de Neurología

Disclosures

I have received honoraria as consultant in advisory boards, and as chairmen or lecturer in meetings, and has also participated or participates at present in clinical trials and other research projects promoted by Biogen-Idec, Bayer-Schering; Merck-Serono, Teva, Novartis, Actelion, Almirall , Roche and Allergan.

"Consideraciones del clínico"

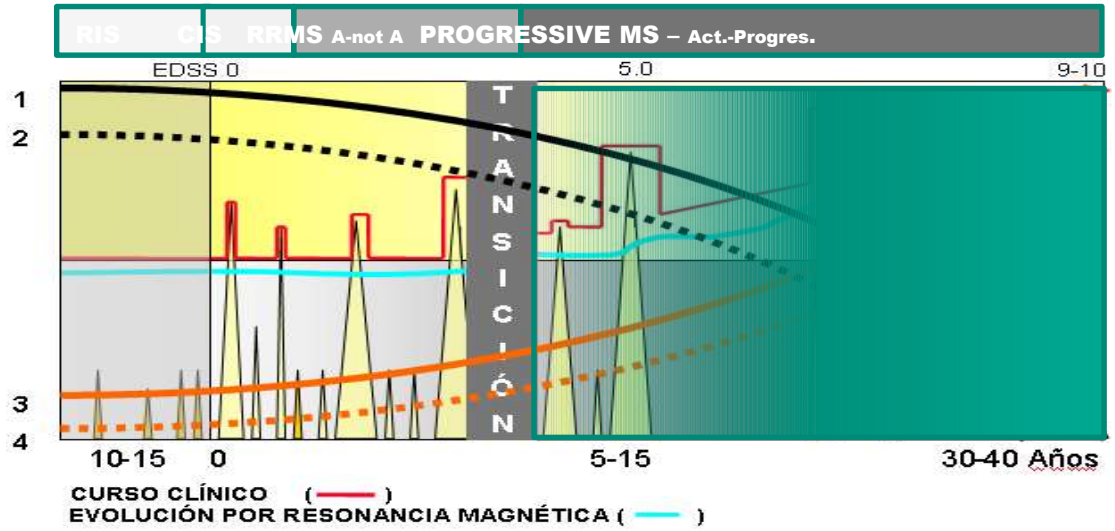
AGENDA

- Proceso de prescripción, ¿cómo se cuenta con el paciente?
- Cuánto pesan las necesidades no cubiertas en la toma de decisión del clínico (patient-related outcomes, conveniencia de los tratamientos).
- Implicación de los datos de vida real en las decisiones del clínico

La esclerosis múliple es una enfermedad compleja

MS EVOLUTION

1. Inflamación / Remielinización (——)
2. Pérdida axonal aguda / Pérdida neuronal (- - -)
3. Pérdida axonal extensa / Pérdida neuronal (——)
4. Desmielinización cortical (· · · ·)



Compensatory Phase
- Adaptative Immune S.
- Altered BBB

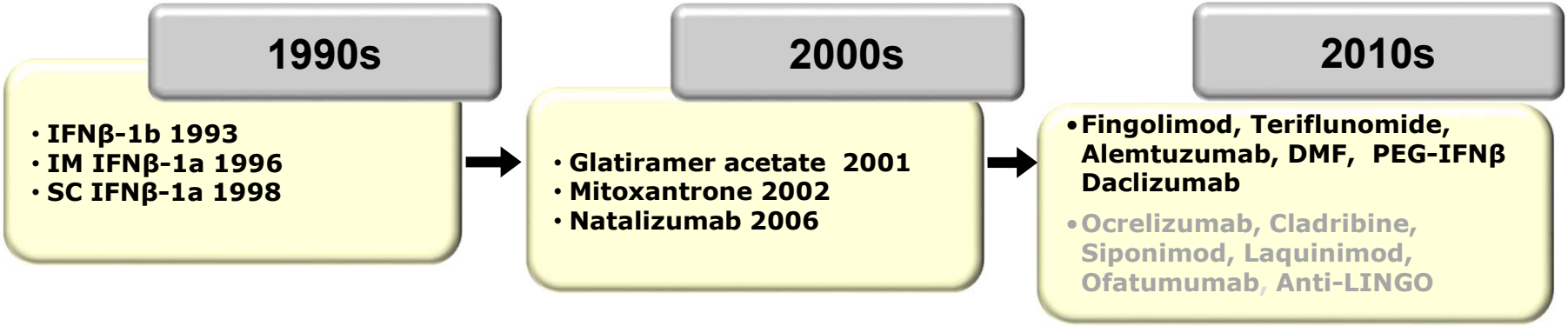
- Restricted focal lesions
- High remyelinative capability (80%)
- OPC differentiation

Non- Compensatory Phase
- Innate immune S (mycroglia)
- Trapped inflammation behind BBB
- B cell follicles
- CNS global inflammation
- Low remyelinative capability (20%)
- Restricted OPC differentiation
- Cortical demyelination

Fernández O. 2014

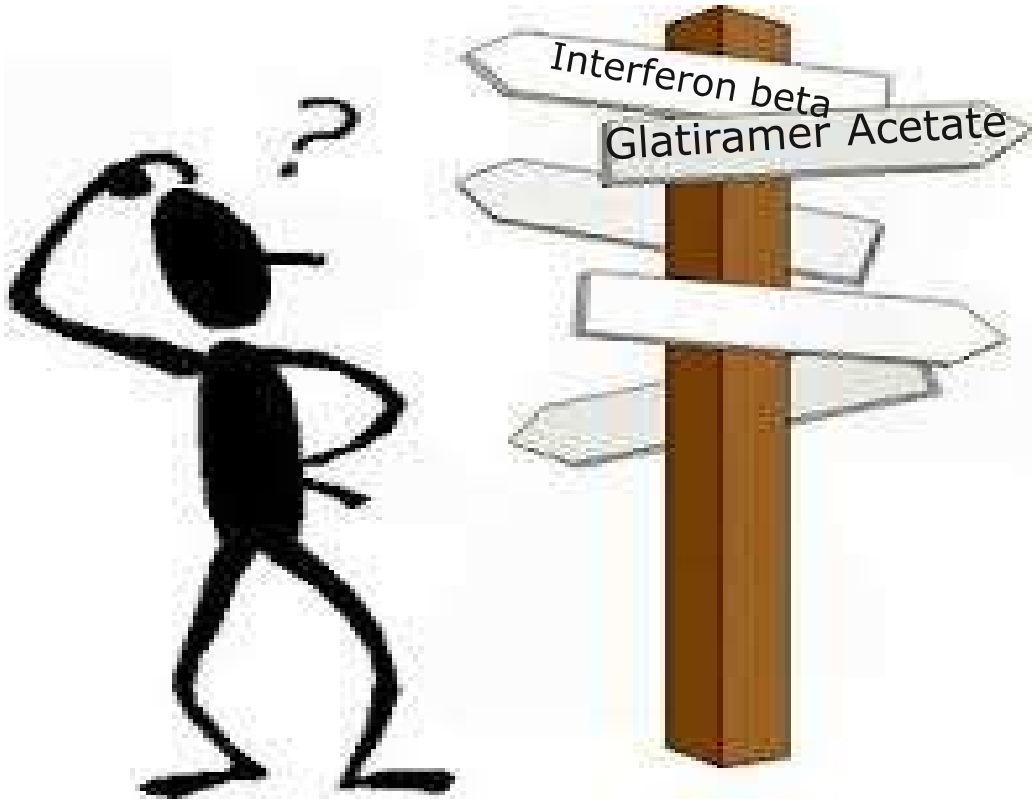
The available therapies

Evolution of availability of drugs in the treatment of MS



IFNβ=interferon beta; IM=intramuscular; SC=subcutaneous; BG-12=dimethyl fumarate; PEG=PEGylated.

The available therapies



Interferon beta 1a s.c.
Interferon beta 1b s.c.
Interferon beta 1a i.m
Pegylated IFNB 1a s.c.
Glatiramer Acetate
Mitoxantrone
Natalizumab
Fingolimod
Teriflunomide
Dimethylfumarate
Alemtuzumab
Daclizumab
BMT
Ocrelizumab
Cladribine
Siponimod
Ofatumumab
Laquinimod

The available therapies

- Interferon beta 1a s.c.
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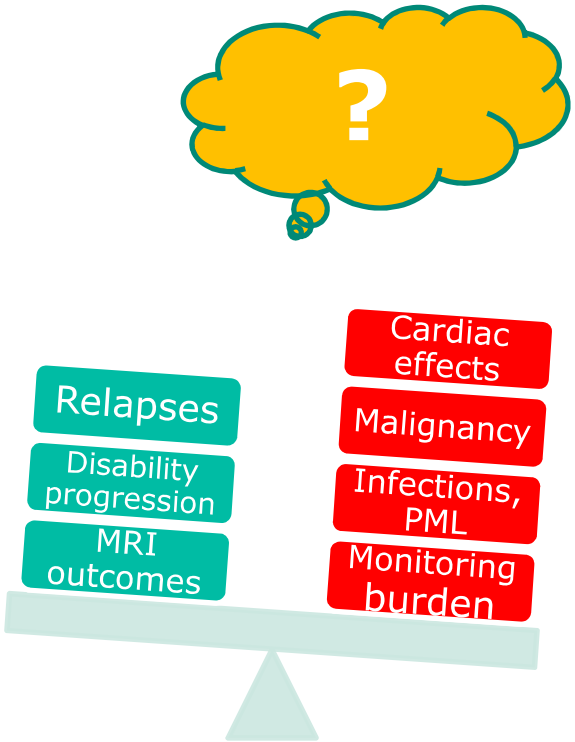
- BMT

- **Daclizumab**
- Ocrelizumab
- Cladribine
- Siponimod
- Ofatumumab
- Laquinimod

* No comercializado en España

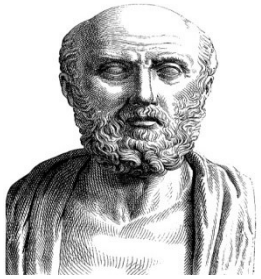
The available therapies – The concept of Risk/Benefit

- **MS is a chronic, debilitating disease and patients require long-term (30-40 y) therapy**[1]
  - However, therapy choices should take into account adequate control of the disease, safety, tolerability and adherence, as well as safety monitoring (and possible unknown long-term or rare adverse events), and concomitant medications[2]
  - **Whenever we escalate the therapy we are changing the benefit / risk balance and the patient has to be informed accordingly**



1. Girouard N & Soucy N. Patient Prefer Adherence 2011;5:101–8. 2. Lugaresi A et al. Neuropsychiatr Dis Treat 2013;9:893–914.
PML, progressive multifocal leukoencephalopathy

The available therapies – The concept of Risk/Benefit



'Primum non nocere'

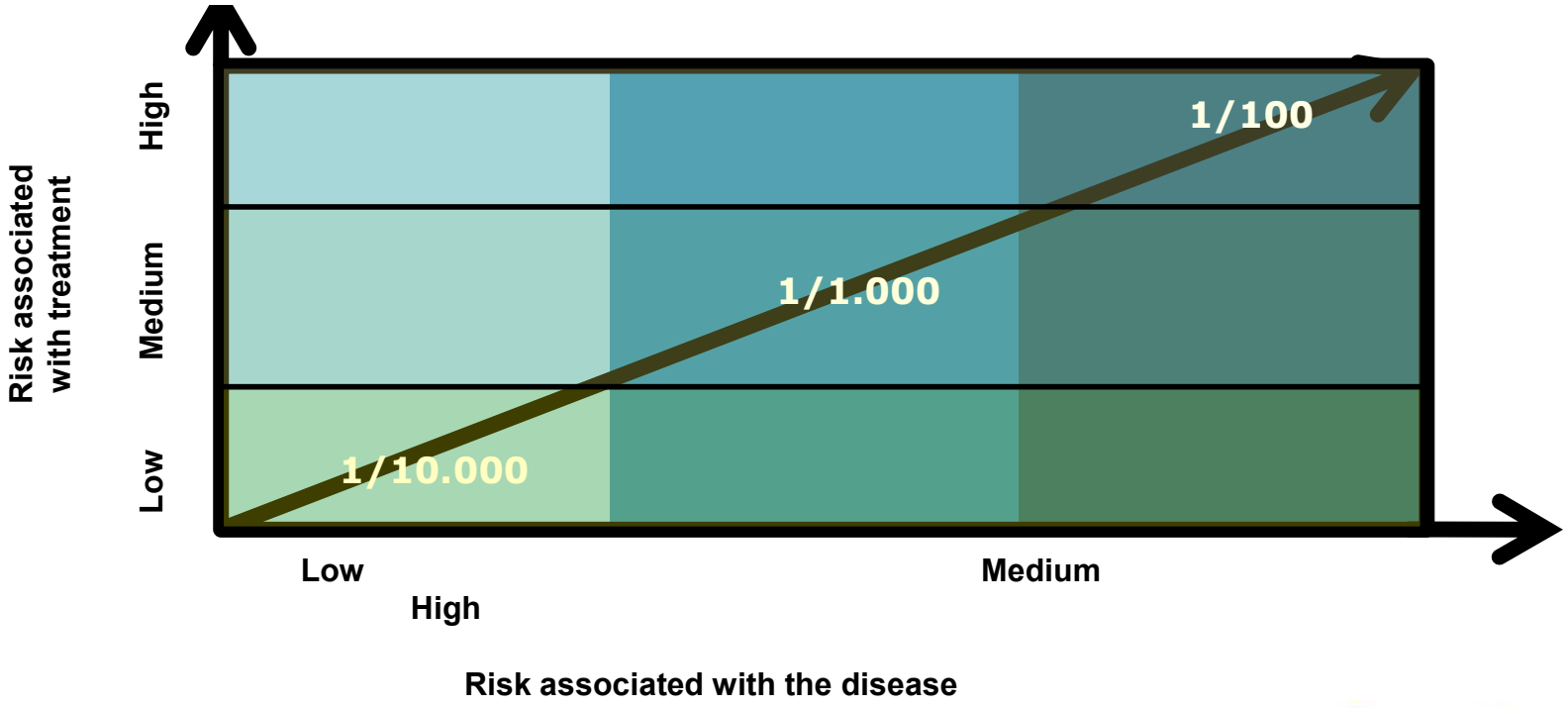
(Ἱπποκράτης; *Hippokrátēs*; **c.** 460 – c. 370 BC)

MS is a severe BUT rarely a lethal disease.
We should avoid the use of medication(s) that have the potential to increase disability, cause more harm, or induce (premature) death

- More **"active"** treatments with important side effects and toxicities are sometimes needed for the treatment of MS, such as in patients:
  - With very aggressive disease from the beginning
  - With obvious and documented treatment failure

he available therapies – The concept of Risk/Benefit

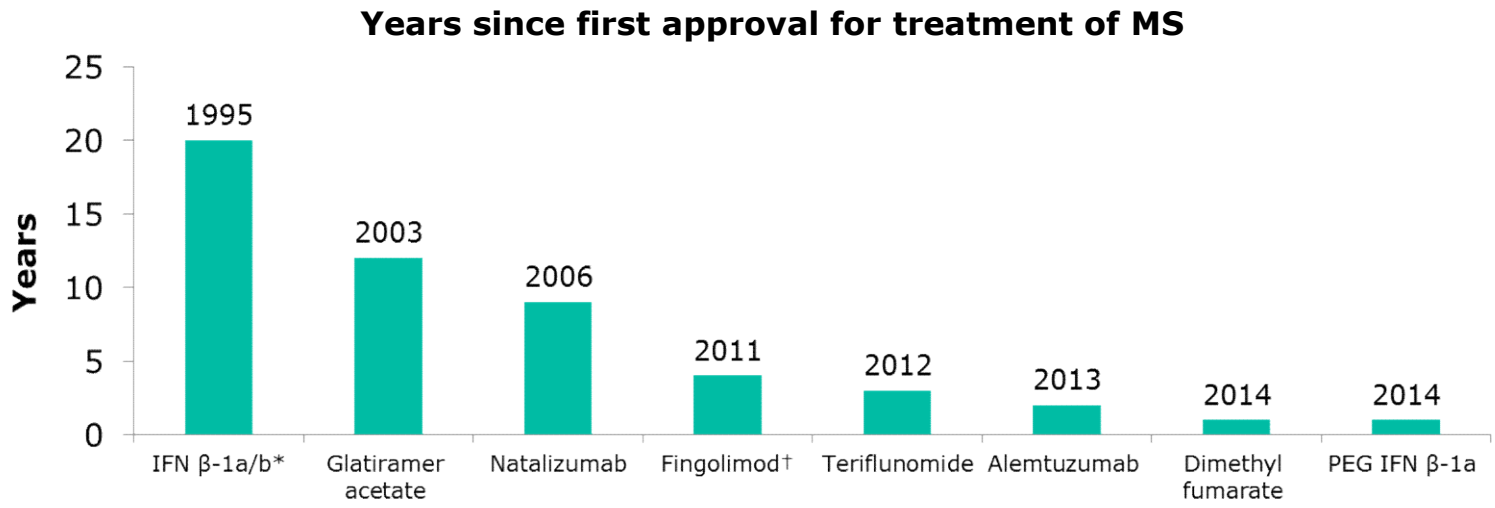
R sociated with treatment vs Risk associated with the disease



Fernández O, et al. Consenso español sobre la utilización de natalizumab (Tysabri®) – Neurología 2011

The available therapies – The concept of Risk/Benefit

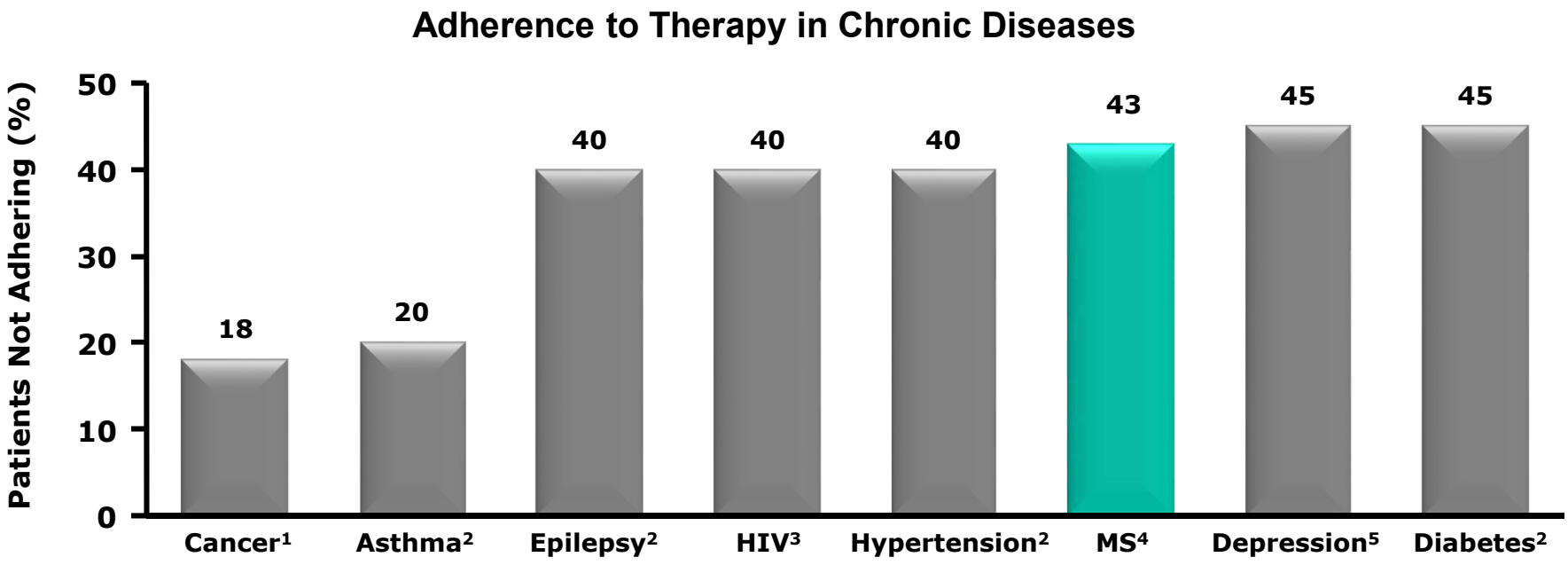
Wealth of experience with different DMDs for MS to inform on benefits and risks



- The first-line therapies have well-characterized safety profiles, with over 20 years of patient and clinical trial experience
- Longer exposure is needed to effectively compare the benefit–risk ratio of new oral DMDs

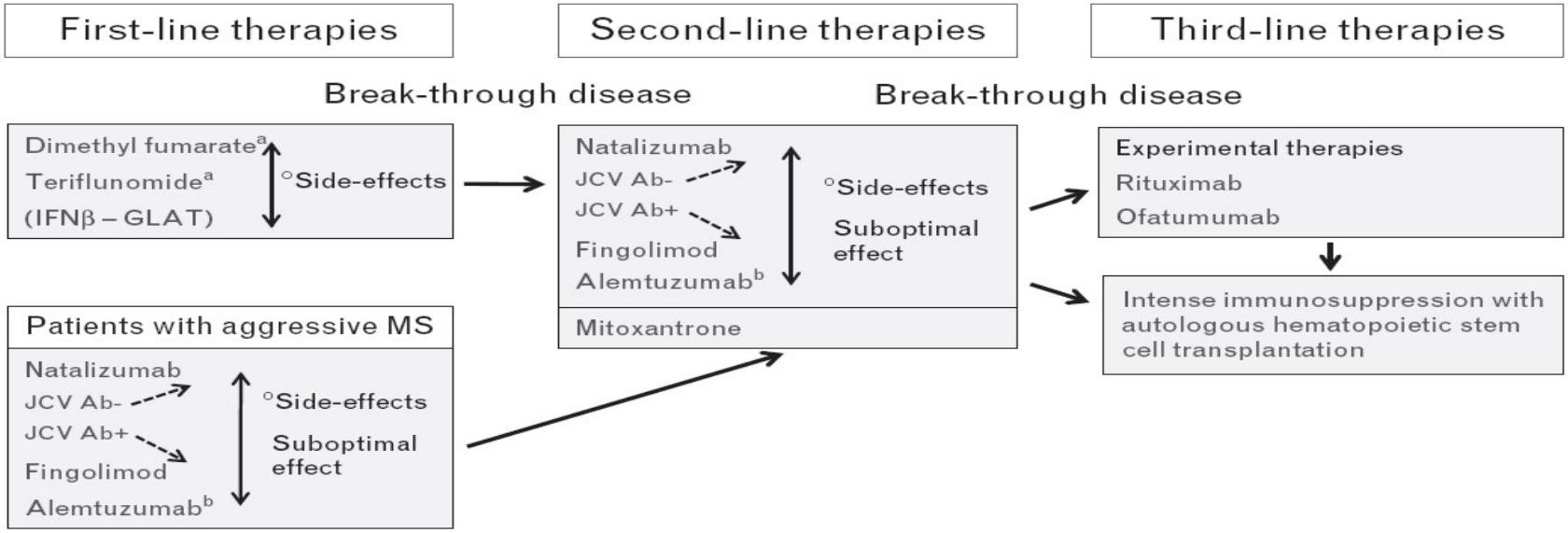
*IFN β-1b subcutaneous injection (250 mcg) every other day - approved 1995;
IFN β-1a intramuscular injection (30 mcg) once weekly - approved 1997;
IFN β-1a subcutaneous injection (22 mcg, 44 mcg) thrice weekly - approved 1998.
†reserved for second-line use in patients with high disease activity despite treatment with at least one disease-modifying therapy, or permitted as first-line therapy in patients with rapidly evolving severe RRMS (see EU SmPC for further details)

The available therapies – The concept of adherence



1. Cuzick J et al. *Lancet* 1999;353:930; 2. Berg JS et al. *Ann Pharmacother* 1993;27(Suppl):S5–S23; 3. Bogart LM et al. *Ann Behav Med* 2010;40:184–190; 4. Lafata JE et al. *J Am Pharm Assoc (2003).* 2008;48:752–757; 5. WHO. Adherence to long-term therapies: evidence for action. 2003. http://apps.who.int/medicinedocs/en/d/Js4883e/3.html#Js4883e.3 Accessed November 1, 2012.

Treatment strategies – Newest proposed tx. algoritm



Sörensen PS. Curr Opin Neurol 2014, 27:246–259

Treatment guidelines – SEN

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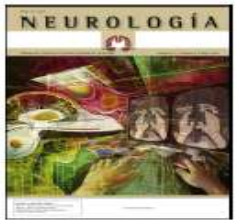


DOCUMENTO DE CONSENSO

Consenso para el tratamiento de la esclerosis múltiple 2016. Sociedad Española de Neurología

A. García Merino[a,*], J. Ramón Ara Callizo[b], O. Fernández Fernández[c], L. Landete Pascual[d], E. Moral Torres[e] y A. Rodríguez-Antigüedad Zarrantz[f]

Treatment guidelines – ECTRIMS-EAN : Consensus statements

General Recommendations
• The spectrum of DMTs should only be prescribed in centers where there is adequate infrastructure to provide: proper patient monitoring, comprehensive assessment, prompt detection, and management of side effects
CIS
• Consider IFN and GA for patients with CIS and an abnormal MRI who do not fulfill MS criteria
RRMS
• Offer early treatment with DMTs to patients with active RRMS • Choosing between the range of available DMTs will depend on: patient characteristics and comorbidities, disease activity/severity, DMT safety profile, accessibility of the DMT
Monitoring Treatment Response
• Consider using MRI combined with clinical measures when evaluating disease evolution • Consider performing a standardized reference brain MRI (usually within 6 months of treatment initiation) and compare it with a MRI performed typically 12 months after treatment initiation. Adjust the timing of both MRIs to account for: therapy MOA (especially the speed of action), disease activity.
Treatment Strategies if Poor Response
• Offer a more efficacious DMT to patients treated with IFN or GA who show evidence of disease activity
Treatment Strategies if Highly Efficacious DMT is Stopped
• Consider offering another highly efficacious DMT • When switching between highly efficacious DMTs, take into account: disease activity, half-life and biological activity of previous DMT, potential for disease activity to resume or rebound (particularly with NTZ)

Otero-Romero S, et al. ECTRIMS 2016; London, England. Abstract 255.

The patient: Other factors

The patient: Other factors

Shared Decision

THERAPEUTIC CHARACTERISTICS

- **Efficacy**
- **Safety**
- **Tolerability**
- **Adherence**
- **Route/frequency of administration**
- **Monitoring**

PATIENT´S PROFILE AND COMORBIDITIES

PATIENT´S PREFERENCES

SOCIOECONOMIC FACTORS

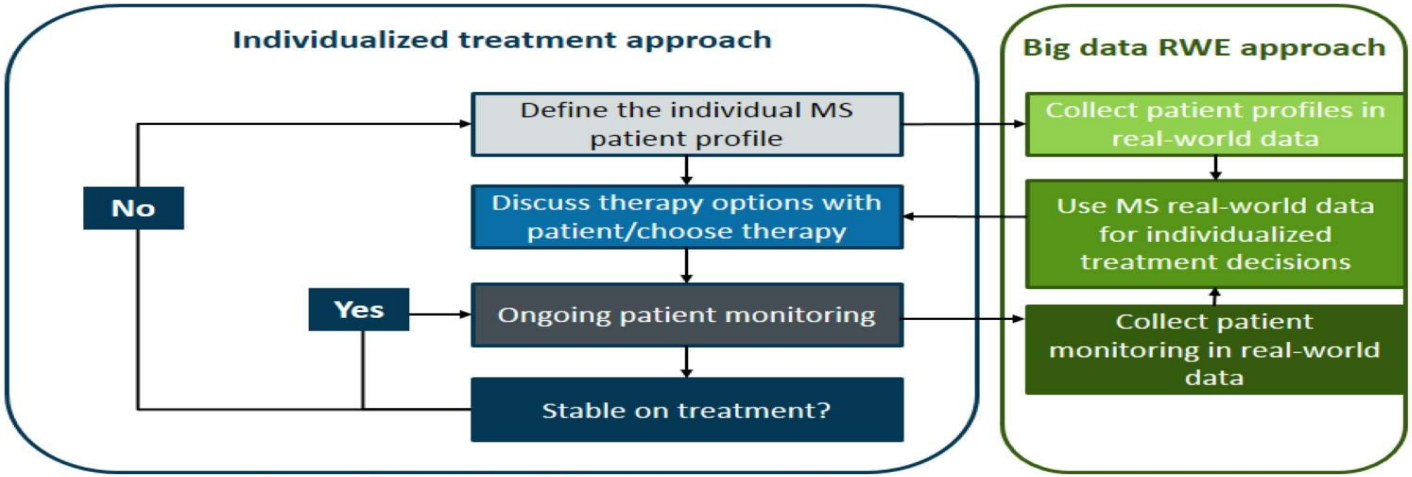
Personalized treatment

“There are no diseases, BUT patients”

(Hippocrates, Claude Bernard, Gregorio Marañón)

Personalized treatment

Combining Individual Treatment and Big Data RWE



- Detailed individual clinical profiling is essential for individual treatment decisions
- Collecting big data can predict disease course and treatment responses, helping with personalized medicine possible

Ziemssen T, et al. *BMC Neurol*. 2016;16:124.

Personalized treatment

Patient´s characteristics

Available Therapies (Efficacy/Safety)

Select the drug with the best Benefit/Risk ratio (EB) for the patient you have in front of you

Clinical	Severity		
PPMS			

Take into account patient´s preferences
Evaluate risk acceptability

Detect early (6-12 months) suboptimal response (activity/progression) and consider another therapy

Agents in advanced phase of approval / development
Daclizumab
Ocrelizumab
Cladribine
Laquinimod

Toma de decisiones colegiada

The patient: Other factors

Shared Decision

- The decision on treatment move away from the physician towards the patient and the health provider/payer
- The therapeutic outcomes are changing and there is no clear consensus
- Shared decision probably helps patients and physicians
- It would help to get closer to patient´s needs