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CONSENSUS DOCUMENT

Spanish Neurology Society consensus document on the use of drugs in multiple sclerosis: escalating therapy

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Multiple sclerosis;
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Abstract
Introduction: Treatment of multiple sclerosis has advanced considerably in the last few years, at the same time as its complexity has increased. The purpose of this consensus document is to provide specific recommendations and rules on the strategy to follow in the treatment of multiple sclerosis in order to modify its course.
Material and methods: Experts on the treatment and clinical research on multiple sclerosis proposed by the Demyelinating Diseases Group of the Spanish Neurology Society (SEN) prepared an initial document with recommendations for the treatment of this disease. The final version of this document was submitted to members of the Demyelinating Diseases Group of the SEN, who were able to make modifications and suggest changes to the final manuscript.
Results and conclusions: A review has been made of the evidence levels and indications for the treatment of the different clinical forms of multiple sclerosis, and recommendations made for the use of drugs. As well as authorised drugs, a review has also been made of other occasionally used products, as well as combined therapy, therapeutic response criteria, levels of treatment changes, and finally a proposal is made on therapeutic escalation.

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PALABRAS CLAVE
Esclerosis múltiple;
Síndrome desmielinizante aislado;
Terapia combinada;
Escalado terapéutico

Documento de consenso de la Sociedad Española de Neurología sobre el uso de medicamentos en esclerosis múltiple: escalado terapéutico

Resumen
Introducción: La terapéutica de la esclerosis múltiple ha avanzado notablemente en los últimos años al tiempo que ha aumentado su complejidad. El propósito de este documento de consenso es presentar recomendaciones y pautas concretas sobre la estrategia que seguir en el tratamiento para modificar el curso de la esclerosis múltiple.
Material y métodos: Expertos en el tratamiento y en investigación clínica en esclerosis múltiple propuestos por el grupo de enfermedades desmielinizantes de la Sociedad Española de Neurología (SEN) elaboraron un documento inicial con recomendaciones para el tratamiento de esta enfermedad. La versión final de este documento fue remitida a los miembros del grupo de enfermedades desmielinizantes de la SEN, quienes pudieron realizar modificaciones y sugerir cambios al manuscrito final. Tras considerar estas enmiendas, el comité de expertos validó el documento final.
Resultados y conclusiones: Se revisan los niveles de evidencia y las indicaciones para el tratamiento de las diferentes formas clínicas de esclerosis múltiple y se hacen recomendaciones de uso de los medicamentos. Además de los fármacos autorizados, se revisan también otros productos ocasionalmente empleados, así como la terapia combinada, los criterios de respuesta terapéutica, los niveles de cambio de tratamiento y finalmente se hace una propuesta de escalado terapéutico.

Preamble

The purpose of this consensus document is to present specific recommendations and guidelines on the strategy to be followed for the treatment of multiple sclerosis to change the course of the disease, without considering the acute, symptomatic or supportive treatment of outbreaks. The authors are experts in treatment and clinical research on multiple sclerosis proposed by the group of demyelinating diseases of the Spanish Society of Neurology.

Introduction

In 1993, the Food and Drug Administration (FDA) approved the first beta interferon for the treatment of multiple sclerosis (MS). These events initiated the launch of clinical research and, towards the end of that decade, the importance of initiating treatment as soon as possible to limit axonal damage was discovered. Progressively, drugs and therapeutic guidelines have been reported and configure the current MS arsenal. Evidence-based medicine (EBM) or use of the information derived from the best studies to make decisions must be supplemented by expert criterion for selecting the best therapeutic option for a specific subject and at a specific time.

Individualised treatment in daily practice must be adjusted to the clinical form of the disease and its progress in each subject. Clinical studies select participants based on a phenotype or disease profile and provide the most effective treatment approach, while the physician knows the individual patient's disease progression. The evidence gained in clinical studies considered decisive and conclusive, and their assessment by the regulatory authority, together with professional experience are all prerequisites for achieving clinical excellence. The aim of these recommendations is to combine personal experience and scientific evidence.

To make these recommendations robust, simple and practical, they have been primarily based on level A evidence, derived from Class I studies, compared against placebo and with a parallel control group. However, it is not always simple to transfer knowledge from a controlled experimental situation to everyday clinical practice. In clinical trials, the variability of experimental subjects should be the minimum possible. In real conditions, this variability is increased and cases appear that are not covered by the experimental conditions. The fact that a specific intervention has proven effective in experimental conditions does not necessary imply its effectiveness when applied in the general population. To the contrary, not all real situations are susceptible to being reviewed under experimental conditions (e.g., low prevalence diseases, exceptional presentations of diseases, comorbidity, polypharmacy, etc.). Therefore, not all clinical decisions can be supported by results previously validated in clinical trials.

Methodology

This consensus document has used the following three levels of evidence:

1. Level A: Class I clinical studies accepted by the regulatory authority for the authorisation of treatment: the main conclusive and decisive studies. Highly recommended.

2. Level B: Class I or II studies that support the usefulness and effectiveness of the studied therapy, but that have not been evaluated or have not been considered conclusive by the regulatory authority. Favourable recommendation.
3. Level C: Class III studies, with evidence from well-designed, non-experimental, descriptive studies, such as comparative studies, correlation studies or case-control studies. Favourable but not conclusive recommendation.
4. Level U: criteria of experts based on clinical experience or documents or opinions of expert committees.

The scientific assessment reports (European Public Assessment Report [EPAR]) of the European Medicines Agency (EMEA) for all products approved for MS treatment were selected and retrieved from the web address www.emea.europa.eu. The studies that the EMEA accepted as valid to back the authorisation were identified. MEDLINE and EMBASE provided Class I and II studies that were not sufficient to support an authorisation or modification of treatment, but that had established an opinion among experts in the therapeutic management of MS. The technical specifications of drugs approved by the Spanish Medicine Agency for MS treatment were obtained at the address www.agemed.es.

In an initial meeting, the panel of experts agreed on the objective of the recommendations document and the levels of evidence to be used. The sections of the document that each had to develop were assigned and the corresponding procedure and timeline were established. After holding several meetings to review and enrich the manuscript on the basis of consensus, the group reviewed the final draft and consolidated the final version of the recommendation document. This document was sent to members of the group of demyelinating diseases of the Spanish Society of Neurology, who were able to make recommendations or modifications to the final manuscript. After considering these amendments, the committee of experts endorsed the final document.

Evidence and indications of the approved treatments in different clinical forms

The first episode of neurological dysfunction is known as clinically isolated demyelinating syndrome (CIS). Its identification is important because most of these patients will develop MS in the course of the years. Around 85-90% of patients with MS begin with the relapsing-remitting form (RRMS), of which a significant proportion progresses to a secondary progressive form (SPMS) after 10-15 years from the onset. The remaining 10-15% start with the primary progressive form (PPMS), with a sustained disability progression. A small number of patients have a progressive-relapsing form (PRMS). From a therapeutic perspective, the EMEA includes all clinical forms showing outbreaks under the term relapsing MS (RMS).

It has been shown that certain drugs are able to modify the course of MS, reducing the number of outbreaks and lesions on magnetic resonance imaging (MRI). There is more doubt about whether these same drugs are able to modify the evolution of residual disability in a clinically significant manner.[1-5] There are arguments suggesting that there is a process of axonal damage, more or less related to inflammation, from the beginning of the disease.[6] This axonal damage would be the pathological substrate of residual disability. Therefore, it has been argued that treatment from the clinical onset of MS would delay the evolution towards significant residual disability.

General recommendations

- People with MS have a right to all available drugs for their form of disease.
- The neurologist is responsible for the treatment of individuals with MS, and must have access to all drugs.
- Drugs authorised for the treatment of MS that have different dosing schedules, routes or methods of administration are not equivalent.

First line of treatment

The first line of treatment includes immunomodulatory drugs authorised for use after the diagnosis has been established. Treatment can be started with any of them and they are interchangeable when a change of drug is considered appropriate.

Clinically isolated demyelinating syndrome

The criteria indicating the use of immunomodulatory drugs in clinically isolated demyelinating syndrome are intended to identify patients at high risk of developing MS. This is defined in the data sheet of the approved products as "patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded and if there happens to be a high risk for developing clinically definite MS". High risk is defined variably according to the information given in the datasheets of each product.[7-10]

Four studies have demonstrated the efficacy of interferon beta (IFN-beta) and glatiramer acetate in the treatment of CIS (table 1). The three studies published[11-13] collect 1,160 cases with CIS and MRI indicative of MS and treated for at least 2 years with IFN-beta (n=639) or placebo (n=521) and with a difference in the rate of conversion at 2 years around 45% in all cases. A metaanalysis[14] of the three studies resulted in a joint odds ratio (OR) of 0.53 with a 95% confidence interval (CI) of 0.41 to 0.71, which is highly significant evidence ($p<0.0001$) that the IFN-beta treatment significantly delayed conversion to clinically definite MS (CDMS) of subjects with CIS. Additionally, these studies showed that treatment with IFN-beta decreased the number and size of brain lesions detected on MRI. After evaluation of these results, the EMEA and the FDA authorised the use of intramuscular (i.m.) IFN-beta-1a and subcutaneous (s.c.) IFN-beta-1b for the treatment of CIS. The Class I study with s.c. IFN-beta-1a, despite having shown efficacy, was not submitted to the regulatory agencies at that moment; at the time of this writing, the results of another trial with this drug in CIS are being awaited. The EMEA and the

Table 1 Studies on clinically isolated demyelinating syndrome (CIS) with level A evidence

Study	Population	Treatment groups	Result
ETOMS (2001)	308 CIS and indicative MRI	154 IFN-β-1a 22 μg s.c./ week; 154 placebo	Conversion risk at 2 years: placebo 45%; IFN-β-1at 34%
CHAMPS (2001)	383 CIS and ≥ 2 MRI lesions	193 IFN-β-1a 30 μg i.m./ week; 190 placebo	Conversion risk at 2 years: placebo 39%; IFN-β-1at 21%
BENEFIT (2006)	468 CIS and ≥ 2 MRI lesions	292 IFN-β-1b 250 μg s.c./ 2 days; 176 placebo	Conversion risk at 2 years: placebo 45%; IFN-β-1b 28%
PRECISE (2009)	481 CIS and ≥ indicative MRI	243 GA 20 mg s.c./ day; 238 placebo	Conversion risk at 2 years: placebo 43%; GA 25%(pending publication of results)

GA: glatiramer acetate; IFN: interferon; i.m.: intramuscular; MRI: magnetic resonance imaging; s.c.: subcutaneous.

Spanish Medicine and Health Products Agency (AEMPS) have recently authorised glatiramer acetate for this indication (table 2).

Relapsing remitting multiple sclerosis

Since the vast majority of subjects with multiple sclerosis begin with the RRMS form, clinical research on this form of the disease has been predominant. In fact, it was in RRMS that the efficacy of disease-modifying drugs (DMD) was first demonstrated and this was one of the first authorised indications. The subjects who participated in these studies presented an active disease, with at least 2 outbreaks in the previous 2-3 years, and the effectiveness of these drugs was mainly manifested as a reduction in outbreak frequency, along with a decrease in cerebral injuries detected by MRI.

The approved drugs for the treatment of relapsing forms of MS are: 250 μg of subcutaneous IFN-beta-1b every other day, 22 or 44 μg of subcutaneous IFN-beta-1a 3 times per week, 30 μg of i.m. interferon (IFN) beta-1a once per week, and 20 mg of s.c. glatiramer acetate daily.

The indication criteria for treatment in RRMS forms require the appearance of 2 or more outbreaks in the last 2 years in the case of IFN-beta-1b and glatiramer acetate, and of 2 or more outbreaks in the past 3 years for i.m. IFN-beta-1a. The latter, s.c. IFN-beta-1a, is authorised for the forms of MS in outbreaks, and its use is allowed from the first outbreak with MRI support (McDonald criteria)[15,16] (tables 3 and table 4).

Table 2 Recommendations for clinically isolated demyelinating syndrome (CIS)

- IFN-beta 1a and 1b and glatiramer acetate used in CIS have been shown to improve the risk of developing multiple sclerosis (MS) significantly
- The purpose of CIS treatment is to prevent the conversion to MS and thus avoid the accumulation of disability
- The presence of a CIS does not in itself imply the need for treatment with disease-modifying drugs (DMD)
- The first demyelinating episode may be treated with DMD in cases with high risk of conversion to MS
  - Presenting 3 of 4 dissemination criteria (DIS) in space (Barkhof criteria)
  - DIS criteria in space according to Swanton criteria
  - Gadolinium enhancing and non-enhancing lesions
  - Intrathecal synthesis of IgG, IgM
- The more factors there are, the greater the probability of conversion and, therefore, the greater the recommendation of treatment

Secondary progressive multiple sclerosis (SPMS)

At present, the two DMD authorised for the treatment of SPMS based on available clinical studies[17,18] that offer level A evidence are s.c. IFN-beta-1b and IFN-beta-1a. The characteristics to be met by individuals to gain access to treatment are having an active form of SPMS, defined by the following criteria:[8,16]

- Having gradually worsened over the previous 2 years: one or more points in patients whose prior EDSS (Expanded Disability Status Scale) score was <5.5, or 0.5 points in patients whose prior EDSS score was 5.5-6.5.
- Having presented at least one outbreak in the previous 2 years.

For patients without clinical evidence of outbreaks, but whose MRI shows inflammatory activity, individualised indication might be considered (tables 5 and table 6).

Primary progressive multiple sclerosis (PPMS)

To date, no clinical study has demonstrated efficacy in patients with PPMS who present an increasing neurological impairment with no outbreaks and that is usually accompanied by few central nervous system lesions on the MRI scan. Due to lack of authorised treatment and the severity of diagnosis, the best clinical criteria is what decides on the treatment in each case, after assessing the risk / benefit ratio (tables 7 and table 8).

Second-line treatment of multiple sclerosis

In MS, a drug is considered as second-line when its use is subject to failure or intolerance of previous first-line treatments.

Table 3 Studies in relapsing remitting multiple sclerosis (RRMS) with level A evidence

Study	Population	Treatment groups	Result
IFNB MSSG (1993)	238 RRMS	115 IFN-β-1b 250μg s.c./2 days; 111 IFN-β-1b 50 μg s.c./2 days; 112 placebo	Outbreaks/year-time to 1st outbreak: IFN-β 250 μg: 0.84/296 days; IFN-β 50 μg: 1.17/180 days; placebo: 1.27/153 days
Cop.1 MSSG (1995)	251 RRMS	125 AG 20 mg s.c./ day; 126 placebo	Outbreaks/year-time to 1st outbreak: GA 20 mg: 0.59/287 days; placebo: 0.84/198 days
MSCRG (1996)	251 RRMS	158 IFN-β-1a 30 μg i.m./week; 143 placebo	Outbreaks/year-progression: IFN-β 30 μg: 0.61/21.9%; placebo: 0.90/34.9%
PRISMS (1998)	560 RRMS	184 IFN-β-1a 44 μg s.c./3 xs; 189 IFN-β-1a 22 μg s.c./3 xs; 187 placebo	Outbreaks/year-time to 1st outbreak: IFN-β 44 μg: 0.87/9.6 months; IFN-β 22 μg: 0.91/7.6 months; placebo: 1.28/4.5 months

GA: glatiramer acetate; IFN: interferon; i.m.: intramuscular; MSSG: Multiple Sclerosis Study Group; s.c.: subcutaneous.

Table 4 Recommendations for relapsing remitting multiple sclerosis (RRMS)

- The goal of treatment is to prevent the recurrence of outbreaks and the accumulation of disability
- The early treatment of multiple sclerosis (MS) is recommended, by applying updated McDonald criteria for early diagnosis
- The following is recommended as first-line treatment in RRMS: IFN-β-1b subcutaneously (s.c.), s.c. IFN-β-1a, intramuscular IFN-β-1a and glatiramer acetate
- In Spain, the use of azathioprine as a first-line drug is allowed
- Likewise, the use of natalizumab is approved as a first choice drug in cases of rapid and aggressive evolution
- Natalizumab and mitoxantrone are indicated as second-line treatment in RRMS

Mitoxantrone

The demonstration of the efficacy of mitoxantrone (Novantrone®)[19] versus placebo made it the first drug approved as second-line treatment in RRMS when there is no response to treatment with immunomodulators and the frequency of relapses and active brain lesions evident on MRI persists. Mitoxantrone is cardiotoxic; it should be administered with a left ventricular ejection fraction > 50% and its use requires ultrasound or radionuclide control of the left ventricular function before and during treatment. The other major risk of mitoxantrone is the development of acute leukaemia, so haematological checks should be carried out during treatment and for several years after completion. As a preventive measure, the total cumulative dose cannot exceed 140 mg/m^2. In fact, it is recommended that the total cumulative dose of 100 mg/m^2 should be exceeded only in individuals who respond and still show signs of activity.[20]

Natalizumab

Natalizumab (Tysabri®) is the only monoclonal antibody approved for MS treatment. It works by blocking leukocyte alpha-4 integrin and thus limiting lymphocyte and monocyte migration through the blood-brain barrier into the central nervous system. There were two ample Phase III studies of RRMS, one with natalizumab in monotherapy[21] and the other in combination therapy with i.m. IFN-beta-1a in subjects with RRMS who did not respond to i.m. IFN-beta-1a. However, this was interrupted for safety reasons because of the appearance of isolated cases of progressive multifocal leukoencephalopathy. Due to this circumstance, the EMEA

Table 5 Class I studies on secondary progressive multiple sclerosis (SPMS)

Study	Population	Treatment groups	Result
Eur Group (1998)	718 SPMS; EDSS, 3-6.5	360 IFN-β-1b 250 μg s.c./2 days; 358 placebo	Probability of not progressing at 1 year/2 years: IFN-β 250 μg: 0.81/0.71; placebo: 0.53/0.65. Outbreaks/year. IFN-β-1b 250 μg: 0.44; placebo: 0.64
SPECTRIMS (2001)	618 SPMS; EDSS, 3-6.5	204 IFN-β-1a 44μg s.c./3 xs; 209 IFN-β-1a 22 μg s.c./3 xs; 205 placebo	Progression. Risk quotient *(hazard ratio)* in subjects with outbreaks: IFN-β 44 versus a placebo: 0.74. Outbreaks/year. IFN-β 44 and 22: 0.50; placebo: 0.71

IFN: interferon; s.c.: subcutaneous.

Table 6 Recommendations in secondary progressive multiple sclerosis (SPMS)

- The SPMS is treatable if it presents outbreaks or inflammatory activity on MRI
- The following are recommended as first-line treatments of SPMS: subcutaneous IFN-beta-1b, subcutaneous IFN-beta-1a
- The use of mitoxantrone is approved as second-line treatment of SPMS with outbreaks
- The use of azathioprine could be considered in SPMS with outbreaks

Table 7 Recommendations for primary progressive multiple sclerosis (PPMS)

- There is no evidence of treatment efficacy with this form of the disease

granted approval of natalizumab as a treatment for patients with no response to first-line drugs or as first option in forms of severe RRMS with a rapid evolution.

Table 9 summarises the two studies which support the authorisation of these two products as second-line MS treatments.

Mitoxantrone and natalizumab are two products with remarkable efficiency in the reduction of disability progression in subjects with an EDSS score of up to 6 points in the limit of ambulation capacity (EDSS <6), outbreak frequency and brain lesions detected by MRI. Their safety profile has positioned them as a second option, due to the risks involved and the tests and controls that must be put in place to minimise them.

Based on the different risk/benefit profile of these two drugs, natalizumab is considered as the first option in the second line of treatment. Both drugs are approved as monotherapy; using them in combination with first-line DMD involves additional risks and is not authorised (table 10).

Other medicines used in MS

With the exception of azathioprine, the drugs listed below do not have an approved indication for the treatment of MS. For them, the evidence levels are lower or have not been sufficiently studied.

Intravenous immunoglobulins (IVIG)

Clinical studies indicate that the main benefit of intravenous immunoglobulin (IVIG) is the reduction in the number of outbreaks, but the heterogeneity of the studies limits the level of evidence. A broad study[22] with different dosing regimes did not show efficacy in reducing outbreaks, EDSS or MRI variables. In this context, the European Federation of Neurological Societies[23] considers IVIG as second-line treatment for RRMS in case of intolerance or concomitant disease. It rejects their use in CIS and SPMS. Treatment with IVIG appears to be safe and probably effective in the prevention of attacks during pregnancy and after birth.[24] None of the IVIG preparations is approved for MS treatment, but they may be considered as an alternative in RRMS treatment when conventional therapies have failed, and in outbreaks during pregnancy and the postpartum period.

Azathioprine

(Note: authorised as a first-line product in Spain, it is included here due to lack of Class I studies).

Table 8 First-line drugs and authorised indications

Drug	Dosage	Administration	Indications
IFN-β-1b (Betaferon®, Extavia®)	250 μg on alternate days	s.c.	CIS which justifies treatment with injected corticosteroids and is considered at high risk of developing MS. RRMS with 2 or more outbreaks in the past 2 years. SPMS with outbreaks
IFN-β-1a (Avonex®)	30 μg once per week	i.m.	CIS which requires treatment with i.m. corticosteroids and is considered at high risk of developing MS. RRMS
IFN-β-1a (Rebif®)	22 or 44 μg 3 days per week	s.c.	RRMS according to the McDonald criteria. SPMS with outbreaks
Glatiramer acetate (Copaxone®)	20 mg daily	s.c.	CIS considered at high risk of developing CDMS. RRMS with 2 or more outbreaks in the past 2 years and capable of walking without aid
Azathioprine (Imurel®)	2.5 mg/kg/day	Oral	RRMS. Optional in SPMS with outbreaks

CDMS: clinically definite MS; CIS: clinically isolated demyelinating syndrome; IFN: interferon; i.m.: intramuscular; MS: multiple sclerosis; RRMS: relapsing remitting MS; s.c.: subcutaneous; SPMS: secondary progressive MS.

Table 9 Class I studies with second-line drugs

Study	Population	Treatment groups	Result
Mitoxantrone. MIMS (2002)	194 RRMS/SPMS	63 MTX 12 mg/m^2/3 months; 66 MTX 5 mg/m^2/3 months; 65 placebo	Average difference 12 mg group versus a placebo: EDSS: 0.24 (CI, 0.04-0.44). Outbreaks: 0.39 (CI, 0.18-0.59). Time to 1st outbreak: 13.7 months
Natalizumab. AFFIRM (2006)	942 RRMS	627 NTZ 300 mg/4 week; 312 placebo	Progression. Hazard ratio (HR): NTZ versus placebo: 0.58 (0.43-0.77). Rate of outbreaks/year: NTZ: 0.26; placebo: 0.81

CI: confidence interval; HR: hazard ratio; MTX: methotrexate; NTZ: natalizumab; RRMS: relapsing remitting MS; SPMS: secondary progressive multiple sclerosis.

Azathioprine is an immunosuppressive purine analogue that has been used in MS for over 25 years, although the studies are small and have methodological limitations. It mainly decreases outbreaks and, to a lesser extent, the progression of disability.[25] Five studies, grouped in one metaanalysis,[26] with data from 1-3 years comparing azathioprine with placebo, showed that azathioprine administration reduced by 20% the relative risk that a patient would present an outbreak. It also demonstrated the effect of the drug in reducing disability, but the number of subjects with that datum was limited. The safety profile of azathioprine is good and the risk of cancer appears linked to treatment duration longer than 10 years and a cumulative dose over 600 g. When considering the risk/benefit ratio, azathioprine could be a therapeutic alternative, but there is still no confirmation through a clinical study with level A evidence.

Cyclophosphamide

Cyclophosphamide is a potent antineoplastic agent that has been used in treatment-resistant MS. The therapeutic regimens tested in MS range from high intravenous induction doses with cyclophosphamide and ACTH for 2-3 weeks and

Table 10 Second-line drugs and their authorised indications

Drug	Dosage	Administration	Indications
Mitoxantrone hydrochloride (Novantrone®)	12 mg/m^2 of body surface every 3 months	i.v. infusion in 5-15 min	High activity RRMS with frequent outbreaks and progression of disability, along with increased T2 lesion load or Gd-enhancing T1 lesions with respect to the previous MRI, being under immunomodulatory treatment. High activity SPMS with frequent outbreaks and progression of disability, along with increased T2 lesion load or Gd-enhancing T1 lesions with respect to the previous MRI, being under immunomodulatory treatment
Natalizumab (Tysabri®)	300 mg every 4 weeks	i.v. perfusion in 1 h	RRMS that has not responded to a full, adequate course of IFN-β (more than 1 outbreak in the previous year and more than 9 T2 lesions or more than 1 GD-enhancing T1 lesion). Rapidly evolving severe RRMS (more than 2 disabling outbreaks in a year and more than 1 Gd-enhancing T1 lesion with respect to a recent MRI or increased T2 lesion load)

IFN: interferon; i.v.: intravenous; Gd: Gadolinium; MRI: magnetic resonance imaging; RRMS: relapsing remitting MS; SPMS: secondary progressive multiple sclerosis.

Table 11 Unapproved drugs and their therapeutic options

Drug	Dosage	Administration	Indications
Unspecific			
IVIG	Variable	i.v.	RRMS, specially in pregnancy and after birth
Plasmapheresis	Not applicable	—	Aggressive MS: corticoresistant outbreaks and/or increase of more than 1 point on EDSS in 12 months
Immunosuppressors			
Cyclophosphamide	Various	i.v.	Refractory MS in < 40 years
Methotrexate	Variable	Oral	SPMS and PPMS

i.v.: intravenous; MS: multiple sclerosis; PPMS: primary progressive MS; RRMS: relapsing remitting MS; SPMS: secondary progressive MS.

monitoring up to 2 years, to low booster doses every 2 months for 2 years on an outpatient basis.[27,28] The pattern of low booster doses for 2 years significantly lengthened the time to sustained progression of disability in subjects aged less than 40 years, but not in those older. Overall, studies have shown that outpatient administration of cyclophosphamide is safe in patients with MS, without objectifying a significant clinical benefit.

Methotrexate

Methotrexate is an antineoplastic that which acts as inhibitor of dihydrofolate reductase. It has the advantage of oral administration and the inconvenience of liver toxicity. A recent review[29] of clinical studies with methotrexate in MS identified two randomized, controlled trials. Only one of them had methodological robustness and monitoring over 3 months. This study was a randomized, placebo-controlled trial in 60 subjects with SPMS and PPMS. It found that treatment with methotrexate produced only minor side effects, reduced disability progression and reduced outbreak number, but did not reach statistical significance after 36 months of monitoring. There are no studies with methotrexate in RRMS.

Plasmapheresis

Plasmapheresis is a therapeutic option for certain patients with an aggressive form of MS who do not respond to treatment, and which seeks to eliminate from the plasma the proinflammatory agents responsible for the aggressiveness of MS. Published data are few and are related to individual cases with severe corticosteroid-resistant outbreaks or to progressive forms with rapid disability increase despite treatment.[30] It is a therapeutic option with limited evidence and which may be considered in individual cases of catastrophic outbreaks and cases of aggressive MS, with rapid disability progression despite treatment. It has recently been used as part of the treatment of natalizumab-associated progressive multifocal leukoencephalopathy.

New therapies under development

There are several products in advanced development with major Class I studies to obtain level A evidence, which the regulatory authority may consider sufficient to permit their use in MS treatment. The range of new products goes from monoclonal antibodies (alemtuzumab, rituximab and daclizumab) to new forms of products already studied in MS, ranging from oral cladribine and laquinimod through immunosupressors that inhibit pyrimidine synthesis (teriflunomide) and sphingosine 1-phosphate agonists (fingolimod). Aside from effectiveness reviews, it will be important to have new products for oral administration (table 11).

Combined therapy

Combination therapy aims to concurrently cover more than one pathogenic MS mechanism to increase efficiency. However, there is no authorised combination therapy or clinical studies providing level A evidence.

The decision to combine medical treatments is taken by the physician for a specific case, depending on experience and best criteria. The other situation is the search for the best combination therapy in groups of patients in clinical studies with the design needed to obtain decisive and conclusive results. A recent[31] review of therapeutic combinations in MS has identified at least 95 different combinations and expressly states that the quality of the studies is limited. The safety-based interruption of two Class I studies with natalizumab in combination with i.m. IFN-beta-1a (AFFIRM study) and with glatiramer acetate (GLANCE study) has frustrated the first opportunities to obtain level A evidence of two combination therapies for RRMS. It has also reinforced the importance of safety in combination therapies. A very careful balance between efficacy, safety, and very detailed information to patients should direct all clinical decisions on this issue.[32,33]

Criteria for therapeutic response

The irregular, unpredictable course of MS and the absence of healing treatments make it difficult to specify response and failure criteria for each treatment. The baseline MS profile or the subject characteristics do not allow the response to be anticipated.[33] In principle, it is easier to detect failure. The response includes the placebo effect, the phenomenon of regression to the average or the natural evolution of the illness and adherence to treatment, in addition to outbreaks and disability evolution. Approved treatments have been shown to improve the course of the

disease in the early years of their administration and only their long term effect remains unknown. However, for ethical reasons, as well as of efficiency and safety, the clinical management of patients with MS requires the use of response or failure criteria to adopt therapeutic decisions for a specific time and subject.

To assess effectiveness, it is considered necessary to undertake a full course of treatment for an estimated period of 6-12 months.

Monitoring of response

To identify response, we have clinical parameters (outbreaks and disability) and MRI parameters. These variables have different weights depending on disease form, which is important with regard to therapeutic approach.

Outbreaks

Outbreaks are a good clinical marker of activity, despite confounding factors such as regression to the average or the difficulty to gauge severity. Furthermore, their relation to disability in the medium to long term is not lineal.[34,35] Finally, the relapse rate is heavily influenced by how patient monitoring is carried out. If monitoring is more frequent, there is a greater possibility of detecting outbreaks. Therefore, although outbreaks offer a measure of disease activity, using them as a single measure of immunomodulatory treatment response should be evaluated with caution.

Progression of disability

MRI shows that there is more cerebral inflammatory activity than is reflected by the RRMS clinical manifestations.[36] This silent inflammatory activity can produce a detectable progression of neurological deficit in successive scans as a marker of poor therapeutic response. It is considered that a one-point increase in EDSS is a significant change in neurological status, especially if it is above EDSS level 3. The increases should be confirmed in time to reject false or temporary increases due to incomplete recovery after a disease outbreak or other medical conditions such as fever. One study observed that the increase of 1 EDSS point confirmed at 6 months provided a sensitivity of 77% and a specificity of 89% to detect an increase in long-term disability.[37] The EDSS is universally established and facilitates comparison of results. It should be considered as the assessment standard and continue to be used, regardless of the use of other scales.

Cerebral lesions

Cerebral MRI detects hyperdense areas, whose appearance is related to clinical activity in both outbreaks and disability. The association between MRI and clinical variables is not very close, and MRI is not yet accepted for surrogate assessment of the effectiveness of studies for an A level of evidence. However, changes objectified on MRI are useful in assessing treatment effect.

Definition of response

Clinical variables, outbreaks and disability all determine treatment response. Additional evidence to support the therapeutic decision making process is provided by MRI.

Clinical variables

Having a validated definition of response is essential in identifying the individuals who continue to have activity after a lack of initial treatment response and may benefit from an early therapeutic change, when the disease has not yet caused irreversible damage. However, there is no validated definition of response and so the best available option is to use the criteria of clinical studies that the regulatory authority has accepted as sufficient evidence. This involves assessing the response adjusted to the interval of 2 years of clinical studies, which seems short for a chronic disease but is the best approximation.

As for the outbreaks, it is considered that subjects have good response when they present less than 1 outbreak in 2 years of treatment, which corresponds to an annualised rate of 0.5, representing half of the criteria for inclusion in the studies. Time between outbreaks is not considered a good parameter.

With regard to disability, treatment failure is considered when there is an increase of 1 point in the EDSS, maintained in time for 6 consecutive months, in subjects with an EDSS≤5.5. When the EDSS is > 5.5, an increase of 0.5 points is considered as failure. Time until the sustained worsening is also an acceptable parameter for assessing response. The proportion of subjects with progression at a given time is not applicable to a specific case in daily practice. The response is considered acceptable if there is no apparent increase in disability at the magnitudes identified.

Radiological variables

An MRI also provides information on disease activity, but the regulatory authority does not consider it as a surrogate variable. However, a T1 lesion (relaxation time 1) hyperintense after gadolinium and/or more than two T2 lesions (relaxation time 2) that are new with respect to an MRI conducted 1-2 years earlier indicate a poor treatment response. MRI may be the criterion that determines the treatment option when the clinical data is not conclusive.

Combined variables

Although it seems reasonable to define the response by a combination of outbreaks and disability, there is a lack of experience and it is not simple. A combination of clinical and radiological data adds the inconvenience that MRI is not accepted as a surrogate parameter for clinical data. Each patient is an independent case and the neurologist will consider how to prioritise the response variables for a specific case and time to decide on the appropriateness of changing treatment.

The primary objective is to prevent disability in the long term. Therefore, although A level of evidence give priority to outbreak frequency, the accumulation of disability must also be considered and the support offered by data from brain lesion MRI and brain atrophy should be considered whenever possible. The evolution of MS activity is the adjustment criterion for individualised treatment.

Change of treatment in multiple sclerosis

At present, drugs to treat MS can be classified into four groups:

1. Approved first-line drugs: IFN-beta-1b, IFN-beta-1a, glatiramer acetate (GA), and, in Spain, azathioprine.
2. Approved second-line drugs: mitoxantrone, and natalizumab.
3. Unapproved drugs, about which there is clinical experience: cyclophosphamide, methotrexate, i.v. immunoglobulin, steroids and drug associations.
4. Drugs registered for other indications that are being investigated for MS: cladribine, mycophenolate mofetil, rituximab, alemtuzumab, etc.

Approved first-line drugs generally have a reasonable tolerability profile, with very little induction of serious adverse effects, although with frequent minor side effects. Their effectiveness is about 30% reduction in relapse rate, that percentage grouping patients with apparently complete response, partial response and lack of response. It is the drug group with the most consolidated safety and efficacy profile.

This range of MS drugs makes it possible to replace a poorly tolerated or ineffective treatment with another of the available ones, in order to achieve the best risk/benefit ratio or treatment optimisation. Treatment risk assessment is easier as experience about exposure to drugs is gained. The most problematic aspect is evaluating benefit in the absence of curative treatment and with the response variability inherent to the illness itself and to each individual. This is the object of the present consensus, and so the prior section has defined and quantified the minimum limit of response for each assessment variable.

Levels of change of treatment

Treatment options are classified into the four levels indicated above, which rank each group. The passage to a superior level represents therapeutic scaling. Moreover, each group contains several drugs and preparations with different interchangeable dosages. This results in dozens of available treatment combinations for the daily management of MS patients.

The possibilities for change between first-line drugs are:

1. Drugs of the same type: IFN-beta.
2. Immunomodulators: IFN-beta and GA.
3. 3 IFN-beta, AG and azathioprine.

In the first group, the reasons for change because of intolerance in relation to the route of administration are clear and rarely raise doubts. A common approach is to replace one low-dose IFN for another at a higher dose and/or frequency of administration in cases of relapse or lesion activity on MRI. There is a B level of evidence showing a benefit in increasing doses and/or frequency, at least to a certain limit. Thus, a dose of 44 μg of IFN-beta-1a was slightly more effective than a dose of 22 μg of the same drug;[3] further, s.c. IFN-beta-1b on alternate days showed improved clinical data and MRI efficacy than IFN-beta-1a in a single weekly i.m. administration,[38] indicative of a better response by increasing dose and/or frequency (however, doubling the dose of IFN-beta-1b to 500 μg did not improve the benefit of the standard dose of 250 μg).[39] Thus, for subjects treated with low IFN-beta doses and having inadequate response, the first option is to increase the IFN-beta dosage before moving to another type of immunomodulator, unless they present persistent high titres of neutralising antibodies. The maximum authorised doses should not be exceeded.

In the second group, because they are two different drugs, there is a theoretical framework to effect change in case of insufficient response or intolerance to treatment. Available evidence shows that the change should be done mainly seeking better tolerability and not better response. A recent comprehensive study[40] with B level evidence showed no difference in clinical response or tolerability between IFN-beta-1a and GA. However, there are several studies providing C level evidence for a change from IFN-beta to GA in cases of intolerance or inefficacy, and vice versa. In one of these studies,[41] on IFN-beta-1b treatment that was changed to GA due to toxicity or ineffectiveness, with a 3-year monitoring period, the subjects who were changed due to inefficacy showed a significant reduction in outbreak number but not toxicity. Another study[42] compared the three possible changes in this group: from one IFN-beta to another, from GA to an IFN-beta and from an IFN-beta to a GA. The changes were always due to inadequate disease activity control, outbreak persistence, MRI activity or disability accumulation; the three groups benefited from the change of drug in reduction of outbreaks, except those who switched to GA. Methodological limitations weighed down the level of evidence, but it seems that for subjects with RRMS without high activity or relapse-associated disability accumulation, the change between these immunomodulators is a safe and reasonable option.

In the third group, controlled experience is very limited. Given that azathioprine belongs to a very different drug group from the immunomodulators mentioned above, it is reasonable to propose the replacement of this drug by GA or IFN in case of intolerance or ineffectiveness. Theoretically, a change in the opposite direction is also reasonable, but it must be considered that the evidence in favour is more tenuous, the expected efficiency may be delayed by months and there is a certain oncogenic risk.

Therapeutic scaling

The change from a first-line drug to a second-line one represents entering the field of therapeutic scaling. The rationale behind therapeutic scaling is the sequential use of drugs that are more effective, but also more toxic, according to a pre-established pattern; this is done in an attempt to maximise the risk/benefit balance, so that the more potentially toxic drugs are reserved for patients with a more aggressive disease. Therapeutic scaling schemes have in their favour level A evidence for approved drugs, but that evidence decreases as the scaling progresses. They have some weak points such as the definition of inadequate

response, on which there is no definitive agreement, and the risk that an overly schematic implementation may involve a loss of critical time in some cases. Several consensuses have been published, from Europe, from German-speaking countries and by the MS Therapy Consensus Group.[43-46]

Treatment should not be scaled seeking better tolerability. After exhausting the options for first-line treatment, the second-line treatment should begin if there is still a lack of response, always in monotherapy, without continuing with any first-line drugs. The second line should start with natalizumab, leaving mitoxantrone as the second and last option, due to its toxicity that limits the treatment period. Response criteria mentioned above in the corresponding section should be applied to decide when to switch to the second line or end it and progress to rescue therapy.

An alternative to scaling schemes is the proposal of induction therapy, which is based on the theory of achieving rapid inflammation control to prevent parenchymal damage and the spread of epitopes. This would be accomplished by the early use of a potent immunosuppressive drug for a limited time, followed by use of an immunomodulator as maintenance. There is limited experience with mitoxantrone followed by interferon or glatiramer acetate,[47,48] but there is currently no sound basis to recommend this option.

The lack of sufficient information on the effectiveness of combination therapy makes it impossible to assign it a specific role within the framework of therapeutic scaling.

Rescue therapies

Rescue therapy is the use of drugs that are not authorised for MS, but are authorised in other autoimmune diseases, or else the introduction of therapeutic combinations of drugs individually approved as monotherapy for MS. The choice of rescue therapy depends on the experience and discretion of the neurologist. Due to safety reasons, the drugs most tested in other diseases should be the first choice. Monotherapy with a drug not approved for MS is preferable to the combination of two approved drugs, because the probability of synergy in the first instance is remote whereas an increase in toxicity is likely in the second.

Therapeutic scaling proposed in MS

0. First line treatment:

- s.c. IFN-beta-1b, s.c. or i.m IFN-beta-1a.
- Glatiramer acetate.
- Azathioprine.

1. Persistence of outbreaks with little or no repercussion on functional state:

- If IFN: increase frequency or dose.
- If IFN at high doses and frequency: evaluate a change to GA.
- If GA: evaluate a change to IFN.

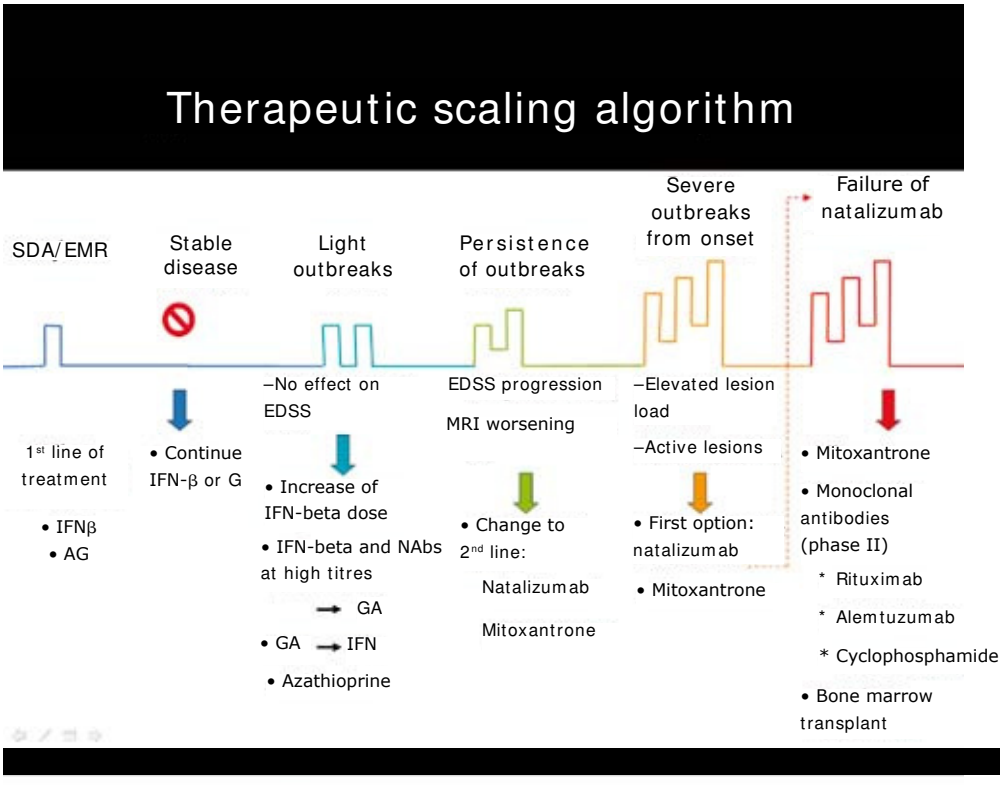

Figure 1 Flow algorithm of treatment. GA: glatiramer acetate; IFN: interferon. Taken from (A. García Merino, A. J. Sanchez).

*If outbreaks continue after having carried out the above options, the association of azathioprine can be assessed (this is not an option endorsed by controlled studies, although it is practiced by some neurologists; see point on azathioprine).

2. Persistence of outbreaks with significant increase in disability, the above treatment option points having been carried out. Patients with aggressive onset: rapid succession of relapses with significant increase in disability:

   - Natalizumab.

3. Patients with intolerance to natalizumab or with low therapeutic response to it:

   - Mitoxantrone.

4. Patients with prior immunosuppression treatments with no control of activity:

   - Natalizumab: wait long enough to have evidence of immunocompetence before starting with natalizumab.
   - In case of lack of response to natalizumab, consider the compassionate use of: rituximab, alemtuzumab or cyclophosphamide.

5. In the two preceding paragraphs, once remission of the disease or exhaustion of the dose of immunosuppressant are achieved, a return to immunomodulatory therapy with an agent different from that used previously can be considered.
6. No response to prior treatments: evaluate bone marrow transplant (Figure 1).

Special situations

Pregnancy and lactation

Treatment with monoclonal antibodies and immunosuppressants is contraindicated during pregnancy and lactation. In general, immunomodulatory treatment is not recommended during pregnancy and lactation.

In pregnant patients with a high relapse rate before starting treatment, the risk of a severe outbreak appearing after stopping interferon beta treatment should be weighed against the possible risk of a spontaneous abortion. A patient who is pregnant or planning a pregnancy during therapy should be informed about potential risks and the possibility of interrupting treatment must be considered.

In principle, the option of administering IVIG should be considered restricted. Women of childbearing age should use appropriate contraceptive measures. The use of IVIG is allowed for the treatment of outbreaks during pregnancy, and steroids from the second quarter. Some authors recommend initiating immunomodulatory treatment immediately after birth to prevent outbreaks during the postpartum period, while others allow a period of lactation when initiating IVIG after delivery.

The use of immunosuppressors, monoclonal antibodies and immunomodulators is not recommended during lactation to prevent adverse effects on the infant.

Paediatric use

IFN-beta and GA can be administered to children with MS, from 12 years of age. When more than one dose is available, the lowest should be administered. There is limited information on the use of immunomodulators in children younger than 12 years, with their use being restricted to specific cases. Higher precautions should be taken in the case of compassionate use of immunosuppressants. Experience with natalizumab in children who do not respond to immunomodulators is very limited.[49]

Epilogue

Due to advances in diagnostic techniques and the imminent arrival of new drugs, it is expected that the recommendations of this consensus should be reviewed periodically.

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