



REVIEW ARTICLE

Consensus statement on medication use in multiple sclerosis by the Spanish Society of Neurology's study group for demyelinating diseases[☆]

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Abstract Treatments for multiple sclerosis therapy are rapidly evolving. It is believed that new drugs will be approved in the near future, thereby changing current indications for treatment. In this context, the Spanish Society of Neurology's study group on demyelinating diseases, which evaluates medication use in MS, has decided to draw up a consensus statement on the current indications and guidelines for multiple sclerosis treatment.

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Documento del Grupo de Consenso de la Sociedad Española de Neurología sobre el uso de medicamentos en esclerosis múltiple

Resumen La terapia de la esclerosis múltiple está en rápida evolución. En un plazo próximo, se prevé la incorporación de nuevos fármacos que pueden modificar las pautas actuales de tratamiento. Mientras tanto, el Grupo de Enfermedades Desmielinizantes de la Sociedad Española de Neurología encargado del consenso sobre la utilización de medicamentos para la EM, ha considerado necesaria una puesta al día de las indicaciones actuales y de los principios de tratamiento de esta enfermedad.

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Introduction

Since interferon beta (IFN- β) was approved as treatment for multiple sclerosis (MS), there have been major advances in our understanding of the disease. Such advances have affected every aspect of MS, including genetics, immunology, anatomical pathology, neuroimaging, and especially

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therapeutic measures. New drugs have been optimised and many more are in the final phases of development. Although treating MS progression is a goal beyond the reach of current drugs, control over the disease's inflammatory phase is improving day by day, and some data indicate that providing treatment in early stages is associated with better long-term outcomes. However, MS remains a serious disease. It is the number one cause of disability unrelated to trauma in young adults, and it may also significantly reduce a patient's life expectancy.¹ Early and appropriate use of available treatments is essential for improving patient prognosis. At present, the treatment objective is to achieve complete control over MS activity, meaning both clinical and neuroimaging manifestations.

It is believed that the European Medicines Agency (EMA) will authorise new drugs in the near future. Meanwhile, the Spanish Society of Neurology's study group for demyelinating diseases, which is responsible for generating consensus statements on medication use in MS, finds it necessary to update general treatment guidelines for this disease.

Indications for treatment for multiple sclerosis

Relapsing-remitting multiple sclerosis

The drugs IFN- β 1a IM (Avonex[®]) or SC (Rebif[®]), IFN- β 1b (Betaferon[®]) and glatiramer acetate (AG) (Copaxone[®]) have grade A recommendations based on level I studies as drugs reducing the frequency of exacerbations in relapsing-remitting MS (RRMS). These recommendations^{2–5} were published between 1993 and 1998 and the drugs are indicated by the EMA and by other regulatory agencies on this basis. It is generally accepted today that a patient receiving these treatments must be 16 or older, with RRMS and an EDSS score below 5.5 (patient able to walk 100 metres unaided and without stopping). Contraindications for treatment include pregnancy, breastfeeding, severe systemic disease, allergy to human albumin, or depression with suicidal thoughts.

Grade A recommendation based on level I clinical trials has also been given for natalizumab (Tysabri[®])^{6,7} and fingolimod (Gilenya[®])^{8,9} in trials controlled with placebo or active comparator. However, owing to the safety profile of these two drugs, the EMA restricted their use to initial treatment of aggressive-onset RRMS with rapid deterioration of neurological function and evidence of inflammatory activity. Other indications are reserved for failure of first-line treatments (IFN- β and GA).

Azathioprine is authorised as RRMS treatment in Spain,¹⁰ but we must point out that there is considerably less evidence of its efficacy than for IFN- β and GA, and that the drug also presents risk of oncogenesis. Azathioprine may be considered when MS is associated with connective tissue disease or in cases in which immunomodulatory agents cannot be used.

Secondary progressive multiple sclerosis

Three main level I studies of IFN have been performed: 2 with Betaferon[®] and 1 with Rebif[®].^{11,12} The first study,

carried out in Europe with Betaferon[®], indicated a net effect on exacerbations and a significant delay in disability progression both in patients with and without exacerbations. However, a US study of the same drug in patients with secondary progressive MS (SPMS) did not find any effects on disability levels. The following study with IFN- β examined Rebif[®] vs placebo at doses of 22 and 44 μ g. Both doses were shown to effectively reduce the exacerbation rate, but favourable results for disability progression were only recorded for patients who had experienced prior exacerbations. Based on these studies, IFN- β has a class A recommendation for SPMS with exacerbations, but it has only been approved for use in this SPMS subgroup.

Mitoxantrone has a class B recommendation based on a level II/III study¹³ determining that the drug was likely to produce discrete improvements in the exacerbation rate, MRI findings, and progression in cases of SPMS with exacerbations. However, its use in clinical practice has decreased considerably due to its cardiotoxicity and associated risk of acute leukaemia.

None of the drugs that have been studied in controlled clinical trials have been shown to be effective for SPMS without exacerbations, and as a result, they have no recognised treatment indications.

Primary progressive multiple sclerosis

Researchers have completed several studies of IFN- β . One systematic review did not find that the drug presented any benefits with regard to disease progression.¹⁴ Other drugs have also been studied in primary progressive MS (PPMS), including GA and rituximab, without results being conclusive. Based on the lack of significant effects on disease progression in studies completed to date, using drugs to modify the course of this form of MS is not recommended at present.

Treatment following a single or isolated demyelinating episode

Single or isolated episodes of demyelination (clinically isolated syndrome) have been examined by several studies using different preparations of IFN- β or GA.^{15–19} The first of these published studies (CHAMPS) used weekly doses of IFN- β 1a IM; the second, weekly doses of IFN- β 1a SC at 22 μ g (ETOMS); the third, IFN 1b (BENEFIT); and the fourth, IFN- β 1a SC at 44 μ g, 1 or 3 times weekly (REFLEX). GA has been examined in a trial named PRECISE. While results differed somewhat from study to study, all showed that early use of IFN- β or GA in clinically isolated syndrome significantly delayed conversion to MS. This was confirmed by both clinical manifestations and by new MR images. For this reason, all drugs listed above have class A recommendations for delaying the onset of new exacerbations or new lesions in MR imaging studies. Health authorities have approved the indication of any of the three types of IFN- β and GA for treating clinically isolated syndrome, using the same doses and frequencies as for RRMS.

The literature offers differing views regarding which patients with clinically isolated syndrome should be treated. It seems reasonable to treat those patients who stand to

benefit the most from treatment, that is, patients at the most risk of severe progression (exacerbations, neurological deterioration). The neurologist should estimate level of risk based on clinical or paraclinical data.

First and second lines of treatment. Treatment failure. Drug escalation

Treatment for MS is evolving rapidly, which is not only due to the incorporation of new drugs, but also to changes in the way the disease is understood and interpreted. For example, adopting the McDonald criteria entails being able to issue a firm diagnosis of the disease after a single episode of demyelination when certain findings appear in the MRI study. As we increase our knowledge of MS, the action and response of different drugs, and the optimisation of biomarkers for different features of the disease, we should also anticipate the possibility of adjusting treatments to each patient's profile in the near future.

When regulatory agencies such as the EMA authorise a specific drug for use in a disease, they do so based on usage indications that point to a positive risk–benefit ratio. Later, other health authorities from individual countries complete further evaluations of these indications in order to determine whether or not to subsidise the medication, and if so, under what conditions. In treating MS, the concepts of 'first line of treatment' (IFN- β , GA, and fingolimod and natalizumab for forms with aggressive onset) and 'second line of treatment' (the latter 2 and mitoxantrone) are established by the regulatory authority's evaluations.

It should be noted that drugs listed in the first line or second line categories are not equivalent. In the case of IFN- β , each of the three preparations differs with regard to composition, route of administration, absorption, and dose. These differences may significantly affect efficacy or tolerability in specific patients. To cite an example from the first line of treatment, GA is not pharmacologically related to forms of IFN- β . Natalizumab and fingolimod are not equivalent treatment alternatives due to their different pharmacological properties and action mechanisms, and the possible role played by the presence or absence of antibodies to the JC virus or by comorbidities such as heart or metabolic disease. Mitoxantrone is only an option in a very few select cases because of its toxicity.

In practice, clinical assessment may establish indications that are not included in drug leaflets and which may be taken from clinical consensus statements. A specialist's evaluation based on available evidence is fundamental for deciding which drug to administer to a specific patient.

The concepts of the first and second line of treatment, which are well-known in the international community, imply the notion of treatment failure. These concepts are a topic of debate due to their excessive strictness and because, as stated above, biomarker availability may be used to determine the treatment best suited to the patient's individual characteristics.

Experts do not agree on the definitions of treatment failure or suboptimal response, but several studies have examined the number of exacerbations, the progression of disability, and MR imaging data to draw up criteria for treatment failure. When one of the initial drugs does not deliver

the desired effect, doctors consider trying drugs listed as the second line of treatment, which have both increased efficacy and a higher level of associated risk. This process involves the idea of treatment escalation.

The Spanish Society of Neurology's study group for demyelinating diseases has elaborated a consensus statement on the use of medications in MS. This document, which is pending review, specifically addresses each of these issues.²⁰

Summary of recommendations

RRMS:

- Initial treatment: IFN- β 1b SC, IFN- β 1a IM, IFN- β 1a SC and GA.
- Aggressive onset MS: fingolimod or natalizumab.
- Initial treatment not effective: fingolimod, natalizumab, mitoxantrone (rarely used at present).

SPMS with exacerbations: IFN- β 1b SC, IFN- β 1a SC, mitoxantrone (rarely used at present).

SPMS without exacerbations: no evidence of there being an effective treatment.

PPMS: no evidence of there being an effective treatment.

Clinically isolated syndrome: IFN- β 1b SC, IFN- β 1a IM, IFN- β 1a SC and GA.

Conflicts of interest

The authors have no conflicts of interest to declare.

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