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MULTIPLE SCLEROSIS TREATMENT AND HOLISTIC PATIENT CARE: CONSENSUS OF THE SPANISH SOCIETY OF NEUROLOGY

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CONCLUSIONS

- This consensus is intended to be a useful tool to improve and standardize MS patient management in clinical practice in Spain.
- The recommendations were developed considering the scientific evidence accumulated and the resources available in Spain.
- Early diagnosis and start of DMTs as soon as possible is considered essential.
- The terminology of treatment lines should be abandoned, since DMTs considered "second-line" are high-efficacy treatments that can be stablished as first option depending on patient and disease characteristics.

INTRODUCTION

- The management of patients with multiple sclerosis (MS) is complicated and entails several challenges, both in diagnosis and treatment[1].
- The growing number of disease-modifying therapies (DMTs) available, the scarcity of accurate biomarkers to predict their effectiveness and safety, and individual patient preferences make therapeutic decision-making very complex[2-4].
- In the recent years, several guidelines were developed to improve the management of patients with MS at a European[5] and national level in other countries[6]. The Spanish Society of Neurology published consensus on 2010, 2013 and 2017[7-9].
- The most recent consensus of the Spanish Society of Neurology, focused on the treatment of the patient with MS, lacked a structured methodology to formulate recommendations[7].
- Since the last consensus, new DMTs were approved, diagnostic criteria were updated, new evidence on the early treatment with high efficacy (HE)-DMTs emerged, and patient-reported outcomes started to be considered important tools to evaluate the patient perception of the disease. In this context, updated recommendations are required.

OBJECTIVE

- This collaborative project of a group of specialized physicians aimed to offer a set of recommendations on the complete management of the MS patient in clinical practice in Spain, including aspects related to diagnosis, treatment and patient follow-up.

METHODS

- For this project, a scientific committee was formed by five members (two of them also acted as coordinators) all of whom are considered experts in MS at the national level.
- The scientific committee conducted a thorough literature review, selected dimensions and items, and invited panellists. After the first round, they reviewed and edited the non-consensus items based on the feedback received and, after the second round, evaluated the non-consensus items. The scientific committee did not participate in the item evaluation to avoid any bias.
- A total of 21 panellists, who are experts on MS, representing different regions of Spain participated in the project. The panellists evaluated the items in the first and second round and provided feedback on the evaluated items.
- The items were classified in 9 dimensions:
  1. Early diagnosis
  2. Early start of DMTs
  3. Escalation vs early start of HE-DMTs
  4. Face-to-face and remote follow-up
  5. Detection of suboptimal response and treatment optimisation
  6. Patient perspective
  7. Biomarkers
  8. Pregnancy
  9. Vaccination
- The recommendations were developed following the Delphi method, characterized by implementing an iterative process, guaranteeing anonymity, and collecting feedback from participants **(Figure 1)**.

Figure 1: The Delphi method process

- The items were defined taking into consideration the latest scientific evidence and the limitations of existing resources.
- The level of agreement was assessed using a 9-point Likert scale. The items were categorized as rejected (1-3), indeterminate (4-6) or accepted (7-9). Consensus was reached if the panellists reached a ≥66.6% agreement.

RESULTS

- Of the 148 items studied, 110 were agreed, of which 102 were accepted in rounds 1 or 2 with a mean (standard deviation) of 86.8% (10.3) in agreement. In fact, 73.5% of the items achieved a consensus percentage >80%. In round 2, no consensus was reached on 34 items, which were evaluated by the scientific committee (8 were consensus and 26 were non-consensus). The 8 items agreed by the scientific committee do not have the percentage of consensus. The main items reaching consensus for each dimension are presented.

Table 1. Diagnosis and initiation of DMTs

Dimension and item	Agreement (%)
Early diagnosis	
In addition to MRI, initial paraclinical evaluation should include measurement of OCBs and IgG in blood and CSF	100
If optic neuropathy is suspected, the visual system should be evaluated by OCT and VEP	90.5
The accuracy of the diagnosis of MS would be increased by the inclusion of optic nerve lesions in the criteria for dissemination in space	76.2
Spinal MRI in the diagnosis is recommended and allows to determine lesions that can guide the therapeutic decision making	95.2
Early start of DMTs	
In patients newly diagnosed with MS, DMTs should be offered to the patient as soon as possible to monitor activity and progression	95.2
A HE-DMT treatment may be started, depending on the treatment characteristics and the clinical and radiological characteristics, the lifestyle and the preferences of the patient	95.2
In patients with a first MS relapse or CIS at risk of progression to MS with high lesion burden and poor prognostic factors, treatment with DMTs should be started	95.2
In patients with a first MS relapse and infratentorial/spinal cord lesions on MRI, DMT treatment should be started	95.2
Escalation vs early start of HE-DMTs	
It is possible to treat with a HE-DMT as a first option, once the patient has been evaluated and the risks and benefits of the treatment have been considered	100
The ultimate goal of MS treatment is the best possible disease control (as measured by NEDA-3) and the best possible quality of life for the patient	81
In a patient with demographic, clinical and radiological poor prognostic factors, it is recommended to start with a HE-DMT	95.2
Therapeutic inertia is a loss of therapeutic opportunity	100

- The optic nerve was not previously considered as a topography required to demonstrate dissemination but being a frequently affected region at the beginning of the disease, its inclusion was suggested. Similarly, MRI findings can help confirming the diagnosis. However, no consensus has been reached on items that indicated the confirmation of a transition to progressive phase by detecting an increase of 20% in the time spent performing the 9HPT or a worsening of ≥4 points in the SDMT at 6-12 months.
- Clinically isolated syndrome (CIS) is defined as a single episode of neurological symptoms suggestive of MS, but no consensus has been reached to consider CIS a first MS relapse. In CIS, one of the worst prognostic factors is the lesional burden in MRI. Early initiation of DMTs is recommended depending on the patient's diagnosis.
- Traditionally, a therapeutic escalation strategy has been used, but based on the accumulated evidence, early initiation with HE-DMTs is suggested. It is recommended to evaluate its effectiveness at 12 months, without reaching consensus on the evaluation by radiological activity at 6 months.

Table 2. Treatment and follow-up

Dimension and item	Agreement (%)
Face-to-face and remote follow-up	
After starting the first DMT, a face-to-face follow-up is recommended based on patient and treatment characteristics and adapted case-by-case	85.7
An MRI should be performed 3-6 months after starting the treatment and annually afterwards	90.5
If not stabilized, a face-to-face follow-up is recommended every 3 months, if possible	95.2
Cognition should be assessed based on validated tools such as SDMT and neuropsychological batteries (BICAMS, BRB-N) if cognitive disorders were detected at screening	90.5
Detection of suboptimal response and treatment optimisation	
In the detection of suboptimal response and change to HE-DMTs, relapses (with or without residual disability), MRI lesions, or progression should be considered in patients treated with moderately effective DMTs	81
The presence of ≥1 relapses between the first and second year from the onset of DMTs would indicate a suboptimal response	73.7
The rapid increase in disability progression (≥1 points in EDSS compared to the year prior to the onset of DMTs) would indicate a suboptimal response	81
Stable patients in a HE-DMT who receive clinical and radiological follow-up and do not present with safety/tolerability problems should maintain their treatment	100
Patient's perspective	
If possible, it is recommended to prioritize the use of validated tools specific for MS	95.2
The recommended frequency to evaluate the patient's perspective using validated tools would be, in addition to depending on each case, at least once a year	76.2
It is recommended to encourage the communication of sexual function problems by the patient	100
It is recommended to encourage the communication of sleep disturbances by the patient	100

- Since biomarkers that are sufficiently accurate to predict the suitability of the chosen DMT are not available, follow-up is crucial after treatment begins. After the initiation of DMT, it has been recommended to follow-up at 3 months and depending on the characteristics of the patient, without reaching consensus on follow-ups at 6-12 months. Telemedicine could complement the face-to-face follow-ups and replace certain face-to-face visits in stable patients without visual, auditory, or cognitive difficulties.
- The appearance of new relapses, new lesions on MRI or the increase in confirmed disability suggest an active course of the disease and, therefore, a suboptimal response to treatment. However, it is difficult to determine the specific number of lesions and relapses or the degree of cumulative disability that defines the suboptimal response. When a suboptimal response is detected, a change of treatment is recommended. For a patient to be considered eligible to initiate HE-DMTs, 1-3 relapses must have been detected.
- To assess the patient's perspective, it is recommended to prioritize the use of validated tools specific to MS to homogenize their use and obtain comparable results. The recommended frequency of evaluation with these validated tools would be at least once a year. No consensus has been reached on validations every 6 months or every 2 years.

Table 3. Biomarkers, pregnancy and vaccination

Dimension and item	Agreement (%)
Biomarkers	
Oligoclonal bands are a useful biomarker in routine clinical practice for predicting disease prognosis	66.7
Oligoclonal bands are a feasible biomarker in routine clinical practice for predicting disease prognosis	66.7
Levels of sNfL are a useful biomarker in routine clinical practice for predicting disease prognosis	FE
OCT is a feasible biomarker in routine clinical practice for predicting disease prognosis	FE
Pregnancy	
In patients who are planning a pregnancy and who do not have clinical and radiological stability, it is recommended to optimize treatment and delay pregnancy by at least 12 months	90.5
In patients treated with DMTs, with a desire to gestation and with a relapse in the last 12 months, it is recommended to delay pregnancy planning	94.7
In the event of unplanned pregnancy, the risk/benefit of each DMT will be evaluated, as indicated in the Summary of Product Characteristics	95.2
In the event that the patient does not wish to breastfeed and DMTs have been discontinued during pregnancy, it is recommended to resume treatment as soon as possible after delivery, assessing the patient's condition	100
Vaccination	
Once the diagnosis of MS has been made, the recommended local vaccination schedule should be completed	100
Before starting immunosuppressive therapy, antibodies to possible relevant infections should be evaluated and the patient should be given appropriate vaccination	95.2
The use of inactivated vaccines is considered safe	100
Live attenuated vaccines should be avoided in patients being treated or recently treated with immunosuppressive DMTs	100

- Few biomarkers have reached the validation phase and fewer have been translated into clinical practice. Therefore, it has been difficult to reach consensus on these items. For example, there is sufficient evidence for the use of sNfL levels to evaluate prognosis, but their use in routine clinical practice is still very limited.
- A broad consensus has been obtained on the items related to pregnancy. In patients planning a pregnancy, the risks should be presented to establish a treatment and pregnancy plan, depending on the risk-benefit profile in each case.
- Finally, since there is an increased risk of infections in patients treated with DMTs, vaccination has been recommended as a preventive strategy. Although there is broad consensus on inactivated vaccines, there is some controversy in the use of live attenuated vaccines. In general, it has been recommended to avoid attenuated vaccines in patients recently treated with DMTs.

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Conflicts of interest

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