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SPANISH SOCIETY OF NEUROLOGY CONSENSUS AND RECOMMENDATIONS ON MULTIPLE SCLEROSIS TREATMENT

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INTRODUCTION

- Patients with multiple sclerosis (MS) face many challenges, both in diagnosis and treatment [1-4].
- There have been many developments including the approval of new DMTs, updating of diagnostic criteria, and the increasing use of early treatment with high efficacy (HE)-DMTs, as well as patient-reported outcomes being considered important tools for assessing patient perception.
- Previous guidelines developed at European and national level [5-9] are not focused on the early use of HE-DMTs, the timed detection of suboptimal response or the use of newly identified biomarkers.
- As a result, updated recommendations are needed.

OBJECTIVE

- The objective of this collaborative project between a group of specialized physicians was to offer suggestions on the complete management of patients with MS in clinical practice in Spain, addressing diagnoses, treatment, and patient monitoring.

METHODS

- The scientific committee for this project was formed by five key opinion leaders in MS at the national level (two of whom also acted as coordinators).
- The scientific committee conducted a comprehensive literature review, selected dimensions and items, and invited panelists. Using the feedback from the first round, they revised and edited non-consensus items, which were evaluated in the second round. In order to avoid bias, the scientific committee did not take part in the item evaluation.
- This project involved 21 panelists, who are MS experts from different regions of Spain. Following the first and second rounds of evaluation, the panelists provided feedback on the 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

Round 1
- 128 items defined by the scientific committee (5 members) were evaluated by 21 panelists
- 92 consensus items
- 36 items did not reach consensus and were reviewed and reformulated or divided

Round 2
- 46 items evaluated by 21 panelists
- 12 consensus items
- 34 items did not reach consensus and were reviewed

Final evaluation
- 34 items evaluated by the scientific committee
- 8 consensus items
- 26 items did not reach consensus

110 consensus items

- Scientific evidence and existing resources were taken into account in defining the items. After each round, non-consensus items were reformulated or divided for clarity.
- Based on a 9-point Likert scale, the items were categorized as rejected (1-3), indeterminate (4-6), or accepted (7-9). A consensus was achieved when panelists reached 66.6% agreement.

RESULTS

- We present a selection of items with relevant clinical implications.

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
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
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
Cycling with injectable and oral DMTs of moderate efficacy, which delays the start of an HE-DMT, represents a loss of therapeutic opportunity	81
Persistent clinical or subclinical activity can cause irreversible neurological damage and allows the activation of molecular pathways that favor progression and that could be avoided by starting with a HE-DMT early	90.5
Patients with a first MS relapse may be considered for HE-DMT, depending on patient characteristics and of the disease, without the need for treatment delay or therapeutic escalation	90.5
After the diagnosis of MS, the choice of initial treatment should not be based on the use of so-called "treatment lines", but mainly on the presence or absence of poor prognostic factors (epidemiological, clinical, radiological and biomarkers) for the appearance of new relapses or progression of disability	94.7
It is recommended to evaluate the effectiveness of early start of HE-DMTs by: Radiological activity at 6 months	57.1

- 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) consists of a single episode of neurological symptoms consistent with MS, but no consensus has been reached to consider CIS a first MS relapse.
- Traditionally, therapeutic escalation strategies have been used, but recent evidence suggests that HE-DMTs should be initiated early, avoiding cycling and therapeutic inertia. The effectiveness of the therapy with HE-DMTs should be evaluated annually, although no consensus was reached on evaluating it by radiological activity at 6 months given its difficulty in routine clinical practice.

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
In general, the clinical activity of the disease that is considered sufficient to make patients treated with moderately efficacy DMTs after a full course (1 year after the DMT effect started) eligible for HE-DMT would be:	
Clinical activity (1 relapse)	FE
Clinical activity (2-3 relapses)	68.4
Stable patients with HE-DMT who receive clinical and radiological follow-up and do not present with safety/tolerability problems should maintain their treatment	100
Stable patients with HE-DMT who receive clinical and radiological follow-up and who do not present safety/tolerability problems, de-escalation should not be performed	95.2
Discontinuation or interruption of medication in highly active patients due to suboptimal response or safety/tolerability should be accompanied by initiation, as soon as possible, with the new high-efficacy therapy, taking into account the disease activity before and during treatment, the pharmacokinetics and biological activity of the previous DMT and the risk of rebound	90.5
If a HE-DMT is not effective or safe, it is recommended to switch the patient to another HE-DMT	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 assess treatment preferences before the start of treatment	95.2
It is recommended to measure satisfaction with treatment, after initiation, using validated tests	90.5

FE: final evaluation

- The absence of biomarkers that predict the suitability of a given DMT makes follow-up essential after treatment begins. Following the initiation of DMT, it has been recommended to follow-up at 3 months and based on patient characteristics, with no consensus reached on follow-up at 6-12 months. Patients without visual, auditory, or cognitive difficulties may benefit from telemedicine as a complement to face-to-face follow-ups.
- Relapses, new lesions on MRI or an increase in confirmed disability suggest an active course of the disease and a suboptimal response to treatment. However, it is difficult to define the suboptimal response in terms of the number of lesions and relapses or the level of cumulative disability. In cases of suboptimal responses, treatment changes are recommended. To be eligible for HE-DMTs, it is necessary to detect at least one relapse. Once a patient is stable with HE-DMTs, if there are no safety or tolerability problems, the treatment should be maintained.
- At least once a year would be recommended for evaluation using validated tools specific to MS, such as FSS, MFIS, MSQoL or NRS-S. There has been no consensus on whether evaluation should occur every six months or every two years.

Table 3. Biomarkers, pregnancy and vaccination

Dimension and item	Agreement (%)
Biomarkers	
Serum levels of light chain neurofilaments are a feasible biomarker in routine clinical practice:	
predictive of disease progression	FE
response to treatment	FE
for follow-up	FE
Oligoclonal immunoglobulin bands (lipidospecific IgM) are a biomarker:	
useful in routine clinical practice to predict the prognosis of the disease	66.7
feasible in routine clinical practice to predict the prognosis of the disease	66.7
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
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

FE: final evaluation

- Few biomarkers have reached the validation stage and fewer are used in routine clinical practice. These items have therefore been difficult to agree on. Serum neurofilament light chain (sNfL) levels are sufficient for evaluating prognosis, but their use in routine clinical practice is very limited.
- In patients planning a pregnancy, the risks should be discussed in order to develop a treatment and pregnancy plan based on the risks and benefits.
- Vaccination has also been recommended for patients treated with DMTs due to an increased risk of infection. Patients recently treated with DMTs are generally advised to use inactivated vaccines.

CONCLUSIONS

- Early diagnosis and start of DMTs as soon as possible is considered essential.
- The terminology of treatment lines should be abandoned, since HE-DMTs considered "second-line" can be stablished as first option depending on patient and disease characteristics.
- Suboptimal response to treatment is defined by relapses, new lesions on MRI or an increase in confirmed disability. The therapeutic attitude to suboptimal response should change and HE-DMTs should be maintained if the patient is stable.
- Few biomarkers are considered feasible in routine clinical practice.

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Conflicts of interest

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