GUIDELINE

Portuguese Consensus for the Evaluation of the Multiple Sclerosis Treatment Response: A Delphi Panel

Consenso Português para a Avaliação da Resposta Terapêutica da Esclerose Múltipla: Painel Delphi

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Abstract

Introduction: Multiple sclerosis management has progressed significantly due to the development of novel treatments. Thus, assessing the patients' treatment response is essential to optimize therapeutic decisions. This study aimed to establish a national consensus on the assessment and monitoring of the response to multiple sclerosis treatment with disease-modifying therapies.

Methods: The Delphi methodology was employed, and two rounds of votes were performed. The statements that did not reach consensus (<80%) in the first round were submitted to a new assessment by the panel.

Results: Thirty-eight Neurologists participated in the first round and 33 participated in the second round (86.8% response rate). In total, 38 statements (71.7%) reached consensus. In a general manner, consensus was reached for the statements related to assessment and monitorization of response to treatment. Statements for which no consensus was reached were related to less established response evaluation criteria, such as assessment by optical coherence tomography. Additionally, a lack of consensus was observed for the statements where the obtained evaluation makes it difficult to define suboptimal response to treatment and for shorter or longer monitoring times.

Conclusion: This work highlights the importance of assessing the response to disease-modifying treatments in patients with multiple sclerosis and provides a set of criteria for this evaluation, established by a comprehensive panel of Portuguese experts. A more comprehensive analysis, which includes different parameters, was consensually agreed to be the best assessment strategy.

Resumo

Introdução: O tratamento da esclerose múltipla registou progressos significativos devido ao desenvolvimento de novas terapias. Assim, a capacidade de avaliar a resposta dos doentes ao tratamento é essencial para otimizar as decisões terapêuticas. Este estudo tem como objetivo estabelecer um consenso nacional sobre a avaliação e monitorização da resposta ao tratamento da esclerose múltipla com terapêuticas

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Metodologia: Foi utilizada a metodologia Delphi e foram efetuadas duas rondas de votação. As afirmações que não obtiveram consenso (<80%) na primeira ronda foram submetidas a uma nova avaliação pelo painel de especialistas.

Resultados: Trinta e oito neurologistas participaram na primeira ronda e 33 participaram na segunda ronda (86,8% de taxa de resposta). No total, 38 afirmações (71,7%) obtiveram consenso. De uma forma geral, foram objeto de consenso as afirmações relacionadas com a avaliação e monitorização da resposta ao tratamento. As afirmações para as quais não se obteve consenso referem-se aos critérios de avaliação da resposta menos estabelecidos, como a avaliação por tomografia de coerência ótica. Adicionalmente, também não se obteve consenso para as afirmações em que a avaliação obtida dificulta a definição de resposta subótima ao tratamento e para tempos de monitorização mais curtos ou mais longos.

Conclusão: Este trabalho realça a importância da avaliação da resposta aos tratamentos modificadores da doença em doentes com esclerose múltipla e apresenta um conjunto de critérios para essa mesma avaliação, estabelecidos por um painel alargado de peritos portugueses. Uma análise mais abrangente, que inclua diferentes parâmetros, foi consensualmente aceite como a melhor estratégia de avaliação.

Introduction

Multiple sclerosis (MS) affects around 2.8 million individuals worldwide and is the most common demyelinating, neurodegenerative and chronic inflammatory disease in young adults.[1,2]

MS treatment management is very challenging due to its long-term nature and uncertain prognosis. In general, periodic neurological re-evaluations and treatment adjustments are needed, with better medium-term outcomes expected if the treatment is started early in the course of the disease.[3-5]

As it has been shown that the natural history of MS can be modified by treatment, several disease-modifying therapies (DMTs) have been developed.[3,6-8] The evolving treatment landscape in MS, with increasingly effective DMTs available, was accompanied by a parallel evolution of the treatment outcomes, becoming progressively more exigent with the ultimate goal of controlling disease activity and preventing irreversible neuronal damage and disability.[9] However, an associated range of complex adverse effects also emerged.[10,11] Thus, treatment management requires an extensive knowledge of the mechanism of action of each treatment and potential side effects, namely regarding immune compromise after chronic immune therapy.[10] Ultimately, the selection of which treatment to use and its maintenance relies on a delicate balance between efficacy, safety and tolerability.

It is, therefore, crucial to correctly assess the treatment response of each patient to consider optimal therapeutic decisions.[3,4,11] However, therapeutic decisions are hindered due to 1) the lack of a shared definition for treatment response in MS, 2) no consensus on which biomarkers should be used to assess treatment response upon treatment with DMTs, 3) the lack of clear instructions concerning the more adequate procedure to switch between DMTs in current guidelines and recommendations on MS treatment and 4) the inability of evidence-based recommendations to solve daily clinical management issues due to high variability in resources and treatment approaches between care units.[3,4]

Notwithstanding these difficulties, early prediction of treatment response is a critical purpose in the field of MS research.[3] In this work, Portuguese Neurologists participated in a Delphi study to reach a national consensus on the strategies to identify and monitor treatment response in MS.

Methods

Consensus on the evaluation of MS treatment response was reached by employing the Delphi methodology.[12] The statements were adapted from a Spanish survey regarding assessment and follow-up of the response to DMT in MS[13] by 7 Portuguese Neurologists. These statements addressed how and when to assess

treatment response and the influence of relapses, disability progression, disease activity, neuropsychological status, and brain volume loss in this assessment. Moreover, it addressed the change of treatment due to lack of response. The statements were made available online to 63 nationwide Neurologists, recognized MS experts, who fulfilled the prerequisite of following at least 50 MS patients per year. Two anonymous voting rounds were performed between July and September 2022. Most statements were evaluated using a Likert scale that assessed agreement (totally agree, agree, disagree, totally disagree) and, for the statements deemed appropriate, a Likert scale that assessed applicability (not applied in clinical practice but useful, applicable in the medium/long term, applicable in the short term, already applied in clinical practice) was also employed. For the statements regarding change of treatment due to lack of response, the options 1) maintain treatment, 2) change of treatment (different mode of action, similar efficacy) and 3) change of treatment (greater efficacy) were provided. Eighty percent of agreement was considered the threshold for consensus. In between rounds, the results of all answers to the questionnaire were qualitatively analyzed and sent to the Delphi panel. In the second round, the statements that do not reach a consensus in the first round were subjected to new voting. To facilitate the interpretation of the results, the evaluations totally disagree/disagree and agree/totally agree were combined under the evaluations disagree and agree.

Results

Of the 63 Neurologists contacted, 38 participated in the first round (60.3% adherence). Of these 38, 33 participated in the second round (86.8% response rate). Consensus was obtained for 37 statements (69.8%) in the first round, being the remaining 16 statements submitted to the second round. From these, only one reached consensus (6.3%) and, thus, 38 of the 53 statements (71.7%) reached consensus (**Fig. 1**). The statements assessed and the respective percentages obtained are presented in **Table 1**.

Treatment response

Regarding treatment response assessment, the panel deemed that the patients should be analyzed every 6 months since the beginning of treatment. Moreover, in the presence of one relapse in combination with new T2 lesions it was considered inappropriate to maintain treatment and perform a reassessment at 6 months. No consensus was reached for maintaining treatment and performing a reassessment at 6 months for patients that had three or more new T2 lesions but that did not experience a relapse.

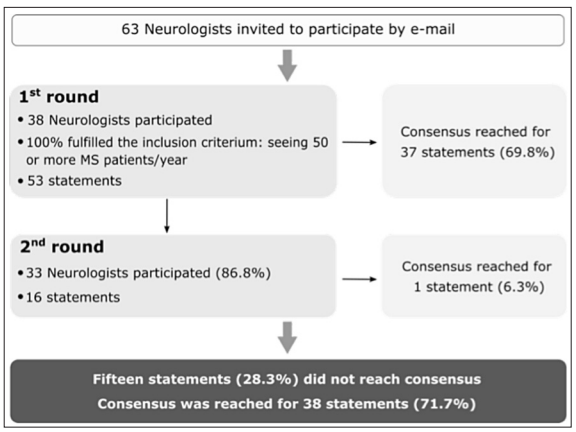

Figure 1. Overview of the rate of response and consensus reached in this study.

The panel consensually agreed that magnetic resonance imaging (MRI), relapses, disability progression, quality of life, cognitive parameters, brain volume loss and treatment adherence should be considered when assessing treatment response.

Relapses

Relapse assessment was regarded as an insufficient measure for determining treatment response. Moreover, it was agreed that the absence of relapses did not hinder the determination of a lack of treatment response.

It was considered that relapse assessment should include the number of relapses since the beginning/change of treatment, their severity, their typology, and time of appearance, namely if they are related to the beginning/change of treatment.

Disability progression

Disability progression was considered as a parameter for assessing treatment response. Consensus was reached on employing a neurological exam and the Expanded Disability Status Scale (EDSS) scale in each appointment to assess disability progression. Additionally, it was considered that disability progression evaluation should be performed using the EDSS scale and at least one other test, such as the 25-foot walk test (25FTW) or the 9-hole peg test (9HPT). The timing for disability pro-

Table 1. Statements submitted for evaluation and the respective percentage of agreement and applicability reached.

Statements	Agree (%)	Disagree (%)	Not applied in clinical practice, but useful (%)	Applicable in the medium/ long term (%)	Applicable in the short term (%)	Already applied in clinical practice (%)
I. Treatment response						
1. To assess treatment response, patients should be assessed every 6 months since the beginning of the treatment.	81.6%	18.4%	-	-	-	-
2. Patients without relapses and ≥ 3 new T2 lesions: maintain treatment and perform a reassessment at 6 months to confirm the adequate control of the disease and assess the treatment response.	21.2%	78.8%	-	-	-	-
3. Patients with 1 relapse and ≤3 new T2 lesions: maintain treatment and perform a reassessment at 6 months to confirm the adequate control of the disease and assess the treatment response.	5.3%	94.7%	-	-	-	-
4. Patients with 1 relapse and ≥3 new T2 lesions: maintain treatment and perform a reassessment at 6 months to confirm the adequate control of the disease and assess the treatment response.	0	100%	-	-	-	-
5. MRI, relapses and disability progression should be analyzed to evaluate treatment response.	100%	0%	2.6%	0	0	97.4%
6. Quality of life should be considered when evaluating treatment response.	100%	0%	15.8%	18.4%	23.7%	42.1%
7. Cognitive parameters should be considered when evaluating treatment response.	100%	0%	13.2%	18.4%	47.4%	21.1%
8. Brain volume loss should be considered when evaluating treatment response.	97.4%	2.6%	57.9%	34.2%	5.3%	2.6%
9. Before evaluating treatment response, adherence to treatment should be analyzed.	100%	0%	0	0	5.3%	94.7%
II. Relapses						
10. Relapse assessment is enough to determine treatment response.	7.9%	92.1%	-	-	-	-
11. Relapse assessment should include the number of relapses since the beginning/switch of treatment.	97.4%	2.6%	-	-	-	-
12. Relapse assessment should include their severity (intensity and/or sequels).	94.7%	5.3%	-	-	-	-
13. Relapse assessment should include the typology (location and/or associated symptomatology)	97.4%	2.6%	-	-	-	-
14. Relapse assessment should include the time of appearance (namely, take into account the onset of action of the medication) and if they are related to the beginning/switch of treatment.	100%	0	-	-	-	-
15. It is possible to define lack of treatment response in the absence of relapses.	92.1%	7.9%	-	-	-	-
III. Disability progression						
16. The patients should be assessed in each appointment using a neurological exam and the EDSS scale.	100%	0	7.9%	5.3%	5.3%	81.6%
17. The assessment of treatment response should take disability progression into account.	100%	0	7.9%	0.0%	10.5%	81.6%
18. Progression can be defined by an increase in EDSS of 1 point if the initial score was ≤5,5 or if an increase of 0.5 points if the initial score was ≥6.	100%	0	0	7.9%	7.9%	84.2%
19. Assessment of disability progression using the EDSS scale should be performed every 3 months.	39.4%	60.6%	48.5%	30.3%	12.1%	9.1%
20. Assessment of disability progression usinsg the EDSS scale should be performed every 6 months.	86.8%	13.2%	7.9%	2.6%	7.9%	81.6%
21. Assessment of disability progression should be performed using the EDSS scale and at least 1 other test (e.g., 25FTW, 9HPT).	94.7%	5.3%	47.4%	13.2%	31.6%	7.9%
IV. Disease activity - assessed by magnetic resonance imaging						
22. Disease activity should be systematically assessed by MRI.	100%	0	7.9%	5.3%	2.6%	84.2%
23. Disease activity should be assessed by MRI with or without contrast.	89.5%	10.5%	2.6%	7.9%	2.6%	86.8%
24. A new baseline MRI should be performed 3-6 months after the onset of treatment to assess treatment response.	86.8%	13.2%	34.2%	7.9%	7.9%	50.0%

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; EDSS: Expanded Disability Status Scale; 25FTW: 25-foot walk test; Gd: gadolinium; 9HPT: 9-hole peg test; MRI: magnetic resonance imaging; OCT: Optical Coherence Tomography; SDMT: Symbol Digit Modalities Test.

Table 1. Statements submitted for evaluation and the respective percentage of agreement and applicability reached. (cont.)

Statements	Agree (%)	Disagree (%)	Not applied in clinical practice, but useful (%)	Applicable in the medium/ long term (%)	Applicable in the short term (%)	Already applied in clinical practice (%)
IV. Disease activity - assessed by magnetic resonance imaging (cont.)						
25. At diagnosis, disease activity should also be assessed by spinal cord MRI.	97.4%	2.6%	15.8%	2.6%	5.3%	76.3%
26. Disease activity should be assessed by MRI every 24 months.	33.3%	66.7%	6.1%	15.2%	9.1%	69.7%
27. Disease activity should be assessed by MRI every 12 months.	97.4%	2.6%	15.8%	7.9%	7.9%	68.4%
28. Disease activity should be assessed by MRI every 6 months.	33.3%	66.7%	63.6%	21.2%	9.1%	6.1%
29. Detection of subclinical activity by MRI is sufficient to define lack of treatment response.	84.8%	15.2%	9.1%	9.1%	9.1%	72.7%
30. The detection of 1 new or 1 enlarged T2 lesion is sufficient to define the lack of treatment response.	33.3%	66.7%	-	-	-	-
31. The detection of 2 new or enlarged T2 lesions is sufficient to define the lack of treatment response.	66.7%	33.3%	-	-	-	-
32. The detection of ≥3 new or enlarged T2 lesions is sufficient to define the lack of treatment response.	94.7%	5.3%	-	-	-	-
33. The detection of 1 lesion T1-Gd+ is sufficient to define the lack of treatment response.	81.6%	18.4%	-	-	-	-
34. The detection of ≥2 T1-Gd+ lesions is sufficient to define the lack of treatment response.	94.7%	5.3%	-	-	-	-
35. The location of the new T2 lesions is important to define the response to treatment.	69.7%	30.3%	-	-	-	-
36. During patient follow-up, spinal cord MRI should be performed regularly to assess disease activity.	45.5%	54.5%	-	-	-	-
V. Disease activity - assessed by biomarkers						
37. At diagnosis, the search for oligoclonal IgG bands in the cerebrospinal fluid should always be performed.	84.2%	15.8%	5.3%	0	2.6%	92.1%
38. At diagnosis, the quantification of neurofilaments in the cerebrospinal fluid should always be performed.	63.6%	36.4%	57.6%	39.4%	3.0%	0.0%
39. Periodic evaluation of the serum neurofilaments should always be performed to determine disease activity and to monitor treatment response.	92.1%	7.9%	57.9	26.3%	15.8%	0
40. Periodic evaluation using OCT should be performed to determine disease activity and to monitor treatment response.	72.7%	27.3%	60.6%	24.2%	9.1%	6.1%
VI. Brain volume loss						
41. Brain volume loss should be included in the evaluation of treatment response.	97.4%	2.6%	65.8%	26.3%	7.9%	0
42. The evaluation or quantification of brain volume loss should be performed periodically.	94.7%	5.3%	68.4%	23.7%	5.3%	2.6%
43. Patients with brain volume loss ≥0.4% should be considered as non-responders to treatment.	69.7%	30.3%	87.9%	12.1%	0	0
VII. Neuropsychological measures						
44. Regarding cognitive parameters, SDMT is a useful tool for the screening of cognitive defects and the monitoring of treatment response.	94.7%	5.3%	28.9%	15.8%	23.7%	31.6%
45. Regarding cognitive parameters, BICAMS is a good battery of tests to monitor treatment response.	92.1%	7.9%	50.0%	15.8%	26.3%	7.9%
46. Neuropsychological evaluations should be performed annually to assess treatment response.	75.8%	24.2%	42.4%	36.4%	6.1%	15.2%
VIII. Change of treatment due to lack of response						
Statements	**Maintain treatment**		**Change of treatment (different mode of action, similar efficacy)**		**Change of treatment (greater efficacy)**	
47. Patients with relapses, with MRI activity and with disability progression, treatment decision should be:	0		0		100%	
48. Patients with relapses, with MRI activity and without disability progression treatment decision should be:	0		7.9%		92.1%	
49. Patients with relapses, without MRI activity and without disability progression, treatment decision should be:	6.1%		18.2%		75.8%	

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; EDSS: Expanded Disability Status Scale; 25FTW: 25-foot walk test; Gd: gadolinium; 9HPT: 9-hole peg test; MRI: magnetic resonance imaging; OCT: Optical Coherence Tomography; SDMT: Symbol Digit Modalities Test.

Table 1. Statements submitted for evaluation and the respective percentage of agreement and applicability reached. (cont.)

VIII. Change of treatment due to lack of response (cont.)			
Statements	**Maintain treatment**	**Change of treatment (different mode of action, similar efficacy)**	**Change of treatment (greater efficacy)**
50. Patients with relapses, without MRI activity and with disability progression, treatment decision should be:	0	5.3%	94.7%
51. Patients without relapses, with MRI activity and with disability progression, treatment decision should be:	0	2.6%	97.4%
52. Patients without relapses, without MRI activity and with disability progression, treatment decision should be:	3.0%	30.3%	66.7%
53. Patients without relapses, with MRI activity and without disability progression, treatment decision should be:	9.1%	15.2%	75.8%

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; EDSS: Expanded Disability Status Scale; 25FTW: 25-foot walk test; Gd: gadolinium; 9HPT: 9-hole peg test; MRI: magnetic resonance imaging; OCT: Optical Coherence Tomography; SDMT: Symbol Digit Modalities Test.

gression assessment using the EDSS that reached consensus was 6 months and the panel unanimously agreed with the definition of progression that considers "an increase in EDSS of 1 point if the initial score was ≤5.5 or if an increase of 0.5 points if the initial score was ≥6".

Disease activity – assessed by magnetic resonance imaging

The panel unanimously agreed that disease activity should be systematically assessed by MRI and consensus was reached for the monitorization to occur annually. It was also agreed that, at diagnosis, disease activity should be evaluated with a spinal cord MRI, too. Moreover, it was considered that the evaluation of disease activity by MRI should be performed with or without gadolinium and that a new baseline MRI should be performed 3 to 6 months after the start of the treatment. It was considered that detection of subclinical activity by MRI is sufficient to define the lack of treatment response. Accordingly, the detection of 3 or more, new or enlarged T2 lesions, 1 or more T1 gadolinium enhancing (Gd+) lesions was considered sufficient to define the lack of treatment response. No consensus was reached regarding the detection of 1 new or enlarged T2 lesions or 2 new or enlarged T2 lesions being sufficient to define the lack of treatment response. Furthermore, no consensus was reached on whether the location of new T2 lesions is important to define the treatment response and if spinal cord MRI should be performed regularly to assess disease activity.

Disease activity – assessed by other biomarkers

Regarding biomarkers, consensus was reached for the search for oligoclonal immunoglobulin G (IgG) bands in the cerebrospinal fluid at diagnosis and for the periodic evaluation of the serum neurofilament light chain (sNfL), to determine disease activity and monitor treatment response. Nevertheless, regarding the applicability of sNfL most participants considered that they are not yet applicable in clinical practice. No consensus was reached for the quantification of neurofilaments in the cerebrospinal fluid at diagnosis, as well as for monitoring treatment response and determining disease activity through periodic evaluations using optical coherence tomography (OCT).

Brain volume loss

Brain volume loss was deemed a parameter that should be included in the evaluation of treatment response and that should be quantified/evaluated periodically. However, the majority of the participants answered that evaluating brain volume loss is currently not applied in clinical practice. No consensus was reached on whether patients with brain volume loss ≥0.4%/per year should be considered as non-responders to treatment.

Neuropsychological measures

The Symbol Digit Modalities Test (SDMT) was considered a useful test for the screening of cognitive defects and the monitoring of treatment response. Additionally, the Brief International Cognitive Assessment for MS (BICAMS) was considered a good battery of tests to monitor treatment response. No consensus was reached on the need to perform neuropsychological evaluations annually to evaluate treatment response.

Change of treatment due to lack of response

The recommendation of a therapeutic change to a DMT with greater efficacy reached consensus for patients with relapses combined with MRI activity and disability progression; with MRI activity without disability progression; without MRI activity and with disability pro-

gression. It was also recommended for patients without relapses but with MRI activity and disability progression. No consensus on whether to maintain treatment, switch to a treatment with a different mechanism of action but with a similar efficacy or switch to a treatment with greater efficacy was obtained for patients that presented only relapses, disability progression or MRI activity, although in all cases, most of the specialists considered the change to a treatment with greater efficacy to be the best option.

Characterization of the population

The Neurologists that participated in both vote rounds worked mainly (48.5%) in central/university hospitals (**Fig. 2A**) and practiced comparably in the north (30.3%), center (27.3%) and south (39.4%) of Portugal (**Fig. 2B**). The less experienced Neurologist had 3 years of medical specialty and the most experienced had 36, being the median (interquartile range) 10 (16). The minimum number of patients with MS that the specialists saw per month was 15 and the maximum was 200, being the median (IQR) 50(50). The lowest percentage of time that the specialists allocated to MS was 3% and the highest was 80%, being the median (IQR) 30 (35) (**Fig. 2C**).

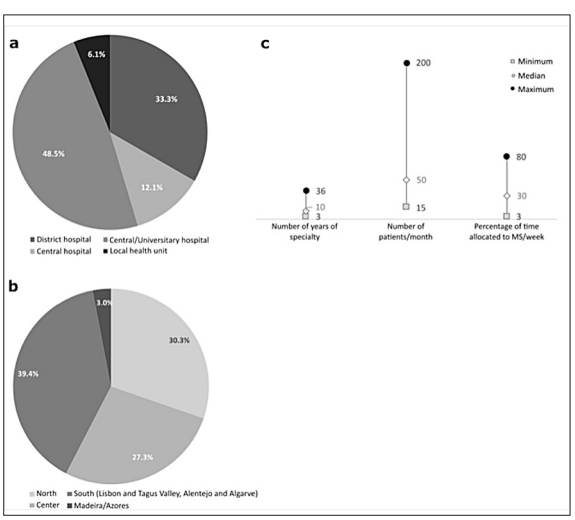

Figure 2. Characterization of the population: type (a) and location (b) of the hospital where the Neurologists practice and number of years practicing the specialty, number of patients with multiple sclerosis seen per month, as well as percentage of schedule allocated to treating multiple sclerosis per week (c).

Discussion

The growing number of novel, more effective DMTs that have become available in the last decades have increased the complexity of MS management.[6] The wider treatment variety, combined with a generally more aggressive approach to the management of MS, has led to the need for outcome measures that can help steer MS management in the direction of personalized medicine.[14,15] These measures should be able to assess the effectiveness of treatment and predict long-term evolution of the disease.[15,16] Usually, suboptimal response to treatment can be identified one or two years before a substantial worsening of disability.[4] Nevertheless, as disability can take decades to become noticeable, the long-term influence of DMTs on disability is unclear.[4] Traditional parameters of treatment efficacy are relapse rate, MRI activity and disability progression.[15] However, new treatment targets, such as No Evidence of Disease Activity (NEDA), which includes a composite of outcomes, have been proposed.[15] Patients that reach NEDA-3 are patients that do not present 1) clinical relapses, 2) confirmed EDSS disability progression and 3) new gadolinium enhancing lesions or new or enlarging T2 lesions.[15] Yet, it is well-known that NEDA does not fully capture all disease activity associated with MS. Findings such as cognitive deterioration or ongoing brain microstructural damage measured by advanced MRI techniques in patients meeting NEDA criteria, provide some direct evidence for this.[17,18] As a matter of fact, NEDA captures essentially the inflammatory component of MS and correlates less with the neurodegenerative process that starts early in the disease course and is ultimately contributing for disease progression.[19]

In this study it was consensually agreed that a more comprehensive analysis, which includes various measures, is the best strategy to prevent suboptimal response to treatment. All participants agreed that quality of life, cognitive parameters, treatment adherence, MRI, relapses, and disability progression should be analyzed to evaluate treatment response. Moreover 97.4% of participants agreed that brain volume loss should also be analyzed. Accordingly, it was consensually considered that relapse assessment is not sufficient to determine treatment response and that it is possible to define the lack of treatment in the absence of relapses. However, the majority considered that some biomarkers still do not have applicability in clinical practice, namely the evaluation of brain volume loss and the monitoring of sNfL. Brain volume loss occurs in MS patients since the early stages of the disease and correlates with increased physical and cognitive disability among MS patients.[20,21]

Additionally, brain atrophy is an important endpoint of phase 3 clinical trials to evaluate the efficacy of DMT therapy.[22,23] Nevertheless, brain atrophy assessment is not a routine clinical procedure for MS patients, and there is a lack of standardization regarding protocols, definitions, interpretations, and reproductivity.[24,25]

It has been proposed in the literature that multiple relapse characteristics should be assessed.[26] Similarly, the panel agreed on the need to evaluate the severity, type, number and time of appearance of relapses.

Regarding disability progression, all the participants agreed with the definition based on EDSS scores change and 86.8% of participants considered that the assessment of this parameter should occur every 6 months. These results support the current recommendations that state that a change in the EDSS score, confirmed at 6 months, allows the distinction between disability progression and relapse-related residual impairment.[27] Moreover, the importance of other tests that complement the assessment performed through EDSS[27] was also recognized by the panel.

MRI assessment for diagnostic, prognostic and monitoring objectives in MS is well established, although a standardized strategy regarding the use of this technique has been hindered by divergences in healthcare systems and clinical practices.[28] Consequently, all participants considered that disease activity should be systematically assessed by MRI. Almost all participants (97.4%) considered that the MRI follow-up interval should be 12 months and not 6 (33.3%) or 24 (33.3%) months. Moreover, it was agreed that a new baseline MRI should be performed 3 to 6 months after the onset of treatment as suggested in the literature, so that monitorization has a treated starting point.[29] It was also agreed that a spinal cord MRI should be performed at diagnosis, as it allows the identification of asymptomatic spinal cord lesions that correlate with short and long-term prognosis.[27]

Consensus was reached on defining the lack of treatment response with a basis on the detection of subclinical activity by MRI. This disagrees with governmental National guidelines, in which the definition of treatment response takes also into consideration the occurrence of a moderate to severe relapse and/or an increase in EDSS.[30] While MRI is fundamental to monitoring treatment response, some studies showed that new lesion formation detected in MRI does not correlate with long-term worsening and disability.[31] Nevertheless, it has been described that subclinical activity correlates with future disability accrual, even while on treatment, and that asymptomatic spinal cord lesions can predict relapses when combined with asymptomatic brain lesions.[3,32]

The higher reliability associated with the assessment of gadolinium-enhancing lesions when compared with new or enlarging T2 lesions,[3] might explain why only the statements that consider 3 or more, new or enlarged T2 lesions, or T1-Gd+ lesions sufficient to define lack of treatment response, reached consensus. Accordingly, in the absence of relapses, the presence of 3 or more T2 lesions was not considered a condition for treatment change and the location of T2 lesions was not considered important to define treatment response. However, in the presence of other clinical symptoms, T2 lesions can indicate lack of treatment response. The panel disagreed with maintaining treatment and reassessing in 6 months when patients presented 1 relapse and new T2 lesions.

The statements from section VIII include a composite evaluation of relapses, disability progression and MRI activity. The only statements where no consensus was reached, were the ones where the patient only presented one of these parameters. Nonetheless, and although these were the only statements where the hypothesis of maintaining treatment was selected, most specialists considered that the best course of action would be to switch the treatment for a more effective one. Additionally, even though the hypothesis of switching the treatment for one with a different mode of action and similar efficacy was provided, this hypothesis never reached consensus, indicating that the primary factor to consider when selecting a different DMT is efficacy and not mode of action. The statement where opinions were more divided was the one where patients only presented with disability progression. This divergence of opinions might be explained by the observation that disability measurements might not closely reflect treatment results at least during the first two years of treatment, since the effect on disability progression usually takes longer to become noticeable.[14] On the other hand, it may also result from the fact that approved DMTs are known to be less effective in the neurodegenerative component of the disease.

Statements for which no consensus was reached usually reflected the limited resources, or the lack of established protocols and specialized professionals in Portuguese hospitals. Consequently, no consensus was reached 1) on whether patients with a brain volume loss

change equal or higher than 0.4% should be considered non-responders to treatment, 2) on the regular assessment of disease activity though spinal cord MRI, 3) on the quantification of neurofilaments in the cerebrospinal fluid, at diagnosis, 4) on annual neuropsychological evaluations and 5) on the use of OCT measurement as an outcome for assessment of MS treatment.

The Neurologists that comprise the Delphi panel follow 50 or more MS patients per year and either dedicated a large percentage of their schedule to patients with MS or had many years of specialty. Thus, the composition of the Delphi panel was comprehensive and suitable to ensure the validity of this study. Moreover, these specialists practice in a myriad of hospitals across mainland Portugal and Madeira, which allowed a consensus representative of the Portuguese reality.

Still, some limitations of this study must be noted. As five specialists only participated in the first round, we cannot exclude the hypothesis that their vote would influence the number of questions that reached consensus in the second round. To adjust the statements to the realities of the clinical practice carried out in Portugal, some techniques and/or resources were not included in the statements. Other issues relevant to clinical practice were not assessed in this questionnaire and would be interesting to consider in future work, namely if the initial EDSS or the age of the patient should influence the monitoring of disease activity; if the frequency of clinical evaluation may influence the accuracy to detect relapses; the existence and dissemination of MRI protocols and the impact on the results when the MRI report is done by trained neuroradiologists compared with less experienced neuroradiologists; the differences in brain volume measurements across different centers; and finally the impact of other issues (e.g. economic) on monitoring disease activity and treatment choices. Additionally, periodic updates to this work will be needed to include technical and pharmacological developments.

Conclusion

In conclusion, this work highlights the importance of assessing treatment response and provides a set of criteria for this evaluation, agreed upon by a comprehensive panel of Portuguese experts. In summary:

- Patients should be analyzed every 6 months since the beginning of treatment and treatment response assessment should include MRI lesion load, relapses, disability progression, quality of life, cognitive parameters, brain volume loss and treatment adherence.
- Relapse rate is not sufficient to determine treatment response and besides the number of relapses, their severity, typology and time of appearance should also be considered.
- Disability progression should be considered when assessing treatment response and should be evaluated using a neurological exam and the EDSS, every 6 months.
- MRI should be employed to evaluate disease activity annually, being the detection of subclinical activity suitable to define the lack of treatment response. Also, a rebaseline MRI should be performed 3 to 6 months after the start of the treatment.
- Oligoclonal IgG bands should be searched in the cerebrospinal fluid at diagnosis and serum neurofilaments should be periodically evaluated to determine disease activity and monitor treatment response.
- Brain volume loss should be quantified/evaluated periodically and considered during the assessment of treatment response.
- Switch of treatment to a DMT with greater efficacy is recommended for patients: 1) with relapses, MRI activity and disability progression, 2) with relapses, MRI activity and without disability progression; 3) with relapses, without MRI activity and disability progression and 4) without relapses but with MRI activity and disability progression.

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Contributorship Statement / Declaração de Contribuição

SB: Conception and design, data interpretation, writing and critical review of the manuscript.

CC, FC, JF, JG, ES, MJS: Conception and design, data interpretation, critical review of the manuscript.

All authors approved the final version to be published.

SB: Conceção e desenho, interpretação dos dados, redação e revisão crítica do manuscrito.

CC, FC, JF, JG, ES, MJS: Conceção e desenho, interpretação dos dados, revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

Responsabilidades Éticas

Conflitos de Interesse: SB recebeu honorários da Janssen, Merck, Roche, Biogen, Bristol Myers Squibb, Novartis e Sanofi-Genzyme. CC recebeu honorários da Janssen, Merck e Roche, Almirall, Biogen, Bristol Myers Squibb, Novartis, Sanofi-Genzyme, Teva e Bayer. FC recebeu honorários da Janssen, Merck, Biogen, Novartis, Sanofi-Genzyme e Roche. JF recebeu honorários da Biogen, da Janssen, da Merck, da Novartis, da Roche, da Sanofi e da Teva. JG recebeu honorários da Janssen, Merck, Roche, Biogen, Novartis e Sanofi-Genzyme. ES participou em conselhos consultivos da Alexion, Argenx, Bayer, Biogen, Genzyme, Merck, Novartis e Roche. ES recebeu uma bolsa da Roche e da UCB. MJS recebeu honorários da Alexion, Almirall, Bayer Healthcare, Biogen, Bristol Myers Squibb, Celgene, Janssen, Merck-Serono, Novartis, Roche, Sanofi-Genzyme e Teva.

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