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ORIGINAL COMMUNICATION

Unveiling preferences in multiple sclerosis care: insights from an Italian discrete-choice experiment with patients and healthcare professionals

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Abstract

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, neurodegenerative disease of the central nervous system, significantly impacting patients' quality of life. Understanding patient and healthcare professional (HCP) preferences for MS treatments is crucial for optimizing therapeutic strategies and improving adherence and outcomes. This Discrete-Choice Experiment (DCE) assesses preferences for various MS treatment attributes among Italian patients and HCPs. The sample included 1069 patients and 186 HCPs. Key attributes evaluated were treatment administration route, frequency, location, and Patient-Reported Outcome Measures (PROMs), such as cognitive impairment, fatigue, and mobility. Data were collected through questionnaires and responses were analyzed to determine the relative importance (RI) and utility of each attribute. Both patients and HCPs highly prioritized PROMs, with cognitive impairments and walking ability being the most critical factors. Patients showed a strong preference for oral administration and treatments administered biannually at home, whereas HCPs preferred hospital-based treatments. The "Time to Progression" attribute was more significant for HCPs than for patients, reflecting different priorities between the groups. The study highlighted the importance of treatment convenience, with patients favoring less-frequent administration schedules and home-based treatment options. This study underscores the necessity of incorporating both patient and HCP perspectives into MS treatment planning. Shared decision-making, which considers individual preferences, can enhance treatment adherence and outcomes. These insights into treatment preferences provide valuable guidance for personalized MS care, aiming to improve patient quality of life and optimize therapeutic efficacy.

Keywords Multiple sclerosis (MS) · Patient preferences · Discrete choice experiment (DCE) · Healthcare professionals (HCPs) · Treatment attributes

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, neurodegenerative disease of the central nervous system. It is marked by inflammation and axonal damage [1, 2] leading to impairment in neurological functions [3]. Additionally, significant brain volume loss (BVL) has been observed, exceeding the amount expected from normal aging [3, 4]. MS is associated with the progression of disability and significantly impacts patients' daily activities and health-related quality of life (HRQoL). Although the exact cause of MS remains unknown, several risk factors have been identified, including genetic predisposition, sex, age, race, climate, infections, vitamin D levels, and smoking [5].

MS has the most significant impact on neurological disability in young adults [1, 2], affecting approximately 2.8 million people worldwide [6]. Usually diagnosed in adulthood, MS is more prevalent in females [7]. Common symptoms include fatigue, chronic pain, impaired mobility, cognitive impairment, and mood disorders, which can vary significantly between individuals [3, 8]. In most cases, MS initially presents with a relapsing–remitting course (relapsing–remitting MS, RRMS) and may eventually progress to a secondary progressive form (secondary progressive MS). In some cases, MS is progressive from the outset (primary progressive MS). The variability in symptoms and the impact on HRQoL is substantial [8].

Relapsing–remitting MS (RRMS) is the most common form of MS [9]. RRMS is characterized by episodes of worsened neurological function and symptoms, followed by periods of partial or complete recovery. The disease course is highly individualized [3]. Approximately 85% of patients initially diagnosed with RRMS experiencing periods of exacerbation and stability [10].

Currently, MS has no cure, and treatment primarily focuses on managing symptoms and slowing disease progression [3]. The main objectives of RRMS therapy are to control disease activity while optimizing tolerability and safety [5]. Disease-modifying treatments (DMTs) target immunological signaling proteins (e.g., interferons and cytokines) or immune cells (e.g., lymphocytes) and have been relatively successful in controlling inflammatory activity such as relapses [10]. First-generation DMTs, including β-interferons and glatiramer acetate, were effective in reducing relapse risk and have generally been well tolerated [2, 11]. Although DMTs cannot cure MS, they can mitigate disease progression and reduce relapse rates [12]. However, they are associated with various adverse events and different administration frequencies, making treatment decisions complex for patients [6]. Despite the advantages of DMTs, treatment discontinuation is common, influenced by factors, such as disease symptoms, comorbidities, and tolerability [13].

New treatments, including infusion therapies (e.g., natalizumab, alemtuzumab, ocrelizumab, and rituximab) and oral therapies (e.g., dimethyl fumarate, teriflunomide, fingolimod, siponimod, and cladribine) [14], have been developed but come with increased risks of severe adverse effects, impacting the risk–benefit balance [2]. While infusion therapies are effective for RRMS, they are associated with progressive multifocal leukoencephalopathy, a potentially disabling and fatal complication, especially with natalizumab [15]. It is common for patients to switch DMTs due to diminished efficacy, adverse events [16], or concerns about long-term complications [17]. This applies to patients with MS who may switch to another DMT if their current treatment is not effective or causes too many adverse events.

Adherence to treatment is essential for reducing acute neurological attacks, relapse severity, hospitalizations, and disease progression [15]. Convenience is a critical factor influencing the choices of both patients and physicians when selecting the most suitable treatment among available therapies, as well as in determining adherence to the prescribed treatment. Moreover, preferences and convenience also play a significant role for stakeholders involved in the development or funding of new medications, as these factors are considered during the approval process in some healthcare systems [18].

In the context of chronic therapies, factors, such as the route, frequency, and location of administration, define "convenience" and can influence both the choice of treatment and adherence to it.

Thus, involving patients in the decision-making is essential for optimizing adherence and achieving the best clinical outcomes [2]. Shared decision-making, which considers patient preferences and goals, can enhance adherence and improve treatment outcomes, ultimately contributing to a better quality of life [9]. Multidisciplinary teams, including neurologists, nurses, and pharmacists, play a crucial role in managing MS, since understanding treatment preferences is vital for effective care [5].

In recent years, there has been growing emphasis on incorporating patient preferences into healthcare interventions, as involving patients in clinical decision-making can improve treatment satisfaction and adherence. Information on patient preferences is valuable for healthcare providers, pharmaceutical industries, and policymakers. One method for evaluating these preferences is conjoint analysis [19]. Discrete choice experiments (DCEs) are frequently employed in healthcare to assess patient preferences for managing conditions such as asthma and cancer. Understanding the key attributes that influence patient preferences for DMTs can help healthcare professionals in managing MS and provide important discussion points for shared

decision-making. However, DCEs can be complex and cognitively demanding, posing challenges for MS patients who experience cognitive difficulties. In an international sample of RRMS patients, dosing regimen, efficacy, and safety profile were identified as equally important treatment attributes, although priorities may vary depending on individual patient characteristics [9].

Physician preferences for MS treatments have not been extensively studied, yet they may significantly impact treatment decisions. The perspective of patients and physicians regarding MS treatment strategies can differ, underscoring the importance of understanding both viewpoints to facilitate effective shared decision-making [20].

This project aims to investigate the preferences of patients, doctors, nurses, and hospital pharmacists for various attributes of MS treatments in Italy using the DCE methodology, a scientifically validated and innovative tool. This tool allows for the exploration of potential differences within each population based on certain conditions (age, disease duration, disease severity, etc.). In addition to evaluating clinical characteristics of treatments, the project seeks to determine whether other variables might influence therapeutic preferences among patients. It also aims to compare these preferences with those of healthcare professionals involved in MS management, including doctors, hospital pharmacists, and nurses.

Methods

The Discrete-Choice Experiment (DCE) is a robust quantitative and statistical methodology based on conjoint analysis. This approach facilitates the evaluation of preferences among various stakeholders, including patients, doctors, payors, and other actors involved in healthcare decision-making, regarding different therapeutic options or disease management strategies.

The DCE methodology consists of several phases, each contributing to the validity and reliability of the results: Definition of the Research Question, Identification and Selection of Attributes and Levels, Construction of Choices, Data Collection, Statistical Analysis, and Interpretation of Results and Conclusions. The primary objective of the DCE is to determine the preferred combination of attributes and levels among different groups, such as clinicians, patients, and decision-makers. Attributes represent the characteristics of the subject under examination, while levels indicate the variations of these attributes. For example, when evaluating available treatments for a disease, attributes might include administration frequency, duration of therapy, and risk of side effects, each with different levels of manifestation.

Attributes and levels are identified through a thorough review of scientific literature, clinical guidelines, and recommendations, or based on clinical experience. These attributes and levels are then randomly combined using specialized software to create various potential treatment scenarios. These scenarios are presented in questionnaires as comparisons between pairs of options, where respondents are asked to choose their preferred alternative. The questionnaires also gather demographic information about respondents (such as age, gender, education, etc.), which allows for detailed analysis and the segmentation of responses into significant groups. Analyzing these responses enables the identification and quantification of the most influential attributes and levels in terms of preferences, thereby establishing a priority order among the different attributes and levels. Separate DCE questionnaires were developed for patients and for clinicians, nurses, and hospital pharmacists (Supplementary Material—DCE study design).

Study design and sample size

This study is based on a cross-sectional survey. MS patients were invited to participate by the Associazione Italiana Sclerosi Multipla (AISM), the Italian Multiple Sclerosis Society. Recruitment was not carried out using formal random sampling methods to obtain a representative sample of Italian MS patients. Rather, the study utilized a convenience sample composed primarily of individuals who voluntarily completed a questionnaire. Participants received a link to the questionnaire as subscribers of the AISM newsletter, which is targeted toward individuals interested in receiving detailed and updated information about MS. Additionally, participants included individuals under the age of 35 who attended national or local events dedicated to young people with MS. Approximately 8800 people with MS were invited to complete the questionnaire, and around 1300 of them filled in all the mandatory fields (Q1 and Q2). This convenience sampling method limits the generalizability of the findings, which may only apply to populations with demographic and clinical characteristics similar to those observed in the sample.

Regarding HCPs, a non-random recruitment procedure was used. Initially, a list of 112 clinicians specializing in MS was compiled to ensure a fair and representative distribution nationwide. These experts received an email containing a detailed explanation of the project's rationale and methodology, a schematic presentation of the DCE and its application, and an invitation to participate in the initiative. During the collection of responses, some clinicians extended the invitation to colleagues with a known interest in the study topic. This increased the total number of invited participants to 156. From the initial list of 112 clinicians, 65 hospital pharmacists working in the clinicians' centers were also selected.

The nurses were involved through the Società Infermieri Sclerosi Multipla (SISM), a professional society affiliated

with the AISM. SISM sent a targeted communication to a mailing list of approximately 1200 members who have participated in CME courses for nurses over the years. This communication was read by 450 nurses.

The design of the DCE is detailed in Table 1. The first version (Q1) presented to both MS patients and HCPs involved 10 attributes, each with 2–4 levels. The attributes were categorized into three main categories: (1) efficacy/safety: according to many RCT [21] as well as DCE studies on MS [13], efficacy was represented with "time until MS progresses" and safety by occurrence of side effects; (2) impact on quality of life due to MS (and potentially mitigated by treatments: this domain was represented by impact of fatigue and cognitive, mood and bladder disorders; (3) administration and management of treatments: via, frequency, setting of administration and scheduling check-ups.

Following the discussion of the Q1 analysis findings, the Scientific Board observed that the levels of the primary efficacy attribute "time until MS progression" (2, 4, 6, and 8 years) were more similar to each other compared to the levels of the quality of life (e.g., for cognitive domain, "- No impact", "- Mild impact: Cognitive impairment impacts less than 25% of my daily activities", "- Moderate impact: Affects my daily activities at least 50% of the time", "- Severe impact: Always present during my daily activities"). Consequently, the importance attributed by patients may have been influenced by the proximity of the predefined levels. Although "time until progression" is commonly used as a principal endpoint in RCT, the Scientific Board suggested reformulating the efficacy attribute to focus on "Impact on walking in the medium–long term (10–20 years)" with the following levels: "- No impact", "- Mild impact: walking with difficulty but independently", "- Moderate impact: walking with support (cane, crutch, walker)", and "- Severe impact: use of a wheelchair". Table 1 presents the designs for both Q1 and Q2 of the DCE.

For sample size calculation, Orme's rule-of-thumb was applied. The minimum required sample size for the DCE was computed as $n \geq 500$*c/ta, where n is the number of respondents, c is the maximum number of levels per attribute (in our study, $c = 4$), t is the number of tasks (in our study $t = 8$), and a is the number of alternatives (in our study, $a = 2$), resulting in $n = 125$ patients. The number of choice tasks was limited to eight for patients based on feedback and suggestions received after testing the questionnaire with a small sample of volunteers. However, for HCPs dealing with MS, we decided to increase the number of choice tasks from 8 to 12 to account for their smaller number compared to MS

Table 1 MS patients' demographic and clinical characteristics of Q1 and Q2 DCE surveys

		Patients' characteristics DCE 1 ($n = 1069$)*	Patients' characteristics DCE 2 ($n = 314$)§
Age (years)	Median (IQR)	45 (37–55)	42 (35–53)
Sex	female	742 (70%)	204 (65%)
Disease duration (years)	Median (IQR)	11 (6–18)	7 (2–13)
On-treatment for MS	*n* (%)	939 (88%)	280 (90%)
MS types	RR *n* (%)	828 (78%)	229 (74%)
	PP *n* (%)	93 (9%)	43 (14%)
	SP *n* (%)	135 (13%)	36 (12%)
EDSS	Median (IQR)	3 (1.5–5.5)	3 (1.5–5.5)
Current treatments	Oral	460 (43%)	130 (41%)
	IV	330 (31%)	116 (37%)
	SC	172 (16%)	32 (10%)
	Intramuscular	#	11 (3%)
Previous treatments	Oral	437 (41%)	134 (43%)
	IV	320 (30%)	105 (33%)
	SC	535 (50%)	86 (27%)
	Intramuscular		58 (18%)
Treatment administration	At home	606 (63%)	171 (59%)
	Hospital	361 (37%)	119 (41%)

*Missing answers: age, $n = 35$; sex, $n = 5$; MS duration, $n = 3$; MS type, $n = 13$, EDSS, $n = 290$, treatment administration, $n = 102$

§Missing answers: age, $n = 15$; sex, $n = 2$; MS duration, $n = 3$; MS type, $n = 6$, EDSS, $n = 107$, treatment administration, $n = 24$

#in DCE1 questionnaire, intramuscular was not considered among the possible closed answers to the questions about current and previous treatments

patients. By applying the above formula, the minimum number of HCP to be recruited was (500*4)/(2*12) = 84. However, even with the adoption of a partial-profile design—where only 5 of the 10 attributes were shown to patients and 7 to HCPs to mitigate task complexity and encourage more focused responses, as recommended by ISPOR guidelines—the appropriate sample size was also estimated using a simulation performed with Sawtooth Software Lighthouse Studio (9.14.2). With a sample size of 1000 patients, the maximal standard error was found to be 0.048, which is below the conventional threshold of 0.05 suggested by Sawtooth guidelines. To ensure that standard errors for main effect utilities were 0.05 smaller, the size was adjusted to 300 patients, resulting in a maximal standard error of 0.051. For 200 HCPs, the simulation indicated a maximal standard error of 0.08, slightly exceeding the 0.05 threshold. However, HCPs are generally less heterogeneous than patients, and a lower standard deviation is likely to yield more precise estimates of HCP preferences.

Details of DCE design are reported in Supplementary Materials—DCE Design.

Since the project is considered an opinion poll, it does not require approval from an Ethical Committee or Institutional Review Board according to Italian law. No sensitive information was requested from the participating clinicians. However, after reviewing the survey presentation and completion instructions, the clinicians provided their informed consent for the collection and analysis of data for the study's purposes.

Statistical analysis

To measure preference weights, we employed the Choice-Based-Conjoint analysis Hierarchical Bayes procedure, as recommended by Sawtooth Software (CBC/HB algorithm). This Bayesian approach integrates the a posteriori probability, which combines the likelihood of a respondent selecting a specific concept given a set of utilities, with the a priori probability, which reflects the consistency of the respondent's utilities with those observed in the rest of the sample. Parameter estimates from this model are interpreted as relative preference weights (PW), representing the average relative preference for one attribute level over others. The mean preference weights were then used to calculate the relative importance (RI) of each attribute. Following the indication of ISPOR ("It is important to elicit respondent-specific health and sociodemographic information to allow for testing for systematic differences in preferences based on these characteristics" [22]), the effects of demographic and clinical characteristics on preferences were assessed. A General Linear Model was used to identify significant and potentially relevant interactions. The model included "Attribute" and "Levels" as within-subjects factors and "Main Characteristics" as between-subjects` factors.

Additionally, Latent Class Analysis was conducted to identify clusters of patients characterized by substantial differences between clusters and low variance within clusters. The optimal number of clusters was determined using the adjusted Bayesian Information Criterion (aBIC).

Results

Demographic and clinical information of the participating patients is detailed in Table 1, while demographic details for the healthcare professional sample are presented in Table 2. As indicated, two distinct patient samples were recruited, because the scientific board raised significant concerns about the formulation of the efficacy attribute (time until MS progresses) in the initial questionnaire (refer to the Study design paragraph above). Participants filled in the questionnaire and completed the choice tasks between May, 14th and June, 23rd 2024.

The two samples differed in terms of MS types (Chi-square = 7.089, df = 2, $p = 0.029$), with a higher proportion of Primary Progressive MS among Q2 patients (14% compared to 9% in Q1). Although the EDSS scores were similar (median = 3 for both samples, Mann–Whitney $p = 0.561$),

Table 2 Demographic characteristics of healthcare professionals (HCP)

		HCP characteristics ($n = 186$)
Age (years)	Median (IQR)	51 (43–58)
HCP	Clinician *n* (%)	99 (53%)
	Nurse *n* (%)	41 (22%)
	Pharmacist *n* (%)	46 (25%)
n of patients followed in the center	Median (IQR)	630 (250–1000)
Type of clinical center	University *n* (%)	62 (33%)
	Public hospital *n* (%)	131 (70%)
	Private hospital *n* (%)	19 (10%)
	Territorial health services *n* (%)	6 (3%)

disease duration was approximately 5 years shorter in Q2 patients than in Q1 patients. This difference was statistically significant after log-transformation to account for log-normal distribution (t-test = 5.05, adjusted df = 456.8, $p < 0.001$, Cohen's D = 0.41). Additionally, Q2 patients were 2.2 years younger than Q1 patients (t-test = 2.852, df = 1331, $p = 0.004$, Cohen's D = 0.19).

The analysis of respondents' preferences can be summarized using two fundamental indices: the Relative Importance (RI) of the attributes, which indicates the significance of each attribute relative to the others (with the total RI summing to 100), and the implicitly stated Utility for each level of every attribute. As illustrated in Fig. 1, based on the preferences of the 1069 patients who responded to DCE 1 (represented by blue bars), the attribute with the highest RI was the impact of cognitive disorders, followed by the other three PROMs (fatigue, emotional disorders, and bladder disorders). The parameter "time to progression" ranks fifth. Among the attributes related to administration mode, frequency was deemed the most important, followed by the route of administration. These two attributes are weighted more heavily for patients compared to the risk of side effects, with a notable difference observed particularly between frequency and side effects. Parameters related to the setting in which therapy is administered and whether visits align with administration times are considered to have a minimal impact.

Healthcare professionals (represented by red bars) exhibited a similar hierarchy of attribute importance to that of patients, with one notable difference: the efficacy attribute, indicated by time to progression. For clinicians, this attribute ranks second in importance, compared to fifth for patients, and is significantly less important only than the impact of cognitive disorders. For clinicians, the frequency of administration is the most relevant drug-specific attribute, holding nearly 2 percentage points more importance than the route of administration.

When patients were given a questionnaire with a reformulated disability attribute (previously indexed by progression times, now by levels of walking autonomy), their preferences

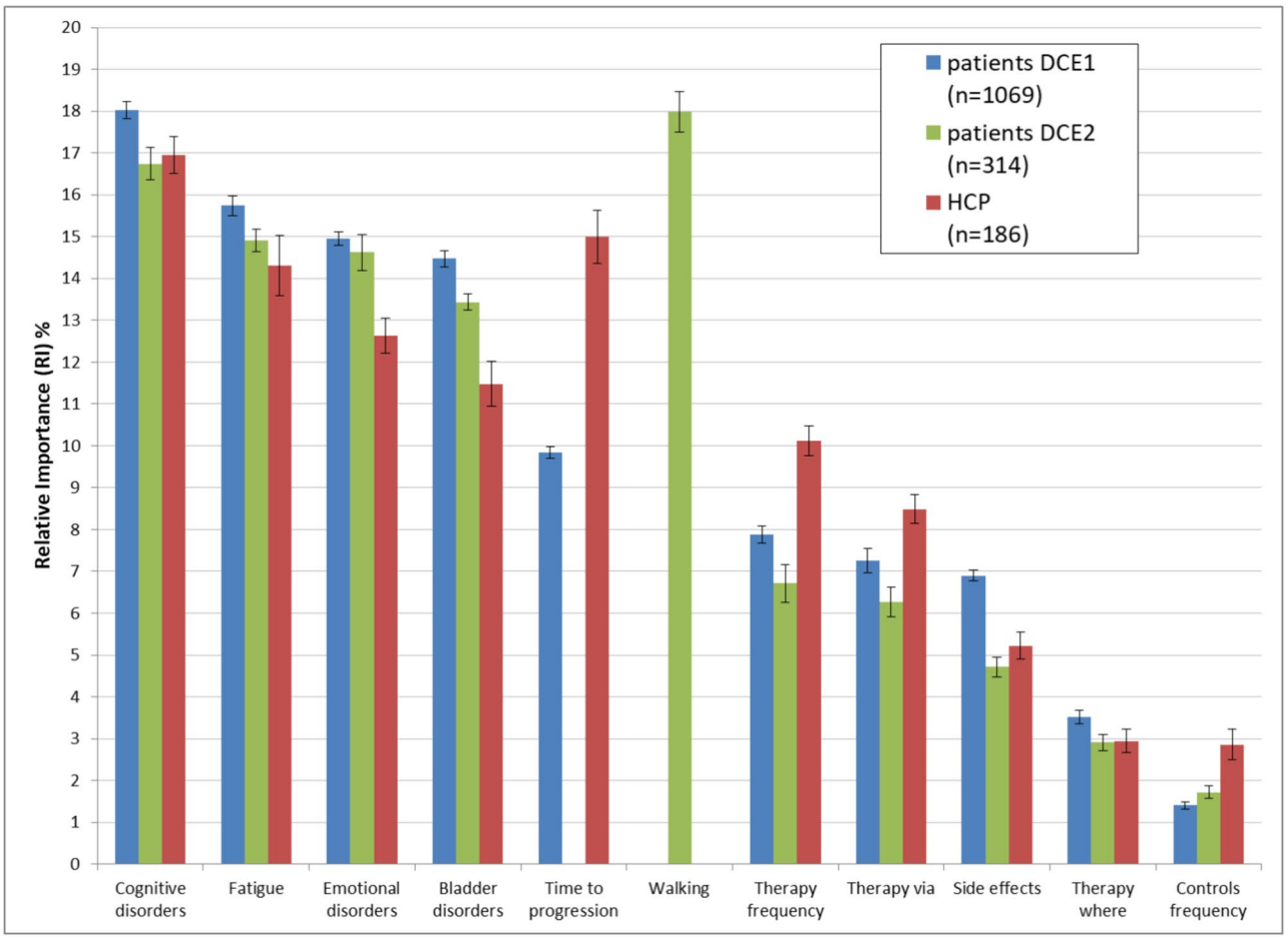

Fig. 1 Attribute preferences analysis resulting from patients and HCP questionnaire. On Y axis % of RI is reported, while on X axis different attributes

(represented by green bars) showed a very significant shift while maintaining the overall hierarchy. The walking autonomy attribute emerged as the most important, commanding about 8% more importance compared to the "time to progression" attribute, but did not alter the relative importance of other attributes. The impact of cognitive disorders on quality of life is greater than that of physical fatigue, which in turn is marginally (though not significantly) more impactful than emotional disorders. In the second DCE, the frequency of administration continues to be a highly significant attribute, although the confidence intervals for this attribute partially overlap.

In Fig. 2, the analysis of utilities for each level emerging from DCE 1 on patients and healthcare professionals demonstrated that the level of highest relative utility corresponds to the condition where cognitive disorders have no impact on daily life activities. For patients (represented by blue lines), the utility implicitly expressed for this condition is slightly higher than that defined by a zero impact of fatigue and emotional disorders, but significantly higher than the condition described by a zero impact of bladder disorders and the maximum progression time (8 years) among those considered.

For healthcare professionals (represented by red lines), the utility of a condition where cognitive disorders have no impact is consistently the highest, although it is only marginally higher than the utility associated with extending disease progression to 8 years. Conversely, the levels associated with the greatest disutilities (negative values) show similar but opposite trends. Comparing the utilities for the "Time to Progression" attribute between patients and clinicians reveals a distinct difference in their preferences.

Regarding therapy administration parameters, it is evident that, if possible, oral intake would result in relatively high utility for both patients (+40; 95% CI: +38, +42) and clinicians (+49; 95% CI: +47, +51). However, particularly for healthcare professionals, the advantage of oral administration would be nullified by daily frequency, a level associated with a disutility of −37 (95% CI: −36, −38) for patients and −52 (95% CI: −49, −54) for healthcare professionals.

As anticipated from the analysis of relative importance, the reformulation of the disability attribute has led to a

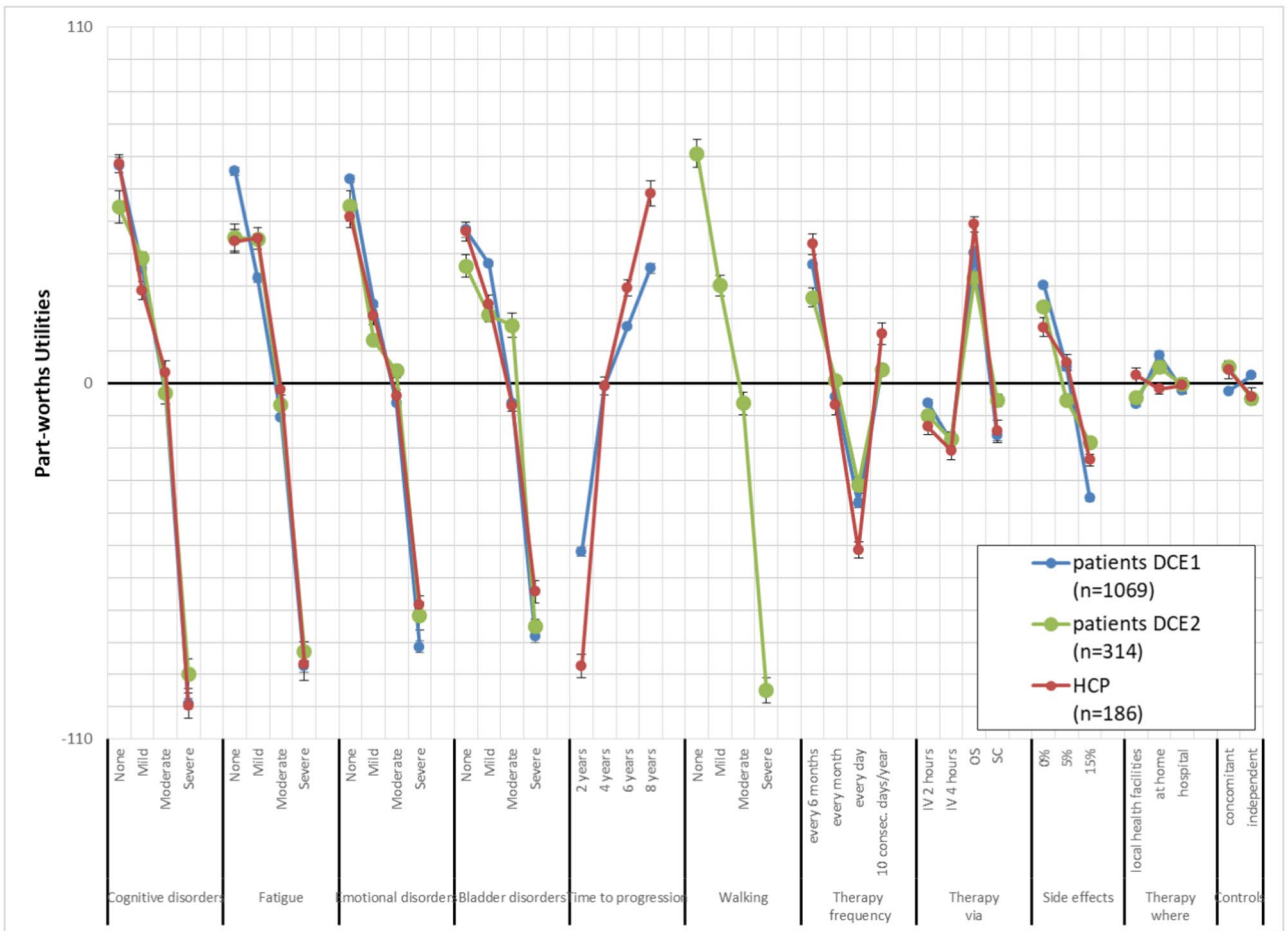

Fig. 2 Analysis of utilities for each level

notable differentiation among levels in terms of walking autonomy (see the green line corresponding to the "walking" attribute in Fig. 2). The condition characterized by long-term walking autonomy is associated with the highest utility for patients, whereas loss of autonomy (wheelchair use) is linked to the highest disutility. Interestingly, a similar level of disutility is observed when cognitive disorders affect all daily activities, underscoring the high relevance of this PROM. Even in the level analysis, the change in the disability attribute does not substantially alter the observed patterns for the other attributes.

Patients' subgroup analysis

The large sample size of DCE1 enabled an assessment of whether preference patterns were influenced by patients characteristics, specifically the type of MS (RR, PP, SP), sex (M, F), age, disease duration, and EDSS (these last three numeric variables were recoded in two levels: below or above median). The interactions between the within-subjects factor level for each attribute and each of the five between-subjects factors are presented in Table S6 of the Supplementary material (to be noted that sum of squares is adjusted for all other effects in the model).

The main point is that even the significant interactions has small effect sizes (eta-squared values never exceeded 0.02), indicating that utilities were slightly influenced by demographic or clinical characteristics. With this in mind, a detailed description of the preference modulators is provided below.

Preferences regarding the levels of "Route and duration of administration" depended solely on age ($p = 0.003$). Patients older than 45 assigned higher utility to the "oral route" and higher disutility to "intravenous for 4 h" compared to younger patients (Sidak adjusted $p < 0.05$, Fig. S1). Considering all patients, 69.3% attributed higher utilities to oral administration than any other via and these patients were older (+2.5 years; 95% CI: +1.1, +3.8; $p < 0.001$) and with larger SM duration (+2.1 years; 95% CI: +1.0, +3.1; $p < 0.001$) than those (30.7%) who preferred other routes. No evidence of differences in terms of sex and EDSS was found ($p = 0.149$ and $p = 0.697$, respectively).

Preferences for the levels of "Frequency of administration" depended only on the Type of MS ($p = 0.035$). However, this effect was small, and none of the pairwise comparisons were significant after adjusting for multiple testing.

Preferences for the levels of "Place of administration" depended only on the type of MS ($p = 0.007$). PP patients did not assign higher utility to home administration compared to hospital administration, while RR and SP patients showed a slight preference for home treatment (Fig. S2).

Preferences for the levels of "Control visits/year" were very slightly dependent only on EDSS ($p = 0.049$), as patients with an EDDS greater than 3 assigned lower utility "In conjunction with therapies administration" (Fig. S3).

Preferences for the levels of "Time to disease progression" depended on both age ($p = 0.002$) and EDSS ($p < 0.001$). Patients younger than 45 attributed higher utility to "8 years" than older patients (Fig. S4). Similarly, less disabled patients (EDSS ≤ 3) attributed higher utility to "8 years" than patients with and EDSS greater than 3 (consistently, Sidak's p value < 0.05, Fig. S5).

Regarding the attributes related to the impact on quality of life (including fatigue, and cognitive, emotional, and bladder disorders), preferences were consistently influenced by age and EDSS ($p < 0.05$). The general pattern observed was that younger and less disabled patients assigned higher utilities to "None" (i.e., no impact) compared to older and more disabled patients (Figs. S6–S13). In particular, concerning bladder disorders, older and more disabled patients assigned similar utilities to both "None" and "Mild" impact on quality of life (Fig. S12–S13).

Preferences for the levels "Risk of occurrence of side effects" were not significantly related to any demographic or clinical characteristics.

HCPs' subgroup analysis

Interactions of the within-subjects factor level for each attribute by Type of HCP (clinicians, nurses and pharmacists) and by Patients of Clinical Centre (below/above 600) are reported in Table S7 of the Supplementary material (to be noted that sum of squares are adjusted for all other effects in the model).

Similar to the subgroup analysis on patients, the main point is that even the significant interactions had small effect sizes (eta-square never exceeded 0.05), indicating that utilities were only slightly modulated by the two instrument variables. Keeping this point in mind, a detailed description of the preference modulators is provided below.

Preferences for the levels of "Route and duration of administration" depended on the Type of HCP ($p = 0.009$). Pharmacists assigned higher disutility to "intravenous for 2 h" than clinicians (Sidak's $p = 0.028$) and lower disutility to "subcutaneous" than clinician (Sidak's $p = 0.005$, Fig. S14).

Preferences for the levels of "Frequency of administration" also depended on the Type of HCP ($p = 0.030$). Pharmacists attributed slightly lower disutility to "every day" compared to clinicians (Sidak's $p = 0.033$) and lower utility to "10 consecutive days/year" than clinician (Sidak's $p = 0.040$, Fig. S15).

Preferences for the levels of "Control visits/year" were significantly influenced by the Type of HCP ($p = 0.013$). Nurses assigned higher utility to "In conjunction with

therapies administration" than the other two categories, particularly pharmacists (Sidak's $p = 0.013$, Fig. S16).

Preferences for the levels of "Time to disease progression" were dependent on both the type of HCP ($p = 0.005$) and the size of the clinical center ($p < 0.004$). Nurses assigned lower disutility to "2 years" compared to clinicians and pharmacists (Fig. S17). Additionally, HCPs working in larger clinical centers (with more than 600 MS patients) assigned higher utility to "8 years" (Sidak's $p < 0.05$, Fig. S18).

Regarding the attributes related to the impact on quality of life, specifically emotional and cognitive disorders, preferences were consistently modulated by the size of the clinical center ($p = 0.022$ and $p = 0.046$, respectively). HCPs in larger clinical centers better discriminated between "none" and "mild" effects of emotional disorders compared to those in smaller centers. Conversely, HCPs in larger clinical centers were less sensitive to differences among "none", "mild", and "moderate" effects of cognitive disorders compared to their counterparts in smaller centers (Figs. S19–S20).

Another potentially relevant variable on preferences was to be followed in primary/secondary centers in comparison to tertiary/university settings. However, this question is largely answered when the effect of by Patients of Clinical Centre (below/above 600) was assessed, since there was a relevant collinearity between type (university vs. other) and size (number of patients > 600 vs. < 600): 76% of university centers vs. 28% of non-university centers had more than 600 SM patients.

Latent class analysis

As reported above, patient preferences for the levels of attributes were only weakly influenced by their demographic or clinical characteristics. However, identifying clusters of patients with distinct choice behaviors can provide additional insights. In DCE studies, segmentation of respondents is typically achieved using Latent Class Analysis (LCA, see Statistical Methods above). We applied this procedure only to our largest sample, i.e., DCE1 (1069 patients), as applying LCA to the other samples (186 HCPs and 314 DCE2 patients) would likely have resulted in small and unreliable clusters.

For the respondents in DCE1, LCA tested segmentations ranging from 2 to 5 clusters. The optimal segmentation was determined based on the adjusted Bayesian Information Criterion (aBIC), with the minimal value achieved for three clusters (aBIC = 8262.27). The relative importance of each attribute within these three clusters is illustrated in Fig. 3.

Cluster 1, the largest group comprising 52.6% of patients, is characterized by a strong emphasis on Patient-Reported Outcome Measures (PROMs). Patients in this cluster primarily chose treatments based on their potential effects on (1) cognitive disorders, (2) emotional disorders, (3) fatigue, (4) bladder disorders, and (5) delaying disease progression. For these patients, other attributes are of much lesser importance.

Patients in Cluster 3, representing 23.1% of the sample, were primarily influenced by the "Route of administration", which was approximately twice as important as the second-ranked attribute, "Fatigue". Additionally, "Frequency of administration" was the third most important attribute, highlighting the significance of treatment administration features for this cluster.

As shown in Fig. 4, patients in Cluster 3 assign high utility to oral administration and low utility to intravenous administration. Although the differences among levels are smaller, they also assign higher utility to "every 6 months" and lower utility to "every day" administration.

Finally, an "intermediate" cluster (Cluster 2, 24.3%) was identified. As represented in Fig. 3, this cluster includes patients whose preferences do not show a clear polarization, with similar relative importance assigned to most attributes.

Multinomial multivariable logistic regression, conducted by cross-referencing cluster membership with demographic and clinical characteristics, indicated that the three clusters could be distinguished primarily by age and EDSS. In Cluster 1 (PROMs-driven), the proportion of younger patients was highest (55% compared to 40% in Cluster 2 and 31% in Cluster 3), and the prevalence of more disabled patients (EDSS > 3) was lowest (37% compared to 62% in Cluster 2 and 54% in Cluster 3). Conversely, Cluster 3 (administration modality-driven) consisted of older and more disabled patients, suggesting that as age and disease severity increase, the focus shifts from PROMs to the practical aspects of therapy management.

Discussion

This study, the first to analyze over 1160 questionnaires from both patients and HCPs, provides valuable insights into preferences for MS treatments in clinical practice. The results highlight the importance of PROMs, particularly cognitive health and walking ability, with time to disease progression also being a significant factor. Patients prioritized oral administration and less-frequent treatments/every 6 months), while HCPs placed greater emphasis on the mode and location of treatment administration, preferring hospital-based settings. The findings underscore the need for personalized treatment discussions that consider both patient-reported outcomes and practical aspect of treatment administrations.

Moreover, our study is aligned with the existing literature and emphasizes the need for shared decision-making to ensure treatment plans that are both effective and aligned

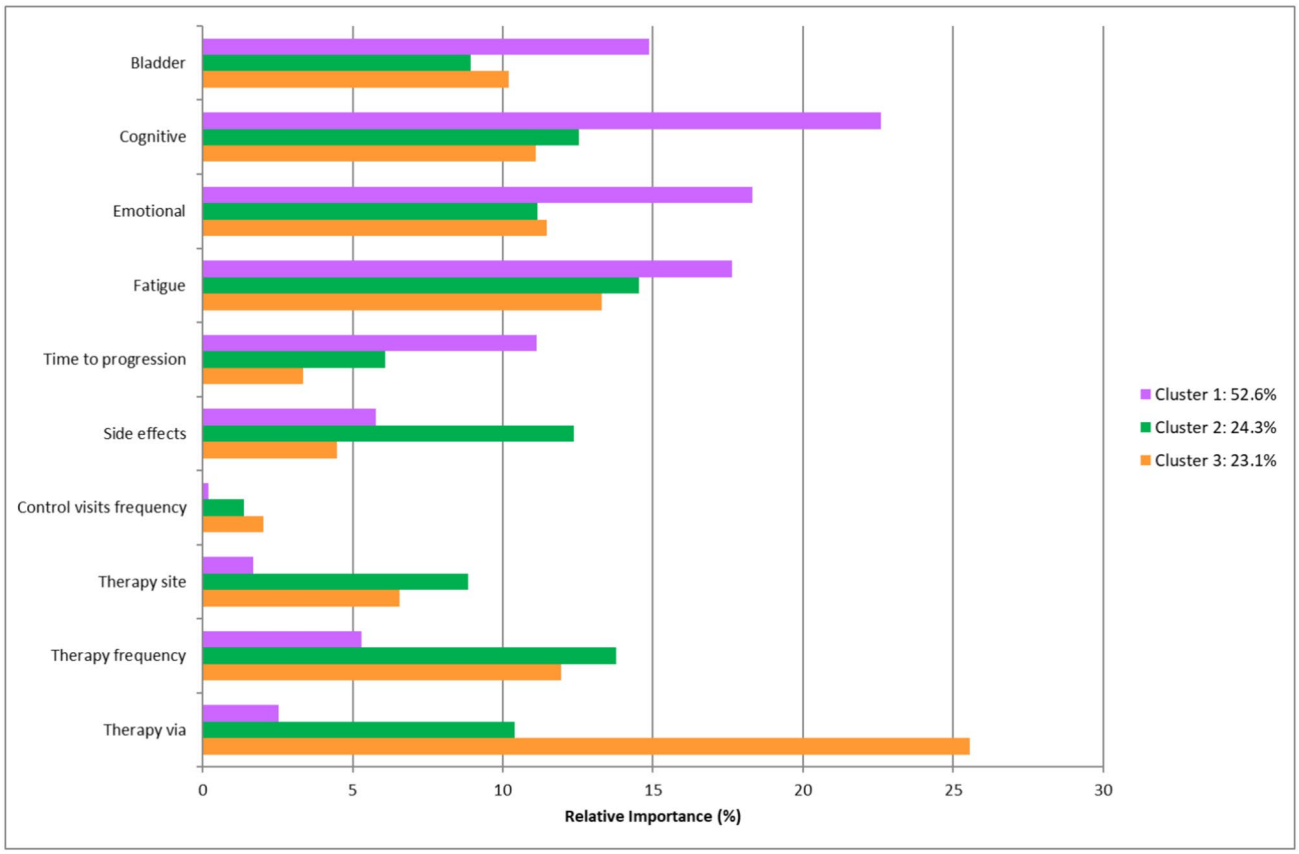

Fig. 3 Relative Importance of each attribute in the three clusters of DCE1 patients obtained by means of Latent Class Analysis

with patient preferences offering guidance for clinical practice in MS management.

Consistent with the study by Tervonen et al. [13], this research highlights a clear pattern where physical abilities, such as the ability to walk or manage physical fatigue (fatigue), are highly prioritized by patients with MS. This underscores the critical need to address these attributes in treatment planning. Kumar et al. [3] demonstrated that RRMS patients in the United States prioritized reducing brain volume loss (BVL) and infection risk, while neurologists focused on preventing life-threatening events and slowing disability progression over 2 years.

The finding that HCPs favor specific treatment modalities and administration settings compared to patients is consistent with the results reported by Bottomley et al. [17] and Utz et al. [18]. These studies highlighted that patient preferred daily oral medications. This preference for oral administration and consideration of treatment frequency was also observed in German studies, where patients similarly prioritized the oral route of administration and treatment schedule [18, 20].

The importance of minimizing side effects, emphasized by Wilson et al. [24] and Garcia-Dominguez et al. [1], was also evident in this patient sample, although to a lesser extent for HCPs. This finding is consistent with Poulos et al. [25], which reported that patients favored less-frequent treatment regimens and sought to delay disability progression.

From the results of this research, the emphasis on cognitive disorders reflects the conclusions of Mansfield et al. [26], who observed that patients place significant weight on improving dosing methods and frequencies, thus influencing treatment adherence. This is crucial as adherence impacts the overall effectiveness of the therapeutic regimen.

Interestingly, the study by Tencer et al. [4] highlighted that both patients and neurologists in the UK prioritized reducing BVL and disability progression, aligning with these findings regarding the importance of "Time to Progression" among HCPs. However, the results also reveal a broader spectrum of preferences among HCPs, highlighting the need for comprehensive discussions regarding treatment settings and administration methods.

Given the chronic nature of MS therapies, factors, such as the route of administration, frequency, and place of administration, are critical "convenience" factors that can influence both treatment choice and adherence. Both MS patients and the doctors are managing their care place significant importance on treatments that can be administered orally or, as a secondary option, subcutaneously. Regarding

Fig. 4 Part Worth Utilities of each level in the three clusters of DCE1 patients obtained by means of Latent Class Analysis

treatment frequency, both groups prefer administration every 6 months. However, patients prefer treatments to be administered at home, whereas healthcare providers favor administration in healthcare facilities.

The heterogeneous preferences observed in this study and others [20, 27] highlight the necessity of shared decision-making in the treatment of MS. Integrating both patient and physician perspectives ensures that treatment plans are more personalized and effective, addressing the unique needs and priorities of each individual.

Discussion: latent class analysis

The Latent Class Analysis (LCA) conducted on the DCE1 sample ($n = 1069$) provides significant insights into the heterogeneity of preferences among MS patients, particularly concerning Patient-Reported Outcome Measures (PROMs). The analysis identified three distinct clusters, each characterized by different priorities and choice behaviors.

Cluster 1: PROMs-driven preferences

The largest cluster, comprising 52.6% of patients, displayed a strong preference for PROMs, emphasizing cognitive and emotional disorders, fatigue, bladder disorders, and time to disease progression. This cluster's focus on PROMs suggests that these patients prioritize outcomes that directly affect their daily quality of life and overall well-being. Cognitive and emotional health, along with the ability to manage fatigue and bladder function, are critical factors in maintaining independence and minimizing the impact of MS on their lives. The inclusion of time to disease progression among the top priorities further underscores the importance of long-term disease management and the desire to delay the worsening of symptoms.

The demographic profile of Cluster 1, characterized by a higher proportion of younger (55%) and less disabled (63% with EDSS ≤ 3) patients, aligns with these preferences. Younger and less disabled patients may be more focused on maintaining their current quality of life and may prioritize treatments that address the daily challenges posed by cognitive and emotional issues, as well as other symptoms like fatigue. The emphasis on PROMs reflects a proactive approach to managing the disease, with these patients likely seeking treatments that offer tangible improvements in their daily experiences.

Cluster 2: intermediate preferences

Cluster 2, which represents 24.3% of the sample, did not exhibit a clear polarization in preferences, showing relatively equal importance across most attributes. This intermediate cluster may represent patients who have a balanced view of treatment options, valuing both the clinical efficacy and practical aspects of treatment. The lack of a dominant preference for any specific attribute suggests that these patients may be more flexible or adaptable in their treatment choices, possibly considering a broader range of factors when evaluating their options.

The demographic characteristics of Cluster 2 were less distinct, with a mix of ages and disability levels, indicating that this group might include patients who are in a transitional phase of their disease or those who are still exploring different treatment approaches.

Cluster 3: administration-focused preferences

The third cluster, accounting for 23.1% of patients, showed a strong preference for the route and frequency of administration, favoring oral administration and less-frequent treatments (every 6 months). This cluster's focus on the practical aspects of treatment administration suggests a priority on convenience and minimizing the disruption to daily life. The preference for oral administration and infrequent dosing may reflect the desire to reduce the burden of treatment, which can be particularly important for patients who are older and more disabled.

The demographic profile of Cluster 3, with a higher proportion of older and more disabled patients (69% with EDSS > 3), supports this interpretation. As the disease progresses and physical abilities decline, the convenience of treatment becomes increasingly important, with patients likely seeking options that simplify their regimen and allow them to maintain as much independence as possible.

Implications for clinical practice

The findings from this LCA highlight the importance of personalized treatment approaches in managing MS. The strong preference for PROMs in Cluster 1 indicates that younger, less disabled patients may benefit from treatments that specifically target cognitive and emotional health, fatigue, and other symptoms that directly impact their quality of life. For these patients, shared decision-making should focus on how treatments can improve these aspects, alongside managing disease progression.

In contrast, the preferences of Cluster 3 suggest that older, more disabled patients may prioritize the practicality of treatment administration. For this group, discussions should emphasize the convenience and ease of treatment, with a focus on options that minimize the physical and logistical burden.

Finally, the intermediate preferences observed in Cluster 2 underscore the need for a balanced approach, considering both the clinical benefits and practical considerations of treatment. This cluster may benefit from a more comprehensive discussion of all available options, weighing the pros and cons of each.

This analysis reveals that MS patients' preferences are not monolithic but vary significantly based on age, disability status, and the specific aspects of their condition they find most burdensome. By understanding these preferences, healthcare providers can better tailor treatment plans to meet the individual needs of their patients, ultimately improving adherence and outcomes. The emphasis on PROMs among a significant portion of patients suggests that treatments aimed at enhancing daily functioning and quality of life will likely be well received, particularly among younger and less disabled individuals. On the other hand, ensuring that treatment regimens are manageable and minimally invasive is crucial for older and more disabled patients.

Conclusion

This study confirms the significant role of cognitive health and treatment administration preferences among both patients and HCPs in Italy. These insights should inform clinical practice by highlighting the need for personalized discussions that consider both patient-reported outcomes and practical aspects of treatment administration. As the first Discrete-Choice Experiment to compare the preferences of four different populations involved in the management of MS within the Italian context and internationally, this study provides valuable guidance on shared decision-making and the promotion of effective care for MS patients.

The results of this study, utilizing the DCE methodology and the first to collect and analyze responses from over 1600 patients and healthcare professionals (HCPs), offer valuable information on preferences for multiple sclerosis (MS) treatments. From the analysis of the results of the two DCEs, it emerges that patients assigned priority to attributes related to Patient-Reported Outcomes (PROMs), particularly the ability to walk (walking) and cognitive disorders, followed by "Time to Progression" of the disease, understood as the time to worsening. In the second DCE, patients attributed even greater importance to "Time to Progression", nearly doubling its value compared to the first, likely because this attribute encompasses walking ability, which is crucial for patients. Regarding convenience factors, patients preferred oral administration and treatment frequencies every 6 months. HCPs, while also valuing cognitive disorders, fatigue, other PROMs, and Time to Progression", placed

greater emphasis on the mode and location of treatment administration, showing a preference for hospital or local healthcare settings over home-based treatments.

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Author contributions All authors have contributed to the study conception and design. Material preparation, data collection, and analysis were performed by CG, MAB, MF, and PP. The first draft of the manuscript was written by PP. The manuscript was revised by CG, MAB, FB, EC, MP, PP, VBM, and MF. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest CG declares speaker honoraria and travel expenses for attending meetings from Bayer Schering Pharma, Sanofi-Aventis, Merck, Biogen, Novartis, and Almirall. VBM received personal compensation for speaking or consultancy from Biogen, Teva, Genzyme, Merck, Novartis, and Almirall. MF is the Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Horizon, Merck, Novartis, Roche, and Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Horizon, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Horizon, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, and Takeda; scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, and Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). MAB, FB, EC, MP, and PP declare no conflict of interest. The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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