

BMJ Open Conjoint analysis to understand preferences of patients with multiple sclerosis for disease-modifying therapy attributes in Spain: a cross-sectional observational study

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ABSTRACT

Objective: To assess patients' preferences for a range of disease-modifying therapy (DMT) attributes in multiple sclerosis (MS).

Design: A cross-sectional observational study.

Setting: The data reported were from 17 MS units throughout Spain.

Participants: Adult patients with relapsing-remitting MS.

Main outcome: A conjoint analysis was applied to assess preferences. A total of 221 patients completed a survey with 10 hypothetical DMT profiles developed using an orthogonal design and rating preferences from 1 (most acceptable) to 10 (least acceptable). Medication attributes included preventing relapse, preventing disease progression, side effect risk, route and frequency of administration.

Results: Patients placed the greatest relative importance on the side effect risk domain (32.9%), followed by route of administration (26.1%), frequency of administration (22.7%), prevention of disease progression (10.0%) and prevention of relapse (8.3%). These results were independent of the Expanded Disability Status Scale score. The importance assigned to side effect risk was highest for patients with a recent diagnosis. Patients who had previously received more than one DMT gave a higher importance to relapse rate reduction than patients receiving their first DMT.

Conclusions: Patient DMT preferences were mainly driven by risk minimisation, route of administration and treatment schedule. The risk–benefit spectrum of available DMT for MS is becoming increasingly complicated. Understanding which treatment characteristics are meaningful to patients may help to tailor information for them and facilitate shared decision-making in clinical practice.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central

Strengths and limitations of this study

- Little is known about the patients' preferences for different attributes of multiple sclerosis (MS) drug therapy.
- This study included a sample of 221 patients with relapsing-remitting MS managed in 17 different MS units at the national level, which allows results to be generalised to community practice. A comprehensive battery of the most important disease-modifying therapy attributes, including efficacy, tolerability, safety and convenience (route and frequency of administration), was analysed.
- The inclusion of a high percentage of patients with short disease duration is the main limitation of the study.

nervous system with genetic and environmental factors involved.¹ Relapsing-remitting MS (RRMS) is the most common clinical form of MS. The first-generation of disease-modifying therapies (DMTs), β -interferons and glatiramer acetate, reduced the risk of relapses, were generally well tolerated and safe.² Recently, an increasing number of new drugs have shown encouraging results for the management of RRMS due to higher efficacies compared with first-line DMTs. Consequently, major changes in the therapeutic management of RRMS are expected in coming years, which can impact on the natural progression of the disease. However, despite improved efficacy, these new agents have been associated with increased risk of serious adverse effects, thus altering the risk–benefit balance.^{2–4} The choice of new drugs should take into account aspects other than efficacy, including mechanisms of action, duration of effect, potential safety problems,

convenience and patient preferences.⁵ In this context, therapeutic decisions are becoming increasingly complex.

In recent decades, there has been a big change in the physician–patient relationship. Patients and health authorities are increasingly demanding a more active role in decision-making processes related to medical care. This approach requires the patient to assess benefits and risks. Thus, in the management of MS, it is important to involve patients in the decision-making process regarding treatment initiation or switching due to the risk–benefit spectrum of the different DMTs available (partially effective and with significant side effect risk).^{6–8}

In the real-world setting, patients evaluate a range of features to make decisions. The analysis of preferences can be used to further improve the knowledge of which treatment attributes are considered the most valuable by patients.⁹ There are different approaches for assessing patient preferences: methods using rating or choice designs to quantify preferences for various attributes of an intervention (conjoint analysis or stated-choice methods) or methods using direct elicitation of monetary values of an intervention (including contingent valuation or willingness-to-pay and willingness-to-accept methods).¹⁰ Conjoint analysis is a multivariate technique in that the implicit values for an attribute of an intervention are derived from some overall score for a profile consisting of two or more attributes. Conjoint analysis has been conducted successfully to assess preferences for a diverse range of health interventions.¹⁰

The objective of this study was to assess the relative importance of a number of hypothetical DMT attributes for patients with RRMS.

METHODS

A multicentre observational cross-sectional study in adult patients with RRMS was conducted in 17 MS units throughout Spain (the EMPOWER study). The study was conducted between January and March 2016.

Patients were enrolled into the study who were aged 18 years or older with a diagnosis of RRMS (2010 McDonald criteria¹¹), an Expanded Disability Status Scale¹² (EDSS) score from 1 to 6, and receiving a DMT for at least the past 3 months prior to inclusion. Written informed consent was obtained from all participants. Investigators included the first 12 consecutive patients who met the inclusion criteria for study participation. Competitive recruitment was established among centres. Study patients were treated by participating neurologists following current clinical practice and according to their judgement.

Conjoint analysis required the definition of hypothetical treatment options in terms of attributes (characteristics) and a subset of levels for each attribute. The DMT attributes and levels were developed through a review of current clinical trial literature and advanced clinical

expertise.^{13 14} A total of five attributes and two to four levels per attribute were defined to take into account the most important characteristics of all available DMTs: preventing relapse, preventing disease progression, side effect risk, route and frequency of administration (table 1). An orthogonal design was used to construct 10 cards containing unique combinations of all five attributes (table 2). Patients were asked to assess the level of each attribute combined to evaluate overall preference for each card relative to the other by first placing each card on a number line from 1 to 10 (1 being the best and 10 the worst possible selection).

Sociodemographic and clinical characteristics of the sample and patient-reported questionnaires were also collected. The EDSS was used to measure disability. Health-related quality of life (HRQoL) was assessed using the EuroQol five dimensions questionnaire (EQ-5D).¹⁵ The nine-item Shared Decision-Making Questionnaire (SDM-Q-9)¹⁶ is a patient-report tool for measuring patients' perceptions of how clinician performance fits the shared decision-making process. Total score ranges from 0 to 45 (the lowest to the highest extent of shared decision-making). Cognitive functioning was assessed using the Medical Outcomes Study Cognitive Functioning Scale (MOS Cog-R scale),¹⁷ a six-item self-report instrument that measures a range of day-to-day problems in several dimensions of cognitive functioning, including memory, attention/concentration and reasoning over the previous 4 weeks. Total scores range from 0 to 100 points, with higher scores indicating greater cognitive performance.

Table 1 DMT attributes and levels

| Attributes | Levels | Description |
|--------------------------------|--------|---|
| Preventing relapse | 2 | Presenting a relapse every 2 years |
| | | Presenting a relapse every 5 years |
| Preventing disease progression | 2 | Preventing the disease from getting worse/progressing for 2 years |
| | | Preventing the disease from getting worse/progressing for 5 years |
| Side effect risk | 2 | Rare but severe, life-threatening side effects (including PML) |
| | | Frequent but mild/moderate side effects |
| Route of administration | 3 | Oral |
| | | Subcutaneous–intramuscular |
| | | Intravenous |
| Frequency of administration | 4 | Daily |
| | | Every 2 days—weekly |
| | | Monthly |
| | | Twice per year |

PML, Progressive multifocal leukoencephalopathy.

Table 2 Set of cards

| Card | Preventing relapse | Preventing disease progression | Side effect risk | Route of administration | Frequency of administration |
|------|------------------------------------|--|---|----------------------------|-----------------------------|
| A | Presenting a relapse every 2 years | Preventing the disease from getting worse/ progressing for 5 years | Rare but severe life-threatening side effects (including PML) | Oral | Daily |
| B | Presenting a relapse every 2 years | Preventing the disease from getting worse/ progressing for 2 years | Frequent but mild/moderate side effects | Subcutaneous–intramuscular | Daily |
| C | Presenting a relapse every 5 years | Preventing the disease from getting worse/ progressing for 5 years | Rare but severe life-threatening side effects (including PML) | Intravenous | Daily |
| D | Presenting a relapse every 5 years | Preventing the disease from getting worse/ progressing for 2 years | Frequent but mild/moderate side effects | Oral | Every 2 days—weekly |
| E | Presenting a relapse every 2 years | Preventing the disease from getting worse/ progressing for 5 years | Rare but severe life-threatening side effects (including PML) | Subcutaneous–intramuscular | Every 2 days—weekly |
| F | Presenting a relapse every 2 years | Preventing the disease from getting worse/ progressing for 5 years | Rare but severe life-threatening side effects (including PML) | Oral | Monthly |
| G | Presenting a relapse every 5 years | Preventing the disease from getting worse/ progressing for 2 years | Rare but severe life-threatening side effects (including PML) | Subcutaneous–intramuscular | Monthly |
| H | Presenting a relapse every 2 years | Preventing the disease from getting worse/ progressing for 5 years | Frequent but mild/moderate side effects | Intravenous | Monthly |
| I | Presenting a relapse every 5 years | Preventing the disease from getting worse/ progressing for 5 years | Frequent but mild/moderate side effects | Subcutaneous–intramuscular | Twice per year |
| J | Presenting a relapse every 2 years | Preventing the disease from getting worse/ progressing for 2 years | Rare but severe life-threatening side effects (including PML) | Intravenous | Twice per year |

Statistical analysis

Relative preferences were derived from rankings assigned by study patients to the 10 hypothetical scenarios, obtaining values ranging from 0 to 10. Rankings had a hierarchical order that showed which cards were more or less preferred on an arbitrary scale. Patient preferences for hypothetical treatment were collected for the overall sample of valid patients and for stratified subgroups according to the EDSS score (1–3.0 and 3.5–6.0) with the aim to check that the preferences remain stable for different levels of disability. An ordinary least squares (OLS) regression model was used to estimate parameters, given that preferences were obtained in terms of ranges.

The model estimated by the OLS method, depending on the attributes and levels, is as follows:

$$y_t = \alpha + \sum \beta_{ij} x_{ij} + e$$

Where:

y_t is the utility for a card t ;

α is the constant or intercept term;

β_{ij} is the utility or part-worth associated with the i -th attribute in the j -th level;

$x_{ij}^1=1$ when the j -th level of the i -th attribute is present in the card t ;

$x_{ij}^0=0$ when the j -th level of the i -th attribute is not present in the card t ;

e is the error term.

The DMT preference card was the dependent variable and attributes used in the definition of the cards were independent variables. Relative (overall) and individual (at patient level) importance assigned to each attribute was derived by dividing the importance of a factor (maximum difference in utility values assigned to the levels) by the sum of all individual importance scores. The relationship between sociodemographic and clinical characteristics of patients, degree of patient disability, HRQoL, cognitive function and role in shared decision-making, and preference for treatment attributes were analysed using bivariate tests. A sensitivity analysis was performed which excluded those patients with inverse preferences (or investments) in efficacy and safety attributes.

Individual importance of each attribute (or level) for obtaining information about factors related to the importance assigned to different attributes was explored according to sociodemographic and clinical variables using bivariate tests.

RESULTS

A total of 221 patients were included in the study. The mean age was 42.1±9.9 years, and 68.3% were female. The mean EDSS score was 2.7±1.5. Patients presented mean SDM-Q-9 and MOS Cog-R total scores of 38.7±8.5 and 41.5±11.1, respectively. The most common current DMTs were first-line injectable therapies (43.9% of patients), followed by fingolimod (19.0%), dimethyl fumarate (15.4%) and natalizumab (12.2%). The main sociodemographic and clinical characteristics of the sample are presented in [table 3](#).

[Table 4](#) describes estimated utilities reported by patients for attributes and levels assessed in hypothetical treatment scenarios. Patients had a higher preference for treatments with better efficacy (presenting a relapse every 5 years and/or preventing the disease from getting worse/progressing for 5 years), lower side effect risk (frequent but mild/moderate side effects), oral administration and lower frequency of administration (twice a year). Pearson's R and Kendall's τ coefficients, which provide measures of the correlation between observed and estimated preferences to assess the model's goodness of fit, showed high correlation coefficients (0.998 and 0.956, respectively). Importance assigned to the different attributes show some differences according to the method used (average or relative importance). Considering the relative importance, the most important attribute for a DMT was tolerability/safety (32.9%), followed by route of administration (26.1%) and frequency of administration (22.7%). Average importance, obtained at the patient level, was slightly different with schedule of administration being the most important attribute (26.9%), followed by side effects (26.8%) and route of administration (25.1%). Estimated utilities reported by patients for attributes and levels were

consistent in groups of patients stratified according to the EDSS score (1.0–3.0 and 3.5–6.0 strata; [figure 1](#)).

The sensitivity analysis performed, excluding those patients who showed individual reversed utilities in efficacy and safety attributes, put greater value in presenting a relapse in 5 years (0.773 vs 0.367) and preventing the disease from getting worse or progressing for 5 years (0.764 vs 0.445), but a minor preference for treatments administered twice per year (0.727 vs 1.137).

[Table 5](#) describes sociodemographic and clinical variables related to individual importance assigned to each DMT attribute. Patients having previously received more than one DMT gave a higher importance to relapse rate reduction than patients receiving their first DMT. The importance assigned to side effect risk was highest for those patients with a recent diagnosis of <1 year.

DISCUSSION

Treatment decisions in MS are becoming difficult after the introduction of several new DMTs with more complicated spectrums of risks and benefits.¹⁸ Involving patients with MS in the decision-making process is key to selecting the treatment that best suits the patient's profile and preferences. In our study, patients placed the greatest importance on the side effect risk domain with 32.9% relative importance, followed by route of administration (26.1%), frequency of administration (22.7%), prevention of disease progression (10.0%) and prevention of relapse (8.3%).

Several studies DMT preferences of patients with MS were recently published.^{12 13 19–28} Such studies evaluated different spectrums of drug attributes. In a sample of 651 patients from the USA, a survey using five efficacy and safety drug attributes found that a delay in years to

Table 3 Main characteristics of the sample

| | EDSS 1.0–3.0 (n=143) | EDSS 3.5–6.0 (n=78) | Total (n=221) | p Value |
|--|-------------------------|------------------------|------------------|---------|
| Age, mean (SD) | 40.0 (9.8) | 46.0 (8.9) | 42.1 (9.9) | <0.001 |
| Gender, female, n (%) | 99 (69.2%) | 52 (66.7%) | 151 (68.3%) | 0.763 |
| Employment status, n (%) | | | | |
| Employed (part-time or full-time) | 92 (64.7%) | 15 (29.5%) | 96 (52.0%) | <0.001 |
| Unemployed | 19 (13.3%) | 9 (11.5%) | 28 (12.7%) | |
| Retired due to RRMS | 10 (7.0%) | 31 (39.7%) | 41 (18.6%) | |
| Retired due to other reasons | 4 (2.8%) | 2 (2.6%) | 6 (2.78%) | |
| Without paid employment | 18 (12.6%) | 13 (16.7%) | 31 (14.0%) | |
| Some level of incapacity for work, n (%) | 31 (21.7%) | 44 (66.5%) | 75 (34.9%) | <0.001 |
| Time of MS evolution (years), mean (SD) | 7.8 (6.5) | 11.7 (6.9) | 9.1 (6.9) | <0.001 |
| Time with DMT treatment (years), mean (SD) | 5.3 (4.1) | 7.2 (4.7) | 6.0 (4.4) | 0.012 |
| Time with current DMT treatment (years), mean (SD) | 3.5 (3.7) | 3.4 (3.3) | 3.5 (3.5) | 0.529 |
| Use of previous DMT treatment, n (%) | 75 (52.4%) | 58 (74.4%) | 133 (60.2%) | <0.001 |
| Presence of relapses, n (%) | | | | |
| Since diagnosis | 125 (87.4%) | 76 (97.4%) | 201 (91.0%) | 0.013 |
| During the past 2 years | 66 (46.2%) | 34 (43.6%) | 100 (45.2%) | 0.714 |
| During the past year | 32 (22.4%) | 20 (25.6%) | 52 (23.5%) | 0.585 |

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS.

Table 4 Utility scores in patients with MS

| | Utility (SD) | Importance (relative) | Importance (averaged) |
|---|----------------|-----------------------|-----------------------|
| Preventing relapse | | | |
| Presenting a relapse every 2 years | −0.367 (0.131) | 8.3 | 10.4 |
| Presenting a relapse every 5 years | 0.367 (0.131) | | |
| Preventing disease progression | | | |
| Preventing the disease from getting worse/progressing for 2 years | −0.445 (0.131) | 10.0 | 11.1 |
| Preventing the disease from getting worse/progressing for 5 years | 0.445 (0.131) | | |
| Side effect risk | | | |
| Rare but severe, life-threatening side effects | −1.457 (0.131) | 32.9 | 26.5 |
| Frequent but mild/moderate side effects | 1.457 (0.131) | | |
| Route of administration | | | |
| Oral | 1.345 (0.195) | 26.1 | 25.1 |
| Subcutaneous–intramuscular | −0.381 (0.175) | | |
| Intravenous | −0.965 (0.195) | | |
| Frequency of administration | | | |
| Daily | −0.877 (0.206) | 22.7 | 26.9 |
| Every 2 days—weekly | −0.527 (0.251) | | |
| Monthly | 0.267 (0.206) | | |
| Twice per year (Constant) | 1.137 (0.251) | | |
| | 5.875 (0.133) | | |

MS, multiple sclerosis.

disability progression was the most important factor for treatment preferences.¹⁹ Risk of progressive multifocal leucoencephalopathy was the second most significant factor while the frequency of relapses had the least overall importance. Treatment frequency and route of administration showed a stronger influence on patient preferences compared with frequency of mild side effects in a German study.¹³ However, no efficacy attributes were assessed. Oral administration was preferred over injections by 93% of patients when treatment frequency and frequency of side effects were held constant.¹³ Poulos *et al*^{20 21} performed studies in the USA and Germany assessing several attributes of injectable treatments using a discrete-choice approach to derive utilities: number of years until MS symptoms get worse, number of relapses in the next 4 years, injection time, frequency of injections, influenza-like symptoms and infection-site reactions. Both studies identified the number of years until MS symptoms get worse as being the most important attribute, followed by influenza-like symptoms, frequency of injections per month and number of relapses in the following years. A study performed by Wilson *et al*²² used different attributes (prevent progression, prevent relapse, prevent changes on MRI, improve symptoms, common and severe side effects, treatment administration and time on market) and established a ranking (0–10) approach to derive utilities. Prevention of disease progression, relapses and changes on MRI were assessed on an annual basis, but taking into account a maximum prevention period of 5 years, the most important attribute was the presence of severe side effects, followed by administration routes. In

addition, a study conducted in Canada, with a sample of 189 patients with RRMS as well as progressive MS using latent-class modelling, concluded that the most important attribute was the avoidance of serious adverse effects.²³

Our findings concur with those of Wilson *et al* using similar attributes to define scenarios and the same elicitation method. Prevention of relapse is not as relevant as preventing side effects.²² We identified main factors related to patient preferences for drug attributes, including previous experience with more than one DMT, number of relapses and HRQoL. Patients with prior DMT treatment gave higher importance to the impact of treatment on the prevention of relapse rate and lower importance to the side effects attribute. In a recent study performed to assess patient preferences for the full spectrum of DMT attributes, patients receiving their first DMT also gave higher importance to type, severity and duration of side effects.²⁴ On the other hand, patients who had previously received multiple DMTs gave higher importance to the effect on relapse rate and its severity. The fact that patients with a longer disease duration tend to prioritise the efficacy profile of DMTs may be indicative of a better understanding of the disease, both from a theoretical and from a practical point of view. Wilson *et al*¹⁴ identified that treatment-naïve patients had no significant relative preference for preventing disease progression, which could be associated with a lower disease activity. In addition, patients receiving the first-line DMTs such as β -interferons or glatiramer acetate displayed more aversion to fatal risk than those receiving the high-efficacy

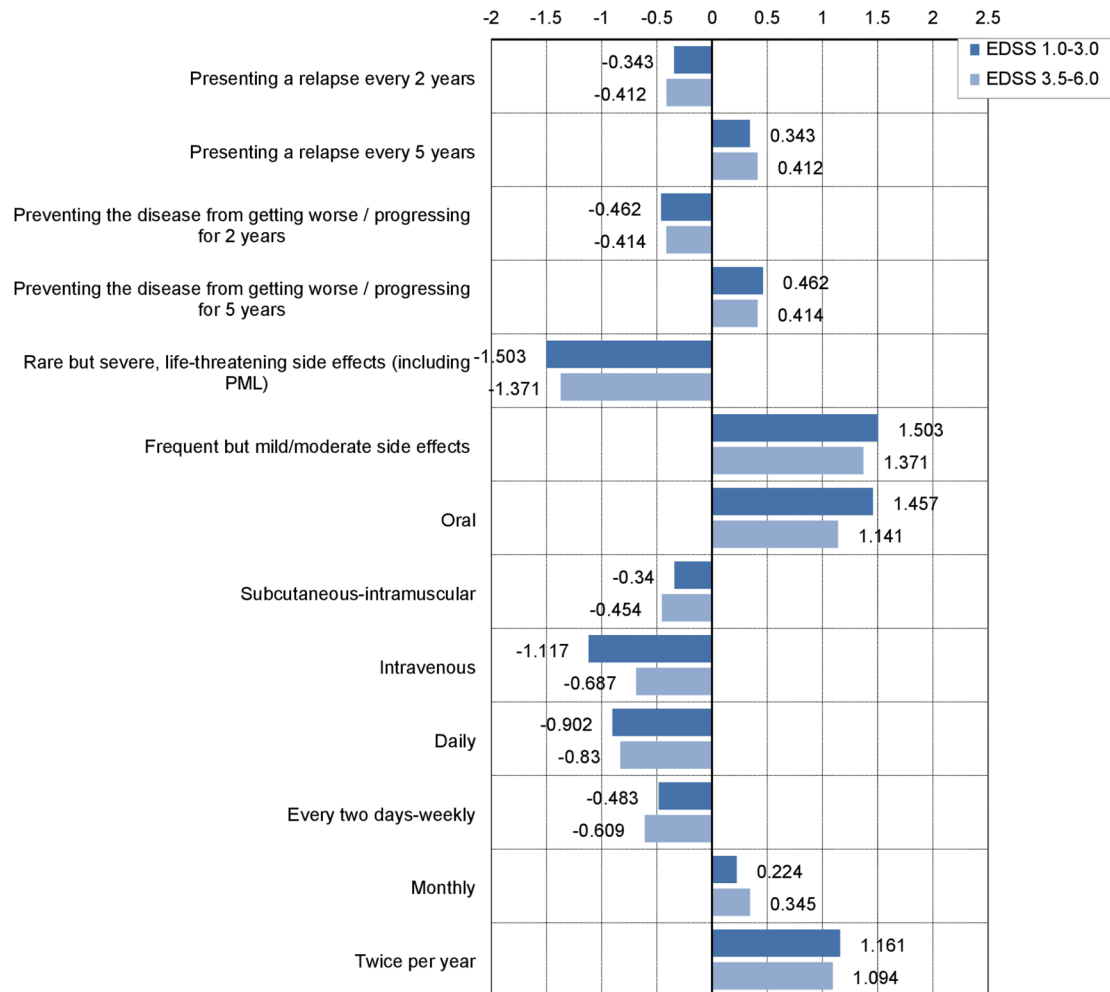


Figure 1 Utility scores for each level of the attribute according to the EDSS score. EDSS, Expanded Disability Status Scale.

DMTs fingolimod or natalizumab. The ability of natalizumab-treated patients to assume therapy-associated risks and the factors involved in such risk acceptance was assessed in a study published by Tur *et al.*²⁸ The authors defined risk acceptance as a multifactorial phenomenon which is partly explained by an adaptive process involving the perception of MS as a more severe disease. Therefore, it would be important to give special attention to patients newly diagnosed in efficacy aspects of available therapies.

Our study has several limitations. First, the sample population included a high percentage of patients receiving their first DMT (39.8%). According to the study results, patients without prior treatment experience had a higher awareness about side effects, reducing the importance assigned to efficacy parameters. This high percentage of patients may explain the higher importance obtained for safety risk. Second, preference studies are classically limited in that the preference weights elicited are specific to the attributes and levels that are presented. It is possible that some attributes that are important to some patients were not included. In addition, the method used to derive utilities is a second

study limitation as utility values and importance derived from conjoint analysis depend on attributes and levels used to define scenarios. Treatment efficacy was assessed in terms of prevention of relapses and disease progression, but not in terms of improving MS symptoms. Previous studies that included both attributes derived a higher importance for the MS symptoms attribute than for the number of relapses.^{20 21} On the other hand, side effect risk was defined in terms of severe and life-threatening adverse events, which could increase the importance assigned to this attribute. However, results obtained by Wilson *et al.*²² using a similar definition for the side effects attribute are aligned with our study. In addition, it is important to consider the number of levels included in each attribute. A higher number of levels tend to be related to higher importance assigned to the attribute, given that a higher variability in response options tends to occur. Finally, another potential limitation is the absence of additional patient factors or characteristics that may impact preferences, such as personality traits. For example, a neurotic personality profile has previously been predicted to have a higher acceptance of natalizumab-associated risks.²⁸

Table 5 Sociodemographic and clinical characteristics and individual importance assigned to each DMT attribute*

| Sociodemographic or clinical characteristics | Preventing relapse | Preventing disease progression | Side effect risk | Route of administration |
|--|--------------------|--------------------------------|------------------|-------------------------|
| Previous DMT treatment | | | | |
| No | 9.0 (10.5) | | | 21.8 (13.2) |
| Yes | 11.3 (10.8) | | | 27.3 (16.0) |
| p Value | 0.027 | | | 0.008 |
| Incapacity for work | | | | |
| Partial incapacity | | 12.1 (7.5) | | |
| Total incapacity | | 17.5 (12.8) | | |
| Absolute incapacity | | 11.8 (7.9) | | |
| Incapacity for severe disability | | 4.6 (4.8) | | |
| Not recognised | | 9.6 (6.5) | | |
| No incapacity | | 10.7 (10.2) | | |
| p Value | | 0.048 | | |
| Anxiety/depression (EQ-5D) | | | | |
| No | | 12.3 (10.1) | | |
| Yes | | 9.6 (8.5) | | |
| p Value | | 0.025 | | |
| Longer time since MS diagnosis (years) | | | | |
| <1 | | | 39.0 (14.4) | |
| 1–2 | | | 17.1 (14.7) | |
| 2–5 | | | 24.0 (16.0) | |
| 5–10 | | | 25.9 (16.7) | |
| 10–20 | | | 30.3 (15.7) | |
| >20 | | | 21.8 (15.7) | |
| p Value | | | 0.001 | |
| Greater number of relapses in the past 2 years | | | | |
| No relapses | | | 28.4 (15.6) | 23.8 (14.0) |
| 1 relapse | | | 27.6 (16.7) | 23.9 (15.7) |
| 2 or more relapses | | | 18.3 (16.6) | 31.1 (16.7) |
| p Value | | | 0.005 | 0.030 |

*Only statistically significant results are included (p<0.05).

DMT, disease-modifying therapy; EQ-5D, EuroQol five dimensions questionnaire; MS, multiple sclerosis.

Despite these limitations, the study also has several strengths. The sample of 221 patients was managed in 17 different MS units at the national level, which allows results to be generalised to community practice. In addition, the sample size was large enough to allow the derivation of preference values according to the degree of disability (EDSS). Finally, a comprehensive battery of the most important DMT attributes, including efficacy, tolerability safety and convenience (route and frequency of administration), was analysed.

Patient preferences for DMT in our study were mainly driven by risk minimisation, route of administration and treatment schedule. There is no evidence that decisions based on patient preferences are better than those based on a drug's efficacy in order to achieve the best possible mid-long-term outcome for the patient. Nevertheless, understanding which DMT characteristics are meaningful to patients may help to tailor information and support decision-making in clinical practice.

Shared decision-making is a cornerstone of patient-centred care. A rating-based conjoint analysis is a feasible method for quantifying the relative preferences of patients with MS. Treatment decisions in MS should be made in collaboration between the neurologist and the

patient, and they should be based on the best available evidence as well as on patient values and preferences.^{29 30}

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Contributors RA and JM developed the research question, designed the study and wrote the protocol. MR and AC performed the statistical analyses. All authors contributed to and have approved the final manuscript.

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Competing interests ER-B, DP and JM are employees of Roche Farma SA. MR and AC are employees of IMS Health.

Patient consent Obtained.

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