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Understanding multiple sclerosis patients´ preferences for disease-modifying therapy attributes

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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. Patients completed a survey with ten 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 minimization, route of administration and treatment schedule. The risk-benefit spectrum of available DMT for multiple sclerosis 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.

Key words: Multiple sclerosis, patient preferences, disease-modifying therapies, rating-based experiment, conjoint analysis

Strengths and limitations of this study

. Little is known about the patients´ preferences for different attributes of multiple sclerosis drug therapy. Non-representative samples of patients and an incomplete number of treatment characteristics explored were the major limitations of previous studies.

. A comprehensive battery of the most important disease-modifying therapy attributes was analysed in a sample of 221 patients managed in 17 different MS Units from across Spain. We found that the most important drug attribute was the side effect risk. The prevention of relapse and delay of disease progression were not as relevant as the safety risk minimization.

. Patients´ preferences should play a key role in treatment decisions.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with genetic and environmental factors involved.[1] Relapsing-remitting multiple sclerosis (RRMS) is the most common clinical form of MS. The first-generation of disease modifying therapies (DMTs), beta-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 to 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 to 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 real life, patients do not make decisions based on a single attribute; rather they evaluate a range of features and then make the final decision. The analysis of preferences can be used to further the knowledge of which treatment aspects are considered the most valuable by patients.[9] There are different methodologies for assessing patient preferences for treatment alternatives based on the description of their main attributes. These methodologies include conjoint analysis, a multivariate technique originally used to estimate the value that people give to the attributes that define products and services. In the healthcare sector, conjoint analysis can be utilised to determine the relative weight of each of the attributes that define the patient preference for a treatment.

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 (EMPOWER study). The study was approved by the institutional review board of the Hospital Universitari Dr. Josep Trueta (Girona, Spain).

Patients were enrolled into the study who were aged 18 years or older with a diagnosis of RRMS (2010 McDonald criteria[10]), an Expanded Disability Status Scale[11] (EDSS) score from 1 to 6, and receiving a DMT for at least the last three months prior to inclusion. Written informed consent was obtained from all subjects. Investigators included the first twelve consecutive patients that 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.[12,13] 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 ten 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).

Socio-demographic 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).[14] The 9-item Shared Decision-Making Questionnaire (SDM-Q-9)[15] 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)[16], a 6-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.

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 scale (1 to 3.0 and 3.5 to 6.0) with the aim to check that the preferences of patients 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 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) between by the sum of all individual importance scores. The relationship between socio-demographic 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 were explored according to socio-demographic 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 socio-demographic 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 tau 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 shown some differences according to the method used (average or relative importance). Considering 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 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 socio-demographic and clinical variables related with 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 less than one year.

DISCUSSION

Treatment decisions in MS are becoming difficult after the introduction of several new DMTs with more complicated spectrums of risks and benefits.[17] Involving MS patients in the decision-making process is key to select the treatment that best suits the patient´s profile and preferences. In our study, patients placed the greatest importance on 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 of MS patient DMT preferences were recently published. Such studies evaluated different spectrums of drug attributes. In a sample of 651 patients from the US, a survey using five efficacy and safety drug attributes found that a delay in years to disability progression was the most important factor for treatment preferences.[18] Risk of progressive multifocal leukoencephalopathy 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.[12] 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.[12] Poulos *et al*. performed studies in US 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, flu-like symptoms and infection-site reactions.[19,20] Both studies identified the number of years until MS symptoms get worse as being the most important attribute, followed by flu-like symptoms, frequency of injections per month and number of relapses in the following years. A study performed by Wilson *et al.* 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 to 10) approach to derive utilities.[21] Prevention of disease progression, relapses and changes on MRI were assessed on 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.[22]

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.[21] 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.[23] On the other hand, patients who had previously received multiple DMTs gave higher importance to the effect on relapse rate and its severity. Wilson *et al.* identified that treatment-naïve patients had no significant relative preference for preventing disease progression, which could be associated to lower disease activity.[13] In addition, patients receiving the first-line DMTs such as beta-interferons or glatiramer acetate displayed more aversion to fatal risk than those receiving the high-efficacy DMTs fingolimod or natalizumab. The ability of natalizumab-treated patients to assume treatment-associated risks and the factors involved in such risk acceptance was assessed in a study published by Tur *et al.*[24] 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.

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. 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 number of relapses.[19,20] 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.* using a similar definition for the side effects attribute, are aligned with our study.[21] In addition, it is important to consider the number of levels included in each attribute. A higher number of levels tend to be related with 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.[24]

Despite these limitations, the study also has several strengths. The sample of 221 patients was managed in 17 different MS Units at 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.

Understanding which DMT characteristics are meaningful may help to tailor information for patients and support decision making in clinical practice. A rating-based conjoint analysis is a feasible method for quantifying the relative preferences of patients with MS. Patient preferences for DMT in our study were mainly driven by risk minimization, route of administration and treatment schedule. Shared decision making is a cornerstone of patient-centred care. 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.[25,26]

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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 ERB, DP and JM are employees of Roche Farma SA. MR and AC are employees of IMS Health. None of the other authors report any conflict of interest.

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 two days-weekly Monthly Twice per year

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 two 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 two 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

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 last 2 years	66 (46.2%)	34 (43.6%)	100 (45.2%)	0.714
	During the last year	32 (22.4%)	20 (25.6%)	52 (23.5%)	0.585

Table 4 Utility scores in MS patients

		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 two days-weekly	-0.527 (0.251)		
	Monthly	0.267 (0.206)		
	Twice per year	1.137 (0.251)		
(Constant)		5.875 (0.133)		

Table 5 Socio-demographic and clinical characteristics and individual importance assigned to each DMT attribute

Socio-demographic or clinical characteristics		Preventing relapse	Preventing disease progression	Side effect risk	Route of administration
Previous DMT treatment	No	9.0 (10.5)			
	Yes	11.3 (10.8)			
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 recognized		9.6 (6.5)		
	No incapacity		10.7 (10.2)		
Anxiety/depression problem (EQ-5D)	No		12.3 (10.1)		
	Yes		9.6 (8.5)		
Longer time since MS diagnosis	< 1 year			39.0 (14.4)	
	1-2 years			17.1 (14.7)	
	2-5 years			24.0 (16.0)	
	5-10 years			25.9 (16.7)	
	10-20 years			30.3 (15.7)	
	>20 years			21.8 (15.7)	
Higher number of relapses in the last 2 years	No relapses			28.4 (15.6)	23.8 (14.0)
	1 relapse			27.6 (16.7)	23.9 (15.7)
	2 o more relapses			18.3 (16.6)	31.1(16.7)

Figure 1 Legend

Utility scores for each level of the attribute according to EDSS score

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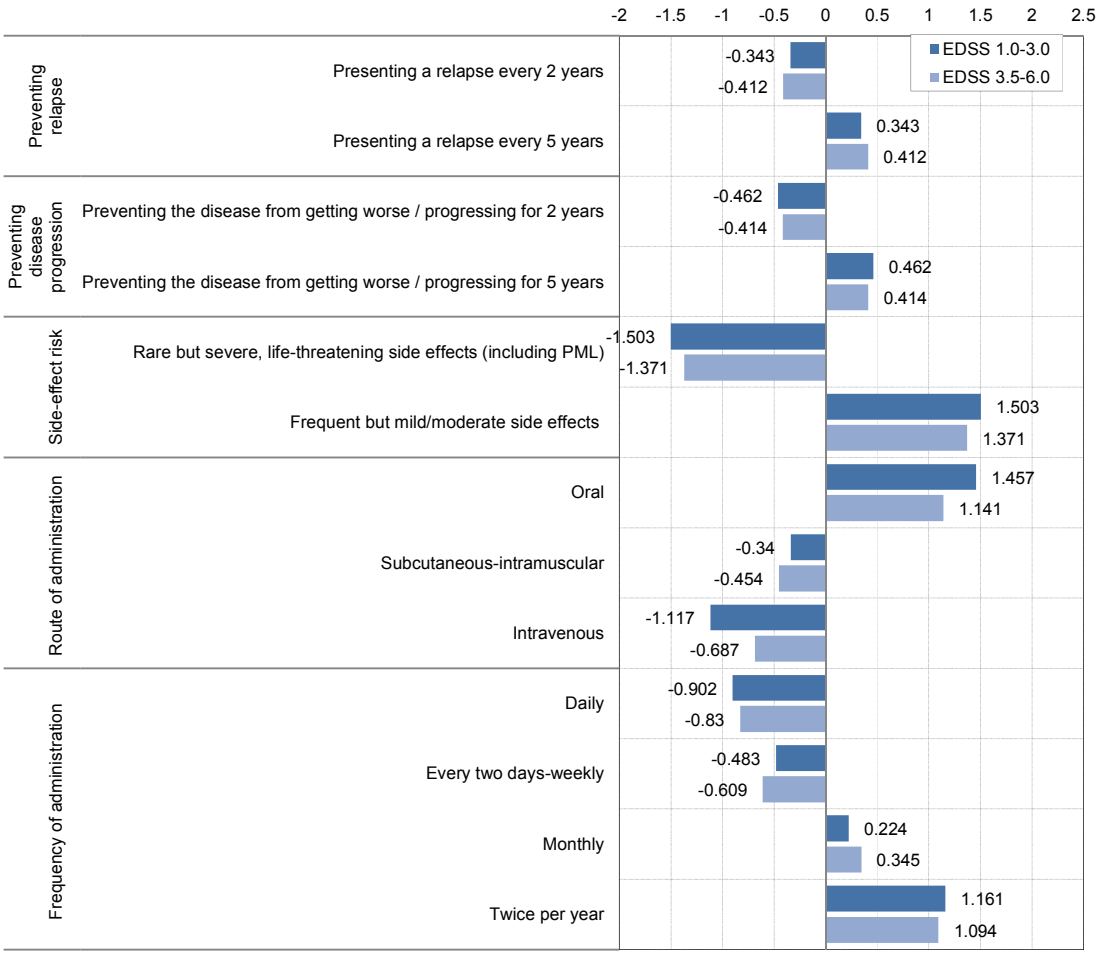
Figure 1. Utility scores for each level of the attribute according to EDSS score



STROBE Statement—checklist of items that should be included in reports of observational studies

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Conjoint analysis to understand multiple sclerosis patients´ preferences for disease-modifying therapy attributes in Spain

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Conjoint analysis to understand multiple sclerosis patients´ preferences for disease-modifying therapy attributes in Spain

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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 ten 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 minimization, route of administration and treatment schedule. The risk-benefit spectrum of available DMT for multiple sclerosis 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.

Key words: Multiple sclerosis, patient preferences, disease-modifying therapies, rating-based experiment, conjoint analysis

Strengths and limitations of this study

. Little is known about the patients´ preferences for different attributes of multiple sclerosis drug therapy.

. This study included a sample of 221 patients with relapsing-remitting multiple sclerosis managed in 17 different MS Units at national level, which allows results to be generalised to community practice. A comprehensive battery of the most important DMT 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.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with genetic and environmental factors involved.[1] Relapsing-remitting multiple sclerosis (RRMS) is the most common clinical form of MS. The first-generation of disease modifying therapies (DMTs), beta-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 to 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 to 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 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 approved by the institutional review board of the Hospital Universitari Dr. Josep Trueta (Girona, Spain) and 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 criteria[11]), an Expanded Disability Status Scale[12] (EDSS) score from 1 to 6, and receiving a DMT for at least the last three months prior to inclusion. Written informed consent was obtained from all subjects. Investigators included the first twelve consecutive patients that 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 ten 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).

Socio-demographic 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 9-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 6-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.

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 scale score (1 to 3.0 and 3.5 to 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 ordinary least squares method, depending on the attributes and levels, is as follows:

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

Where:

t is the order or preference assessment of the stimulus t

α is the constant term

β ij is utility or part-worth associated with the i-th attribute in the j-th level

x ij $= 1$ if the j-th level of the i-th attribute is present in the stimulus t

x ij $= 0$ if the j-th level of the i-th attribute is not present in the stimulus t

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) between by the sum of all individual importance scores. The relationship between socio-demographic 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 were explored according to socio-demographic 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 socio-demographic 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 tau 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 shown some differences according to the method used (average or relative importance). Considering 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 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 socio-demographic and clinical variables related with 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 less than one 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 MS patients in the decision-making process is key to select the treatment that best suits the patient´s profile and preferences. In our study, patients placed the greatest importance on 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 of MS patient DMT preferences were recently published.[12,13,19-28] Such studies evaluated different spectrums of drug attributes. In a sample of 651 patients from the US, a survey using five efficacy and safety drug attributes found that a delay in years to disability progression was the most important factor for treatment preferences.[19] Risk of progressive multifocal leukoencephalopathy 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*. performed studies in US 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, flu-like symptoms and infection-site reactions.[20,21] Both studies identified the number of years until MS symptoms get worse as being the most important attribute, followed by flu-like symptoms, frequency of injections per month and number of relapses in the following years. A study performed

by Wilson *et al.* 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 to 10) approach to derive utilities.[22] Prevention of disease progression, relapses and changes on MRI were assessed on 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 longer disease duration tend to prioritize the efficacy profile of DMTs may be indicative of a better understanding of the disease, not only from a theoretical but also from a practical point of view. Wilson *et al.* identified that treatment-naïve patients had no significant relative preference for preventing disease progression, which could be associated to a lower disease activity.[14] In addition, patients receiving the first-line DMTs such as beta-interferons or glatiramer acetate displayed more aversion to fatal risk than those receiving the high-efficacy 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] 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 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.* using a similar definition for the side effects attribute are aligned with our study.[22] In addition, it is important to consider the number of levels included in each attribute. A higher number of levels tend to be related with 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]

Despite these limitations, the study also has several strengths. The sample of 221 patients was managed in 17 different MS Units at 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 minimization, route of administration and treatment schedule. There is no evidence that decisions based on patient preferences are better than those based on 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]

Figure 1. Utility scores for each level of the attribute according to EDSS score

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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 ERB, DP and JM are employees of Roche Farma SA. MR and AC are employees of IMS Health. None of the other authors report any conflict of interest.

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 two days-weekly Monthly Twice per year

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 two 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 two 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

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 last 2 years	66 (46.2%)	34 (43.6%)	100 (45.2%)	0.714
	During the last year	32 (22.4%)	20 (25.6%)	52 (23.5%)	0.585

Table 4 Utility scores in MS patients

		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 two days-weekly	-0.527 (0.251)		
	Monthly	0.267 (0.206)		
	Twice per year	1.137 (0.251)		
(Constant)		5.875 (0.133)		

Table 5 Socio-demographic and clinical characteristics and individual importance assigned to each DMT attribute*

Socio-demographic 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 recognized		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	< 1 year			39.0 (14.4)	
	1-2 years			17.1 (14.7)	
	2-5 years			24.0 (16.0)	
	5-10 years			25.9 (16.7)	
	10-20 years			30.3 (15.7)	
	>20 years			21.8 (15.7)	
	p-value			0.001	
Greater number of relapses in the last 2 years	No relapses			28.4 (15.6)	23.8 (14.0)
	1 relapse			27.6 (16.7)	23.9 (15.7)
	2 o 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)

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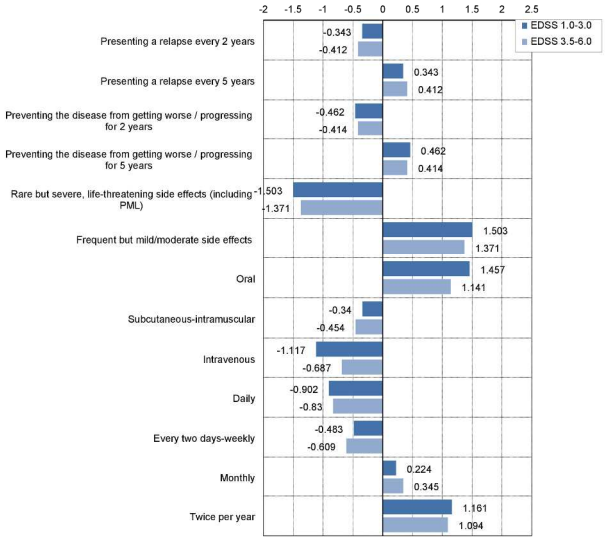

Figure 1. Utility scores for each level of the attribute according to EDSS score

209x297mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Conjoint analysis to understand multiple sclerosis patients´ preferences for disease-modifying therapy attributes in Spain: A cross-sectional observational study

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Conjoint analysis to understand multiple sclerosis patients´ preferences 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 ten 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 minimization, route of administration and treatment schedule. The risk-benefit spectrum of available DMT for multiple sclerosis 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.

Key words: Multiple sclerosis, patient preferences, disease-modifying therapies, rating-based experiment, conjoint analysis

Strengths and limitations of this study

. Little is known about the patients´ preferences for different attributes of multiple sclerosis drug therapy.

. This study included a sample of 221 patients with relapsing-remitting multiple sclerosis managed in 17 different MS Units at national level, which allows results to be generalised to community practice. A comprehensive battery of the most important DMT 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.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with genetic and environmental factors involved.[1] Relapsing-remitting multiple sclerosis (RRMS) is the most common clinical form of MS. The first-generation of disease modifying therapies (DMTs), beta-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 to 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 to 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 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 approved by the institutional review board of the Hospital Universitari Dr. Josep Trueta (Girona, Spain) and 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 criteria[11]), an Expanded Disability Status Scale[12] (EDSS) score from 1 to 6, and receiving a DMT for at least the last three months prior to inclusion. Written informed consent was obtained from all subjects. Investigators included the first twelve consecutive patients that 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 ten 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).

Socio-demographic 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 9-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 6-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.

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 scale score (1 to 3.0 and 3.5 to 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 ordinary least squares 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

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

$x_{ij} = 0$ 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) between by the sum of all individual importance scores. The relationship between socio-demographic 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 were explored according to socio-demographic 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 socio-demographic 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 tau 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 shown some differences according to the method used (average or relative importance). Considering 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 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 socio-demographic and clinical variables related with 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 less than one 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 MS patients in the decision-making process is key to select the treatment that best suits the patient´s profile and preferences. In our study, patients placed the greatest importance on 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 of MS patient DMT preferences were recently published.[12,13,19-28] Such studies evaluated different spectrums of drug attributes. In a sample of 651 patients from the US, a survey using five efficacy and safety drug attributes found that a delay in years to disability progression was the most important factor for treatment preferences.[19] Risk of progressive multifocal leukoencephalopathy 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*. performed studies in US 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, flu-like symptoms and infection-site reactions.[20,21] Both studies identified the number of years until MS symptoms get worse

as being the most important attribute, followed by flu-like symptoms, frequency of injections per month and number of relapses in the following years. A study performed by Wilson *et al.* 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 to 10) approach to derive utilities.[22] Prevention of disease progression, relapses and changes on MRI were assessed on 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 longer disease duration tend to prioritize the efficacy profile of DMTs may be indicative of a better understanding of the disease, not only from a theoretical but also from a practical point of view. Wilson *et al.* identified that treatment-naïve patients had no significant relative preference for preventing disease progression, which could be associated to a lower disease activity.[14] In addition, patients receiving the first-line DMTs such as beta-interferons or glatiramer acetate displayed more aversion to fatal risk than those receiving the high-efficacy 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] 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 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.* using a similar definition for the side effects attribute are aligned with our study.[22] In addition, it is important to consider the number of levels included in each attribute. A higher number of levels tend to be related with 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]

Despite these limitations, the study also has several strengths. The sample of 221 patients was managed in 17 different MS Units at 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 minimization, route of administration and treatment schedule. There is no evidence that decisions based on patient preferences are better than those based on 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]

Figure 1. Utility scores for each level of the attribute according to EDSS score

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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 ERB, DP and JM are employees of Roche Farma SA. MR and AC are employees of IMS Health. None of the other authors report any conflict of interest.

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 two days-weekly Monthly Twice per year

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 two 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 two 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

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 last 2 years	66 (46.2%)	34 (43.6%)	100 (45.2%)	0.714
	During the last year	32 (22.4%)	20 (25.6%)	52 (23.5%)	0.585

Table 4 Utility scores in MS patients

		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 two days-weekly	-0.527 (0.251)		
	Monthly	0.267 (0.206)		
	Twice per year	1.137 (0.251)		
(Constant)		5.875 (0.133)		

Table 5 Socio-demographic and clinical characteristics and individual importance assigned to each DMT attribute*

Socio-demographic 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 recognized		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	< 1 year			39.0 (14.4)	
	1-2 years			17.1 (14.7)	
	2-5 years			24.0 (16.0)	
	5-10 years			25.9 (16.7)	
	10-20 years			30.3 (15.7)	
	>20 years			21.8 (15.7)	
	p-value			0.001	
Greater number of relapses in the last 2 years	No relapses			28.4 (15.6)	23.8 (14.0)
	1 relapse			27.6 (16.7)	23.9 (15.7)
	2 o 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)

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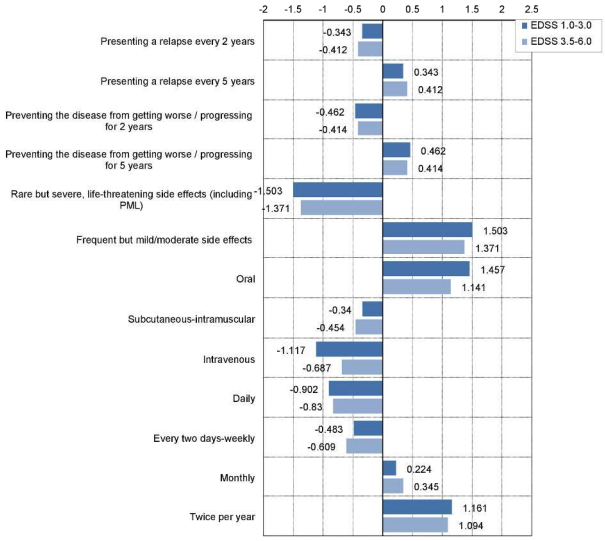

Figure 1. Utility scores for each level of the attribute according to EDSS score

209x297mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page 1)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 4)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 5)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 5)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 5)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants (Page 5)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Pages 5 and 6)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Pages 5 and 6)
Bias	9	Describe any efforts to address potential sources of bias (Page 6)
Study size	10	Explain how the study size was arrived at (Page 6)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy (Pages 6 and 7)
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page 7)
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 7 and Table 3)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures (Pages 7 and 8)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Pages 7 and 8; Tables 4 and 5)
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Not applicable)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Pages 8 and 9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 10)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Pages 10 and 11)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 10)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 12)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.