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ARTICLE

Multiple sclerosis risk perception and acceptance for Brazilian patients

Percepção e aceitação de risco em pacientes brasileiros com esclerose múltipla

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ABSTRACT

The perception of multiple sclerosis (MS) severity and risk associated with therapies might influence shared decision making in different countries. We investigated the perception of MS severity and factors associated with risk acceptance in Brazil in 96 patients with relapsing-remitting MS using a standardized questionnaire and compared this with two European cohorts. Multiple sclerosis was perceived as a very severe disease and the risk of developing progressive multifocal leukoencephalopathy due to natalizumab was seen as moderate to high. Seventy-six percent considered a risk of 1:1,000, or higher, an impediment for natalizumab use. Older age was the only variable associated with higher risk acceptance and our patients showed a more conservative profile than German and Spanish patients. Our patients perceived MS severity and progressive multifocal leukoencephalopathy risk similarly to elsewhere, but their willingness to take risks was more conservative. This should be considered when discussing therapeutic options and it might have an impact on guideline adaptations.

Keywords: multiple sclerosis; natalizumab; risk-taking; risk assessment, decision making.

RESUMO

A percepção de gravidade da esclerose múltipla (EM) e riscos associado a terapias podem influenciar a escolha de tratamento em diferentes países. Investigamos a percepção da gravidade da EM e fatores associados à aceitação de risco em 96 pacientes com EM remitente-recorrentecom um questionário e comparamos com duas coortes europeias. A EM foi percebida como muito grave e o risco de desenvolver leucoencefalopatia multifocal progressiva devido ao natalizumabe, como moderado a alto, sendo que76% consideraram um risco de 1: 1.000 ou maior como impeditivo deseu uso. Idade mais avançada foi a única variável associada àaceitação de risco mais elevado e nossos pacientes revelaram um perfil mais conservador do que os pacientes alemães e espanhóis. Esses dados devem ser considerados ao discutir opções terapêuticas e pode ter impacto nas adaptações de diretrizes locais.

Palavras-chave: esclerose múltipla; natalizumabe; assunção de riscos; medição de risco; tomada de decisões.

Multiple sclerosis (MS) is an inflammatory and demyelinating disease that typically manifests in young adulthood and is the major cause of disability and socio-economic burden in persons younger than 50 years of age in many countries[1,2]. Fortunately, new drugs are available and approved by regulatory agencies, which can reduce or even halt the damage caused by MS, including the long-used disease-modifying therapies (disease-modifying drugs: interferon beta and acetate glatiramer) and the recently-introduced natalizumab, fingolimod, teriflunomide, dimethyl-fumarate and alemtuzumab[3]. Nevertheless, these drugs have variable side effects and risk-benefit profiles that need to be suited to each patient's disease severity and even personal preferences[4].

Although many guidelines have been published suggesting how to choose the best first-line medication for each patient and how to monitor disease activity and drug switching[3,5,6,7],

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the shared decision-making process in MS is strongly influenced by an individual's risk perception, which is dynamic and influenced by the personal, emotional, social, and experiential factors of both the patient and the neurologist[8,9] and might differ from one culture to another. Indeed, it has already been demonstrated that the way a doctor communicates the treatment options for MS might influence the patient's decision[10].

The aim of this study was to investigate the perception of MS severity in a cohort of Brazilian patients and access their knowledge of the risks associated with natalizumab, a drug with a well-known risk-benefit profile[11], and their willingness associated with risk acceptance of a hypothetical drug risk profile, and compare the results with previously published studies performed with similar methodology in Germany[12] and Spain[13].

METHODS

We consecutively invited patients with relapsing-remitting MS to answer a standardized questionnaire, aiming to get their impressions on the severity of MS, the risks resulting from natalizumab treatment and the factors involved in risk acceptance and decision-making. The interviews took place during their regular clinical appointment, from January through October 2016 at two centers specialized in caring for people with MS – the Neuroimmunology Clinic at Universidade Federal de São Paulo and the Universidade Federal de Goiás. This study was modeled after the work by Tur et al.[13], in which the first author had participated, and upon previous contact and authorization from the lead author, with the intention of a cross-cultural comparison. The Ethics Committee of the Universidade Federal de São Paulo approved the study and the patients provided written informed consent to participate as part of an observational study on demyelinating diseases.

Prior to answering the questionnaire, all patients were given a handout containing information about MS and its natural clinical course, the drugs available in Brazil for treating MS and the label information for natalizumab, including efficacy (two-year benefits defined from Phase III trial results as a 68% reduction in clinical relapse rate, 42% slowing of disability, and 90% reduction in new brain lesions)[14]and the risk of developing progressive multifocal leukoencephalopathy (PML) as presented on the Brazilian label (102 cases from 2006 to 2011, with risk up to 8:1,000)[14]. The handout was given to all patients and caregivers who agreed to participate and they were allowed adequate time to read and discuss the information prior to answering the questionnaire.

Knowledge of the risk for developing PML under natalizumab use was evaluated by five multiple choice answers, ranging from 1:100,000 to 1:200; and these same choices were again offered as indicators that the potential PML risk patients considered high enough to stop natalizumab or make them unwilling to receive the drug. Assessment of the perception of MS severity was performed with a survey containing visual analog scale questions, whose possible values ranged from 0 to 10, as has been used previously[12]. Patients were asked to answer to what extent they judged MS to be a severe disease, where 0 = MS is not at all a severe disease, and 10 = MS is the most severe disease you can think of.

For the assessment of risk acceptance we presented the same five hypothetical therapeutic scenarios used by Tur et al.[13], to maintain the uniformity of the results for further comparison. Briefly, patients were asked to what extent they would like to be prescribed a given drug if the associated annualized risk of a serious secondary effect was 1:2,000,000 (very low risk), 1:600,000 (low risk), 1:5,000 (intermediate risk), 1:100 (high risk), and 1:50 (very high risk). Patients answered using a visual analog scale, the possible values of which ranged from 0 to 10 (0 = I would not like to receive this drug at all; 10 = I would like to receive this drug without any doubt).

To help patients understand the risks associated with each therapeutic scenario, we also presented five events totally unrelated to MS, the associated risks of which were similar to those of the hypothetical therapeutic scenarios: to die during an airplane flight (1:2,000,000); to win the lottery (1:600,000); to die in a car accident (1:5,000); to be diagnosed with epilepsy (1:100); and to be diagnosed with breast cancer (1:50, women's risk). Therefore, we obtained risk-acceptance scores (RAS) for each therapeutic scenario, with higher RAS indicating acceptance of higher risk. The number of years of formal education (years of schooling) was recorded by directly asking the patients, considering the first year of elementary school in Brazil (usually at six years old). Clinical and demographic data were retrieved from each patient's medical record by the attending neurologists and comprised age of onset, years of schooling, disease duration, history of disease modifying drug use and the expanded disability status scale(EDSS)[15].

Personality traits were evaluated with the NEO Five-Factor Inventory-Revised (NEO-FFI-R), validated for Brazilian Portuguese[16], by means of 60 questions (12 questions per personality trait), with scores ranging from 0 to 4. The NEO-FFI-R explores five personality traits: neuroticism, extroversion, openness, agreeableness, and responsibility. The analysis of this questionnaire was carried out by trained neuropsychologists (Elias I. and Mendonça A.).

Demographic and clinical data are presented as mean +/- standard deviation and n (percentages). Considering the lower prevalence of MS in Brazil, and the later availability of natalizumab (late 2011)[14], we did not divide the patients into groups by their use of or indication for natalizumab, and thus performed a general analysis of the whole cohort.

To evaluate if the five personality traits predicted different RAS, we used a multivariate general linear model (GLM). We evaluated each RAS independently and an additional item was created based on the last two questions, where we averaged the answers obtained for high-risk scenarios (1:100) and very high-risk scenarios (1:50), generating a variable called an ***averaged RAS***, which indicated the degree of acceptance of high

and very high treatment-associated risks, as conducted by Tur et al.[13]. For the multivariate GLM, we used the five original questions plus the averaged RAS as dependent variables predicted by the five personality traits as continuous covariates. Multivariate GLM was preferable as some of the six questions are strong to moderately correlated with each other, whereas separate linear regression would inflate false discovery rates.

In another multivariate GLM, we used the same six RAS measures as dependent measures predicted by sex, age, years of schooling, disease duration, EDSS score, and natalizumab use (yes/no). In both multivariate GLM (i.e., one investigating personality traits as dependent variables and the other socio-economic and clinical features on RAS), if one of the predictors was shown to be statistically significant via Pillai's trace (with an adopted level of significance at 0.05), we further proceeded to evaluate in which degree of the RAS it was a predictor. For the latter investigation, because there were six dependent variables, the level of significance was reduced to 0.05/6;in other words, in the last step of the GLM analysis, any of these five questions plus the averaged RAS could be proclaimed as significantly being predicted by the independent variables only if the pertinent p-value identified in the between-subjects test was less than 0.05/6 (i.e., lower than 0.0083)[17,18]. All analyses were performed with Graph Pad Prism version 7.0b and SPSS version 24.

Table 1. Sociodemographic and clinical data from the 96 participating patients.

Age (years, mean +/- SD)	39.3 (+/- 11.9)
Years of schooling (years, mean +/- SD)	12.6 (+/- 3.0)
Age at first relapse (years, mean +/-SD)	30.2 (+/- 10.5)
Disease duration (years, mean +/-SD)	9.1 (+/- 6.8)
Current treatment (n, %)	
Interferon Beta 1a IM	7 (7%)
Interferon Beta 1a SC	13 (13%)
Interferon Beta 1b SC	7 (7%)
Glatiramer acetate	20 (21%)
Fingolimod	29 (30%)
Fumarate	2 (2%)
Teriflunomide	4 (4%)
Natalizumab	12 (13%)
No treatment	2 (2%)
Duration of current treatment (years, mean +/-SD)	3.5 (+/- 3.4)
Number of previous treatments (n, %)*	
0 (only received current treatment)	32 (33%)
1	35 (36%)
2	21 (22%)
3	4 (4%)
4	3 (3%)
5	1 (1%)
Current or previous use of natalizumab (n, %)	20 (21%)
EDSS** at the moment of interview (mean +/- SD)	2.6 (+/- 1.5)
Progression index*** (mean +/- SD)	0.4 (+/- 0.4)

Data is presented as mean +/- standard deviation and n (%); *Previous treatments include: interferon-beta 1a IM, interferon-beta 1a SC, interferon-beta 1b SC, glatiramer acetate, fingolimod, teriflunomide, natalizumab, IV immunoglobulin, azathioprine, cyclophosphamide or mitoxantrone; **Progression index: current EDSS divided by total disease duration in years; ***EDSS: expanded disability status scale[15].

RESULTS

One hundred patients were invited and 96 answered the questionnaire, the latter patients being included in the final analysis (Table 1). All patients received at least one disease-modifying therapy for MS during their follow-up and 20 had used natalizumab (Table 1). In general, patients considered MS to be a severe disease and understood the risks associated with natalizumab; most patients considered the risk of developing PML as moderate to high, and 76% considered 1:1,000 a risk sufficient to impede its use (between 1:100,000 and 1:200) (Table 2).

There was no evidence that personality traits could predict any of the six RAS, as the p-values for the Pillai's trace were higher than 0.05 (Table 3).Given that the research question of interest was conceptualized as a multivariate one in

Table 2. Answer profile for the 96 patients.

Disease severity perception of MS (0 = MS is not at all a severe disease; 10 = MS is the most severe disease you can think of)	7.3 (+/- 2.4)
Knowledge of the risk for developing PML under natalizumab use	
1:100,000	14 (15%)
1:10,000	12 (13%)
1:1,000	37 (39%)
1:500	8 (8%)
1:200	25 (26%)
Putative progressive multifocal leukoencephalopathy risk patients considered high enough to stop or be unwilling to receive natalizumab	
1:100,000	10 (10%)
1:10,000	13 (14%)
1:1,000	27 (28%)
1:500	13 (14%)
1:200	33 (34%)
Opinion on the risk of developing PML under natalizumab use (VAS; 0 = very low risk, 10 = very high risk)	5.9 (+/- 2.9)
Impeditive risk for use of a theoretical drug (VAS; 0 = unlikely to accept, 10 = very likely to accept risk)	
1:2,000,000	5.5 (+/- 3.9)
1:600,000	5.4 (+/- 3.5)
1:5,000	4.4 (+/- 3.5)
1:100	3.0 (+/- 3.4)
1:50	2.5 (+/- 3.3)
Personality traits	
Neuroticism	50.5 (+/- 9.3)
Extroversion	48.1 (+/- 9.5)
Openness	44.8 (+/- 9.4)
Agreeableness	48.4 (+/- 8.7)
Responsibility	50.3 (+/- 7.4)

Answers are displayed as mean (+/- standard deviation) when answered in a visual analog scale (VAS) and n (%) when answered as multiple choices.

the first instance, and the lack of evidence that personality traits could influence the RAS, the univariate results (the between-subjects test) obtained in subsequent analyses were of no particular interest (i.e., evaluating which personality trait would predict the RAS in each separate question).

However, clinical and sociodemographic features evaluated by Pillai's trace showed age as statistically significant (Table 3). We then investigated in which RAS profiles age was a predictor for, and observed statistical significance for high RAS and the averaged RAS (high plus very high) (Table 3), indicating that the older the patient, the higher the scores for high risk ($\beta = 0.092$, p-value = 0.006) and for the averaged RAS ($\beta = 0.088$, p-value = 0.007), i.e., older patients tended to accept higher risks. When performing the model without the averaged RAS as an outcome, age was still significant for predicting the high risk of RAS ($\beta = 0.092$, p-value = 0.006).

The comparison between the answers profile for this population and two previously published cohorts with similar methodology[12,13], revealed that our patients perceive MS severity and the risks associated with natalizumab similarly, but their RAS is lower than for patients from these two European cohorts (Table 4 and the Figure).

DISCUSSION

This study revealed that Brazilian patients interviewed in two different centers perceived MS as a very severe disease and understood the risks associated with natalizumab, a drug with a well-known risk-benefit profile, but their willingness to take risks with a hypothetical drug was lower than patients interviewed in Germany and Spain[12,13] (Table 4 and Figure). Moreover, only age was significantly associated with RAS, with older patients willing to take higher risks.

Although the presence of high neuroticism scores in patients with MS have been associated with higher levels of anxiety and depression[19], and that individuals with MS presenting with higher neuroticism tend to be more concerned about their illness[20], none of the personality traits evaluated by the NEO-FFI-R predicted a RAS for this cohort. Clinical features, such as the EDSS, disease duration and the use of natalizumab also did not correlate with RAS, results similar to those previously reported in Spain[13], reflecting the complexity of the decision-making processes beyond the evaluation of clinical data only.

Table 3. Pillai's trace for personality traits, sociodemographic and clinical features and tests of between-subjects effects for age as a predictor for risk acceptance scores.

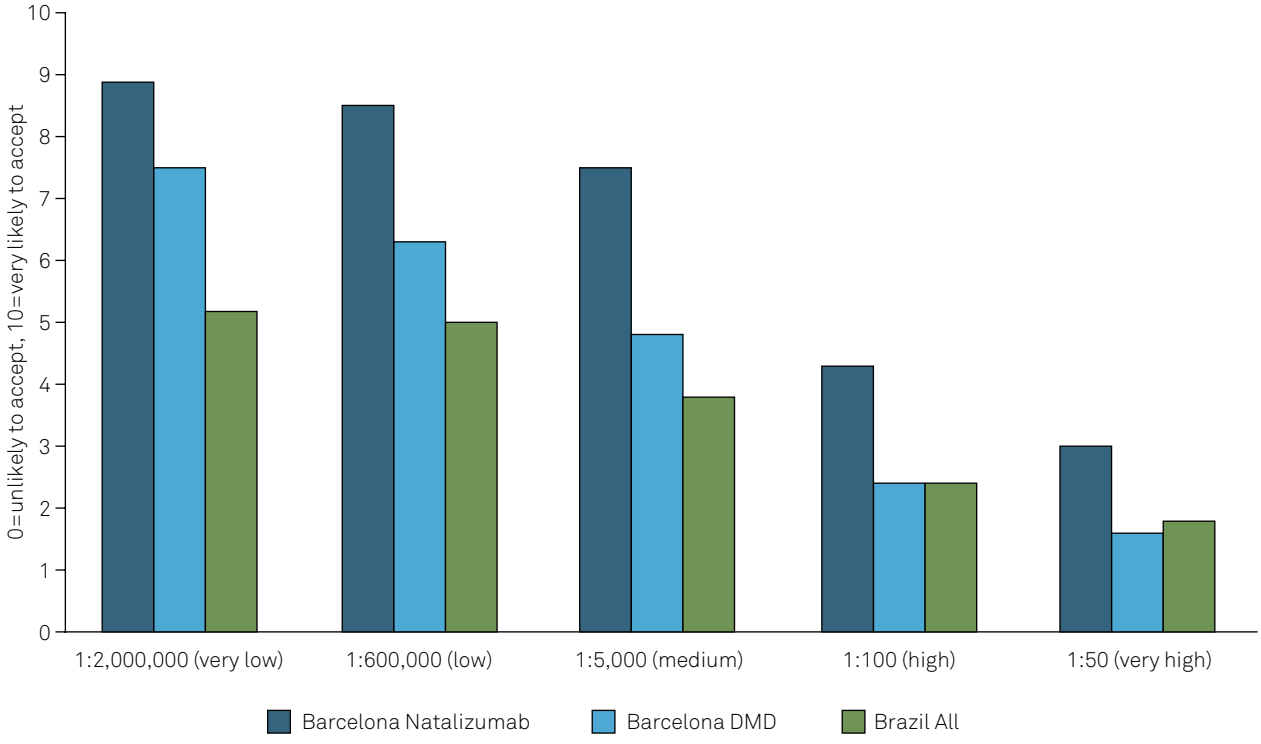
Personality traits						
Effect	Value	F	Hypothesis df	Error df		p-value
Neuroticism	0.009	0.159	5	86		0.977
Extroversion	0.029	0.51	5	86		0.768
Openness	0.053	0.96	5	86		0.447
Agreeableness	0.034	0.613	5	86		0.691
Responsibility	0.059	1.069	5	86		0.383
Sociodemographic and clinical features						
Effect	Value	F	Hypothesis df	Error df		p-value
Sex	0.077	1.425[b]	5	85		0.224
Natalizumab	0.099	1.863[b]	5	85		0.109
Disease duration	0.099	1.874[b]	5	85		0.107
EDSS	0.039	0.683[b]	5	85		0.638
Years of schooling	0.027	0.468[b]	5	85		0.799
Age	0.12	2.319[b]	5	85		0.05
Tests of between-subjects effects for age as a predictor for risk acceptance scores						
Source	Risk-acceptance scores	Type III sum of squares	df	Mean square	F	p-value
Age	Very low	232.656	1	232.656	1.942	0.167
	Low	229.368	1	229.368	1.971	0.164
	Medium	36.607	1	36.607	3.147	0.08
	High	84.794	1	84.794	7.871	0.006
	Very high	70.181	1	70.181	6.33	0.014
	Average High and very high	77.315	1	77.315	7.512	0.007

df: degrees of freedom.

Table 4. Attitude towards risk acceptance in populations with distinct cultural backgrounds.

Variable	Heesen 2010[12]	Tur 2013[13]	Tur 2013[13]	Bichuetti 2017 (present study)
	All	NTZ	DMD	All
Number of patients evaluated	69	114	22	96
Age (years, mean)	40	38	39	39
Disease duration (years, mean)	11	13	5	9
Previous or current natalizumab use (n, %)	69 (100%)	114 (84%)	22 (0%)	20 (21%)
Disease severity perception of MS*	8.5 (6.5-9.5) median (range)	7.0 +/- 2.0 mean +/- SD	7.6 +/- 1.8 mean +/- SD	7.3 (+/- 2.4) mean +/- SD
Attitude towards risk acceptance				
Natalizumab-associated PML risk**	4.5 (1.7-6.0)	NA	NA	5.9 (+/- 2.9)
Putative progressive multifocal leukoencephalopathy risk patients considered high enough to stop or not willing to receive natalizumab.				
1:100,000 (very low)	7%			-
1:5,000 (low)	10%			-
1:100 (high)	54%			-
1:10 (very high)	29%			-
1:100,000	-	NA	NA	10%
1:10,000	-			14%
1:1,000	-			28%
1:500	-			14%
1:200	-			34%
Impeditive risk for use of a theoretical drug***				
1:2,000,000 (very low)	NA	8.9 (+/- 1.9)	7.5 (+/- 2.3)	5.2 (+/-3.7)
1:600,000 (low)		8.5 (+/- 2.2)	6.3 (+/- 2.7)	5.0 (+/-3.3)
1:5,000 (medium)		7.5 (+/- 2.8)	4.8 (+/- 3.1)	3.8 (+/-2.7)
1:100 (high)		4.3 (+/- 3.5)	2.4 (+/- 2.0)	2.4 (+/-2.7)
1:50 (very high)		3.0 (+/- 3.4)	1.6 (+/- 1.8)	1.8 (+/-2.6)
1:100 + 1/50 (high and very high)		3.7 (3.4)	2.0 (+/- 1.9)	2.8 (+/- 3.3)

NTZ: patients who received natalizumab in the Barcelona cohort; DMD: patients who received first-line disease modifying therapies in the Barcelona cohort; NA: not available from published scientific report. VAS: visual analog scale; *0: MS is not at all a severe disease; 10: MS is the most severe disease you can think of; **VAS; 0: very low risk, 10: very high risk); ***VAS; 0: unlikely to accept, 10: very likely to accept



Barcelona Natalizumab: patients that received natalizumab in the Barcelona cohort; Barcelona DMD: patients who received first-line disease modifying therapies in the Barcelona cohort.

Figure. Impeditive risk for use of a theoretical drug in the Spanish and Brazilian cohorts.

The ability to take risks was not influenced by the years of schooling (Table 3); thus, we suppose that all patients interpreted the questionnaire equally, and the presence of variables not evaluated directly, such as religious beliefs, social class and access to private healthcare services, might influence the profile of risk acceptance in some patients. These and other unmeasured elements are possibly behind the fact that our patients also had a lower threshold for stopping or not being willing to receive natalizumab, compared to German patients[12].

Fox et al.[21] performed a large survey with patients from the North American Research Committee on Multiple Sclerosis Registry (5,446 participants) using an online standard gamble paradigm: cure MS with the risk of immediate painless death in sleep or the two-year benefits of the use of natalizumab defined in the Phase III trial results as a 68% reduction in clinical relapse rate, 42% slowing of disability, and 90% reduction in new brain lesions, but with a risk of PML[22].Although performed with a distinct methodology, this study revealed that three-quarters of the participants had a tolerance for risks lower than 1:1,000, i.e., many people with MS are risk averse and are not willing to take high risks for greater benefits. Distinct from this study and Tur's investigation[13],the North American Research Committee on Multiple Sclerosis Registry showed that patients with greater disability tolerated greater risks for a treatment that would either cure their MS or slow disease progression. However, it seems unclear whether this is a characteristic of North American patients or if this result is related to the study design and sample size.

The measurement of risk-acceptance behaviors may vary between cultures and, in a huge country like Brazil, this aspect needs to be taken into consideration, preventing us from generalizing the current results to the whole country, especially as two centers do not represent the whole Brazilian population. Our study was modeled after Tur's work[13], which is a little different from Heesen's study[12], restricting direct comparison of this cohort to the German patients. Furthermore, we evaluated a young patient population with a mean disease duration of only nine years, with low-to-moderate disability and with most of them having received only one or two disease modifying drugs. However, the opinion of patients with longer disease duration and greater disability could show more disease perception and risk-acceptance than presented here. One might say that older patients are at higher risk for cognitive impairment and, since this study was not designed to evaluate cognition, this could bias the results presented in Table 3. On the other hand, it is known that a higher EDSS score and disease duration are also related to cognitive impairment in MS[23,24], and these two variates were not associated with higher risk-taking behaviors, thus reassuring that an older age might, indeed, be an independent factor for risk-acceptance.

The positivity for the John Cunningham virus (JCV) was not used as a predictive variable in this study as we measured a hypothetical drug risk-benefit profile, and thus JCV positivity would not be related to this scenario. Furthermore, since we commonly test for the JCV only in patients using natalizumab – our only choice of a more aggressive treatment at the time this study was performed – the small number of participants who used natalizumab would preclude giving significant statistical results.

Most disease-modifying therapies are made available in Brazil many years after they are approved in the United States and the European Union. Thus, Brazilian doctors and patients need a few more years to get used to new medications. As examples, while natalizumab was approved worldwide in 2006, it was made available in Brazil only in late 2010 and fingolimod was made available in Brazil only in 2015 and to few patients due to restrictions in public access and reimbursement[14]. For these reasons, we have used cyclophosphamide and mitoxantrone for severe and breakthrough disease for longer periods than elsewhere, making many patients switch from natalizumab to other drugs very early and thus reducing its percentile of usage. The fact that this study was not designed to compare the effect of one drug versus another, as well as the variety of current treatments used by patients in this cohort, preclude us from making an adequate and reliable comparison of the use of each specific drug on the risk-taking behavior, which would be more adequately evaluated in a larger and specifically-designed study.

Considering the fast-changing scenario for treating MS, we conclude that knowing one's patients' risk-taking profiles is important for treatment discussion and shared decision-making[9], which may vary between different countries.

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