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Risk perception in natalizumab-treated multiple sclerosis patients and their neurologists

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Abstract

Background: Natalizumab is associated with the potentially life-threatening side-effect progressive multifocal leukoencephalopathy (PML). Little is known about patients' and physicians' risk estimates and attitudes towards natalizumab treatment.

Methods: Consecutive natalizumab-treated patients ($n = 69$) and neurologists ($n = 66$) in two centres and cooperating private practices received an evidence-based three-page information leaflet about natalizumab-associated PML and an evaluation sheet.

Results: After reading the information, patients were significantly more likely than physicians to intend continuation of natalizumab treatment and willing to accept higher risks of PML: 49% of physicians would stop treatment at a PML risk of 2 : 10,000 or lower, while only 17% of patients would do so ($p < 0.001$). This difference could not be explained by risk calculation abilities or lack of understanding. Both groups overestimated natalizumab treatment effects.

Conclusion: Patients had a significantly worse perception of multiple sclerosis as a malignant disease. We conclude that patients were willing to accept a higher risk of PML than neurologists. Coherent with their perception of risks and benefits, patients were also more willing to continue treatment. Open information about treatment-related risks is appreciated and might support shared decision making.

Keywords

multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy, risk perception, shared decision making

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Introduction

Multiple sclerosis (MS) is characterized by many uncertainties, ranging from diagnosis and prognosis to the value of immunomodulatory treatments.[1,2] Some studies have shown that these uncertainties can be communicated to patients without increasing worries and concerns.[3] Other studies have shown that physicians and patients might not agree about certain issues, for example values of bodily functions and role preferences, as well as the timing of information delivery.[4,5] While it has been demonstrated that patients with MS can be educated to manage risk calculations as, for example, relative and absolute risk reduction,[6] no comparative studies of patients' and physicians' views on benefit and risk perception of potentially risky medical treatments are available.

A shared decision-making approach has been suggested to be particularly important for those medical decisions were there is no single 'best' therapeutic option, especially in chronic conditions such as MS.[7] The goal of this approach is to enable patients to make

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decisions coherent with their values, rather then pushing towards selecting one particular treatment option.[7]

Natalizumab (Tysabri®), a humanized monoclonal antibody targeting the α4-integrin on leucocytes, has been approved for the treatment of patients with very active, treatment-naive relapsing-remitting MS or as an escalation strategy after failure of first-line therapy.[8,9] Although highly effective and viewed as superior to first-line agents, its use has been limited by the occurrence of progressive multifocal leukoencephalopathy (PML), a rare but severe opportunistic encephalitis caused by the ubiquitous JC virus.[10] During the last year there was a substantial increase in reports of PML in patients with MS undergoing natalizumab treatment with, as of May 2010, 49 cases, corresponding to a risk rate of approximately 1 : 1000 in patients treated for 2 years or more.[11] Therefore, experts have advocated an informed re-consent for patients on natalizumab after 2 years of treatment.[12]

Since natalizumab is a treatment where potentially high benefits go along with severe risks, a shared decision-making approach seems to be an ideal way to decide about the start or continuation of therapy. For this purpose, patients and physicians are required to have a good understanding of benefits and adverse effects to be expected from natalizumab. It has been shown that not only patients, but also physicians often have difficulties understanding probabilistic information about treatment effects.[13] Therefore, evidence-based patient information is considered as a prerequisite for proper decision making.[14,15] The process of shared decision-making based on evidence-based patient information can be called informed shared decision making.[3]

The goal of this study was to investigate prerequisites for informed shared decision making on natalizumab treatment. We assessed risk tolerance of patients with MS and treating physicians in relation to numerical skills, personal beliefs and perceived benefit of natalizumab.

Methods

Participants

All consecutive patients treated with natalizumab or patients within the decision process about natalizumab treatment between September and November 2009 were asked to participate at the university-based outpatient clinics in Hamburg ($n = 45$) and Regensburg ($n = 24$) (for demographic data see Table 1). Patients were asked to fill in the questionnaire in the MS clinic before natalizumab infusion ($n = 64$), or at their visit in the MS clinic while in the decision process to start natalizumab ($n = 5$). All patients agreed to participate. We included a Northern and a Southern German cohort to enhance generalizability of the findings. All neurologists from the Department of Neurology at the University Medical Center Regensburg ($n = 32$) as well as all neurologists in private practice or heading neurology departments in Hamburg ($n = 160$) were contacted to fill in the questionnaire. The response rate was $n = 26$ (81%) in Regensburg and $n = 40$ (25%) in Hamburg. This work is part of a larger project with different interventions on informed shared decision making in multiple sclerosis, approved by the Ethics Committee of the Hamburg Chamber of Physicians.

Table 1. Demographic data of patients with multiple sclerosis and physicians

MS patients				
	all ($n = 69$)	Regensburg ($n = 24$)	Hamburg ($n = 45$)	p
Age, y	40 (34–46)	42 (33–46)	38 (34–46)	0.605
Female/male	45/24	19/5	26/19	0.085
Disease duration, y	11 (6–17)	15 (10–19)	8 (5–15)	< 0.001
EDSS ($n = 56$)	4 (2.5–5)	4 (3–6)	3.5 (2.5–5)	0.410
Natalizumab infusions	23 (17–33)	31 (23–34)	20 (13–31)	0.002
Physicians				
	all ($n = 66$)	Regensburg ($n = 26$)	Hamburg ($n = 40$)	p
Age, y	40 (31.5–48.5)	33 (28–41)	45 (33–52)	0.003
Female/male	31/35	10/16	21/19	0.261
Working experience, y	11 (3.5–20)	8 (1–15)	16 (5–23)	0.017
MS expertise°	1 (1–2)	2 (1–2)	1 (1–2)	0.02

Data represent median values and interquartile ranges in brackets. For scale meaning see methods section. All p-values are based on Mann–Whitney U-tests, apart from sex comparisons, which were based on Chi-square tests. EDSS = Expanded Disability Status Scale; y = years.
° = refers to a 4-point Likert scale with 1 = low and 4 = high.

Information leaflet

A three-page leaflet was prepared explaining the current status of knowledge about natalizumab-associated PML as of August 2009. Participants were asked whether: (i) the information was relevant; (ii) they understood the leaflet; (iii) the information was familiar; (iv) the information was reassuring or threatening; and (v) the extent of the information was appropriate (see Supplementary Data File). Based on studies showing that physicians have similar difficulties in dealing with risks as patients, we used the same leaflet for both groups.[13]

Evaluation

Demographic data and disability status, measured by the Expanded Disability Status Scale,[16] were obtained. Physicians were asked about their years of clinical expertise. Self-estimated MS expertise was rated on a 4-point Likert scale with 1 indicating low and 4 indicating high expertise.

Participants were asked to calculate the risk of PML in natalizumab-treated patients based on four choices of rough estimates: 1 : 100,000, 2 : 10,000, 1 : 1000 and 5 : 1000. The actual known case number at the time of the survey initially was 15, later 23 of 60,000 treated patients, corresponding to a risk between 1 : 4000 and 1 : 3000. Given an estimated risk of lower than 1 in 1000 in October 2009, 'about 1 : 1000' and 'about 2 : 10,000' were accepted as the right answers. In addition, we assessed general risk calculation abilities with an index question from a risk questionnaire (item 9 from the Medical Data Interpretation test).[17]

To assess individual risk tolerance, participants were asked at which PML risk they would stop natalizumab treatment in themselves (patients) or in patients being under their care (physicians). Participants had to choose between risk rates of 1 : 100,000, 2 : 10,000, 1 : 100 and 1 : 10.

As moderating factors of risk perception, we assessed participants' perceived severity of MS on a visual analogue scale (VAS). For assessment of risk perception we used the format as suggested by Boeije and Janssens,[18] stressing expected wheelchair dependency as a highly relevant factor. To analyse perceived efficacy of natalizumab, participants had to estimate how many patients with and without natalizumab would be wheelchair-bound in 10 years and how many patients would not be able to walk more than 100 m. For each task, 11 choices were presented: <10, 10, 20... up to 100 of 100 treated patients. In the same format, participants were asked about results of natalizumab studies regarding the number of patients being progression-free through 2 years of treatment.

Statistical analysis

Median results and interquartile ranges were calculated. Nonparametric tests comparing patients' and physicians' answering patterns were performed using the Mann–Whitney *U*-test. Correlations were obtained using Spearman's correlation coefficient rho. Sex and risk calculation abilities were compared using chi-square tests.

Results

Perception of MS and of the benefits and risks of natalizumab

Patients perceived MS to be more malignant than did physicians (Table 2), and perceived natalizumab to be more effective than did physicians on some dimensions,

Table 2. Perception of multiple sclerosis disease course and of the benefits of natalizumab

	Patients	Physicians	*p*
MS as malignant disease (VAS)*	8.5 (6.5–9.5)	6.5 (5.7–8.2)	<0.001
1-year risk of walking distance <100 m°			
without natalizumab	40% (20–50)	10% (0–30)	<0.001
with natalizumab	10% (<10–30)	<10% (<10–20)	0.062
10-year risk of becoming wheelchair-bound°			
without natalizumab	40% (20–60)	30% (20–40)	0.081
with natalizumab	10% (<10–30)	10% (<10–20)	0.956
Patients without progression after 2 years treatment with natalizumab°	50% (30–70)	50% (30–70)	0.931
General natalizumab-associated PML risk (VAS)*	4.5 (1.7–6.0)	3.1 (1.8–5.0)	0.195
Continue natalizumab treatment (VAS)*	9.0 (5.1–9.5)	6.1 (3.7–7.5)	<0.001

Data represent median values and interquartile ranges in brackets.
*Visual analogue scale (VAS) range 0–10 with 10 representing high malignancy, high risk, high willingness to continue treatment. °percentage estimates as: <0, 10, 20, 30, 40,...up to 100. All *p*-values are based on Mann–Whitney *U*-tests.

but not others. On average, patients thought that natalizumab reduces the risk of getting a maximum walking distance below 100 m from 40% to 10%. Physicians gave much lower estimates of a reduction (from 10% to <10%). Less-pronounced differences were shown for estimations of benefits of natalizumab in reducing the risk of being wheelchair-bound within the next 10 years: patients estimated the effects of reducing the risk from 40% to 10%, and physicians from 30% to 10%. In contrast, both patients and physicians assumed that the pivotal studies showed 50% of patients being progression-free due to natalizumab in a period of 2 years.

General PML risk was perceived moderate on a VAS with no significant difference between patients and physicians. However, subjective perceived risk of patients was considerably lower than the attributed risk in general (2.7 vs. 4.5 on a VAS, $p < 0.001$).

Risk behaviour attitude

Patients would accept higher risks of PML than physicians ($p < 0.001$). While 49% of physicians would stop treatment at an event rate of 2 : 10,000 or lower, only 17% of patients would do so (Figure 1). Some 48% of physicians and 54% of patients would stop at an event rate of 1 : 100, while 29% of patients but only 3% of physicians would accept higher risks.

Importantly, these effects cannot be explained by a substantially lower risk understanding of patients. We found significant differences between patients and physicians in the general (92% vs. 76%, $p = 0.01$) and PML-specific (95% vs. 79%, $p = 0.005$) risk calculation tasks. However, there was no difference in the acceptable risk of PML between patients who answered the general risk calculation question or the PML risk estimate correctly or not ($p = 0.807$ and $p = 0.341$, respectively). Also, perception of MS was uncorrelated with the acceptable risk of PML among patients (rho = −0.15, $p = 0.216$) and physicians (rho = −0.02, $p = 0.889$). Finally, the perception of the efficacy of natalizumab with regard to reducing the risk of limiting the walking distance or the risk of getting wheelchair-bound was uncorrelated with the acceptable risk of PML (rho = 0.08, $p = 0.337$ and rho = 0.13, $p = 0.153$, respectively), which identically held true when looking at patients and physicians separately. Treatment status had no influence, as five patients not yet treated showed the same risk tolerance pattern as those already on treatment.

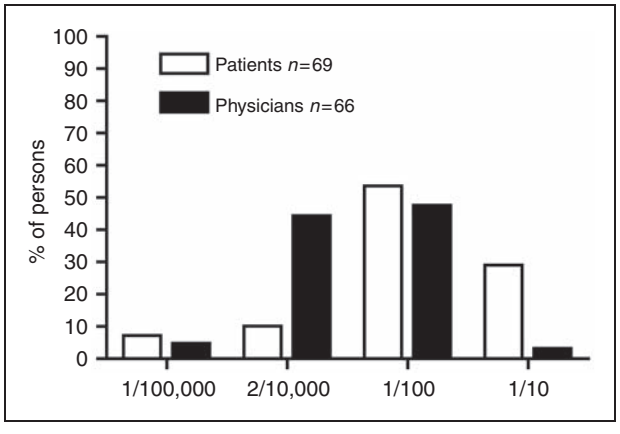

Figure 1. Putative progressive multifocal leukoencephalopathy risk making patients and physicians stop natalizumab.

In total, patients' willingness to continue treatment as measured by a VAS was significantly higher than that of physicians (9.0 vs. 6.1 on a VAS, $p < 0.001$) (Table 2). Patients were more likely to intend continuing treatment if they perceived the general or personal risk of PML as low (rho = −0.55, $p < 0.001$ and rho = −0.70, $p < 0.001$, respectively), their personal benefit of natalizumab as high (rho = 0.51, $p < 0.001$), thought a higher risk of PML to be acceptable (rho = 0.38, $p = 0.001$), or the estimated benefit of natalizumab to reduce the risk of becoming wheelchair-bound as high (rho = 0.35, $p = 0.004$).

Discussion

In this study, we evaluated risk calculation abilities and attitude towards natalizumab in patients with MS and neurologists after reading an evidence-based information leaflet about natalizumab-associated PML.

Patients' estimates of treatment effects and side-effects did not differ much from those of physicians, although patients perceived the specific risk reduction with regard to preventing a limited walking distance as higher. Both patients and physicians overestimated the benefit of natalizumab in treatment trials. While both thought that 50% were progression-free due to natalizumab over a 2-year treatment trial period, the AFFIRM study showed that this number was only 12%.[8] As a limitation, we did not ask for effects on relapse rates, which – particularly for patients – might be easier to use as surrogates of treatment effects.

Natalizumab-treated patients accepted higher risks than physicians, independent of their ability to deal with risk information in general. None of the variables assessing perception of the general benefit of natalizumab or the view on the severity of their disease were related to the risk they would accept. Instead, the difference between patients and physicians in the willingness to accept higher levels of risks was genuine. While more than 80% of natalizumab-treated patients would accept PML risks higher than 2 : 10,000, nearly 50% of neurologists would stop treatment at this event rate. This is congruent with evidence that patients may be

willing to accept higher risks in exchange for therapeutic benefits.[19]

Patients performed slightly worse in calculating risks than physicians. However, this ability was not related to the intention to continue therapy. Instead, decisions about whether to continue treatment or not were dependent on patients' individual preferences. Coherent with their higher acceptance of PML risk, patients were more strongly in favour of continuing natalizumab even in light of the new risks, while physicians showed more ambivalence, although the overall risk perception of getting PML was the same in physicians and patients.

Decisions are commonly evaluated as good if they are internally consistent with risk perception, values and preferences, and based on a realistic estimate of risks and harms,[20] which was the case in our patients.

This study has some limitations. First, our sample with 69 patients was small. Since we included all consecutive patients being treated with natalizumab at two different medical centres, we still believe that our data represent the population of patients with MS well. Second, the physician cohort in Hamburg is likely to be biased as the response rate was low. Assuming that neurologists in practice with an interest in MS would have been more prone to reply, the overall critical attitude towards the PML risk might even be higher in a representative cohort.

Recently, Hauser and Johnston pointed out that physicians are biased in decision making by the recall of a recent case or experience – for example an adverse outcome – which can bias physicians and unduly influence subsequent decision making and risk presentation.[21] Stopping the drug at an event rate of 2 : 10,000, as 49% of the neurologist in our survey suggested, might not be adequately tailored to patients' needs, given their high disease activity prior to natalizumab therapy.

Taken together, our data indicate that MS patients see their disease as more malignant than neurologists and are willing to take higher risks. However, patients and physicians considerably overestimated treatment benefits, emphasizing the need of understandable, evidence-based information. Physicians, pharmaceutical companies and health regulatory agencies should not be worried that patients with MS are not able to bear up-to-date balanced and open information, assuming that that benefits and harms are communicated transparently.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

Competing Interests

Dr. Heesen reports study grants from Merck-Serono and travel and educational grants from Biogen-Idec, Teva-Sanofi-Aventis, and Bayer-Schering. Dr. Kleiter reports study grants from Merck-Serono and travel and educational grants from Biogen Idec, Teva-Sanofi-Aventis, Merck-Serono, and Bayer-Schering. Drs. Nguyen, Schäffler, Kasper, Köpke, and Gaissmaier report no disclosures.

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