Benefit–risk perception of natalizumab therapy in neurologists and a large cohort of multiple sclerosis patients

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Abstract

Background: Natalizumab (NAT) is associated with the risk of progressive multifocal leukoencephalopathy (PML). Risk stratification algorithms have been developed, however, without detectable reduction of PML incidence. Objective: To evaluate to which extent patients and physicians understand and accept risks associated with NAT treatment. Methods: Prospective observational cohort study in German MS centers (n = 73) among NAT-treated MS patients (n = 801) and their neurologists (n = 99). Patients included in this study had mean disease duration of 10.2 years and a mean NAT treatment duration of 24 months. Results: More than 90% of patients and physicians voted for shared decision making or an informed choice decision making approach. Patients and physicians perceived a similar threat from MS as serious disease and both overestimated treatment benefits from NAT based on trial data. Men perceived MS more severe than women and perception of seriousness increased with age in both groups and in patients as well with increasing disability. Although patients evaluated their PML risk higher, their risk acceptance was significantly higher than of their neurologists. Risk stratification knowledge was good among neurologists and significantly lower among patients. Conclusion: While patients and physicians seem to have realistic risk perception of PML and knowledge of risk stratification concepts, the threat of MS and the perception of treatment benefits may explain the ongoing high acceptance of PML risk.

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1 Introduction

Natalizumab (NAT) is one of the most effective immunotherapies for relapsing-remitting multiple sclerosis (RRMS). In the pivotal trial AFFIRM, NAT increased the number of relapse-free patients by 26% and the number of patients free from progression by 12% compared to placebo after two years (absolute risk reductions) [1].

While NAT is generally well tolerated, patients treated with NAT have an increased risk of progressive multifocal leukoencephalopathy (PML) when positive for John Cunningham virus (JCV). Based on 638 cases in 152,000 treated RRMS patients, PML risk is currently estimated at 4.15/1000 [2]. Factors associated with PML risk include (I) prior therapy with immunosuppressants, (II) duration of NAT therapy > 2 years, and (III) positive serostatus for anti-JCV antibodies (JCV-ab) [3–5]. A three-stage algorithm enables PML risk stratification for individual patients [5]. In addition it has been shown that the level of JCV-ab might be a further risk factor for development of PML [6]. Of 372 PML cases, 8% were asymptomatic at diagnosis, and 76% survived with disability [9,10]. There is an ongoing discussion if the risk stratification algorithm really helps to reduce PML incidence and a lack of understanding among neurologists has been discussed as reason [11]. In fact the cumulative risk of PML beyond month 24 has doubled since 2012 (3.85, now 6.36 in 1000). NAT continuation is complicated by a relevant rebound of disease activity after NAT withdrawal [7,8].

Shared informed decision-making has been shown to be the patient-preferred decision-making approach in MS [12–14]. An adequate level of knowledge about the efficacy of NAT and the magnitude of PML risk...
in the individual situation are important prerequisites enabling neurologists and patients to make informed decisions on the initiation or continuation of NAT therapy. Apart from a divergence of risk knowledge, there is also a divergence of risk perception in patients and neurologists, which may interfere with the process of shared decision-making [15]. Physicians might have an incomplete understanding of patient preferences and values which is also the case in MS [16]. A previous study, performed soon after reintroduction of NAT, showed that MS patients receiving NAT are willing to accept higher risks than their treating neurologists, and that this discrepancy was not due to a misconception of actual risks [17].

The present study aimed to reassess previous findings in a larger cohort and to examine the following topics among NAT-treated patients and their physicians: autonomy preferences regarding treatment decisions, perception of severity of MS and of PML risk, perception of efficacy of NAT, knowledge about results of pivotal NAT trials, knowledge about PML risk stratification, and PML risk tolerance.

PERCEPTION of risk in patients and physicians on NAT (PERCEPT) was a multicenter cohort study from a standard clinical care setting. CONSIDERing NAT benefits and risks (CONSIDER) was an investigator-initiated complementary study to get a more detailed insight on patients' knowledge and attitude. This paper reports on cross-sectional data from both studies.

2. Patients and methods

2.1. Study design

PERCEPT, a prospective, multicenter, non-interventional observational study, was conducted in German clinics and private practices experienced in MS treatment. Study visits were performed at baseline and 1, 2, 6 and 12 months after baseline. CONSIDER, an investigator-initiated complementary study in patients participating in PERCEPT, assessed NAT efficacy and knowledge about side effects in more detail. Data were obtained at baseline and 1 and 12 months after baseline. Both studies were initiated in November 2011, last patient's last visit was in August 2014.

2.2. Participants

Participants were neurologists and NAT-treated RRMS patients. Participating MS centers were recruited through the German wide network of account managers of Biogen Idec. Neurologists were asked to include all consecutive patients already treated with NAT or in whom NTZ therapy is planned. Inclusion criteria for patients were: age ≥ 18 years, diagnosis of RRMS, and treatment with NAT within the licensed indication in Germany [18].

2.3. Demographic and disease-related data

Patients were asked for their age, gender, year of first symptoms, year of diagnosis, previous MS therapies/immunosuppressive therapy, relapses in the year before inclusion/the year before starting NAT, date of starting NAT, JCV-ab status, adverse events-serious adverse events. The latter were reported according to applicable regulations of German drug authorities. Patients were asked for their reasons to start NAT and to evaluate their status of health and quality of life. To quantify disability the Expanded-Disability-Status-Scale score (EDSS) [19] was obtained. Symbol-Digit-Modalities-Testing [20] was included as an optional measure. Physicians were asked for their age, gender, work place, self-rated MS expertise (from excellent to limited, 4-point Likert scale), and reasons for starting or stopping NAT.

2.4. Questionnaires

All questionnaires (see Appendix A) were answered by patients and physicians.

2.4.1. Autonomy preferences

Participants were asked for their autonomy preferences in a medical encounter, for general medical issues and for decisions regarding NAT therapy [21,22]. Physicians were asked for situations in which they were patients themselves.

2.4.2. Knowledge on NAT study results

The knowledge on AFFIRM study results [1] was tested. Participants were asked for the chance to stay progression free for a 2-years-interval without therapy (placebo arm) and during NAT therapy. Percentiles from 0 to 100 from 100 patients were presented for choice. In addition participants in the CONSIDER subgroup were asked about their perceived beneficial effect of NAT. These questions were presented separately from the risk tolerance questions.

2.4.3. Evaluation of MS

Participants were asked to rate the severity of MS as a disease in general on a visual analogue scale (VAS; 1 = ‘benign’, 25 = ‘severe’). Physicians were additionally asked to evaluate the severity of MS in the individual NAT-treated patient. Patients were asked to assess impact of wheelchair dependency.

2.4.4. PML knowledge

Seven multiple choice questions on PML risk factors were presented to participants. A mean knowledge score was calculated based on the number of correct answers ranging from 0 to 7 points.

2.4.5. PML risk tolerance and perception

Participants were asked for a theoretical risk at which they would stop NAT treatment [17]. Risk rates of 0.1–500 in 1000 were presented. As a plausibility check they were also asked at which risk they would just tolerate the PML risk. Participants were asked for their assessment of PML risk in general on a VAS (1 = ‘low’, 25 = ‘high’). In addition patients were asked for their perceived personal risk.

2.4.6. JCV-ab testing

Participants were asked if they think that JCV-ab testing is helpful or not (1 = definitely useful, 2 = somehow useful, 3 = less useful, 4 = not at all useful, 4-point Likert scale).

2.5. Ethical approval

PERCEPT and CONSIDER were approved by the ethics committee of the Hamburg Chamber of Physicians (PV3983 10.4.2012, PV3955 5.1.2012) and the local ethical committees of the participating centers. All participants gave written informed consent.

2.6. Statistical analysis

Categorical variables were compared using chi-squared tests. Ordinal variables were compared using Mann-Whitney U tests (between subjects) and Wilcoxon U tests (within subjects). Interval scaled variables were compared using t-tests. Bivariate relations were assessed as Pearson correlations. Multivariate predictions were conducted using multiple regression models, and we report standardized coefficients.
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