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Discontinuation of disease modifying treatments in middle aged multiple sclerosis patients. First line drugs vs natalizumab☆

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ABSTRACT

Background: Several disease-modifying drugs (DMD) are available for the treatment of MS, and most patients with relapsing-remitting disease are currently treated. Data on when and how DMD treatment can be safely discontinued are scarce.

Methods: Fifteen MS patients, treated with natalizumab for > 5 years without clinical and radiological signs of inflammatory disease activity, suspended treatment and were monitored with MRI examinations and clinical follow-up to determine recurrence of disease activity. This group was compared with a retrospectively analysed cohort comprising 55 MS patients treated with first-line DMDs discontinuing therapy in the time period of 1998–2015 after an analogous stable course.

Results: Natalizumab discontinuers were followed for on average 19 months, and follow-up data for 56 months were available for first-line DMD quitters. Two-thirds of natalizumab treated patients experienced recurrent inflammatory disease activity, and one third had recurrence of rebound character. In contrast, 35% of first-line DMD quitters had mild recurrent disease activity, and no one exhibited rebound.

Conclusions: Withdrawal of a first-line DMD after prolonged treatment in middle-aged MS patients with stable disease appears to be relatively safe, while natalizumab withdrawal in a similar group of patients cannot be safely done without starting alternative therapy.

1. Introduction

During the last two decades several disease modifying drugs (DMD) have become available for multiple sclerosis, and today most patients with relapsing remitting MS (RRMS) receive treatment. Considerable effort has been put into proving the efficacy of these drugs, less so whether and when it is time to stop treatment. Treatment discontinuation is discussed in later years [1], but with some exceptions little is known about the consequences of withdrawing treatment and its practice has been labelled “increasingly tricky” [2]. Natural history shows that inflammation tends to diminish with age [3]. Consequently, most patients will reach a point when DMD treatment is no longer beneficent.

Despite that first line DMDs, such as interferons, were introduced two decades ago, surprisingly little is known about potential risks of stopping treatment and disease course after withdrawal. Disease activity returned promptly in a cohort of patients treated with interferons for 25 months [4]. The cohort comprised mainly younger patients with high levels of pre-treatment inflammatory activity and a fairly short treatment period. In one recent large register study, containing patients with a longer duration of treatment and stable disease course, recurrent inflammation was not observed to the same degree [5].

The α4 integrin blocking agent, natalizumab (NTZ) is an effective suppressor of CNS inflammation and a potent DMD for RRMS [6,7]. On the downside, long-term NTZ treatment is associated with a risk for progressive multifocal leukoencephalopathy (PML). When this problem was first encountered [8], NTZ treatment was halted globally in February 2005. Patients from the pivotal trials of NTZ, with an average treatment time of 28 months, were prospectively followed after the treatment suspension. Return of disease activity, (relapse or its surrogate marker contrast enhancing lesion on MRI) ensued in many patients, mainly within 4–7 months [9]. This reactivation was independent of NTZ exposure time and occurred irrespective of whether

☆ During the publication procedure of this paper a similar study has been published, where 221 RRMS patients discontinued first-line DMT after at least 12 months of treatment and at least 2 years of follow-up [36]. Patients older than 45 years, with treatment more than four years without evidence of clinical or radiological disease activity, had a high likelihood of remaining relapse-free after DMT discontinuation, thus in accordance with our conclusion concerning first-line DMT.

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another treatment was commenced. A similar risk was observed in the RESTORE study, where patients were randomized to stop or continue NTZ therapy, but again after relatively short treatment duration [10].

From a theoretical vantage point it is conceivable that suspension of NTZ treatment could lead to rebound activity, which was also suggested by some early studies [11,12]. This supposition was emphatically rejected in the report by O'Connor et al. [9] The definition of rebound activity is not unproblematic however, and the analysis made was restricted to the group level, potentially masking unfavourable consequences for individual patients. Later investigators could demonstrate rebound activity with severe relapses in 10–30% of patients [13,14].

Such reports describe relatively young patients with short treatment duration. In a real-life clinical setting stopping DMD treatment is most likely to be attempted in older patients treated for a longer time, thereby expected to remain relatively stable. One purpose of the present study was to prospectively investigate whether NTZ could be safely discontinued in predominantly older patients treated with NTZ without signs of inflammatory activity for at least 5 years. Additionally, we compared the outcome with a retrospectively analysed cohort of patients who stopped first line DMDs after a similar period of stability.

2. Patients and methods

2.1. Natalizumab prospective study

RRMS and progressive relapsing MS (PRMS) patients treated with NTZ for at least 5 years without signs of inflammatory disease activity were eligible for the study. During treatment, inflammatory disease activity was evaluated by biannual clinical follow-up including Expanded Disability Status Scale (EDSS) grading and annual MRI brain scan. Patients were invited to participate at a routine follow-up visit and gave informed consent.

According to protocol clinical evaluation with EDSS grading and MRI was scheduled at the last infusion of NTZ, and at 3, 6, and 10 months afterwards. After this, patients were followed according to what was considered appropriate to their individual situation. Patients were instructed to contact the clinic without delay if symptoms indicating a relapse would occur, whereby an extra visit was made and an extra MRI was obtained.

MRI of the brain and the spinal cord was performed at 3 T. All T1-weighted sequences were performed after intravenous injection of the gadolinium-based contrast agent (GBCA), gadobutrol (Gadovist®, Bayer Schering Pharma, Berlin-Wedding, Germany), at a dose of 0.1 mmol/kg body weight (see Appendix for technical details). GBCA enhancing and new non-enhancing T2 lesions were counted separately by an experienced neuroradiologist. For assessment of radiological rebound activity, the volume of contrast enhancing lesions was visually compared to that in every previous MRI.

Primary endpoint was clinical relapse or GBCA enhancing lesions on MRI. A clinical relapse was defined as an acute worsening of neurological function lasting ≥24 h not attributable to an external cause such as increased body temperature or acute infection. Secondary endpoints were EDSS change at 10 months of follow-up, number of new or enlarging T2 lesions on MRI scans and number of patients with rebound activity. Rebound activity was defined as a relapse with a larger EDSS increase or a larger volume of GBCA enhancing lesions on an MRI scan than ever seen in this individual.

2.2. First-line DMD retrospective study

The Swedish MS Register (http://www.msreg.net) was established in 2001 and is partly funded by the Swedish National Board of Health and Welfare. The coverage of Uppsala County is >90% of the estimated prevalence. All patients from Uppsala County in the register were scrutinized to identify those that for any reason had stopped treatment with first line DMDs, i.e. interferons, glatiramer acetate, and intravenous immunoglobulin. Treatment with intravenous immunoglobulins was used as an alternative for patients not tolerating the side effects of interferons and glatiramer acetate.

Table 1
Reasons for discontinuation of first-line DMD treatment 1998–2015.

Treatment failure	40
Conversion to SPMS	47
SPMS before start of treatment	31
Other	10
(Patient's own decision; side effects, pregnancy)	
RRMS, clinically stable disease	55

Totally 183 patients stopped such treatment 1998–2015. Table 1 summarizes the reasons for discontinuation; 55 patients (interferons, n=42; glatiramer acetate, n=9; intravenous immunoglobulin; n=4) discontinued treatment due to stable disease, i.e. freedom from relapse or progression for five years (MRI was not performed regularly in these patients). These constitute the study cohort. Patient records were scrutinized to check the veracity of the register data. Then, data regarding gender, age, disease duration, treatment type, treatment duration, follow-up time, relapses, and EDSS scores were collected. Furthermore, conversion to secondary progressive MS, SPMS, was assessed. Patients were considered to have entered a progressive phase if their EDSS score increased by ≥1 step, confirmed after 6 months, in the absence of relapses.

2.3. Statistical assessment

Due to the unequal size of the two cohorts, statistical comparison was made with restriction. Some outcome differences are obvious; unpaired Student's t-test, chi-square test, and the Mann-Whitney test were applied when p-values were considered of importance.

3. Results

3.1. Natalizumab prospective study

3.1.1. Patient characteristics

Fifteen patients (13 RRMS, two PRMS), out of a pre-planned twenty, were included. Their characteristics are summarized in Table 2. When the first relapses (see below) were encountered, further recruitment was halted for ethical reasons. Treatments before NTZ were interferon-β (n=8), glatiramer acetate (n=2), intravenous immunoglobulin (n=2), and mitoxantrone (n=2). Eleven patients tested positive for JC virus antibodies, seven of these with index value above 1.5, associated with an increased risk for PML [15]. Median follow-up time was 19 months.

Table 2
Baseline clinical data.

	NTZ	First line-DMD	p-Value
N	15	55	
Female/male	10/5	38/17	
Median age at treatment start (range)	42 (26–65)	37 (18–62)	
Median age at treatment stop (range)	50 (32–72)	42 (25–68)	0.15
Mean disease duration at treatment stop	16	11	
Mean ARR in year prior to start (SD)	2.3 (±1.2)	1.7 (±0.9)	0.016
Mean treatment time (months)	68	68	