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# Natalizumab discontinuation in a Dutch real-world cohort

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ABSTRACT

*Objective:* To determine characteristics of multiple sclerosis patients that discontinued natalizumab treatment in a real-world cohort.

*Methods:* Data was collected from an ongoing observational cohort study of all natalizumab treated patients at the Amsterdam UMC.

*Results:* Of 253 patients who ever received natalizumab treatment, 147 have discontinued treatment. The most frequent reason for treatment discontinuation was JC-virus (JCV) positivity.

*Conclusions:* JCV positivity seems the most frequent reason for natalizumab discontinuation. The heterogeneity in treatment switches reflects the advances made in treatment options, and underlines the need for adequate patient counselling.

## 1. Introduction

Natalizumab has become one of the most widely used high-efficacy treatment options in patients with relapsing-remitting multiple sclerosis (RRMS). Identifying characteristics of patients discontinuing natalizumab treatment and reasons for discontinuation could help improve clinical decision making regarding the initiation of specific high-efficacy therapies in RRMS. Recently two large retrospective studies were published identifying reasons for natalizumab treatment discontinuation. (Conway et al., 2020); (Bigaut et al., 2020) Conway et al. suggested environmental factors such as smoking to be associated with shorter treatment duration with natalizumab. They only briefly mentioned the risk of progressive multifocal leukoencephalopathy (PML). (Conway et al., 2020) Bigaut et al. suggested JC-virus (JCV) positivity to be an important reason for treatment discontinuation in a large cohort of French patients. (Bigaut et al., 2020) Since the availability and indications of natalizumab treatment differ between countries and national guidelines vary, we here report our large MS Center Amsterdam patient cohort treated with natalizumab.

## 2. Methods

We collected data from an ongoing observational cohort study that includes all natalizumab treated patients at the MS Center Amsterdam. Individuals still using natalizumab on the closure date of data collection (9$^{th}$ of April 2020) were excluded from further analysis. We collected standard clinical descriptives, including the Extended Disability Status Scale (EDSS), total number of natalizumab infusions, reason for discontinuation and to which type of disease modifying therapy (DMT) the patient switched after natalizumab discontinuation. We also registered if a second treatment switch was done afterwards, and if so, to which treatment the patient switched. In addition, we collected JCV status and if JCV seroconversion occurred during natalizumab treatment. Furthermore, we collected MRI data from date of discontinuation of natalizumab to two years after. We analysed this data for disease activity, which we defined as more than one new T2 lesion or one or more gadolinium enhanced lesion(s) during the two years follow-up. If more than one reason for discontinuation was presented, the decisive reason was assigned as the reason of discontinuation. Pregnancy was counted as reason of discontinuation if a patient stopped natalizumab due to pregnancy and decided not to resume treatment afterwards. If patients did resume treatment afterwards, they were not counted as having discontinued treatment. Patients were classified as restarting natalizumab treatment if they discontinued natalizumab for more than six months before restarting (except in the case of pregnancy).

## 3. Results

### 3.1. Patient and treatment characteristics

253 patients were identified as having ever used natalizumab, of whom 147 patients discontinued treatment. Characteristics of patients that discontinued treatment are summarized in Table 1. Mean age at discontinuation of natalizumab was 39.8 years (supplementary table 1), and 66.4% was female. Patients received an average of 68 infusions. The majority of patients (103 (70.1%)) stopped natalizumab treatment because of the perceived risk of PML, due to JCV positivity. 5 patients (3.4%) discontinued because they developed PML. 8 patients (5.4%) discontinued due to disease progression, 3 (2.0%) due to pregnancy, 12 (8.2%) due to an allergic reaction or antibodies, 2 (1.4%) due to side effects, 4 (2.7%) due to the patients preference for another therapy, 3 (2.0%) due to clinical stabilisation, and the remaining 7 patients (4.8%) due to other, or unknown, reasons (see also supplementary table 2 and 3)Treatment switches are summarized in Fig. 1. Most patients (85.7%) switched to another treatment after natalizumab discontinuation. A documented second treatment switch was made in 52 patients (35.4%). Of the 14 patients who stopped DMT during their first treatment switch and 8 who remained as such after natalizumab discontinuation, none did

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**Table 1**
Patient characteristics.

| | | | | |
|---|---|---|---|---|
| **Cohort characteristics (*n*=147)** | | | | |
| Age at start, mean (SD) | | | 35 | (9.7) |
| Age at discontinuation, mean (SD) | | | 39.8 | (9.8) |
| | <45, *n* (%) | | 98 | (66.2%) |
| | 45-55, *n* (%) | | 39 | (26.5%) |
| | >55, *n* (%) | | 10 | (6.8%) |
| Sex, *n* (%) | | Male | 50 | (34.2%) |
| | | Female | 97 | (66.4%) |
| Age at diagnosis, mean (SD) | | | 27.7 | (8.8) |
| Age at onset, mean (SD) | | | 29.8 | (9.0) |
| Disease duration years, mean (SD) | | | 18.6 | (7.2) |
| MS type, *n* (%) | Start NTZ | RR | 144 | (98.0%) |
| | | SP | 1 | (0.7%) |
| | | Unknown | 2 | (1.4%) |
| | Stop NTZ | RR | 140 | (95.2%) |
| | | SP | 5 | (3.4%) |
| | | Unknown | 2 | (1.4%) |
| Time treated in weeks, median (IQR) | | | 225.0 | (110.2-360.9) |
| EDSS, median (IQR) | Start NTZ | | 4.0 | (2.5-5.5) |
| | Stop NTZ | | 4.0 | (3.0-5.0) |
| JCV status at stop NTZ, *n* (%) | Negative | | 13 | (11.6%) |
| | Positive | | 128 | (84.4%) |
| | Unknown | | 6 | (4.1%) |

Patient characteristics. Abbreviations: SD: standard deviation; MS: Multiple Sclerosis; NTZ: natalizumab; RR: relapsing-remitting MS; SP: secondary progressive MS; IQR: interquartile range; EDSS: expanded disability status scale.

so due to having progressed to SPMS. No specific differences in patient characteristics were identified between patients that switched to second-line treatment, first-line treatment, or no DMT.

Most of the patients that were included in this report, discontinued natalizumab treatment before extended interval dosing was implemented in clinical practice. A small amount of included patients did use extended interval dosing, as a part of a trial that was conducted in our center (van Kempen et al., 2020). Of the 147 patients that discontinued natalizumab treatment, 13 have received extended interval dosing of natalizumab with an interval of 5-6 weeks.

### 3.2. JCV-status and seroconversion

Of the patients that discontinued natalizumab treatment, 13 were JCV negative at the time of natalizumab discontinuation, and 128 patients were JCV positive (of 6 patients JCV status at discontinuation was unknown). In at least 49 patients (33.3%)) JCV seroconversion occurred during natalizumab treatment, and 47 patients were already JCV positive at the start of natalizumab treatment (of 38 patients JCV status at the start of natalizumab treatment was unknown). In the total population treated with natalizumab, JCV seroconversion occurred in at least 57 patients (22.5%).

Of the 13 patients that were JCV-negative at the moment of natalizumab discontinuation, 3 stopped treatment due to an allergic reaction and/or antibodies (23.1%), 3 due to disease progression (23.1%), 2 due to stable disease (15.4%), 2 due to patient preference (15.4%), 1 due to pregnancy (7.7%), and 2 due to other reasons (15.4%). After natalizumab discontinuation, most of these 13 patients did not use another DMT (53.8%), 2 switched to ocrelizumab (15.4%), 2 received aHSCT (15.4%), 1 switched to interferon-beta (7.7%) and 1 restarted natalizumab (7.7%).

### 3.3. Disease course after natalizumab discontinuation

#### 3.3.1. Radiological disease activity

Of the 14 patients that stopped DMT completely after

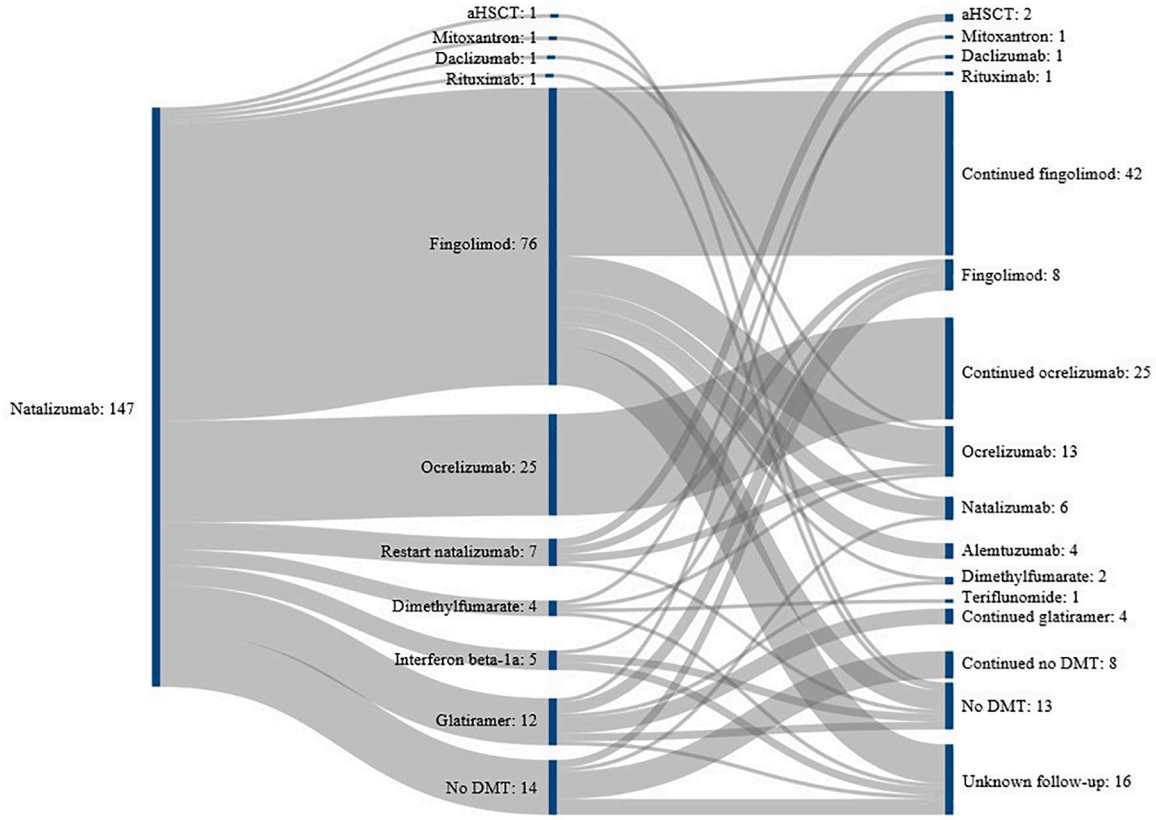


**Fig. 1.** Sankey diagram of first and second treatment switch
Sankey diagram of first and second switches after discontinuation of natalizumab treatment. The number of patients making each switch is depicted in the figure. 16 patients were lost to follow-up after their initial switch.

discontinuation of natalizumab, 5 (35.7%) showed radiological disease activity in the two years after discontinuation. Median time to the detection of disease activity on MRI was 9.8 months (IQR 5.9-12.5). In the group that switched to first-line DMT, radiological disease activity was observed in 15 patients (71.4%) with a median time of 6.1 months to activity (IQR 2.5-10.3). In the group that switched to second-line DMT (including fingolimod, mitoxantrone and aHSCT), activity was observed in 40 patients (35.7%) with a median time of 6.2 months to activity (IQR 4.5-9.9). This information is also depicted in supplementary figure 1.

#### 3.3.2. Clinical disease activity

Of the 14 patients that stopped DMT completely after natalizumab discontinuation, 4 (28.6%) experienced one or more clinical relapse in the two years after discontinuation. Of the 22 patients that switched to first-line DMT, 14 (63.6%) experienced one or more clinical relapse in the two years after natalizumab discontinuation. Lastly, in the group that switched to second-line DMT, 27 patients (24.3%) experienced one or more clinical relapse in the two years after natalizumab discontinuation. This information is also depicted in supplementary figure 1. In addition, in the group that discontinued DMT completely, 3 patients (21.4%) showed signs of secondary progression in the two years after discontinuation. In the group that switched to first-line DMT and second-line DMT, 5 patients (22.7%) and 20 patients (18.0%) respectively showed signs of secondary progression in the two years after natalizumab discontinuation.

#### 3.3.3. Patients with PML

As stated, 5 patients discontinued natalizumab treatment because they developed PML. These cases were discovered during the natalizumab pharmacovigilance protocol of the VUmc. 3 patients were symptomatic, and 2 were (largely) asymptomatic at the moment of diagnosis. All 5 patients were treated according to the standards of that time (Vennegoor et al., 2015), and all symptomatic patients at least partially recovered. 4 patients switched to glatiramer acetate, and 1 patient switched to fingolimod. In addition, 2 patients developed asymptomatic PML after switching from natalizumab to ocrelizumab treatment. These patients have been extensively described by Toorop et al. and both had a mild disease course. (Toorop et al., 2021)

## 4. Discussion

We identified reasons for natalizumab treatment discontinuation in our large single-centre patient cohort, and we found JCV positivity and associated risk of PML to be the most frequent reason for natalizumab discontinuation. In current literature, the risk of PML as reason for discontinuation ranges between 31-75% of NTZ discontinuers in papers published in 2014 or later. (Bigaut et al., 2020), (Sorensen et al., 2014; Vidal-Jordana et al., 2015; Salhofer-Polanyi et al., 2014; Lo Re et al., 2015; Iaffaldano et al., 2015) This variation could be explained by multiple factors, such as the year of natalizumab discontinuation, the availability of other treatment options and differences in monitoring of JCV-status and knowledge of PML risk at the time.

In addition, we identified treatment switches after natalizumab discontinuation. In our cohort most patients initially switched to either fingolimod or ocrelizumab, mainly depending on the year they switched and availability of these therapies at that moment. Currently all our MS patients are screened for JCV status prior to starting second-line therapy and those positive for JCV generally start with ocrelizumab rather than natalizumab. Other treatment switches also occurred. 51 patients (34.7%) switched a second time to another type of DMT, discontinued completely or switched back to natalizumab. The heterogeneity of treatment switches and number of switches is however something to be noted. We face a growing complexity during our outpatient clinics with patients with multiple DMTs in their medical history. This may lead to a potential risk of unexpected side-effects or side-effects that have an altered course due to understudied combinations of DMT. (Toorop et al., 2020)

In conclusion, we have generated a brief overview of all patients that discontinued natalizumab treatment in our patient cohort. Recognising reasons for treatment discontinuation and treatment decisions made in our patient cohort can be helpful in future clinical decision making regarding natalizumab treatment.

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## Declaration of Competing Interest

E.M.E. Coerver, M.H.J. Wessels, Z.Y.G. van Lierop, Z.L.E. van Kempen, and E.M.M. Strijbis report no disclosures

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.102974.

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