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### **Highlights**

- This is the first study to evaluate natalizumab at home during one-year follow-up.
- Patients have a very positive experience of the home natalizumab administration.
- The home natalizumab administration improve the patients' quality of life.
- The home natalizumab remains effective and safe.

# **Switching from natalizumab administration at the day hospital to administration at home. A 1 year prospective study of patient experience and quality of life in 30 consecutive patients with multiple sclerosis (TYSAD-35).**

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## **ABSTRACT**

**Background:** In the context of the COVID-19 pandemic, French health authorities allowed the home administration of natalizumab by a healthcare-at-home service. We evaluated the patients' perception of care quality following the transition from day-hospital to home natalizumab administration.

**Methods:** Thirty relapsing-remitting multiple sclerosis (MS) patients treated with natalizumab were prospectively evaluated for one year after changing onto a home treatment procedure, using MusiCare, the first MS-specific questionnaire to evaluate patient experience and MusiQol. A numerical rating scale score for satisfaction and a dedicated questionnaire concerning patient experience were completed after each infusion. The primary endpoint was the mean difference in MusiCare score between baseline and 12 months.

**Results:** From June 2020 to November 2021, 306 infusions were performed at home. Three patients withdrew from the study (one lost to follow-up and two preferred to return at the day hospital). No worsening of patient experience or quality of life was observed. The mean scores of the MusiCare dimensions were higher at 12 months than at baseline, significantly for the "relationship with healthcare professionals" ( $p=0.0203$ ). The MusiQol global score remained stable but the coping and friendship dimensions were significantly better at M12 than at baseline ( $p=0.0491$  and  $p=0.0478$ , respectively). The satisfaction questionnaire highlighted some pain during the infusions (21.8%) and contradictions between healthcare professionals (17.2%). The mean score for satisfaction with care was 9.1/10. No safety concerns were identified.

**Conclusion:** The positive experience of patients with home natalizumab administration provides an important opportunity to improve the quality of patient care.

## **INTRODUCTION**

Natalizumab is a disease-modifying treatment for very active forms of relapsing-remitting multiple sclerosis, which has been shown to be effective in a number of studies<sup>1-4</sup>. It is administered intravenously, at a dose of 300 mg every four weeks, at the day hospital. Treatment via the

subcutaneous route has also been available in France since March 2021 (two 150 mg injections)<sup>5,6</sup>. Natalizumab is generally well tolerated, but headaches, asthenia, and mild infections (ear-nose-and-throat or urinary) have been reported in some cases. Allergic reactions, rarely severe (1% of them), are reported in 3 to 4% of patients, justifying treatment and monitoring in a hospital environment<sup>1,4</sup>. Furthermore, natalizumab can cause progressive multifocal leukoencephalopathy (PML) in patients seropositive for JC virus (cumulative risk of up to 3%). JC virus serology tests should therefore be performed rigorously, every six months, with the discontinuation of natalizumab in cases of seropositivity<sup>4,7,8</sup>.

MS patients are generally young and active, with children at home. Regular visits to the hospital therefore impose significant personal and professional constraints. The need for such visits can also make these patients and their families feel that they are facing a serious illness<sup>9,10</sup>.

The COVID-19 pandemic has recently led to radical changes in the organization of healthcare, including the administration of immunosuppressants for MS, from the points of view of both healthcare professionals and patients. At the end of April 2020, following the first lockdown of the French population, the French High Authority for Health (HAS) temporarily authorized the administration of natalizumab by the intravenous (IV) route to patients at home, via a home-hospitalization structure (HAD). The healthcare model for hospitalization at home in France was defined by Law No. 91 748 of July 31, 1991, and depends on dedicated medical and paramedical teams in a given area. Beyond the context of the pandemic and the need to ensure the continued treatment of these patients (risk of rebound when natalizumab is stopped)<sup>11</sup>, the decision of the HAS was based on a few previous experiences, particularly in Australia, reporting encouraging results for safety, efficacy, and patient satisfaction<sup>12–15</sup>. Indeed, it is essential to take the patients' viewpoint into account (in addition to the clinical criteria of efficacy and safety) when implementing of new modes of organization for their care<sup>16,17</sup>. Tools have, therefore, been available for several years for evaluating the care results from the patients' point of view (Patient-Reported Outcome Measures - PROMs), and the patients' experience of the new care organization (Patient-Reported Experience Measures - PREMs)<sup>18,19</sup>. MS-specific tools have been developed for measuring quality of life and experience related to the quality of the care path of these patients, and these tools are widely used in clinical studies<sup>20,21</sup>. In France, the two reference tools are MusiQol (PROMs) and the more recently developed MusiCare (PREMs)<sup>22,23</sup>.

Before the COVID-19 pandemic, patients natalizumab treatment attended the day hospital for monthly infusions. In Rennes district (with almost 1 million inhabitants), this treatment was provided by the neurology department of Rennes University Hospital. Following HAS authorization of treatment at home at the end of April 2020, we developed a care protocol for the administration of natalizumab infusions at home, in collaboration with the local home hospitalization service (HAD-35). The objective of the TYSAD-35 study was to assess prospectively the patients' experience of this new practice (MusiCare), together with their quality of life (MusiQol), and satisfaction, during the first 12 months of this experiment, and, finally, the safety of the procedure in terms of tolerance.

## MATERIALS AND METHODS

**Design:** We performed a prospective, observational, descriptive study.

### **Population**

Until 2020, patients had never been treated with natalizumab at home in France. Home-healthcare services, such as HAD-35 (one of the partners in the TYSAD-35 study) provide care for patients at home, within a defined area and with defined human resources (medical and paramedical health professionals). For this reason, the maximum number of patients who could be treated at home was set at 30.

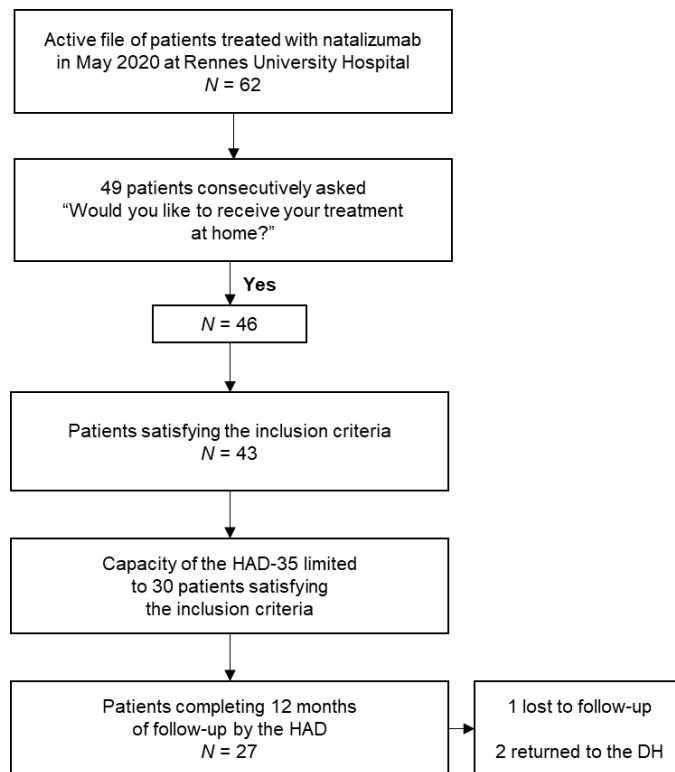
The participants were recruited from the active list of 62 patients treated with natalizumab in the day hospital (DH) of the neurology department of Rennes University Hospital. Between June 2020 and January 2021, 49 consecutive patients visiting the DH for natalizumab infusion were asked whether they would like to be treated at home. The first 30 patients meeting the following inclusion criteria who agreed were included.

### **Inclusion criteria**

The inclusion criteria were: 1) patient aged at least 18 years, 2) MS diagnosis confirmed according to the 2017 McDonald criteria, 3) treatment with natalizumab at the DH for at least six months, 4) negative six-monthly results of serological tests for JC virus infection, 5) desire to be treated at home expressed by the patient, 6) residence within the geographic area covered by HAD-35, and 7) non-opposition to clinical research and subject not under legal protection (ward of court or conservatorship).

**Procedure:** our MS team co-wrote with the local home hospitalization service (HAD-35) a standardized care protocol for the administration of natalizumab infusions at home and shared information about MS and natalizumab. HAD infusions were performed in the same way as at the DH (same dose, route of administration, monitoring, etc.), after validation by a neurologist of our department during a teleconsultation planned within 48 hours before the infusion. A report was sent to the HAD to authorize the infusion. The patients were seen every six months at the DH of Rennes University Hospital, for serological tests for JC virus infection, and for clinical and neurological evaluations. They received the corresponding monthly natalizumab infusion during this visit.

Figure 1. Flow chart



### Data collected

The following data were collected at inclusion: the sociodemographic characteristics of the patients (age, sex, professional status, family situation, etc.), clinical data relating to the disease (EDSS score at M0), and data relating to their natalizumab treatment (start date, duration of exposure). During the follow-up of 12 months after the transfer from the DH to HAD care, the following data were collected: EDSS score at M6 and M12, radiological activity, as assessed by MRI, the occurrence of relapses, and adverse effects imputable to the treatment.

The impact of this new organization of care, from the patients' viewpoint, was evaluated by collecting:

- Data on the overall experience of the patients based on responses to the Musicare questionnaire (Copyright © 2022 Mapi Research Trust-All rights reserved), which is specific to MS and contains 35 items describing the following five dimensions: information about the disease in general, treatments and additional examinations, relationships and communication with healthcare professionals, time required to access care, and perception of the site of care. This questionnaire allows patients to assess the quality of their care pathway in a global manner rather than focusing specifically on infusion at home. It was completed by the included patients before the start of home infusions and then after 12 months of HAD care.
- Data on patient satisfaction and experience immediately after each infusion, collected with a numerical rating scale from 0 to 10 and a questionnaire designed for this study and based on a recognized tool (PPE-15<sup>24</sup> (Supplemental material 1)).

- Quality-of-life data collected with the MS-specific questionnaire, MusiQoI<sup>22</sup>, which contains 31 items describing the following nine dimensions: daily activity, psychological well-being, relationships with friends, symptoms, relationships with family members, relationships with healthcare professionals, emotional and sex life, coping, and rejection. Each of the patients included completed this questionnaire before the start of the first infusion at home, and after each monthly infusion, over a period of 12 months.

All information was obtained prospectively from patients, who completed forms online with Sphinx IQ2 survey software – version 7.4.5.1.

### **Ethics**

This study was approved by the Ethics Committee of the Rennes University Hospital (No. 35RC21\_8924\_TYS-HAD-35) and complies with the obligations of law number 78-17 of January 6, 1978, relating to data processing, files, and liberties. All participants signed a written informed consent form before inclusion.

## **STATISTICAL ANALYSES**

### **Descriptive analyses**

The sociodemographic and clinical characteristics of the patients and their disease are described with the mean and standard deviation (SD) for continuous variables and frequencies with percentages for qualitative variables.

### **Analysis of the questionnaires**

After analyzing the shape of the distributions of the scores for each dimension, patient experience (MusiCare), and quality of life (MusiQoI), were evaluated, with the results expressed as means and standard deviations for the whole population. The scores for each dimension were treated identically. The means for each dimension (and of the overall score for MusiQoI) between M0 and M12 were compared using non-parametric paired Wilcoxon tests.

For the measurement of patient satisfaction with each infusion, the responses to the questionnaire corresponding to a negative experience during an infusion at home were recorded and are presented as the percentage of patients reporting such experiences.

We used a significance threshold of 5% for all comparisons. All statistical analyses and calculations of scores were performed with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

## **RESULTS**



In total, 46 (94%) of the 49 consecutive patients answered in the affirmative when asked whether they wished to receive treatment at home, regardless of their place of residence, duration of treatment, or JC serology status. The main reasons given for wishing to switch to this mode of care or for refusing it are indicated in Table 1.

**Table 1. Desire or refusal to be treated with natalizumab at home (N = 49)**

Reasons	N	%
<b>In favor of home infusions</b>	<b>46</b>	<b>94.0 %</b>
Time saved / Reduced traveling time	28	57.1 %
Better material comfort	9	18.3 %
Fits in better with professional activity	4	8.1 %
Change in view of the disease (less serious)	3	6.0 %
Lower risk of viral infection (COVID-19)	2	4.0 %
<b>Against home infusions</b>	<b>3</b>	<b>6.0 %</b>
Negative or worrying image of the infusion and the sick parent for the children	2	4.0 %
Feeling safer in a hospital environment	1	2.0 %

N = Number

### Characteristics of the 30 patients included in TYSAD-35:

The demographic and medical characteristics of the patients included in the study are presented in Table 2. The patients were young, with a median age of 38.1 years (range: 25-58 years); most were working (60%), living with a partner (73%), and with dependent children (70%). The clinical activity of the disease was well controlled before inclusion. The patients had been on natalizumab treatment for a median of 5.45 years (range: 2.7-14.0 years).

**Table 2. Demographic and clinical characteristics at inclusion (N = 30)**

Age at inclusion† (years)	38.1	25 – 58
Age at diagnosis† (years)	26.2	17 – 51
Duration of MS† (years)	9.5	3.3 – 23
RR form (N)	29	96.0 %
Age at start of NTZ† treatment (years)	32.2	20 – 53
Duration of exposure to NTZ† (years)	5.45	2.7 – 14
Another maintenance treatment during the year (N)	0	0.0%
Seronegative for JC virus in test performed less than 6 months ago (N)	30	100%
ARR (12 months before M0)	0.0	0 – 1
EDSS at M0†	2.0	0.0 – 5.5

†median, range. RR = recurrent-remitting, N = number, NTZ = natalizumab, ARR = annual relapse rate.

### Follow-up of patients by the HAD service

Thirty patients were initially included; 27 (90%) were followed for the 12 months of the home treatment experiment and three left the study prematurely. One patient returned to the DH for treatment due to poor venous access, making it impossible to continue home infusion after the first three sessions. The second patient preferred to return to DH management after four infusions for personal reasons, being a healthcare professional at our establishment. The third patient was lost to follow-up after seven infusions, despite repeated attempts at contact by healthcare professionals from the DH and HAD service. In total, 306 infusions were performed at home during the 12 months of follow-up.

### Natalizumab at home: the patients' perspective

#### - Experienced quality of this new care pathway

- Primary endpoint: MusiCare. Twenty-six patients completed the MusiCare questionnaire at M0 and M12. The overall experience of the patients included improved between M0 and M12 for all the dimensions and it was significant for the dimension "experience of relationships with healthcare professionals" (ability to listen, empathy, relationship based on trust) (Table 3).

Table 3. Patient experience: MusiCare at M0 and M12 (N = 26)

MusiCare Dimensions	M0		M12		P value
	Mean	Standard deviation	Mean	Standard deviation	
Experience of information about the disease in general	74.8	20.5	78.8	20.4	0.4577
Experience of information about the treatment and examinations	81.4	17.9	82.8	18.4	0.9914
Experience of relationships with healthcare professionals	81.8	19.8	91.5	13.2	<b>0.0203</b>
Perception and experience of access to care	69.0	13.6	72.0	20.5	0.0972
Conditions of reception at care sites	67.9	16.1	75.0	17.7	0.0995

<sup>†</sup> P value < 0.05

- Mean overall satisfaction with home infusions was high, at 9.1/10, and remained constant throughout the follow-up period. However, an analysis of the 294 satisfaction questionnaires completed by the 30 patients after each infusion at home identified several areas of patient

dissatisfaction. The most frequently cited points of dissatisfaction were: “contradictory responses provided by the various healthcare actors” (17.2%) and “physical pain during the procedure” (21.8%). Similarly, the information shared with patients and their families was sometimes not entirely satisfactory. Finally, several patients felt that their involvement in therapeutic decisions and in the management of their disease could be improved (Table 4).

**Table 4. Proportion of criteria deemed unsatisfactory by patients over the 12 months of the study, for the 294 questionnaires completed.**

	<b>N</b>	<b>%</b>
Comprehension of the practitioners' answers to questions	4	1.4 %
Comprehension of the nurses' answers to questions	25	8.6 %
Contradictory responses from different healthcare professionals	50	17.2 %
Answers given by the practitioner concerning state of health and treatments	6	2.1 %
Medical discussions in front of the patient as if the patient was absent	9	3.1 %
Involvement in therapeutic decisions/disease management	28	9.7 %
Healthcare with respect and dignity	7	2.4 %
Answers given by the nurse concerning state of health and treatments	2	0.7 %
Ability of the medical team to listen	3	1.0 %
Presence of physical pain	63	21.8 %
Pain management by the medical team	14	8.5 %
Information available to family	26	9.0 %
Contact person known in case of questions after the infusion	24	8.5 %

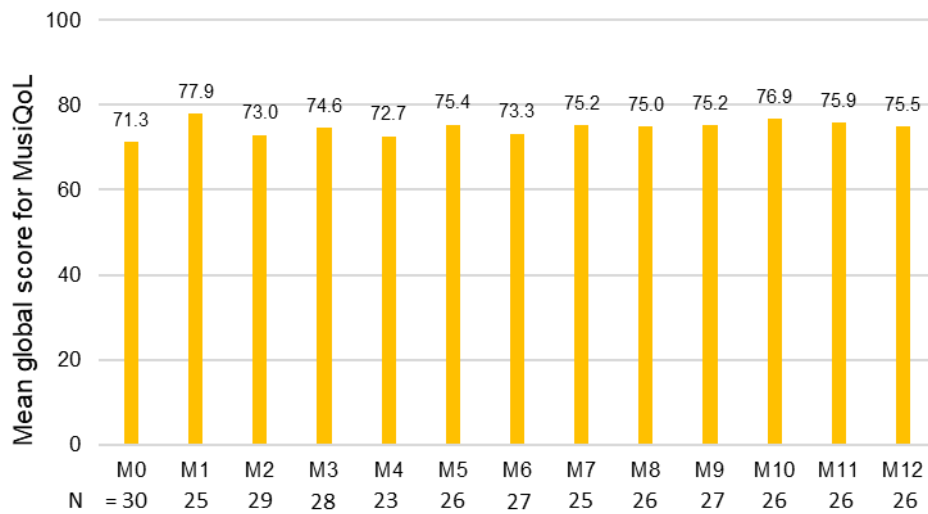
N = Number

#### - Quality of life

MusiQoL global score increased over the months, although this result was not significant (Figure 2). Twenty-six patients completed the MusiQoL questionnaire at M0 and M12. For these patients, a significant increase was observed in the scores for the “friendship” ( $p = 0.0478$ ) and “coping” ( $p = 0.0491$ ) dimensions (Table 5).

**Table 5. Quality of life: MusiQoL at M0 and M12 (N = 26)**

<b>MusiQoL</b>	<b>M0</b>		<b>M12</b>		Significance of difference between M0 and M12
	Mean	Standard deviation	Mean	Standard deviation	
<b>Daily living activities</b>	65.4	22.6	65.4	24.9	0.8566
<b>Psychological well-being</b>	62.5	25.2	67.8	23.6	0.0660
<b>Symptoms</b>	74.3	22.2	75.6	26.8	0.8398
<b>Relationships with friends</b>	66.0	23.6	72.1	28.1	<b>0.0478</b>
<b>Relationships with family members</b>	82.0	20.9	80.3	23.8	0.7144
<b>Emotional and sex life</b>	68.5	31.3	70.0	26.8	0.6395
<b>Coping</b>	67.8	24.8	75.5	26.3	<b>0.0491</b>
<b>Rejection</b>	85.6	28.9	87.5	27.4	0.5156
<b>Relationship with the healthcare system</b>	80.4	13.3	82.5	15.5	0.5031
<b>Global score</b>	72.4	14.3	75.5	16.3	0.0864

**Figure 2. Change in mean global score for the MusiQoL questionnaire**

N = number of questionnaires completed for each period.

### Adverse events

No allergic reactions, not even minor, were reported. No adverse events were recorded apart from mild headaches and asthenia during treatment. On three occasions, the team of HAD nurses encountered difficulties with peripheral venous access, which led to one of these patients resuming treatment at the DH. Only one infusion had to be postponed due to reflex syncope just before initiation of the infusion.

### Progression of multiple sclerosis

Multiple sclerosis activity remained low throughout the follow-up period in all 27 patients who completed follow-up. None of the patients experienced flare-ups. EDSS score remained stable at 2.0. Annual follow-up by brain MRI showed that lesion load was stable in all patients who completed follow-up. No seroconversions were observed for the JC virus.

## DISCUSSION

The context of the COVID-19 pandemic provided an opportunity to establish home infusions of natalizumab, which had already been requested by neurologists and patients but had not previously been approved by the French health authorities. We present here the first French study to evaluate this new procedure. This study included the largest number of infusions (306 in total) of natalizumab at home assessed to date, providing us with sufficient information to demonstrate the feasibility of this new practice. Its implementation, within the HAD care model, required the creation of a specific treatment protocol, the training of HAD healthcare professionals, the sharing of medical information between services, and close coordination between the actors of the neurology department DH at Rennes University Hospital and the HAD. As in the study by Shultz et al., the patients included in TYSAD-35 were very enthusiastic about this new practice, for organizational and logistical reasons

(time savings, fewer medical visits) in particular, consistent with the characteristics of this population of young patients, little neurological impact of their disease, living with their families and continuing to work. Finally, the fear of contracting COVID-19 during visits to the DH was only rarely identified as a reason for wishing to be treated at home. All the patients had been on natalizumab treatment for more than two years (sometimes up to 14 years), accounting for their lack of concern about the risk of a serious allergic reaction. Such reactions are rare in practice, and have been reported to occur essentially at the time of the first or second infusion<sup>1</sup>. Consequently, a switch from DH to HAD treatment could be proposed to patients after a minimum period of six months, as in the study by Schultz et al.

The treatment protocol established specifically for this new organization of care was quickly assimilated and applied by the HAD. As a result, no infusion was postponed or not carried out due to logistical or organizational difficulties. However, three patients withdrew from the study. Two preferred to return to DH management, one because of poor venous access and the other worked at the hospital and found that this organization was more suitable. The third patient was lost to follow-up for several months and the cessation of treatment was accompanied by a resumption of disease activity. These findings suggest that the HAD management model is a suitable option for most patients but should not be systematic, especially when more general adherence to treatment and follow-up are likely to be difficult. Access to both options should be maintained to take patient preferences into account.

This study is original because we prospectively measured, in real-life conditions, the impact of this new mode of care on the care quality from the patient's point of view, an essential perspective in the context of this innovative organization of care. We measured care quality from the patients' perspective with tools of the PREMs and PROMs types.

The patients' experience of this mode of treatment was evaluated immediately after each monthly infusion and over the long term, at the end of the 12 months of follow-up. This approach and the tools used made it possible to highlight a generally very positive experience with the HAD management of natalizumab infusions. Indeed, the mean score of each dimension of MusiCare has increased at the end of the 12 months of follow-up. The difference was significant for the dimension concerning the patients' experience of their relationships with healthcare professionals. These observations suggest that good adherence to the proposed care model is likely, particularly as the HAD healthcare team was completely new to the patients and not specialized in MS or its care, unlike the DH team. Similarly, the maintenance of an overall positive experience in terms of the quality of the information received and access to care suggests that the proposed model of collaboration between the HAD and the reference neurology team met the expectations of patients. These results are consistent with those reported by Juaton et al. in their recent study of home care in Australia, in which a qualitative approach based on interviews was used to study the 12 patients receiving such care<sup>14</sup>. They are also consistent with the findings of another Australian group that used questionnaires to ask several dozen patients

with neurological diseases, including multiple sclerosis, about their preferences in terms of location for long-term infusion treatment (mostly natalizumab). Most of these patients expressed a preference for having their infusions at home<sup>9</sup>. In addition to the MusiCare tool, specifically validated for patients with MS and taking into account the entire care pathway, we developed a tool for assessing patient experience inspired by the French version of the PPE-15, and we used a numerical rating scale to assess the overall level of patient satisfaction. The results obtained with these two tools highlighted a very positive experience at the end of each infusion but also identified areas for the improvement for this new organization of care from the patients' viewpoint. For example, patients sometimes felt that the answers provided by healthcare professionals to questions were contradictory and the infusion procedure was sometimes painful. Information of this type is useful for guiding the necessary feedback-based discussions between the HAD and neurology teams to harmonize practices, based also on the sharing of theoretical knowledge about the disease and the technical specificities related to the frequency of infusions.

In evaluations of care results, principally with the MusiQoL tool, we noted an improvement in the overall score for quality of life and a significant improvement in the dimensions relating to relationships with friends and coping. These results can be interpreted as indicating a better psychological adaptation to the disease and the way it is seen by others. Shultz et al. used other tools not specific for MS, but their results are consistent with ours.

No serious adverse effects, particularly of an allergic nature, were identified. Nevertheless, the risks had been anticipated by the creation of a dedicated protocol. According to this protocol the drug was administered in a safe environment, with twice-yearly visits to the DH to perform serological tests for JC virus and neurological evaluations, and for regular validation of the continuation of treatment according to the proposed procedure. This home procedure did not reduce our capability of detecting potential PML as teleconsultations were performed before each natalizumab home infusion and JC virus status were checked every 6 months.

This experimental study had several limitations, including, in particular, the absence of a control group and a small sample size. Furthermore, all the patients included were volunteers. Our results are therefore preliminary and require confirmation, which is the objective of the TYSATHOME study currently underway in France, with the same design but the aim of including more than 300 patients. This study will also provide additional information, at national level, about the cost of this type of treatment relative to treatment in a hospital setting. With a view to perpetuating this practice for patients treated with natalizumab, administration by the subcutaneous route should enable HAD services to care for more patients, as less time will be required for monitoring after the injection.

## CONCLUSION

Our study demonstrates that home injections of natalizumab are feasible for patients with multiple sclerosis. This new practice has a positive impact on the experience of patients relative to hospital care, while remaining safe and effective for disease control. This therapeutic perspective is promising and of interest for patients who would like to be treated at home, which should help to establish its maintenance in the long term.

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