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Access, satisfaction, adherence and safety to subcutaneous natalizumab compared to intravenous natalizumab in multiple sclerosis in a real-life cohort: first report from Latin America

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Abstract

Background: Subcutaneous natalizumab (scN) was recently approved in Argentina for people with multiple sclerosis (pwMS). The impact of this change in this population is unknown.

Objectives: To evaluate the use, access and satisfaction of scN and correlate it with clinical and demographic variables. Desing: cross-sectional study was conducted, surveying pwMS who received scN and ivN from public and private MS Centres since its approval.

Methods: Treatment adherence was assessed using the MS Treatment Adherence Questionnaire (MS-TAQ) and satisfaction using Treatment Satisfaction of Questionnaire for Medication (TSQM). Clinical and demographic variables were also recorded. Results: 84 pwMS were included, 58.3% female, mean EDSS: 2.4 ± 1.2, mean age: 34.8 ± 10.8 years, mean disease duration: 7.8 ± 4.5 years, mean time under *N*: 43.7 ± 28.7 months, 45.2% naïve of prior disease modifying treatments, 77.4% ($n = 65$) under scN (60.7%, $n = 51$ are switchers from ivN, 49% due to difficult access to an infusion centre); and 22.6% 8 ($n = 19$) under ivN. The main barrier for change from iv to sc was the refusal from health insurance. Of the total of pwMS, 42% ($n = 36$) had a delay or lack of at least one dose from their social insurance, all from public hospitals. We found an association between scN use and high scores on the convenience items of TSQM ($p < 0.0001$, $X^2 = 74$), unlike ivN. Regardless of route of administration, most of pwMS showed high percentages of satisfaction in the effectiveness and global satisfaction items, without differences between ivN and scM.

Conclusion: We found a high rate of change to scN from ivN, associated with a higher score in the comfort and convenience items in people receiving scN, compared to ivN. Access barriers should be addressed in order to improve treatment comfort.

Keywords: access, adherence, multiple sclerosis, natalizumab, satisfaction, subcutaneous, treatment

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Introduction

Multiple sclerosis (MS) is a demyelinating, autoimmune and inflammatory disease of the central nervous system with and degenerative component, characterised by the presence of clinical manifestations in relation to the topography of the compromised areas. Furthermore, MS is the most common disease within the group of demyelinating diseases and is the main cause of non-traumatic disability in young adults.[1,2] Argentina

is considered a low MS prevalence country, with an estimated prevalence of 38.2 per 100,000 inhabitants.[3]

In recent years, there has been a very important development with respect to the available disease modifying treatments (DMTs), especially for relapsing and remitting forms of MS (RRMS), which has improved the prognosis of these people with MS (pwMS).

DMTs in general seek to suppress or modulate the immune system and reduce inflammation, slowing disease progression and helping prevent relapses. These drugs are administered via injection, (e.g. beta interferons, glatiramer acetate, ofatumumab), infusion (e.g. ocrelizumab, alemtuzumab, natalizumab), or as oral formulation (e.g. fingolimod, siponimod, dimethyl fumarate, teruflunomide).[4] In particular, the high efficacy therapies (HETs) have radically changed the natural history of the disease.[5,6]

Natalizumab (Tysabri®), a monoclonal antibody directed against the α4 fraction of integrins α4β1 and α4β7, was the first HET for RRMS, approved by European Medicines Agency (EMA) in 2006 in its intravenous formulation (ivN). Its efficacy and safety versus placebo were demonstrated in the AFFIRM phase III trial.[7] Subsequently, the ongoing Tysabri Observational Programme (TOP), including 6148 patients worldwide, demonstrated that it maintained its efficacy and safety profile over a 10-year period.[8]

Most recently, the subcutaneous formulation of Tysabri® (scN) was approved in 2021 by EMA, and in 2023 in Argentina, based on the results of DELIVER and REFINE studies.[9,10] Currently, in the context of shared decision-making process between neurologist and pwMS, since both routes of administration are equivalent with respect to their efficacy and pharmacodynamics and differ only in their route of administration, the neurologist can offer to pwMS the possibility of choosing one or the other depending on the patient's profile and preference. Furthermore, since the EMA approval of iv and scN, through 31st July 2023, natalizumab (iv or sc), Tysabri®, has been administered to 264,276 patients with a total of 1,117,808 patient-years of exposure, and scN has been administered to 21,406 patients (corresponding to 24,659 patient years of exposure).[4]

Although a European study has evaluated adherence and satisfaction comparatively between both formulations, such data are currently lacking in Latin America. The impact of this change on this population remains unknown. Therefore, the objective of this study is to evaluate the use, access and satisfaction with subcutaneous natalizumab (scN) in our country and to explore its correlation with clinical and demographic variables.

Methods

A cross-sectional study including pwMS who received scN and ivN from public and private MS Centres from Argentina was carried out involving three MS centres: Hospital Italiano de Buenos Aires, CUEM-Hospital Ramos Mejía, and Hospital HIGA San Martín de La Plata.

Patient recruitment for this study was conducted consecutively, between January and March 2024. Surveys were sent consecutively to all patients treated with natalizumab at the hospitals who met the inclusion criteria, as they attended their follow-up visits. The surveys were not anonymised and were administered to all patients at the end of a follow-up neurological consultation. Accordingly, the data were provided by the treating physicians and extracted from medical records within no more than 1 month of the consultation and survey completion. No patient experienced a relapse during this period.

The inclusion criteria were pwMS over 18 years of age, MS diagnosis according to the 2017 McDonald diagnostic criteria[11] and currently receiving iv or scN (Tysabri®) treatment. Data from those who fully answered the online self-administered survey were included.

Administration of subcutaneous natalizumab followed national regulatory guidelines. According to the local package insert, the first six injections – both in treatment-naive patients and in those previously treated with intravenous natalizumab – were administered at the respective healthcare centres under supervision by qualified health professionals.

This study protocol was approved by the Ethics Board of Hospitals involved (protocol N°7066) and Plataforma de Registro Informatizado de Investigaciones en Salud de la Ciudad de Buenos

Aires (PRIISA BA) number 1233, approved on 12 September 2023. Online/virtual informed consent was granted by each patient. Informed consent was obtained in written electronic form through the online platform prior to participation.

Questionnaires

To evaluate the satisfaction with natalizumab treatment, the on line Treatment Satisfaction Questionnaire for Medication (TSQM) v 1.4 validated in Latin American Spanish was used.[12,13] This questionnaire comprises 14 items across four domains: effectiveness, side effects, convenience and global satisfaction, which asks about the use of the medication over the previous 2–3 weeks or since the patient's last use. There are three items for effectiveness, global satisfaction and convenience, and four items regarding side effects. In this case, the 14 questions were rated using a 7-point Likert-type scale (from 1 – extremely dissatisfied to 7 – extremely satisfied) and classified into 4 categories: treatment effectiveness (questions 1–3), side effects (questions 4–8), convenience (questions 9–11) and global satisfaction (questions 12–14).

It should be noted that each question in the treatment effectiveness (questions 1–3), convenience (questions 9–11) and global satisfaction (questions 12–14) domains was scored on a Likert scale from 1 to 7. Each domain comprises three questions, with individual scores summed to yield a maximum of 21 points per domain. The side effects domain includes five questions. The first question asks whether the patient experienced any side effects because of the medication. If a side effect was reported, the subsequent four questions assess the degree of physical and mental discomfort, interference with quality of life and dissatisfaction caused by the side effect.

To assess adherence, the on line MS Treatment Adherence Questionnaire (MS-TAQ) validated in Latin American Spanish was used.[13] It's a rating scale that quantifies the barriers to adherence, side effects and coping strategies experienced by MS patients. The questionnaire includes 23 items about different factors that affect medication adherence such as the effort involved in its use, other concomitant diseases, related side effects, shared decision-making and difficulties in access.[14] Each of the different questions has a variable number of options (4 or 5) which allow an ordinal evaluation, except for those relative to missing doses, which evaluate whether there was forgetfulness, delays and the number of them.

Ad hoc questions were specifically added to analyse the use of natalizumab. These included the current route of administration; whether a different route had been used previously; if a change in route had occurred, the reason for the change; if the patient had wanted to change but was unable to do so, the reason why; the barriers to accessing the desired formulation; and, if the patient did not want to change, the reason for this decision.

The questionnaires employed in this study are provided in Supplemental File 1.

Additionally, demographic and clinical data of the patients who responded to the survey were obtained.

Statistical analysis

All statistical analyses were performed using Graph Pad Prisms V10. Descriptive analyses of all variables were conducted. The results were shown as frequencies, percentages, ranges, mean and standard deviation values. Comparisons between groups were analysed using Chi-square or Fisher's exact tests for categorical variables and, for continuous variables, analysis of variance (ANOVA) with Bonferroni post hoc correction or Kruskal–Wallis test with Dunn post hoc analysis, as appropriate. Effect sizes were calculated for all main comparisons (Cramér's V or ϕ for Chi-square/Fisher's exact tests, and η^2 or partial η^2 for ANOVA). Although GraphPad Prism V10 does not explicitly provide interpretation thresholds, we followed Cohen's conventional benchmarks – small = 0.1, medium = 0.3, large = 0.5 for Cramér's V/ϕ; and small = 0.1, medium = 0.25, large = 0.4 for ANOVA (f) – to aid in the interpretation of effect magnitude. Statistical significance was set at $p < 0.05$.

Results

The survey was administered to 118 patients, of whom 84 completed the questionnaires. Thirty-four patients did not attend their scheduled follow-up visits during the study period (January–March 2024) and therefore could not be surveyed. All of these patients were being treated at the CUEM Ramos Mejía centre. There were no

other reasons for excluding patients. Furthermore, all surveyed participants completed the entire questionnaire, with no missing data.

The clinical and demographic characteristics of these patients are shown in Table 1. Of all patients who answered to the survey, 58.3% ($n=48$) were female. The mean EDSS was 2.4 ± 1.2, the mean age was 34.8 ± 10.8 years and the mean disease duration was 7.8 ± 4.5 years. Concerning prior disease modifying therapies (DMTs) used, 54.8% ($n=46$) received other DMTs before starting natalizumab treatment. Fingolimod was the most used DMT 30.4% ($n=14$). Besides, regarding health coverage, 30.9% ($n=26$) of pwMS did not have any type of social security; therefore, natalizumab was supplied by the government. For this situation, the sample is considered representative of the national population, as 30.9% of participants relied exclusively on the public healthcare system. This proportion is comparable to national data from the 2022 National Population, Household, and Housing Census, which reported that 35.8% of the Argentine population lacks social security, private health insurance, or coverage by state health plans.[15]

Regarding natalizumab, the mean time under treatment was 43.7 ± 28.7 months, and 10.7% ($n=9$) were positive for JCV. All patients had a low index (below 0.9), and none had a history of immunosuppressant use prior to initiating natalizumab treatment. Additionally, 32.1% ($n=27$) was receiving extended interval dosing (EID). Of the total sample, 77.4% ($n=65$) is under scN, of which 60.7%, $n=51$ is switcher from ivN.

The reasons for changing from ivN to scN were difficulties in accessing the infusion centre ($n=25$, 29.8%), following by absence from work ($n=19$, 22.6%), change on daily routine ($n=4$, 4.8%) and waste of time ($n=3$, 3.6%; Figure 1). Additionally, 94.7% ($n=18$) of patients with multiple sclerosis (pwMS) who remained on ivN expressed a preference to switch to scN. Only 1 of the 19 patients receiving ivN preferred to continue with the intravenous route. In those patients who requested a switch from ivN to scN but were unable to achieve it, the main barrier to this change was the refusal from health insurance (100% of cases). In all cases of refusal, the patients

Table 1. Demographic and clinical characteristics of the included patients.

Variable	*n* = 84
Gender, *n* (%)	
Female	49 (58.3)
Male	35 (41.7)
Age (Mean, SD)	34.8 (10.8)
Disease duration in years (Mean, SD)	7.8 (4.5)
Time under natalizumab in months (Mean, SD)	43.7 (28.7)
Current EDSS (Mean, SD)	2.4 (1.2)
Prior DMT use (*n*, %)	
Yes	46 (54.8)
No (Naive)	38 (45.2)
Last DMT (*n*, %)	
Interferon	11 (23.9)
Teriflunomide	6 (13.04)
Dimethylfumarate	10 (21.7)
Fingolimod	14 (30.4)
Cladribine	2 (4.39)
Glatiramer acetate	3 (6.5)
Current natalizumab (*n*, %)	
Iv	19 (22.6)
Sc	65 (77.4)
switchers from iv	51 (78.4)
sc from treatment onset	14 (21,6)
JCV status (*n*, %)	
Positive	9 (10.7)
Negative	75(89.3)
Health coverage (*n*, %)	
Without health insurance	26(30.9)
Private/national social security programmes	58 (69.1)

DMT, disease modifying treatment; EDSS, Expanded Disability Status Scale; Iv, intravenous; JCV, John Cunningham virus; Sc, subcutaneous.

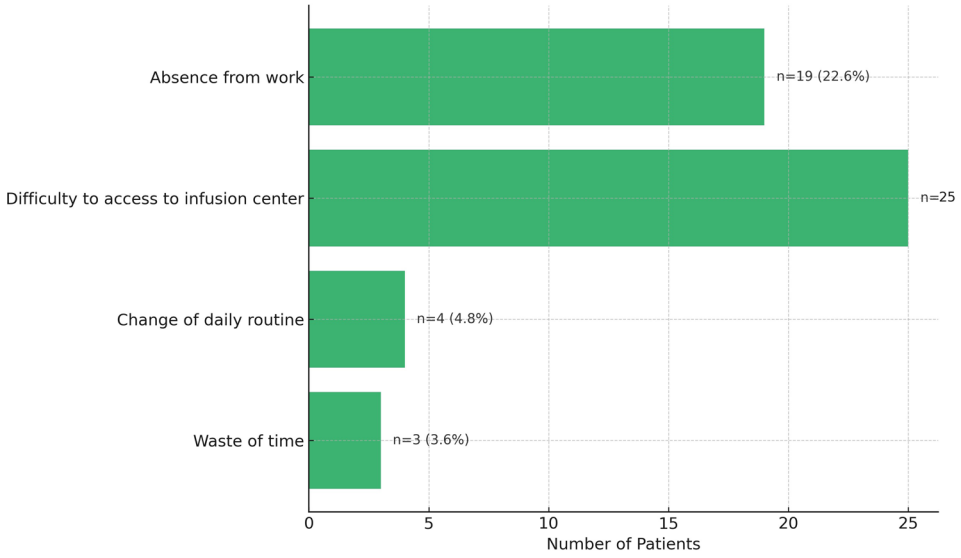

Figure 1. Reasons for change from intravenous natalizumab to subcutaneous natalizumab.

chose to continue with EID, expressing greater comfort with the lower frequency of infusions.

When we analyse the TSQM results, we found significant differences in convenience scores between pwMS under scN versus ivN, and an association between scN use and high scores on the convenience items of TSQM ($p < 0.0001$, $X^2 = 74$, Cramér's $V = 0.94$, very large effect), unlike ivN. Regardless of route of administration, most of pwMS showed high percentages of satisfaction in the effectiveness and global satisfaction items, without differences between ivN and scN. Besides, side effects were reported by 10.8% ($n = 7$) in scN group versus 10.6% ($n = 2$) of ivN group, without significant differences (Figure 2). In patients receiving scN, all reported adverse events were injection site reactions. Of the two patients with ivN, one of them reported headache and the other rashes during the infusion. No cases of progressive multifocal leukoencephalopathy (PML) were found. It should be noted that these side effects did not interfere with physical and mental health in 100% of cases and were reported as mild. They also did not affect overall satisfaction with the medication.

With the MS-TAQ questionnaire, we observed an association between the use of scN with high scores in compliance with dosing and effortless treatment compliance ($p < 0.033$, $X^2 = 6.8$, Cramér's $V = 0.28$, small-to-medium effect; $p < 0.004$, $X^2 = 15.4$, Cramér's $V = 0.42$, medium to large effect, respectively) compared to ivN (Figure 3). In relation to the barriers to access natalizumab, both iv and sc, of total of pwMS analysed, 42% ($n = 36$) had a delay or lack of at least one natalizumab dose, due to failure to deliver medication from their health insurance. In this case, all patients are treated in the public health sector.

Discussion

The introduction of DMTs has led to reductions in disease activity and improvements in quality of life for people with MS.[16] Despite the benefits of DMTs for MS, several problems are associated with their use, including inconvenient methods and schedules of administration and significant side effects.[17] The number of DMTs, particularly for RRMS, has increased significantly in recent years. DMTs differ not only in their efficacy and safety/tolerability but also in the treatment burden associated with their initiation, route and frequency of administration, maintenance therapy and monitoring. All these factors can significantly impact the quality of life, even though DMTs are effective in preventing new relapses, MRI activity and disability progression. Moreover, the side effects of the treatment may be more relevant to the patients than the potential for delayed disease progression, especially in those with a disease duration of more than 5 years.[18,19] Furthermore, one study found that while efficacy was the most

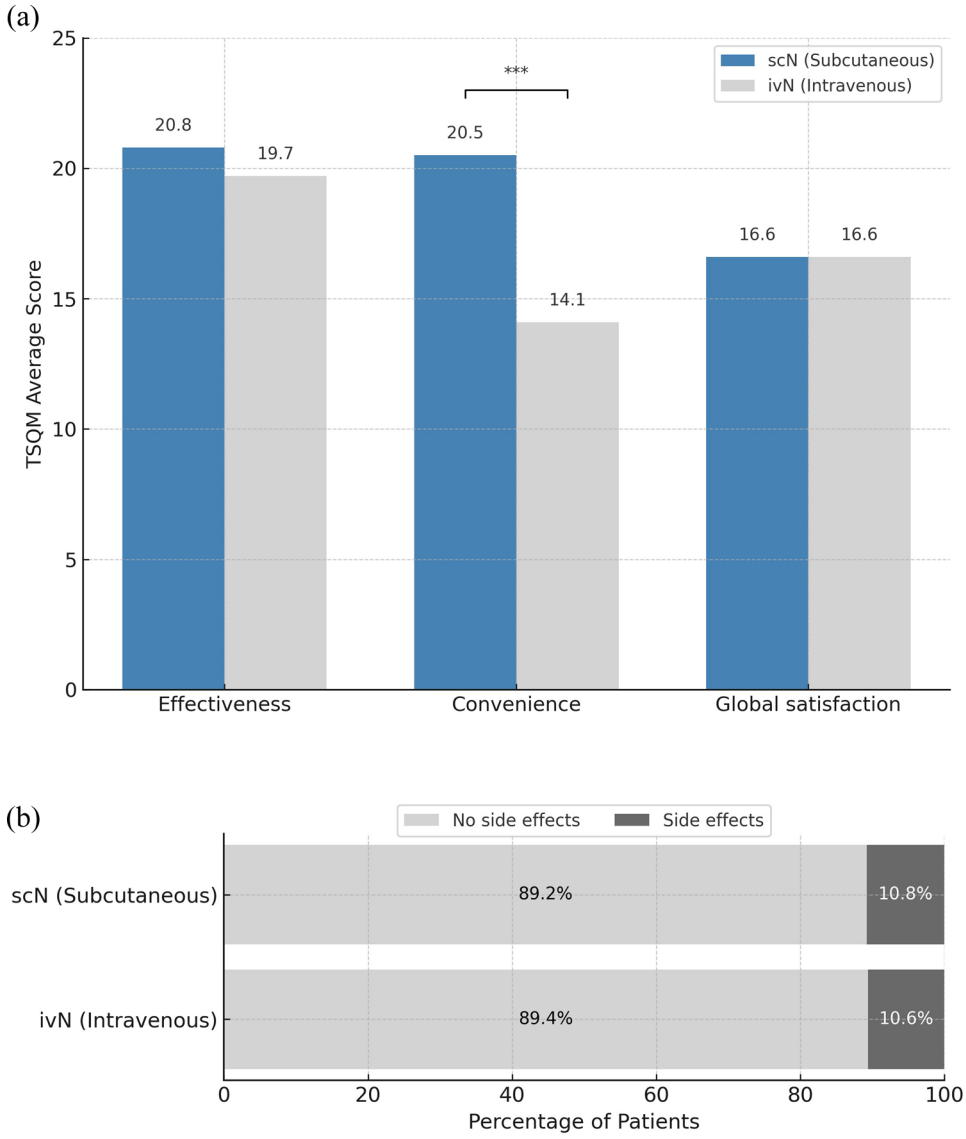

Figure 2. Results of Treatment Satisfaction Questionnaire for Medication V 1.4. (a) Effectiveness, convenience and global satisfaction. (b) side effects.
ivN, intravenous natalizumab; scN, subcutaneous natalizumab.
***$p \leq 0.001$.

important factor in preference among DMTs, patients highly valued avoidance of injection discomfort and convenience of administration when choosing a DMT.[20] Overall, these issues associated with the use of DMTs may negatively impact an individual's adherence to therapy. Consequently, maintaining good adherence is essential to optimise long-term treatment outcomes.[21] In fact, the proportion of non-adherent patients on DMTs has been reported to be as high between 25% and 45% with platform therapies.[22,23] In contrast, adherence, preference and satisfaction with HETs in RRMS are poorly addressed. Only one European study investigated these aspects in patients with ivN compared with scN.[4] Based on these data, our study evaluated treatment satisfaction, preferences, adherence and access to scN compared with ivN, owing to the limited availability of such data in our region.

In this study, we evaluated adherence using the MS-TAQ questionnaire and assessed barriers to

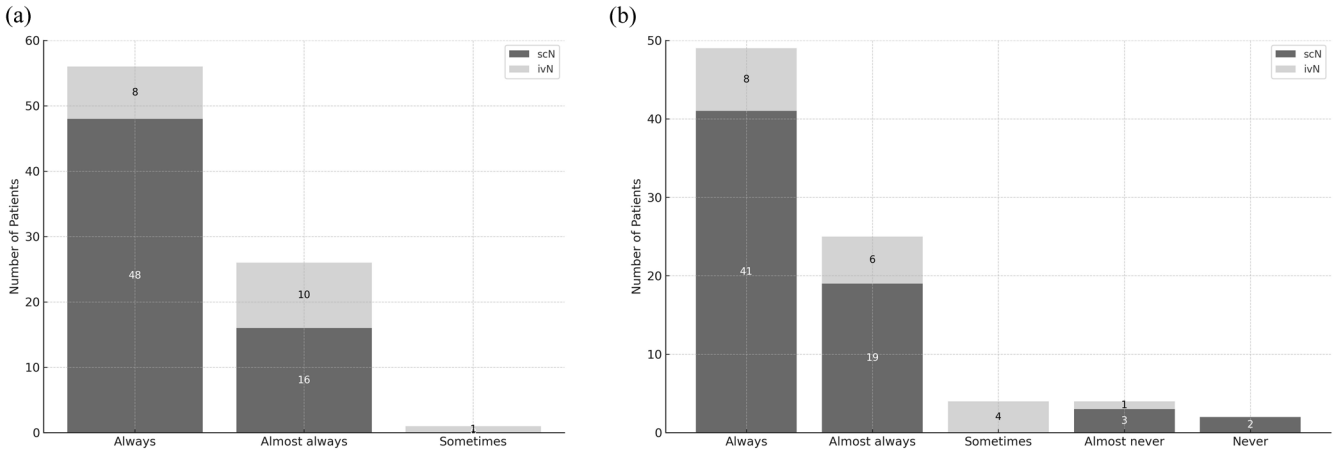

Figure 3. Results of MS-TAQ. (a) Compliance with dosing. (b) Effort involved in natalizumab use.
ivN, intravenous natalizumab; scN, subcutaneous natalizumab.

access to natalizumab, both intravenous and subcutaneous, using an ad-hoc questionnaire. We observed a loss of adherence in a subset of people with multiple sclerosis (pwMS), which resulted in delays in dosing. This was primarily due to a lack of timely delivery of doses by health coverage providers in most of these patients. The existence of barriers to access available DMTs in the Latin American (LATAM) pwMS not only for natalizumab but also for all DMTs were assessed by Carnero Contentti and colleagues.[24] The vast majority of patients included in this study had private or local social security coverage (national social security programmes). PwMS receiving care in the public sector, without any health insurance, is not adequately represented. However, in this study, approximately half of the patients lacked healthcare insurance, rendering them particularly vulnerable in terms of accessing DMTs. It is important to highlight that, beyond barriers to DMT access, numerous challenges remain in achieving genuinely patient-centred care within our region. Substantial knowledge gaps persist regarding MS epidemiology, societal factors, healthcare system dynamics and the perspectives of individual healthcare practitioners and patients.

A study conducted by our group in 2020, prior to scN approval, that evaluated adherence to available DMTs (beta interferon, glatiramer acetate, teriflunomide, dimethyl fumarate, iv natalizumab, ocrelizumab, fingolimod, rituximab and azathioprine) using MS-TAQ in LATAM showed an overall adherence of 78.1%.[13] In this study, patients receiving infusion therapies were significantly more likely to belong to the adherent group and to engage in shared decision-making with their neurologist and family. Lower EDSS and treatment duration were independent predictors of adherence.[13]

This study also assessed treatment satisfaction of ivN versus scN using TSQM. We found that, regardless of route of administration, most of pwMS showed high percentages of satisfaction in the effectiveness and global satisfaction items, without differences between ivN and scN. In contrast, significant differences were found in comfort/convenience items, with a higher score in the people receiving scN, compared to ivN. The SISTER study[4] is the only real-world evidence study that evaluates preference for sc versus ivN in RRMS patients. The primary objective was to compare patients' preference for route of administration and satisfaction with scN versus ivN at baseline and at subsequent visits up to 12 months. Secondary objectives included drug utilisation, clinical outcomes, safety and treatment satisfaction in a real-world care setting. In this study, the use of the TSQM II revealed that baseline treatment satisfaction was higher in the cohort who switched from ivN to scN compared with the two starter cohorts (iv and sc). While overall treatment satisfaction remained stable in the scN switcher cohort, comparable increases were observed in both starter cohorts from Month 6 onwards, which then remained stable through Month 12.[4]

Other studies evaluated satisfaction with natalizumab treatment using the TSQM tool but only

in pwMs under ivN. In a randomised controlled study of intravenous natalizumab 6-week dosing (Q6W) versus continued 4-week dosing(Q4W) for RRMS NOVA study, no significant differences between Q6W and Q4W groups in change from baseline in TSQM items were observed.[25] Furthermore, in a study performed by Glanz and colleagues, ivN-treated participants reported greater satisfaction with the ability of the medication to treat or prevent their condition than IFNβ-1a IM-treated participants using TSQM.[16] Another LATAM study including pwMS under all DMTs approved until 2020, pwMS treated with infusion therapies (natalizumab, ocrelizumab and rituximab) were significantly more satisfied with the amount of time it takes the medication to start working. Additionally, patients treated with injectable drugs (interferons and glatiramer acetate) experienced more side effects in comparison with patients treated with infusion therapies and oral drugs (teriflunomide, dimethyl fumarate and fingolimod).[13]

In relation to the costs associated with the mode of administration, although this was not evaluated in our study, Hincapie and colleagues from the USA showed that out-of-pocket costs of therapy were the main driver of preference among DMTs for MS, illustrating the need to consider patients' treatment preferences within the context of the healthcare provision that they receive.[26] In line with these findings, the EASIER study demonstrates that scN administration will consistently reduce consumption of patient and healthcare professional times per procedure and associated costs. With the adoption of the sc route of natalizumab in nine Italian MS centres, healthcare professionals estimated a 50% reduction in patient procedure time and 55% lower healthcare professional active working time. This translated into a 63% cost reduction for the MS centre per natalizumab administration procedure.[27] Additionally, a study carried out in Spain, showed benefits in terms of direct and indirect cost. ScN use was associated with cost savings for the healthcare system by avoiding drug preparation, reducing administration time and freeing up infusion suite capacity. Additional cost savings could be derived from regional hospital administration of scN by reducing productivity loss.[28]

Regarding safety, we found a low rate of side effects, both for scN and ivN, similar to those reported in the DELIVER, REFINE and SISTER studies. Besides, the type of side effect was also similar to that found in these studies.[4,9,10] Additionally, in our cohort, all patients had a low anti-JCV index (<0.9), and none had previously received immunosuppressive therapy before initiating natalizumab. Because of this, no patients had a risk of PML greater than 6 in 10,000.[29–31] These findings are relevant when assessing the risk of PML. As previously reported, both subcutaneous (scN) and intravenous natalizumab (ivN) formulations are considered equivalent in terms of safety profile and associated risk of PML.

Finally, one limitation of our study is the relatively small number of patients included, which reflects low frequency of MS in our country. Most recent estimate reported a prevalence of 38.2 per 100,000 inhabitants in 2016.[3] Furthermore, not all patients are treated with monoclonal antibodies. A recent local study reported that only 19% of pwMS were receiving HET among 2450 cases.[32] In addition, due to the cross-sectional design of this study, causal inferences cannot be reliably made. Lastly, another limitation was the potential for response bias, as only 84 out of 118 eligible patients completed the questionnaires. However, the demographic and clinical characteristics of respondents and non-respondents were comparable, which may reduce the likelihood of significant bias.

Conclusion

We found a high rate of change to scN from ivN, associated with a higher score in the comfort and convenience items in people receiving scN, compared to ivN. Access barriers should be addressed in order to improve treatment comfort.

Declarations

Ethics approval and consent to participate

We confirm that we have read and understood *Therapeutic Advances in Neurological Disorders*'s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study protocol was approved by the Ethics Board of Hospitals involved (protocol No. 7066, PRIISA BA 12331), approved by [CEPI-HIBA] on 12 September 2023. Online/virtual informed consent was granted by each patient. Informed consent was obtained in written electronic form through the online platform prior to participation.

Consent for publication
Not applicable.

Authors' contributions
Berenice A. Silva: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Franco Santajuliana: Investigation; Resources; Writing – review & editing.

Magdalena Casas: Investigation; Resources; Writing – review & editing.

Luciana Lázaro: Investigation; Resources; Writing – review & editing.

Cecilia Pita: Investigation; Resources; Writing – review & editing.

Leila Cohen: Investigation; Resources; Writing – review & editing.

Guido Rinaldi: Investigation; Resources; Writing – review & editing.

Ricardo Alonso: Investigation; Resources; Writing – review & editing.

Jimena Míguez: Investigation; Resources; Writing – review & editing.

Sofía D'Alessandro: Conceptualisation; Data curation; Investigation; Resources; Software; Supervision; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The datasets used and analysed in this study are available from the corresponding author upon reasonable request.

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Supplemental material
Supplemental material for this article is available online.

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