Effectiveness of Subcutaneous Natalizumab in Multiple Sclerosis: Real-World Evidence from a Finnish Registry Study

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Introduction

- Multiple sclerosis (MS) is a chronic, inflammatory neurodegenerative disease of the central nervous system driven by autoreactive T cells.[1]
- The majority (≥85%) of patients initially present with a relapsing-remitting phenotype (RRMS) which often later develops into secondary progressive MS (SPMS).[1]
- Natalizumab is a high-efficacy disease-modifying therapy that was originally available as an intravenous (IV) infusion for patients with highly active RRMS. A subcutaneous (SC) formulation was approved by the European Medicines Agency in 2021.[2,3]
- SC administration may reduce healthcare resource use and related costs compared with IV infusion. Evaluating real-world treatment outcomes after switching from IV to SC is essential to determine whether these potential benefits can be achieved without compromising the quality of care.[4–6]

Objective

To evaluate the real-world effectiveness of SC natalizumab in patients with highly active RRMS, including:

- those who switched from IV administration,
- those who initiated natalizumab directly with the SC formulation, and
- subgroups based on dosing intervals

Methods

- This retrospective registry study included adult RRMS patients who had ≥1 SC administration of natalizumab between April 2021 and October 2023.
- Patients were identified from electronic health records across three Finnish university hospitals (Helsinki, Turku, and Tampere). Data were supplemented with records from the Finnish MS Registry.
- Index was defined as the date of first administration of SC natalizumab, either as a switch from IV formulation or direct initiation. The study baseline period covered 18 months before the index date, and patients were followed up until the end of the study period or death.
- Two subgroups were defined:

  1. **IV-to-SC switchers**: patients with ≥1 IV natalizumab infusion prior to SC initiation; further subdivided into those receiving standard interval dosing (SID: <5 weeks) and extended interval dosing (EID: ≥5 weeks) under SC treatment

  2. **SC-first users**: patients with no prior natalizumab use before SC initiation

- Effectiveness was assessed by changes in annual relapse rate (ARR) and expanded disability status scale (EDSS) at 12 months post-SC initiation. ARR at baseline and at 12 months was calculated as the number of relapses during the respective 12-month period divided by total person-time.
- In a subset of patients (n=74), disease activity was evaluated based on the change in total number of T2 lesions in magnetic resonance imaging (MRI) scans between baseline and 12-month follow-up (categorized to: no change, increase, or decrease). MRI scans closest to index and the 12-month timepoint (within a ±6-month window) were used.
- Treatment persistence of natalizumab SC was analyzed by Kaplan-Meier survival analysis. Discontinuation was defined by the last recorded dose. For patients without a recorded discontinuation, discontinuation was assumed after 14 weeks of previous natalizumab SC recording.
- Statistical differences within and between groups were tested using appropriate parametric or non-parametric methods, with significance levels adjusted for multiple comparisons.

Results

Patient characteristics

- The study included 179 IV-to-SC switchers (median follow-up 22.8 months) and 43 SC-first users (10.8 months). Median (Q1, Q3) age at index was 40 (32, 46) for the IV-to-SC switchers and 33 (27, 39) for SC-first users. In both subgroups, ≥70% of patients were females (**Table 1**).

Table 1. Patient characteristics

		IV-to-SC switchers (n=179)	SC-first users (n=43)
Median age, years (Q1, Q3)	At diagnosis	29 (23, 35.5)	28 (23.5, 34)
	At index date	40 (32, 46)	33 (27, 39)
Sex, n (%)	Female	133 (74%)	30 (70%)
	Male	46 (26%)	13 (30%)
MS phenotype, n (%)	RRMS	165 (92%)	39 (91%)
	PPMS or SPMS	3 (2%)	0 (0%)
	Unspecified	11 (6%)	4 (9%)
JCV status at baseline, n (%)	Tested	131 (73%)	38 (88%)
	Negative	106 (81%)	23 (61%)
	Positive	10 (8%)	15 (39%)
	Unknown	15 (11%)	0 (0%)

IV, intravenous; JCV, John Cunningham virus; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; Q1, first quartile; Q3, third quartile; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.

Treatment persistence

- Among IV-to-SC switchers, the probability of continuing treatment was 88% (95% CI 0.83–0.93) at 12 months and 81% (0.74–0.87) at 24 months (23-month estimate as proxy) (**Figure 1**).

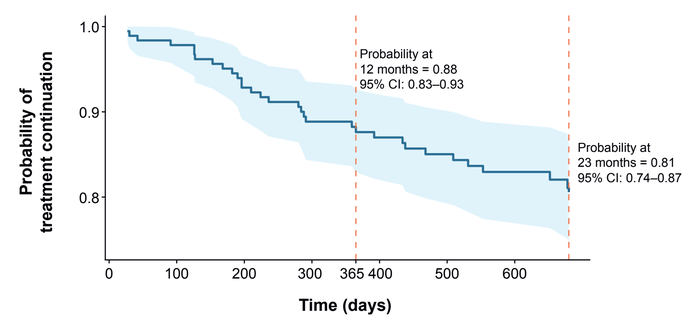

Figure 1. Treatment persistence of natalizumab SC across the follow-up among the IV-to-SC switchers.

Annual relapse rate

- Among IV-to-SC switchers, mean ARR was 0.10 (SD 0.28) at baseline and 0.08 (0.71) at 12 months post-SC initiation (Δ=0.02; p<0.05). In SC-first users, ARR decreased from 0.88 at baseline to 0.00 at 12 months (p<0.0001) (**Figure 2A**).
- Among IV-to-SC switchers, the SID subgroup (n=83) had an ARR of 0.16 (1.0) at 12 months post-SC initiation. In the EID subgroup (n=84), fewer than three relapses occurred, preventing reporting of ARR due to privacy restrictions. (**Figure 2B**).

Neurological function and disease activity

- EDSS scores remained stable with mean (SD) values of 2.7 (1.7) at baseline and 2.9 (1.6) at 12 months in IV-to-SC switchers.
  - In the SID subgroup, EDSS scores were 2.4 (1.6) at baseline and 3.0 (1.8) at 12 months.
  - In the EID subgroup, EDSS scores were 3.0 (1.9) at baseline and 2.6 (1.5) at 12 months.
- At the 12-month follow-up, disease activity (T2 lesion counts) remained unchanged compared to baseline in 90% (n=48, patients with MRI data available) of IV-to-SC switchers (**Table 2**).
  - Similar results were observed with different dosing schedules: 87% of patients in the SID subgroup and 93% in the EID subgroup had stable lesion counts (**Table 2**).

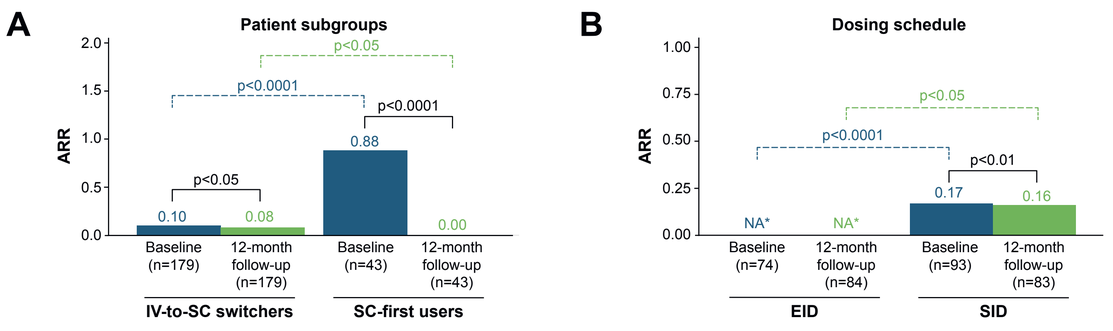

Figure 2. Annual relapse rate (ARR) at baseline and 12-month follow-up in A) intravenous to subcutaneous (IV-to-SC) switchers and SC-first users, and B) by dosing schedule (extended interval dosing or standard interval dosing [EID/SID], among the IV-to-SC switchers). *Results for groups with <3 relapses cannot be displayed due to data privacy restrictions under the Finnish *Act on the Secondary Use of Health and Social Data (552/2019)*.

Table 2. Change in disease activity from baseline to follow-up at 12 months, based on MRI.

T2 lesion count	IV-to-SC switchers (n=74*)		EID (n=43*)		SID (n=27*)	
	Patients (n)	Proportion	Patients (n)	Proportion	Patients (n)	Proportion
Decreased	0	0	0	0	0	0
Increased	<3	NA	<3	NA	<3	NA
Same	48	0.90	27	0.93	20	0.87
Unknown	3	0.06	<3	NA	<3	NA

EID, extended interval dosing; IV, intravenous; MRI, magnetic resonance imaging; SC, subcutaneous; SID, standard interval dosing. *Analyses based on fewer patients due to limited data availability (exact counts not shown for data protection). In addition, the patients with dosing intervals >10 weeks and with out-of-normal dosing trajectories were excluded from the EID/SID categorization.

Conclusions

SC natalizumab remained effective after switching from IV. It also demonstrated significant effectiveness in SC-first users. EID did not compromise effectiveness. However, as these results are observational and descriptive in nature, no causal conclusions can be drawn.

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