Subcutaneous Natalizumab Administration in Relapsing-Remitting Multiple Sclerosis: Results of the EASIER 2 Study

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OBJECTIVE

To evaluate patient time, healthcare professional (HCP) working time, healthcare resource consumption, costs, and patient quality of life (QoL) associated with subcutaneous (SC) administration of natalizumab in relapsing-remitting multiple sclerosis (RRMS), compared to intravenous (IV) administration as measured in the EASIER study from the perspectives of the MS center, the patient, and the society.

CONCLUSIONS

SC natalizumab compared to IV natalizumab administration significantly reduces administration procedure times, healthcare resource consumption, and associated costs, while improving patient experience and quality of life, independent of disability level.

Introduction

- Multiple sclerosis (MS) is a chronic and disabling disease that primarily affects young adults in their working years.
- MS has a direct impact on patients' functionality and quality of life, leading to increased use of healthcare and non-healthcare resources, and a reduction in work capacity and productivity.
- **Natalizumab** is used to treat patients with highly active relapsing-remitting MS (RRMS).
- It controls and reduces inflammation, decreases axonal damage, and delays the progression of motor and cognitive disability.
- It is administered intravenously (IV) via slow infusion lasting approximately 60 minutes or subcutaneously (SC) through two injections administered within 30 minutes between each other.
- In the EASIER study, before the availability of SC natalizumab in Italy, the administration times and costs for IV natalizumab were measured

Methods

EASIER 2 study

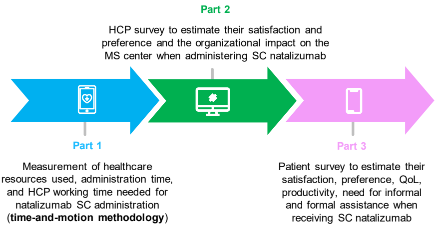
- **EASIER 2** was a multicenter, observational, cross-sectional study carried out in 14 Italian MS centers (*Figure 1*).
- Patients involved were adults with RRMS presenting to the MS center for the scheduled administration of natalizumab, as part of the clinical routine.

Study Design

- EASIER 2 study was made of **3 parts** (*Figure 2*):
  - **part 1:** time-and-motion study conducted to measure healthcare resources and working time needed in clinical practice for natalizumab SC administration using a digital-data-collection-tool operated directly by healthcare professionals (HCPs);
  - **part 2:** HCP structured questionnaire-based assessing preferences and impact on MS center organization;
  - **part 3:** patient survey on patient time, satisfaction, preferences, quality of life and burden of natalizumab administration on patient life.
- In addition to the descriptive statistics on the data collected from the 14 centers, SC procedure times (HCP time, patient time, and chair time) were estimated using a random-intercept regression model to account for potential organizational differences among participating centers.
- The comparison between SC and IV infusion times was conducted using a similar random-intercept regression model adjusted for patient history. This analysis was limited to the 8 centers involved in both the EASIER and the EASIER 2 studies.
- An economic evaluation was conducted using collected data to calculate the impact of SC administration vs IV administration (according to the previously conducted EASIER study) including direct healthcare costs, direct non-healthcare costs, and indirect costs, respectively, in the perspectives of MS center, patient, and society. Unit costs for healthcare resources were obtained from the accounting of the participating centers; other costs (HCP working time, caregiving needs, and productivity losses) were sourced from official data.
- Study indicators are reported in *Figure 3*.

Figure 1. EASIER 2 study: Italian MS center locations.

Figure 2. EASIER 2 study design.



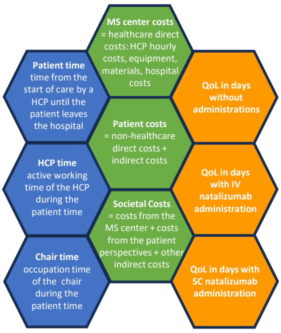


Figure 3. EASIER 2 study indicators.

Results

Baseline characteristics

- The enrolled patients had an average age of 40 years. Patients had undergone a mean of 62 previous IV administrations and 4 previous SC administrations.
- Traveling to the MS center to receive treatment resulted in a loss of 4.2 hours per administration. 57% of patients had paid employment, and these individuals had to take a mean of 3.8 hours off work to travel to the MS center and receive SC natalizumab administration. About 51% had been going to the center accompanied by caregiver(s) (relative and/or friend).

Treatment Time

- In total, 14 Italian MS centers measured 274 SC natalizumab administration procedures. Patients spent on average 26.6 minutes at the MS center, with 13.5 minutes of active HCP working time and 27.3 minutes of chair occupancy.
- The time estimates obtained from the random-intercept regression model from the 8 centers participating in both the EASIER and the EASIER 2 studies (*Table 1*) showed that, compared to IV, SC administration reduced patient time by 77,4%, HCP working time by 34.8%, and chair time by 74.2%. They were consistent with those obtained when analyzing all the 14 centers.

Table 1. Differences in patient time, HCP time, and chair time between SC (EASIER 2 study) and IV (EASIER study). Analysis conducted in the 8 centers participating in both the studies.

	Adjusted* mean difference SC vs IV (minutes)	95% CI	Reduction %
Patient time	-114.0	-126.8 to -101.2	-77.4%
HCP time	-8.7	-11.6 to -5.7	-34.8%
Chair time	-82.5	-92.4 to -72.7	-74.2%

*estimated with a generalized linear regression model with random intercept adjusted by number of previous IV and SC administrations

These results were consistent with those obtained when analyzing all the 14 centers.

Economic Analyses

- When national costs were considered, this translated into cost reductions from all perspectives considered (*Table 2*) with a reduction of 60.6%, 13.5%, and 33.7% respectively for the MS center, the patient, and the Italian society per each SC natalizumab administration procedure vs IV administration.

Table 2. Economic analyses results per visit.

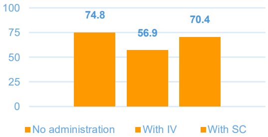
Total costs	SC administration (€)	IV administration (€)	Difference (€; %)
MS center perspective	13.01	32.67	-19.66 (-60.6%)
Patient perspective	45.03	52.05	-7.02 (-13.5%)
Society perspective	118.44	177.62	-59.18 (-33,7%)

SC = subcutaneous; IV = intravenous; CI = Confidence Interval; MS = Multiple sclerosis; HCP = healthcare professional

Quality of life (QoL)

- QoL scores (scale 0–100) were higher on SC days (mean 70.4) than IV days (mean 56.9) administration, corresponding to a 13-point improvement ($p<0.001$) (*Figure 4*).
- The effect of method of administration was confirmed through a linear regression model adjusted for age, gender, previous experience with natalizumab IV and SC, occupation (paid work Yes vs No)
- In a further analysis the model was also adjusted for the EDSS variable included as a continuous parameter and as a dichotomous parameter (EDSS < 4 or ≥ 4)
- Higher disability (Expanded Disability Status Scale [EDSS] ≥4) was associated with lower overall QoL scores, but the benefit of SC over IV was consistent across EDSS levels.

Figure 4. QoL assessment of a day based on the type of administration (VAS scale 0–100).



Preferences

- Among patients, **86% preferred SC administration**, mainly due to shorter center time, less physical discomfort, and lower emotional burden.
- **All HCPs reported a favorable opinion** on SC administration, with 82% expecting or have already observed improvements in MS center organization and shorter patient waiting lists.

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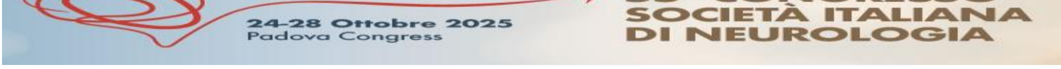
Competing Interests: MF: is Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi; speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda; scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme; he receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla; LMEG: has received funding for travel to attend scientific events or speaker honoraria from Merck, Biogen Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd., Roche, Novartis, Bayer Schering Pharma, Alexion and Neuraxpharm; VBM: disclosed travel/meeting expenses from Novartis, Janssen, Roche and Merck and speaking honoraria from Merk, BMS, Biogen, Novartis, Roche and Almirall; AC: has served on advisory boards and/or received honoraria for speaking or consultation fees from Biogen, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, BMS, Amgen, Almirall, Alexion; CC: in the last two years I received personal compensation for advisory board, speaking and travel grants from Biogen, Novartis, Merck Serono, BMS, Roche; RT: has served on advisory boards and/or received honoraria for speaking or consultation fees from Alexion, Almirall, Biogen, CSL behring, Janssen-Cilag, Merck-Serono, Novartis, Roche, Sanofi-Genzyme; GL: received research grants and honoraria as a speaker and member of advisory boards by: Alexion, Bristol, Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Almirall, Allergan, Merz, Ipsen, Roche; AR: received a grant for the organization of a scientific congress or speaker honoraria from Biogen Idec, Sanofi, Merck Serono, Bristol, and Roche; FM: received compensation for speaking activities, travel grant, and participation in advisory board from Biogen, Bristol-Myers Squibb, Novartis, Roche, Sanofi-Genzyme, and Merck-Serono; PV: has received speaker's honoraria and consulting fee, honoraria for advisory boards from Biogen Idec, Novartis, Merck Serono, Sanofi Genzyme, and TEVA; PP: has received speaker honoraria and consulting fees from Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; GM: is an Advisory Board member of Biogen Idec, Sanofi Genzyme, Merck-Serono, Novartis, and TEVA, and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, and TEVA. She is the principal investigator in clinical trials for Actelion, Biogen Idec, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, and TEVA; MV: Biogen, Sanofi, TEVA, Merck, Roche; SM: Consultation and speaking fees from Sanofi-Genzyme, Biogen-Idec, Merck Serono, Novartis, Celgene-Bristol-Myers Squibb Company, Teva; CZ: received compensation for speaking activities, and/or consulting services, from Alexion, Astrazeneca, Biogen, Bristol-Myers Squibb, Janssen, Merck, Novartis, Roche, Sanofi; LP: is the co-owner and an employee of AdRes, which has received project funding from Biogen; DP, LS: are employees of and may hold stock in Biogen

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