Natalizumab for Multiple Sclerosis: an observational study related to drug administration, and expectations about benefits and risks

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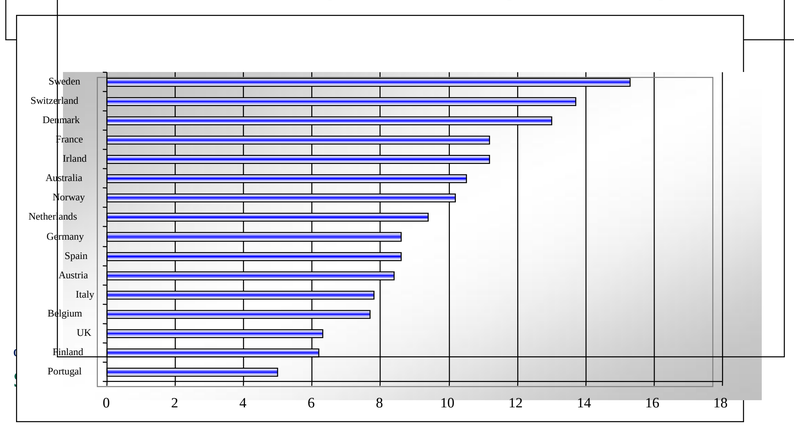
Background

The emergence of new pharmacological therapies for Multiple Sclerosis (MS) poses some challenges: Natalizumab was approved for the treatment of relapsing–remitting MS in 2004.
Natalizumab is a humanized monoclonal antibody against the cellular adhesion molecule $\alpha 4$ integrin. Natalizumab is administered by intravenous infusion every 28 days, while other therapies were administered daily or 3 times a week. The drug is believed to work by reducing the ability of inflammatory immune cells to attach to and pass through the cell layers lining the blood-brain barrier. Natalizumab has proven effective in preventing relapses, cognitive decline and significantly improving quality of life in people with MS. Despite its efficacy has been confirmed by several clinical trials, the use of Natalizumab has been limited after Progressive Multifocal Leukoencephalopathy (PML) was identified as a rare but serious brain infection associated with its assumption.
The collection of pharmacovigilance data is essential for monitoring safety of Natalizumab, its effectiveness and patients' acceptance of risks and expectations from the treatment.

Use of Natalizumab in European countries (data of 2009)



Data and methodology

The main objective of the research project has been to monitor all adverse events occurred during the treatment with Natalizumab and to create a Regional registry on the use of Natalizumab for Relapsing Remitting Multiple Sclerosis (RRMS) patients.
All consecutive RRMS patients treated at the six most important neurological centres in Sicily (IRCCS Centro Studi Neurolesi, Policlinico of Palermo "P. Giaccone", Policlinico of Catania "G. Rodolico", Policlinico of Messina "G. Martino", Ospedali Riuniti Villa Sofia-Cervello of Palermo, IRCCS "San Raffaele Giglio" of Cefalù) have been included in the analysis: the Natalizumab patients' population in Sicily is of 280 patients. The project started in the first months of 2012 and, at April 30th, 2012, observations about **107 patients** are already available.
A questionnaire has been administered to all patients; they have been asked about their clinical condition, satisfaction with Natalizumab and their acceptance of the risk associated to the treatment. The questionnaire has been filled by the patients, helped by psychologists and counsellors. Some of the questions included in the questionnaire are the **MSQol 54** items on daily activities and judgments about their own health.
Moreover, disability status, measured by physicians through the **Expanded Disability Status Scale** (EDSS), were obtained. Data show a clear picture of the Natalizumab patients' population (see tables 1 and 2).

Table 1: descriptive statistics and patients' clinical conditions

Variable	Mean	Std. Dev.	Min	Max
Age	37	9.2	15	59
Age at diagnosis	28	9	10	54
Gender	0.26	0.44	0	1
Married	0.57	0.49	0	1
Years of disease	10	6.4	1	33
Number of relapses	8.23	7	0	40
Last relapse <6months	0.31	0.47	0	1
Last relapse <12months	0.35	0.48	0	1
Severity of last relapse	0.38	0.49	0	1
Evaluation on health status:				
Excellent	0.04	0.20	0	1
Very good	0.13	0.34	0	1
Good	0.19	0.39	0	1
Sufficient	0.46	0.50	0	1
Poor	0.21	0.41	0	1
Health status before the diagnosis (0 to 10)	8.36	1.96	3	10
Evaluation on health status comparing to 12 months ago				
Much better	0.16	0.37	0	1
Slightly better	0.18	0.39	0	1
Same	0.45	0.50	0	1
Worse	0.14	0.35	0	1
Much worse	0.10	0.30	0	1
EDSS	3.14	2.08	0	7
Compliant (yes/no)	0.91	0.27	0	1
Disadvantages (yes/no)	0.52	0.50	0	1
Years of treatment	6.23	4.20	0	20

Table 2: items from MSQOL 54

Activities and Limitations (1=strong limitations; 2= slight limitations; 3=no limitations)	Mean	Std. Dev.	Min	Max
Vigorous activities	1.49	0.70	1	3
Moderate activities	2.12	0.77	1	3
Lifting or carrying groceries	1.92	0.81	1	3
Climbing several flights of stairs	1.77	0.77	1	3
Climbing one flight of stairs	2,25	0.75	1	3
Bending, kneeling, stooping	1.89	0.83	1	3
Walking more that 1 km	1.74	0.85	1	3
Walking more than 500 m	2.01	0.77	1	3
Waling more than 100	2.37	0.73	1	3
Bathing and dressing	2.55	0.60	1	3
Assessment for some dimensions (1=definitely true; 2=mostly true; 3=not sure; 4=mostly false; 5=definitely false)				
I seem to get sick easier	3.54	1.20	1	5
I am health as anybody I know	3.30	1.31	1	5
I expect my health to get worse	2.65	1.21	1	5
My health is excellent	3.74	1.08	1	5

Table 3: uncertainty and knowledge of risk

Uncertainty and information - major fears	Mean	Std. Dev.
Limitations in everyday activity	0.19	0.39
Loss of independence	0.68	0.47
More severe disability	0.42	0.50
More information about the disease	0.83	0.37
Source of information: physicians	0.78	0.41
Source of information: internet, media	0.73	0.45
Source of information: patients	0.32	0.47
Knowledge of risk associated to Natalizumab and its acceptance	**0.91**	**0.28**
0.001% risk (1/100,000)	0.79	0.41
0.01% risk (1/10,000)	0.65	0.48
0.10% risk (1/1,000)	0.38	0.49
Benefit 50%, risk 0.1%	0.57	0.49
Benefit 90% risk 0.1%	0.66	0.47
Benefit 100% risk 1%	0.52	0.5

The explanatory variables concerns patients's clinical situation (age, number of relapses, years of disease) and their perception about their health status before the disease, their knowledge of disease and their beliefs about the higher probability of worsening in the next 5 years.

Since data about knowledge of risks and information about Natalizumab have been collected, a preliminary regression analysis has been run by applying a logit model. Here the dependent variable is the circumstance that the patient declares to receive a positive utility from the treatment (yes/no).

Table 4: A preliminary logit estimation

Dependent variable: "Does the patient receive a positive utility from the therapy with Natalizumab?" (yes/no)	Coefficient (Std. errors in brackets)	t-test	Marginal effects (Y- positive utility from Natalizumab yes/no = 0.856)
Age	-0.153 (0.467)	-0.33	-0.001 (0.005)
Number of relapses	0.161 (0.116)	1.39	0.019 (0.014)
Assessment of health status before the disease	0.644** (0.232)	2.77	0.079** (0.026)
Knowledge about risks	0.175 (0.973)	0.02	0.002 (0.120)
Years of disease	-0.202* (0.098)	-2.05	-0.024* (0.012)
Upper limit of worsening	-0.066** (0.023)	-2.82	-0.008** (0.002)
Constant	0.837 (2.780)	0.30	
Wald c^2 = 13.39; Prob> c^2 = 0.0372			
Log pseudolikelihood = 24.090185 ; Pseudo R2= 0.317			

Some remarks

Patients' knowledge about the disease, more than the knowledge about risks of Natalizumab appears to be a relevant factor in determining a positive utility, comparing to other disease modifying drugs (such a interferons). Natalizumab appears to be accepted especially by **young patients**; there is a negative correlation between the years of disease (and previous treatment) and the positive judgment about Natalizumab.
The assessment of health status before the disease onset (that shows a positive correlation with the dependent variable) as well as the negative correlation with the variable signalling the upper limit of worsening, confirms the positive judgments given by patients to the new therapy, in spite of its risks.

Conclusions

This study represents the preliminary stage of a research started at the end of 2011 and currently being carried in Sicily. At the moment, a network between the main neurological centres dispensing Natalizumab has been established. The descriptive analysis reported here shows patients'characteristics and their first assessment of Natalizumab. The most of patients declare themselves satified with the treatment, mainly because of the absence of collateral effects. Patients are, overall, well informed about risks of Natalizumab and about the course of the disease.

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