BIG MS DATA NETWORK

Treatment discontinuation in the Big Multiple Sclerosis Data Network: a descriptive analysis

Tim Spelman[1,2], Melinda Magyari[3,4], Per Soelberg Sørensen[3], Nils Koch-Henriksen[3,5], Helmut Butzkueven[2,6], Sandra Vukusic[7-9], Maria Trojano[10], Pietro Iaffaldano[10], Fabio Pellegrini[11], Robert Hyde[11], Leszek Stawiarz[1], Jan Hillert[1] on behalf of the Big MS Data Network: a collaboration of the Danish MS Registry, Italian MS Registry, Swedish MS Registry, MSBase and OFSEP

[1]Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden, [2]MSBase Foundation, Melbourne, Australia, [3]The Danish Multiple Sclerosis Registry, Department of Neurology, Rigshospitalet, Copenhagen, Denmark, [4]Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark, [5]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [6]MS and Neuroimmunology Research, Central Clinical School, Alfred and Box Hill Hospitals, Monash University, [7] Service de Neurologie, sclérose en plaques, pathologies de la myéline et neuro-inflammation, and Observatoire Français de la Sclérose en Plaques, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Lyon, F-6977, France, [8] Centre des Neurosciences de Lyon, INSERM 1028 et CNRS UMR5292, Lyon, F-69003, France, [9] Université Claude Bernard Lyon 1, Faculté de Médecine Lyon-Est, Villeurbanne, Auvergne-Rhône-Alpes, F-69622, France, [10]Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari Aldo Moro, [11]Biogen International GmbH, Zug, Switzerland

Introduction

Multiple sclerosis (MS) is a life-long disease where disability typically develops over decades. For almost 20 years, disease modifying drugs (DMDs) have been available to reduce attack frequencies, focal inflammatory brain lesions and development of disability. Changes in product availability, reimbursement and treatment recommendations have led to a growing interest for identifying reliable predictors of DMD discontinuation and to study how discontinuation on a prescribed drug may differ between specific drugs, between countries, over time and calendar year (of licensing new drug) by using observational data from major clinical MS registries.

Aim

To describe the frequency of DMD discontinuation recorded across the pooled Big MS Data Network (BMSD) and to compare patterns of discontinuation between countries and time periods.

Methods

Treatment episodes and associated patient data complying to minimum dataset requirements were individually extracted from the five contributing datasets and then pooled into a single combined dataset. Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD) or median and inter-quartile range (IQR) as appropriate. Alluvial flow plots were used to illustrate treatment sequences. All analyses were conducted in R (R Foundation for Statistical Computing).

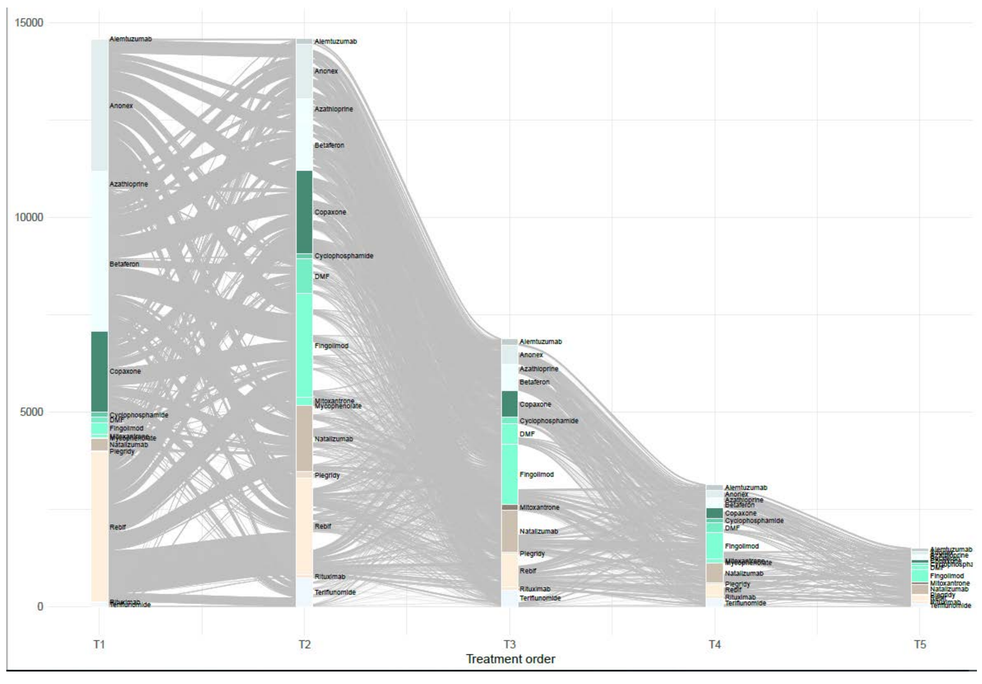
Results

- A total of 110326 patients contributing 269,822 DMD treatment episodes were included in the analysis (Table 1).
- A total of 184,013 (68.2%) DMTs were discontinued during the observation period. IFNβ accounted for the largest proportion of observed treatments in the pooled data (116,551 treatment episodes; 43.2%), followed by natalizumab (NAT) (33,974; 12.6%), glatiramer acetate (GLA) (32,324; 12.0) and fingolimod (FTY) (19,675; 7.3%).
- The incidence of discontinuation was lowest in FTY (19.7 discontinuations per 100 person-years (PY) of treatment; 95% CI 19.2-20.1), followed by NAT (22.6/100 PY; 95% CI 22.2-23-0), IFNβ (23.3/100 PY; 95% CI 23.2-23.5) and GLA (25.8/100 PY; 95% CI 25.4-26.2).

Table 1: Discontinutions by data source

Factor	Denmark	Sweden	OFSEP	Italy	MSBase	Total
Treatment episodes - n	14252	38229	65535	79816	71990	269822
Number of individual patients	7990	15983	24616	26985	34752	110326
Treatment discontinuations - n (%)	8936 (62.7)	24704 (64.6)	45966 (70.1)	59590 (74.7)	44817 (62.3)	184013 (68.2)

Figure 1: Treatment switches; all patients 1996 onwards*



*Limited to patients who discontinued index treatment and started at least 1 post-index treatment. Only first 5 treatments displayed.

Results

Where reason for treatment discontinuation was documented, lack of efficacy was the most frequently reported across the pooled data (23.2%), followed by adverse or side effects (16.1%) and intolerance (13.8%) (Table 2). Whilst inefficacy accounted for the largest proportion of treatment discontinuations in both OFSEP and MSBase, side effects & adverse events were the primary reported drivers of discontinuation in the Swedish, Danish and Italian registries. Figure 1 illustrates the flow of treatment switches across all included patients switching at least once from 1996 onwards. Figure 2a-e illustrates the same flows disaggregated by country/dataset and limited to 2007 onwards (switching population, first 5 treatments per patient displayed only).

Table 2: Reason for discontinuation

Factor	Category	Denmark	Sweden	OFSEP	Italy	MSBase	Total
DMT discontinuations		n=8936	n=24704	n=45966	n=59590	n=44817	n=184013
Reason for discontinuation – n (%)	**Lack of efficacy**	N/A	5524 (22.4)	12020 (26.2)	3088 (5.2)	5402 (12.1)	26034 (14.1)
	Disease progression / EDSS progression / EDSS 7+	1963 (22.0)	N/A	N/A	515 (0.9)	1740 (3.9)	4218 (2.3)
	Lack of tolerance (local, general, biological)	N/A	N/A	8867 (19.3)	3686 (6.2)	2938 (6.6)	15491 (8.4)
	Adverse event / Side effects	3019 (33.8)	5760 (23.3)	881 (1.9)	4881 (8.2)	3604 (8.0)	18145 (9.9)
	Allergic reaction	N/A	N/A	N/A	3204 (5.4)	333 (0.7)	3537 (1.9)
	Convenience	47 (0.5)	N/A	4098 (8.9)	2011 (3.4)	2272 (5.1)	8428 (4.6)
	Pregnancy (planned or confirmed), contraception cessation	372 (4.2)	1450 (5.9)	2320 (5.1)	779 (1.3)	1812 (4.0)	6733 (3.7)
	Scheduled Stop	N/A	N/A	6682 (14.5)	310 (0.5)	5155 (11.5)	12147 (6.6)
	Non-adherence / non-compliance /no motivation	1698 (19.0)	N/A	N/A	2455 (4.1)	402 (0.9)	4555 (2.5)
	Neutralizing antibodies	636 (7.1)	637 (2.6)	N/A	N/A	N/A	1273 (0.7)
	Deceased	266 (3.0)	N/A	N/A	N/A	N/A	266 (0.1)
	Secondary Progressive MS	N/A	1109 (4.5)	N/A	N/A	N/A	1109 (0.6)
	Other	0 (0.0)	6954 (28.1)	1734 (3.8)	805 (1.4)	1013 (2.3)	10506 (5.7)
	Not reported / Unknown	935 (10.5)	3270 (13.2)	9364 (20.4)	37856 (63.5)	20146 (45.0)	76887 (41.8)

Figure 2a: Treatment switching in the Danish MS Registry (2007+)

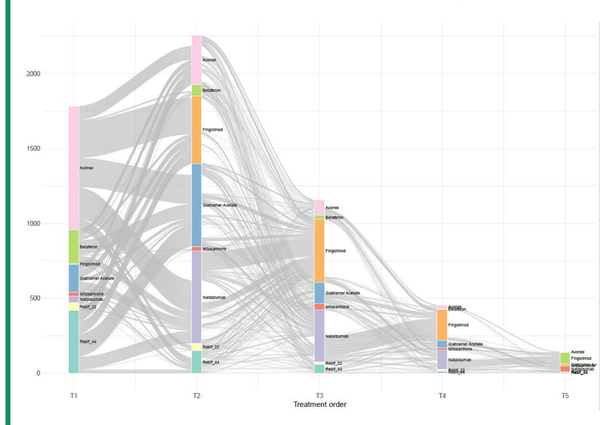


Figure 2b: Treatment switching in the Swedish MS registry (2007+)

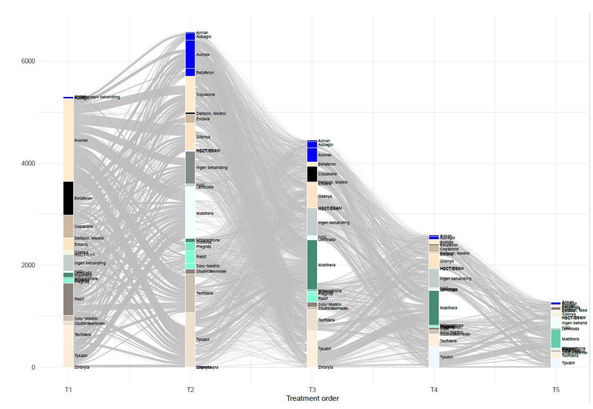


Figure 2c: Treatment switching in OFSEP (2007+)

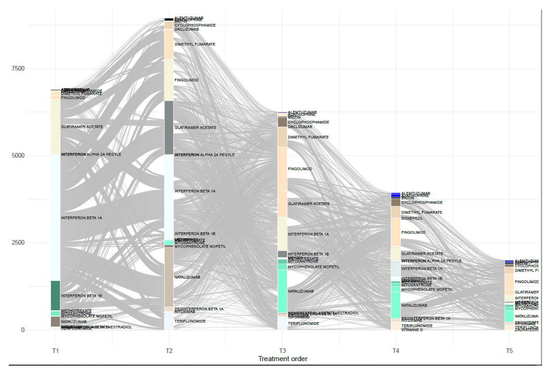


Figure 2d: Treatment switching in the Italian MS registry (2007+)

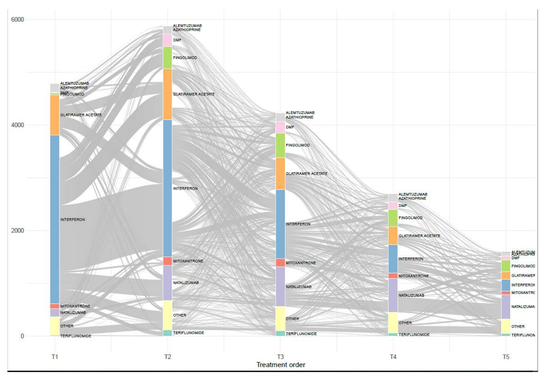
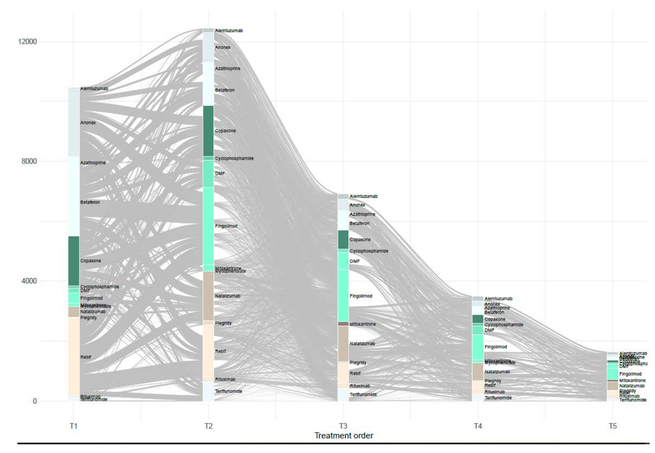


Figure 2e: Treatment switching in MSBase (2007+)



Conclusion

Discontinuation of disease-modifying treatment is a frequent event across countries and product. Individual patient treatment pathways are complex and highly variable. Lack of efficacy, side effects/adverse events and intolerance are the primary drivers of premature treatment discontinuation.

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