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SWITCHING THERAPIES ANALYSIS IN MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT

Introduction: disease-modifying treatments (DMTs) for relapsing multiple sclerosis (MS) have been available starting from the 1990s. Since then, the therapeutic landscape has progressively expanded, so the choice of MS treatment to date is challenging and switching of immunotherapies is often required. The aims of this study were i) to describe and analyse in a real-world setting the reasons of DMTs switches in the court of patients belonging to the MS Centre at the IRCCS Mondino; and ii) to provide real-life insights into currently applied therapeutic strategies.

Patients and methods: non-interventional, retro-prospective study, which included MS patients actively referred to the MS Center at IRCCS Mondino, who switched DMT in the years 1994–2020. The key outcome variable was the main reason to switch DMT, as documented in medical charts based on failure of therapy, safety, patient's wish/tolerability, adverse events (AEs), pregnancy planning, and other.

Results: of the total of 355 enrolled MS patients, 68.75% (242) were female and mean age of MS onset was 30.29 years old (± 9.26). A total of 682 switches occurred in this population. The main reason to DMT switch was treatment failure, defined as the presence of clinical or radiological MS activity (43.32%) followed by patient's wish/tolerability (25.36%), safety (13%), other (9%), adverse events (6%) and pregnancy planning (4%). Reasons for DMT switching differed by year of switch ($p < 0.002$).

Discussion: the method I followed, which is unique in the recent literature, has to be considered an alternative and complementary approach to standard real-world evidence analysis, typically focusing on single treatment (or treatments) rather than the patient and the very event. This study improved current awareness on these dynamics, better characterizing everyday practice switch trends with the ultimate goal of improving disease management and patient care.

1. INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). The disease has a heterogeneous course and the most frequent form is the relapsing one, which begins in about 85% of patients and is characterized by neurological deficits (relapses) followed by the total or partial restoration of functions. About 50% of patients initially diagnosed with a relapsing form, after about 10-15 years of natural history [1], evolve to the secondary progressive form of the disease, which is characterized by progressive accumulation of neurological disability for which few therapies are currently available [2].

Disease-modifying treatments (DMTs) have been available starting from the 1990s. Since then, the therapeutic landscape has progressively expanded, so the choice of MS treatment to date is very complex and heterogeneous [3,4]. In particular, the therapeutic scenario for MS currently consists of 13 DMTs - distinguished in Italy, by the Local Health Authority (AIFA, Agenzia Italiana del FArmaco) between first and second lines according to the risk/benefit ratio. The group of first line DMTs includes: interferon beta 1 a/b (IFN-β), glatiramer acetate (GA), teriflunomide (TFU), dimethyl fumarate (DMF); while the groups of second line DMTs includes: natalizumab (NTZ), fingolimod (FTY), alemtuzumab (ALEM), daclizumab (DAC, was withdrawn from the market in 2018), ocrelizumab (OCRE), and cladribine (CLAD). Furthermore, among the DMTs there is also mitoxantrone (MTX), which has been approved as a treatment in very active forms of the disease when there are no therapeutic alternatives. The effects and mechanisms of action of these MS drugs are summarized in **Table 1.** Unfortunately, although all these DMTs are able to significantly modify the disease by delaying evolution in the progressive phase, none of them are able to cure MS. Indeed, pivotal studies and post-marketing data have shown that only a limited percentage of patients are completely free from disease activity during treatment, while effectiveness is only partial for most patients [5,6]

Treatment	Dosage	Route	Frequency of Dosing	FDA/ EMA Approval (year)	Target	Mechanism of Action	Effects	Side Effects	Ref.
IFN-β 1b	250 mcg	s.c.	Every other day	1993	APCs, T cells	Modulates the cytokine expression profile via the induction of an anti-inflammatory/ reduction in pro-inflammatory expression; blocks migration of lymphocytes across BBB.	Reduced number of exacerbations and improved MRI measures of disease activity in the brains (*vs* placebo)	Injection-site reactions, flu-like symptoms, leukopenia, deranged liver enzymes, and disthyroidism, tolerance (anti IFN antibodies)	7–10
IFN-β 1a	30 mcg	i.m.	Once weekly	1996					
IFN-β 1a	22-44 mcg	s.c.	3 Times/ week	2002					
Pegylated IFN-β 1a	125 mcg	s.c.	Every 14 days	2014					
Glatiramer Acetate	20 mg	s.c.	Daily	1996	APCs, $CD4^+$ T cells, antigen-specific suppressor T cells	Modulates cytokine expression profile to an anti-inflammatory phenotype (i.e. IL-10, TGF- β); induces antigen-specific suppressor T cells; reduces of antigen presentation; corrects of $CD8^+$ T cell regulatory deficit	Reduced relapse rate and accumulation of disability (*vs* placebo); decrease in T2 lesions	Injection-site reactions, transient systemic post-injection reactions (i.e. chest pain, flushing, dyspnea, palpitations, and/or anxiety) and lipodystrophy (with long-term therapy)	11,12
	40 mg	s.c.	3 Times/ week	2014					
Teriflunomide	14 mg	os	Daily	2012	Mitochondrial DHODH	Modulates T cell responses (active metabolite of leflunomide)	Reduced relapse rate, disability progression and MRI activity	Diarrhea, nausea, alopecia, hair thinning, and elevated alanine aminotransferase levels	13–16

							vs placebo		
Dimethyl fumarate	240 mg	os	Twice daily	2013	Nrf2 Pathway	Activates the Nrf2-dependent antioxidant response	Reduced relapse rate, disability progression and MRI activity (*vs* placebo)	Flushing, gastrointestinal symptoms, and PML (rare)	[17–19]
Natalizumab	300 mg	i.v.	Every 4 weeks	2006	α4 subunit of α4β1 VLA-4 integrin	Prevents the migration of leukocytes across the BBB into the CNS	Reduced relapse rate, disability progression and MRI activity *vs* placebo	Allergic reactions, liver toxicity, headache, fatigue and PML, tolerance (anti natalizumab antibodies)	[19–24]
Fingolimod	0.5 mg	os	Daily	2010	Modulates S1P receptors (type 1,2,3 and 5)	Prevents CCR7 positive lymphocytes, including naive and central memory T cells, from exiting lymph nodes	Reduced relapse rate, disability progression and MRI activity (*vs* IFN-β 1a)	Bradycardia and atrioventricular conduction block during initiation, risk of varicella-zoster virus infections, elevated liver enzymes and macular oedema	[19,25,26]
Mitoxantrone	12 mg/m^2	i.v.	Every 3 months	2000	Topoisomerase II	B and T cell suppression/ migration inhibition	Reduced relapse rate, disability progression and MRI activity (*vs*	Leukemia and cardiotoxicity	[19,27]

							placebo and *vs* IFN-β 1a)		
Alemtuzumab	12 mg	i.v.	5 Days of therapy at month 0; 3 days at month 12.	2013 (EMA) 2014 (FDA)	CD52	Complement- and antibody-dependent cellular cytotoxicity on T, B and NK cells	Reduced relapse rate, disability and MRI activity *vs* IFN-β 1a	Acute cytokine release syndrome (within few hours from the treatment), autoimmune diseases (i.e. Graves disease, idiopathic thrombocytopenic purpura and Goodpasture syndrome)	[28–30]
Ocrelizumab	600 mg	i.v	Twice a year		CD20	Elicits depletion of B cells via several mechanisms: antibody dependent cell mediated cytotoxicity and complement dependent cytoxicity and apoptosis.	In RMS: reduced relapse rate, disability progression and MRI activity (*vs* IFN-β 1a) In PPMS: slowed progression of MS and reduced and MRI activity (*vs* placebo)	Infusion related reactions, increased risk of infections including upper and lower respiratory infections, herpes, and hepatitis B reactivation. Hypogammaglobulinemia. Neutropenia. PML.	[31–33]
Cladribine	3.5 mg/Kg	os	Over two years	2018	lymphocytes	Selectively depletes peripheral lymphocytes without a major impact on cells of the innate	Reduced relapse rate, disability progression	6% rate of severe lymphocyte suppression (lymphopenia) (levels lower than of normal). Headache,	[34]

	immune system.	and MRI activity (*vs* placebo)	sore throat, common cold-like illness and nausea

Table 1. Currently approved treatment for MS in Italy. Abbreviations: APC: antigen presenting cell; BBB: blood-brain barrier; CNS: central nervous system CNS; CCR: CC chemokine receptor; DHODH: dihydroorotate dehydrogenase; EMA; European Medicine Agency; FDA: Food and Drugs Administration; IFN: interferon; IL: interleukin; i.m.: intramuscular; i.v.: intravenous; MRI: magnetic resonance imaging; mcg: micrograms; mg: milligrams; MS: multiple sclerosis; NK: natural killer; Nrf: nuclear factor erythroid 2 related factor 2; os: per os; PML: progressive multifocal leukoencephalopathy; S1P: sphingosine1–phosphate; s.c.: subcutaneous; TGF: transforming growth factor; VLA: very late antigen.

In such a varied therapeutic scenario, the evaluation of the relationship between benefits and risks of each treatment is challenging; thus, the study of the rationale for choosing in favour of one DMT or the other is increasingly important - especially when faced with the need to replace an on-going therapy (switch) due to failure of effectiveness, poor tolerability or safety reasons.

In these circumstances, there are several factors to consider and which should guide the clinician to disentangle the different algorithms: i) MS is a complex disease characterized by both inflammatory and neurodegenerative processes, for which no DMT is specific; ii) MS is a heterogeneous disease characterized by an extreme variable onset and course, thus different treatments can be more or less effective in each individual case; iii) no DMT heals from MS and at least 30% of patients are thought to have a suboptimal response to treatment during first years of treatment [35]; iv) the safety profile of DMTs can vary in the individual patient, so the neurologist must adapt and personalize the choices; vi) DMTs are effective if taken regularly, but adherence is often linked to the tolerability profile of the drug, which is specific and sometimes peculiar to individual patients [35–38].

The goal of this study was to describe and analyse in a real-world setting the reasons of DMTs switches in the court of patients attending to the MS Centre at the IRCCS Mondino. This study will likely pave the road for next future specific analytical studies in a well-characterized population with the ultimately aim to identify the most suitable therapy for the individual patient.

2. PATIENTS AND METHODS

2.1 Study design and patients

This single centre non-interventional, retro-prospective study was conducted between October 2017 and August 2020 at Multiple Sclerosis Centre of IRCCS Mondino Foundation.

In this study, switches from any DMT for MS to another were investigated.

The study was conducted in accordance with the guidelines for good pharmaco-epidemiological practice and the applicable laws and regulations.

All treatments were required to conform to the standard of care and the current respective summaries of product characteristics and prescribing information.

Information regarding the treatment before and after the switch was collected using the drug perception software ("file F") of the IRCCS Mondino; reasons for switching (including specification of AEs) were recorded retrospectively using medical records.

2.1.2 Inclusion criteria

- 18 years old at the time of signing the informed consent
- Clinically definite MS according to Poser criteria [39]
- Being followed at MS Centre at IRCCS Mondino
- Switching DMT between 1994 and 31.8.2020
- At least 1 visit at the MS Centre within the previous 2 years (i.e. 1.7.2018 to 30.6.2020).
- Being capable of giving signed informed consent

2.1.2 Exclusion criteria

- Not meeting all inclusion criteria

2.1.2 Patient population selection

According to the administrative records, MS diagnosis is defined with the following ICD-9-CM code 340. I review and screened according inclusion/exclusion criteria the 1507 340-coded MS patients actively referred to the MS Centre at IRCCS Mondino, Of those, I rejected 25 patients due to an inconsistency between the diagnosis and the code. Other 596 MS patients were excluded because they were naïve to DMT, while other 477 MS patients were excluded because they did never switch the DMT.

Of the 409 eligible MS patients, I drop out 54 MS patients (total of 174 records) because valid data of minimum data-set were incomplete. Therefore, I enrolled a total of 355 MS patient (for a total of 682 records). **Figure 1.**

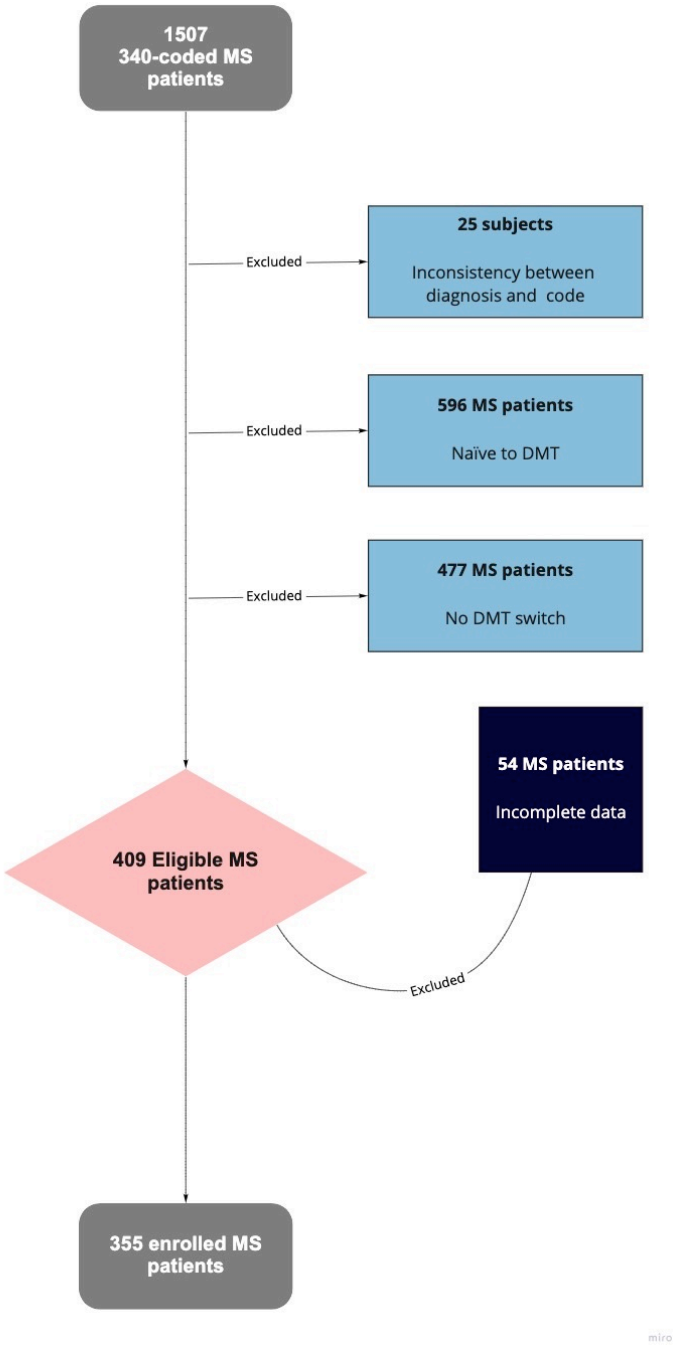


Figure 1 Patient selection. Abbreviation: DMT: disease modifying therapy; MS: multiple sclerosis

2.2 Outcome measures

The key outcome variable was the reason to switch DMT, as documented in medical charts based on failure of therapy [occurrence of clinical relapses, disability worsening, magnetic resonance imaging (MRI) findings of inflammatory activity], safety, patient's wish/tolerability (patient's desire, poor tolerability, inconvenient application form), adverse events (AEs), patient's reasons (woman's wish to become pregnant), and other. Only one answer was possible, which was the main reasons of DMT switch. Of note clinical and radiological MS activity was intended as at least one relapse or at least one gadolinium enhancing or a new area at MRI.

Further outcome measures were recorded: demographical data (gender and date of birthday) and clinical data at the time of MS onset (date of MS clinical onset - month and year, Bayesian Risk Estimate for MS at Onset - BREMSO score) [40]. Additionally, for all patients and each DMT, I recorded: DMT type, DMT start and withdrawal date; Expanded Disability Status Scale (EDSS) score at DMT start and withdrawal; the Multiple Sclerosis Severity Score (MSSS) at DMT start and withdrawal. EDSS score at DMT start was clustered into two groups according to patients' walking ability: low EDSS (EDSS score 0-3.5, a.k.a. unrestricted/fully ambulatory) and high EDSS (EDSS score ≥ 4.0, a.k.a. restricted walking ability). DMT start date was grouped into two groups according the advent of the first oral DMT on Italian market, which represents a watershed in MS therapeutic approach: before fingolimod Local Health Authority (AIFA) approval (i.e. before 22.11.2011) and after fingolimod AIFA approval (i.e. after 22.11.2011).

Additionally, MS disease activity on each DMT was reviewed and data were recorded according a 6-months disease "rebaseline" time point. Thus, the following time-lapses were analysed: the first 6 months of DMT (i.e *pre-rebaseline)* and the time-lapse after the first 6 month of DMT (i.e. *post-rebaseline*). During *pre-rebaseline* and *post-rebaseline* the following variables were collected if available: date of first relapse, number of relapses and date of the first observed MS radiological activity, defined as the presence of gadolinum (Gd)-enhancing lesions and or presence of new or enlarging T2 lesions compared to the previous MRI scan.

Thanks to the aforementioned variables the following variables were calculated: age at MS onset, age at DMT start, age at DMT withdrawal, MS duration at DMT start, time to treatment discontinuation (TTD), multiple sclerosis severity score (MSSS) at DMT start, time to first clinical relapse during *pre-rebaseline*, time to first clinical relapse during *post-rebaseline,* time to first observed radiological activity during *pre-rebaseline*, time first observed radiological activity during *post-rebaseline* and the annualized relapse rate (ARR) during *post-rebaseline.*

The minimum data set included: DMT type, reason to DMT switch, patient's demographics, date of MS onset, and DMT start and withdrawal date.
Data from patient charts regarding reasons to switch and baseline and clinical characteristics were recorded retro-prospectively. AEs leading to a switch from a DMT to another DMT were analysed retro-prospectively.
Database was ordered as following: variables were organized into columns while switches (a.k.a. records) were organizes into raw. I was able to group all the switches that belonged to a defined PwMS via a numeric "code" variable.

2.3 Expanded disability status scale (EDSS)

The Expanded disability status scale (EDSS) is used for assessing neurologic impairment in MS [41]. It includes eight functional systems and the EDSS steps ranging from zero (normal) to ten (death due to MS). The functional systems are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral and other functions.

2.4 Multiple Sclerosis Severity Score (MSSS)

The Multiple Sclerosis Severity Score (MSSS) describes the severity of MS at a given time. It is calculated using an algorithm that adjusts EDSS according to the corresponding disease duration [42]. In order to quantify the neurological impact of MS, the MSSS was calculated for each record at the begin and at the withdrawal of a DMT

2.5 BREMSO score

Bayesian risk estimate for MS at onset (BREMSO) score is the result of a statistical Bayesian approach to model the natural history of MS patients, in order to determine the individual risk of reaching confirmed clinical end-point. This model allows to calculating an individual risk score for each patient by taking into account demographic characteristics and clinical events at the onset of the disease. Each factor is associated with a specific statistical "weight", the Bayesian local relative risk (LRR), which is used to calculate the BREMSO score. In detail, BREMSO score is calculated at individual patient's level according to following algorithm [40]: 0.05 x age (in decades) + (-1.07) (if female gender) + 0.93 (if sphincter onset) + 0.62 (if pure motor onset) + 0.81 (if motor-sensory onset) + 0.32 x number of neurological functional systems (FSs) involved at onset + 0.52 (if sequel after onset). BREMSO

can be used to create matched cohorts or to adjust the comparison of outcome between arms in real-world observational cohorts [43].

2.6 Annualized relapse rate (ARR)

The annualized relapse rate (ARR) was calculated as the total number of relapses experienced in the group divided by the total number of days in the study for the group, and the ratio multiplied by 365. The total number of days on a DMT is defined as the number of days from the date of the first DMT collection (which coincides with the first dose) to the date of the last DMT collection.

2.7 Statistical analysis

The analysis of this study was exploratory, and used primarily descriptive statistical methods.

Continuous variables were summarized with number of observations, mean, standard deviation (SD), median, minimum, maximum, and the 25% and 75% percentiles.

Categorical variables were displayed by absolute and relative frequencies (percentages). Percentages for categorical variables were based on all non-missing values (=100%).

I used inferential methods (e.g. confidence intervals) in selected analyses, and results were interpreted in an exploratory manner.

I evaluated the effect main reasons of DMT switch (i.e. clinical MS activity, radiological MS activity, safety issues and patient's wish/tolerability) for the main variables. For the following continuous variables, I applied a univariate ANOVA analysis: age at MS onset, age at DMT start, BREMSO, MS duration at DMT start, EDSS at DMT start, TTD, EDSS Delta and MSSS at DMT start. When a main effect ($p<0.05$) was obtained, I used a *post hoc* test for paired comparison between groups (Bonferroni). For the following categorical variables, I applied a Pearson's chi squared test: sex (female/male), AIFA DMT classification (first line *versus* second line), relapse free during *pre-rebaseline* (yes/no), relapse free during *post-rebaseline* (yes/no), MRI activity during *pre-rebaseline* (yes/no).

Data analysis was performed via STATA V14.

3. RESULTS

3.1 Baseline patient and disease characteristics

Of the total of 355 enrolled MS patients, 68.17% (242) were female. Mean age of MS onset was 30.29 years old (± 9.26) and median BREMSO score was -0.03 (min; max -0.92; 4.36). During the observational period, a total of 682 switches occurred within the enrolled 355 patients with MS (PwMS). In details, 355 records, 351 records,161 records, 77 records and 28 records referred to the first, second, third, fourth and fifth switch within the same patients, respectively. Only 10 records pertained to more than 5 DMT switches**, figure 2**. **Table 2** summarized population's general characteristics according to the number of the switches. The majority of the 682 switches within the analysed population involved injectable therapies (i.e. interferon and glatiramer acetate), followed by dimethyl fumarate, natalizumab, teriflunomide and fingolimod (**figure 3**).

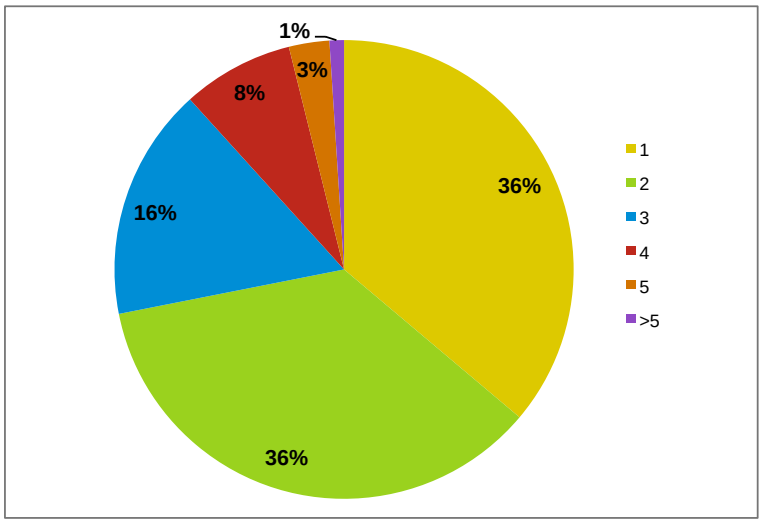


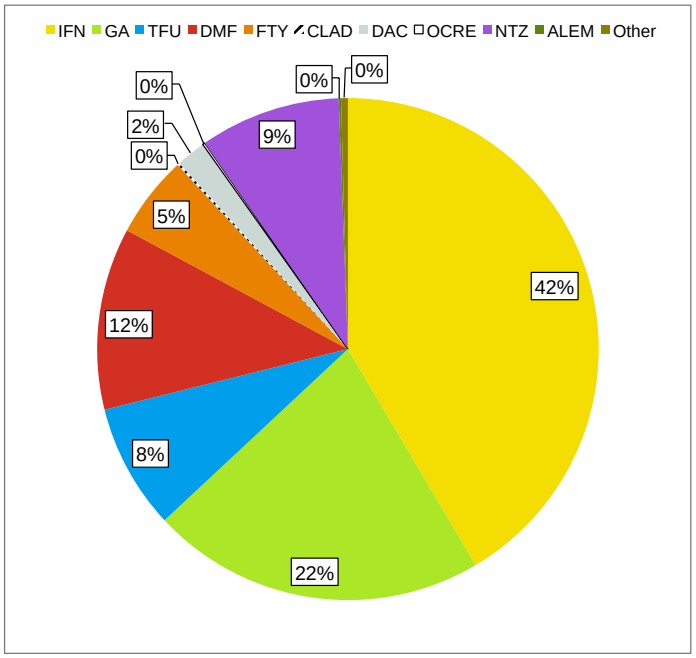
Figure 2: the pie graph represents the percentage of records according to the number of switches within the 355 MS patients

Characteristics of 355 MS patients	
Gender, n(%)	
Female	242 (68.17)
Age at MS onset (yrs), median (min-max)	29.27 (11.26-59.14)
BREMSO, median (min; max)	-0.33 (-0.7; 4.36)
Age at 1st DMT start (yrs), mean (SD)	36.16 (9.78)
Age at 2nd DMT start (yrs), mean (SD)	39.97 (10.34)
Age at 3rd DMT start (yrs), mean (SD)	41.86 (9.74)
Age at 4th DMT start (yrs), mean (SD)	42.52 (9.77)
Age at 5th DMT start (yrs), mean (SD)	42.19 (9.81)
MS duration at 1st DMT start (yrs), median (min; max)	2.75 (0; 14.40)
MS duration at 2nd DMT start (yrs), median (min; max)	7.44 (0.19; 35.65)
MS duration at 3rd DMT start (yrs), median (min; max)	11.39 (0.83; 33.70)
MS duration at 4th DMT start (yrs), median (min; max)	13.02 (3.09; 33.42)
MS duration at 5th DMT start (yrs), median (min; max)	14.74 (5.13; 25.53)
EDSS at 1st DMT start, median (min; max)	1.0 (0; 7.5)
EDSS at 2nd DMT start, median (min; max)	1.5 (0; 7.5)
EDSS at 3rd DMT start, median (min; max)	1.5 (0; 7.5)
EDSS at 4th DMT start, median (min; max)	2.0 (0; 7.5)
EDSS at 5th DMT start, median (min; max)	2.0 (0; 6)
TTD (yrs) at 1st switch, median (min; max)	2.19 (0.07; 13.96)
TTD (yrs) at 2nd switch, median (min; max)	2.45 (0.; 15.05)
TTD (yrs) at 3rd switch, median (min; max)	1.88 (0; 13.8.725)
TTD (yrs) at 4th switch, median (min; max)	1.61 (0.00; 8.66)
TTD (yrs) at 5th switch, median (min; max)	0.75 (0.08; 5.50)

Table 2: Demographic and disease characteristics of the 355 PwMS

ARR: BREMSO: Bayesian Risk Estimate for MS at Onset; EDSS: expanded disability status scale; DMT: disease modifying treatment; SD: standard deviation; TTD: time to treatment discontinuation; yrs: years.

3A



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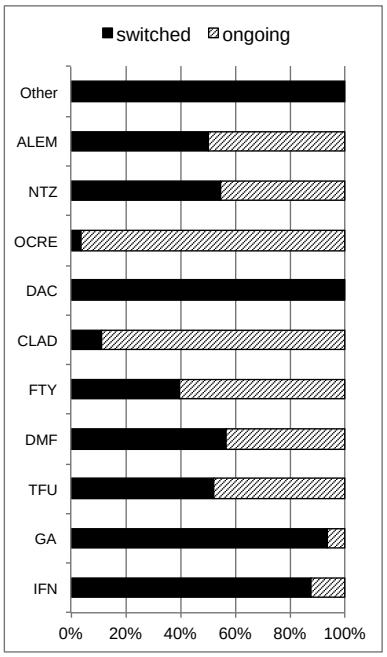

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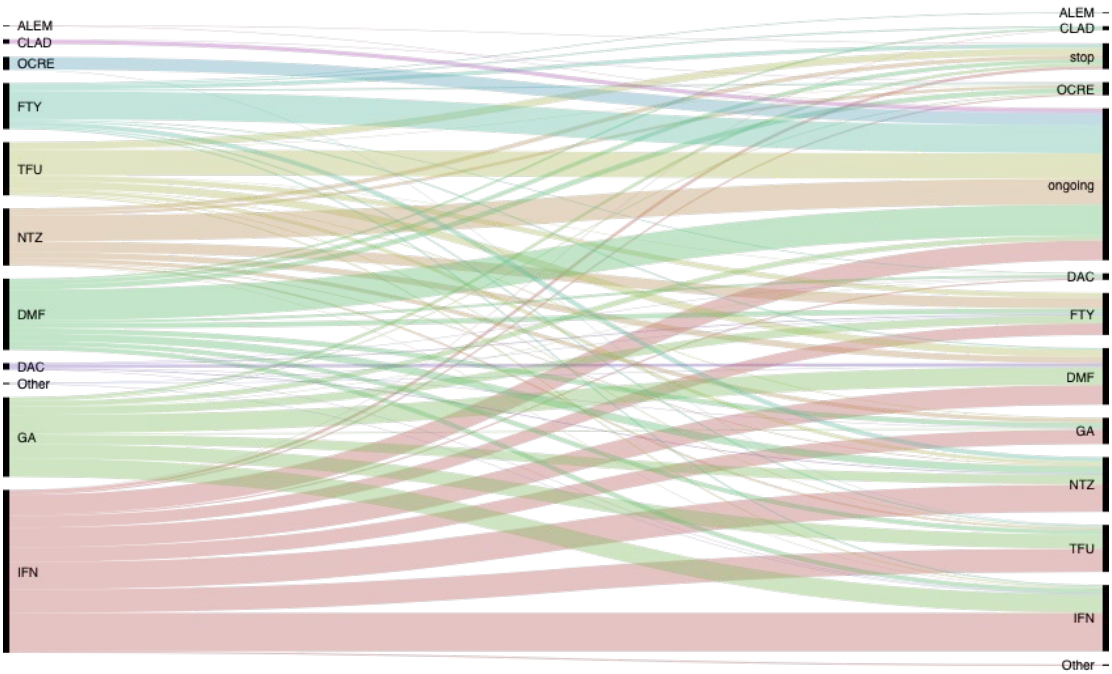

Figure 3. The pie graph represents the 682 switches according to the DMT within the 355 PwMS (**3A**); the bar graph represents the proportion between switched DMT and ongoing DMT according to the DMT type within the 355 PwMS (**3C**); the alluvial graph represents the 682 switches within the 355 PwMS (**3C**). Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide;

3.3. Reasons for switching DMT

Of the total of the 682 records (355 PwMS), the main reason to DMT switch was tolerability/patient wish (n=173) followed by clinical disease activity (n=171), radiological disease activity (n=124), safety (n=91), other (n=58), adverse events (n=42), and pregnancy planning (n=23), **figure 4.**

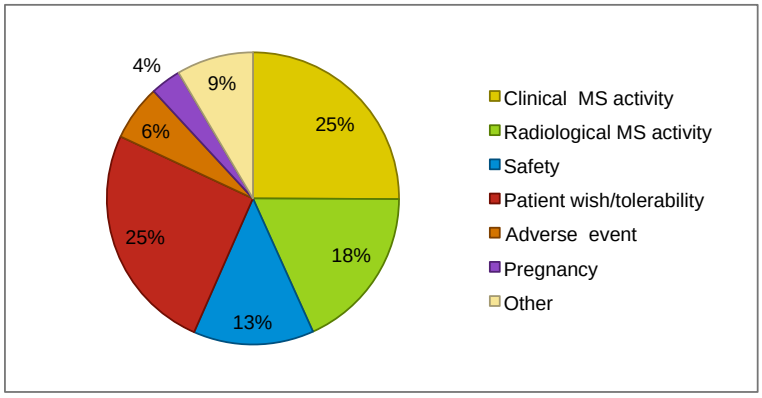

Figure 4: The pie graph represents the main reason of DMT switch within the 682 records.

The main reason of DMT switch differed according to the number of the switch, **figure 5.**

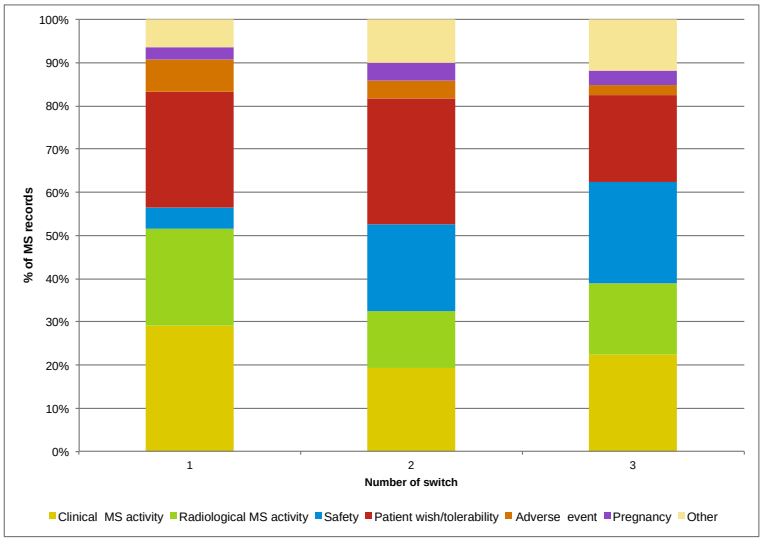

Figure 5: the bar graph represents the main reason of DMT switch grouped by first, second and third DMT switch within the 682 records.

Reasons for switching DMT differed significantly by year of switch, between 1999 and 2020 ($p < 0.002$), **figure 6.**

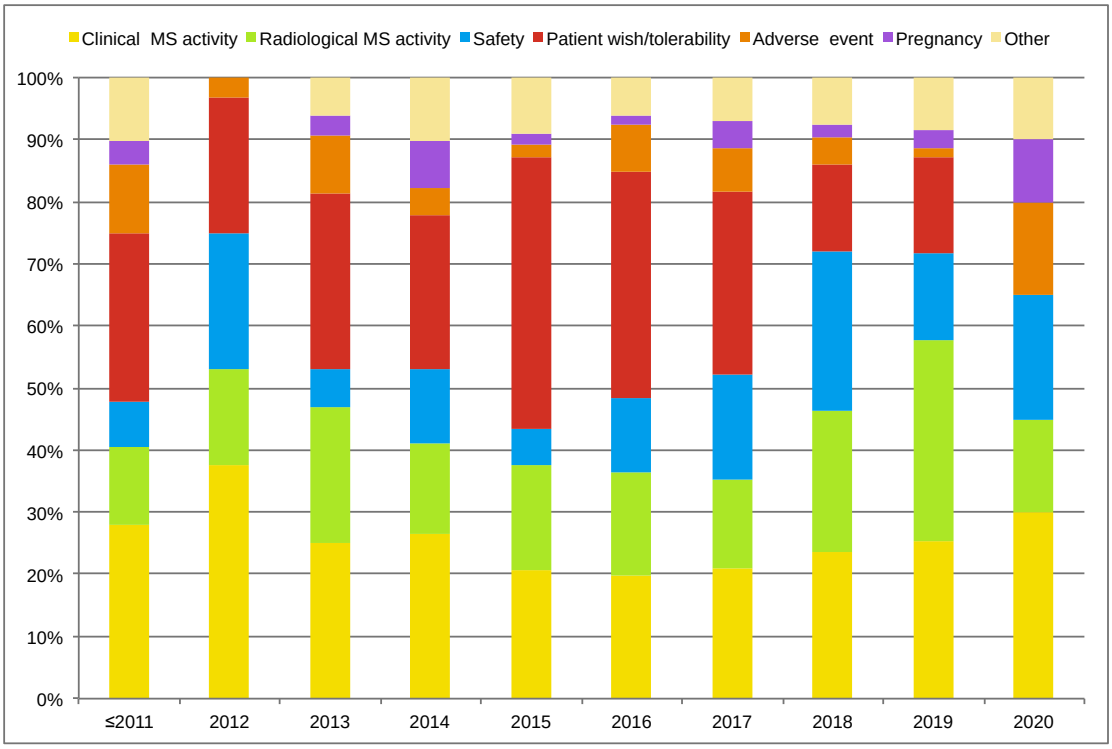

Figure 6: the bar graph represents the main reason for switching DMT by year

3.3.1 Reasons for switching DMT: clinical MS activity

One hundred and thirty-five MS patients (total of 171 records) switched DMT due to clinical MS activity. **Table 3** reports their characteristics.

In general, 69.01% of the records were female. At DMT start, the mean age was 35.46 (±10.34) and 88.96% of records had a low EDSS score (<3.5). Before switching, 44.44% of records were on IFN-β preparations, 27.49% on glatiramer acetate, 8.77% on teriflunomide, 11.11% on dimethyl fumarate, 6.43% in fingolimod and only one case was on alemtuzumab. The percentage of records that already had one or more former immunotherapy switches was 39.77%, while for the remaining 60.23% % that was the first switch.

Mean TTD was 3.16 years (± 3.01).

The overall variation of EDSS from DMT start to DMT withdrawal was 0.55 point (± 0.88); in detail the median of the delta was 0 point (-0.5; 4.0) and 1.5 point (0; 3.5) in those records with EDSS score of 0-3.5 and of ≥ 4, respectively.

DMTs before and after the switch are provided in **figure 7**.

Characteristics	Number of switches	
Gender, n(%)	171	
Female		118 (69.01)
Male		53 (30.99)
Age at MS onset (yrs), median (min-max)	171	26.49 (12.38-50.66)
Age at DMT start (yrs), mean (SD)	171	35.46 (10.34)
Age at DMT withdrawal (yrs), mean (SD)	171	38.62 (10.44)
BREMSO, median (min; max)	166	-0.33 (-0.7; 4.36)
Number of switch, n(%)	171	
1		103 (60.23)
2		38 (22.22)
3		19 (11.11)
4		9 (5.26)
5		1 (0.58)
>5		1 (0.58)
MS duration at DMT start (yrs), median (min; max)	171	4.7 (0; 32.19)
DMT type (n%)	171	
Interferon beta		76 (44.44)
Glatiramer acetate		47 (27.49)
Teriflunomide		15 (8.77)
Dimethyl fumarate		19 (11.11)
Fingolimod		11 (6.43)
Daclizumab		-
Cladribine		-
Ocrelizumab		-
Natalizumab		-
Alemtuzumab		1 (0.58)
other		-
DMT AIFA classification	171	
First line, n%		158 (92.40%)
Second line, n%		13 (7.60%)
EDSS at DMT start, median (min; max)	154	1.5 (0; 7.5)
0-3.5, n (%)		137 (88.96)
>=4, n (%)		17 (11.04)
EDSS at DMT withdrawal, median (min; max)	154	2 (0;8.5)

EDSS Delta, mean (SD)	154	0.55 (0.80)
MSSS at DMT start,	154	2.43 (0.04; 9.80)
TTD (yrs), median (min; max)	171	2.00 (0.07; 13.96)
Pre-rebaseline		
Relapse free patients, n (%**)**	143	95 (0.66)
Number of clinical relapse, mean (SD)	143	0.41 (0.64)
Time to first clinical relapse, (months), mean (SD)	48	2.94 (1.96)
Time to first radiological activity (months), mean (SD)	33	3.92 (1.77)
Post-rebaseline		
Relapse free patients, n (%)	143	42 (29.37)
Number of clinical relapse, mean (SD)	143	1.23 (1.29)
Time to first clinical relapse (months), median (min;max)	101	19.1 (7.06; 165.2)
ARR	143	0.322
MRI activity free patients, n (%)	143	59 (41.26)
Time to first radiological activity, median (min; max)	84	16.35 (6.63; 165.2)

Table 3: Baseline records and disease characteristics of the 135 MS patients (171 records) who switched DMT due to clinical MS activity.

ARR: annualized relapse rate; BREMSO: Bayesian Risk Estimate for MS at Onset; EDSS: expanded disability status scale; DMT: disease modifying treatment; MRI: magnetic resonance imaging; MSSS: multiple sclerosis severity scale; SD: standard deviation; TTD: time to treatment discontinuation; yrs: years.

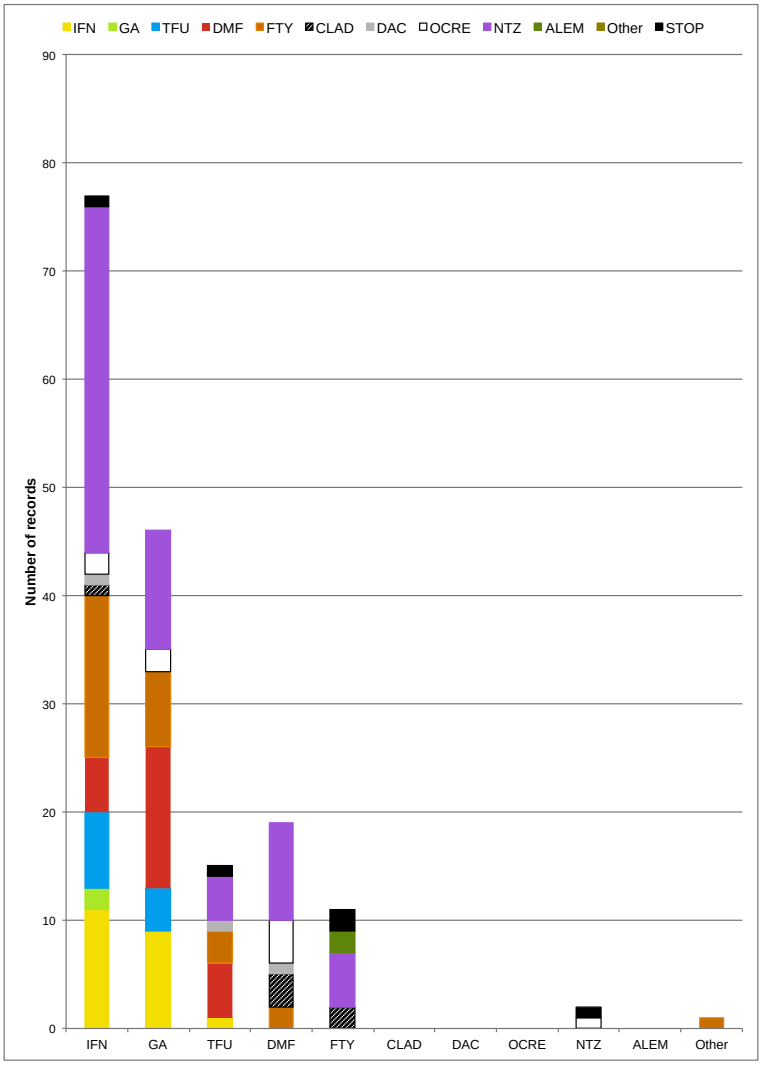

Figure 7: Switch FROM analyse within switchers due to clinical MS activity. The bar graph represents the DMT switches from first DMT, which is reported on x-axes to another DMT, which is reported on y-axes. Of note, there are some cases of switch from IFN to IFN, that is because there are 4 different MS approved formulations of IFN.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

Overall, the most prevalent choice of DMT after the switch due to clinical MS activity was natalizumab (35.67%), followed by fingolimod (16.37%) and dimethyl fumarate (13.45%). Clustering the analysis by the date of fingolimod AIFA approval, the most prevalent DMT was natalizumab for both groups, followed by interferon-beta in the pre-approval group and by fingolimod in post-approval group, **table 4 and figure 8.**

	Overall	PRE fingolimod AIFA approval	POST fingolimod AIFA approval
Interferon-beta, n(%)	21 (12.28)	13 (36.11)	8 (5.93)
Glatiramer acetate, n(%)	2 (2.17)	2 (2.50)	-
Teriflunomide, n(%)	11 (6.43)	-	11 (8.15)
Dimethyl fumarate, n(%)	23 (13.45)	-	23 (13.45)
Fingolimod, n(%)	28 (16.37)	4 (11.11)	24 (17.78)
Daclizumab, n(%)	3 (1.75)	-	3 (2.22)
Cladribine, n(%)	6 (3.51)	-	6 (4.44)
Ocrelizumab, n(%)	9 (5.26)	-	9 (6.67)
Natalizumab, n(%)	61 (35.67)	15 (41.67)	46 (34.07)
Alemtuzumab, n(%)	2 (1.17)	-	2 (1.48)
other, n(%)	-	-	-
STOP, n(%)	5 (2.92)	2 (5.56)	3 (2.22)
Total, n	**171**	**36**	**135**

Table 4: DMT type prescriptions after the switch within switchers due to clinical MS activity.

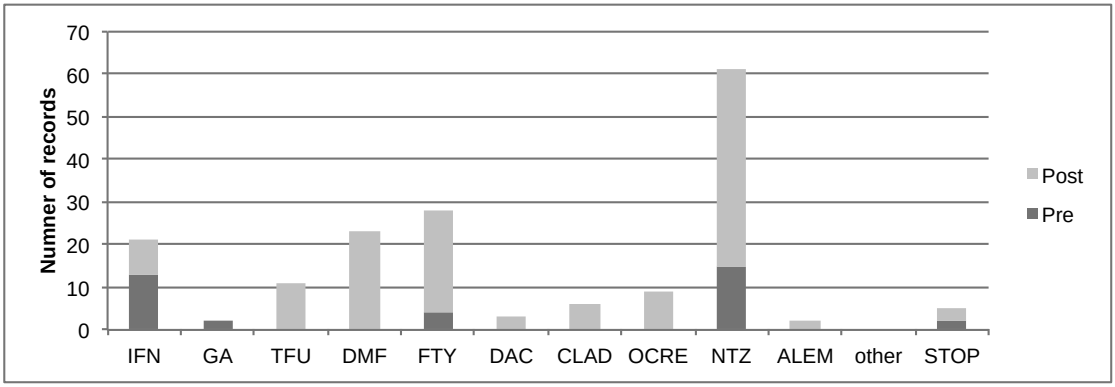

Figure 8: Switch TO analysis within switchers due to clinical MS activity. The bar graph represents the switches to the new DMT, or to DMT withdrawal (i.e. STOP). Different colours have been applied to the switches before (dark grey) and after (light grey) fingolimod AIFA approval. Of note, before AIFA approval, FTY have been used in compassionate study, this explains FTY prescription before AIFA approval.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

3.3.2 Reasons for switching DMT: radiological MS activity

One hundred and seven MS patients (total of 124 records) switched DMT due to radiological MS activity. **Table 5** reports their characteristics.

In general, 66.13% of the records were female. At DMT start, the mean age was 37.94 (± 8.83) and 91.45% had a low EDSS score. Before switching, 38.71% of records were on interferon-beta, 33.87% on glatiramer acetate, 7.26% on teriflunomide, 12.90% on dimethyl fumarate, 5.65% in fingolimod, and only one case was on cladribine and alemtuzumab. The percentage of records that already had one or more former immunotherapy switches was 36.29%, while for the remaining 63.71% that was the first switch.

Mean TTD was 3.33 years (± 2.93).

The overall variation of EDSS from DMT start to DMT withdrawal was 0.34 point (±0.61); in detail the median of the delta was 0 point (-1.0; 2.5) and 0.25 point (0; 2.5) in those records with EDSS score of 0-3.5 and of ≥ 4, respectively.

DMTs before and after the switch are provided in **figure 9**.

Characteristics	**Number of switches**	
Gender, n(%)	124	
Female		84 (66.13)
Male		42 (33.87)
Age at MS onset (yrs), median (min-max)	124	30.35 (12.48-59.14)
Age at DMT start (yrs), mean (SD)	124	37.94 (8.83)
Age at DMT withdrawal (yrs), mean (SD)	124	41.28 (9.28)
BREMSO, median (min;max)	117	0.02 (-0.92; 2.94)
Number of switch, n(%)	124	
1		79 (63.71)
2		26 (20.97)
3		14 (11.29)
4		4 (3.23)
5		1 (0.81)
>5		-
MS duration at DMT start (yrs), median (min;max)	124	4.28 (0.17; 23.03)

DMT (n%)	171	
Interferon-beta		48(38.71)
Glatiramer acetate		42 (33.87
Terfilunomide		9 (7.26)
Dimethyl fumarate		16 (12.90)
Fingolimod		7 (5.65)
Daclziaumb		-
Cladribine		1 (0.81)
Ocrelizumab		-
Natalizuamb		1 (0.81)
Alemtuzumab		-
other		-
AIFA DMT classification	124	
First line, n (%)		115 (92.74)
Second line, n(%)		9 (7.26)
EDSS at DMT start, median (min; max)	117	1.0 (0; 6.5)
0-3.5, n (%)		107 (91.45)
>=4, n (%)		10 (8.55)
EDSS at DMT withdrawal, median (min; max)	118	1.5 (0; 7.0)
EDSS Delta, mean (SD)	117	0.34 (0.61)
MSSS at DMT start,	117	2.382 (0.086; 9.092)
TTD (yrs), median (min; max)	124	2.37 (0.06; 12.67)
Pre-rebaseline		
Relapse free patients, n(%**)**	117	106 (90.60)
Number of clinical relapse, mean (SD)	117	0.08 (0.28)
Time to first clinical relapse, (months), mean (SD)	11	2.91 (2.16)
Time to first radiological activity (months), mean (SD)	33	3.92 (1.77)
Post-rebaseline		
Relapse free patients, n(%)	117	84 (71.79)
Number of clinical relapse, mean (SD)	117	0.45 (0.90)
Time to first clinical relapse (months), median (min;max)	33	25.26 (7.06; 87.20)

ARR		0.13
MRI activity free patients, n(%)	117	13 (11.11)
Time to first radiological activity, median (min;max)	104	12.05 (6.63; 149.56)

Table 5: Baseline records and disease characteristics of the 107 MS patients (124 records) who switched DMT due to radiological MS activity

ARR: annualized relapse rate; BREMSO: Bayesian Risk Estimate for MS at Onset; EDSS: expanded disability status scale; DMT: disease modifying treatment; MRI: magnetic resonance imaging; MSSS: multiple sclerosis severity scale; SD: standard deviation; TTD: time to treatment discontinuation; yrs: years

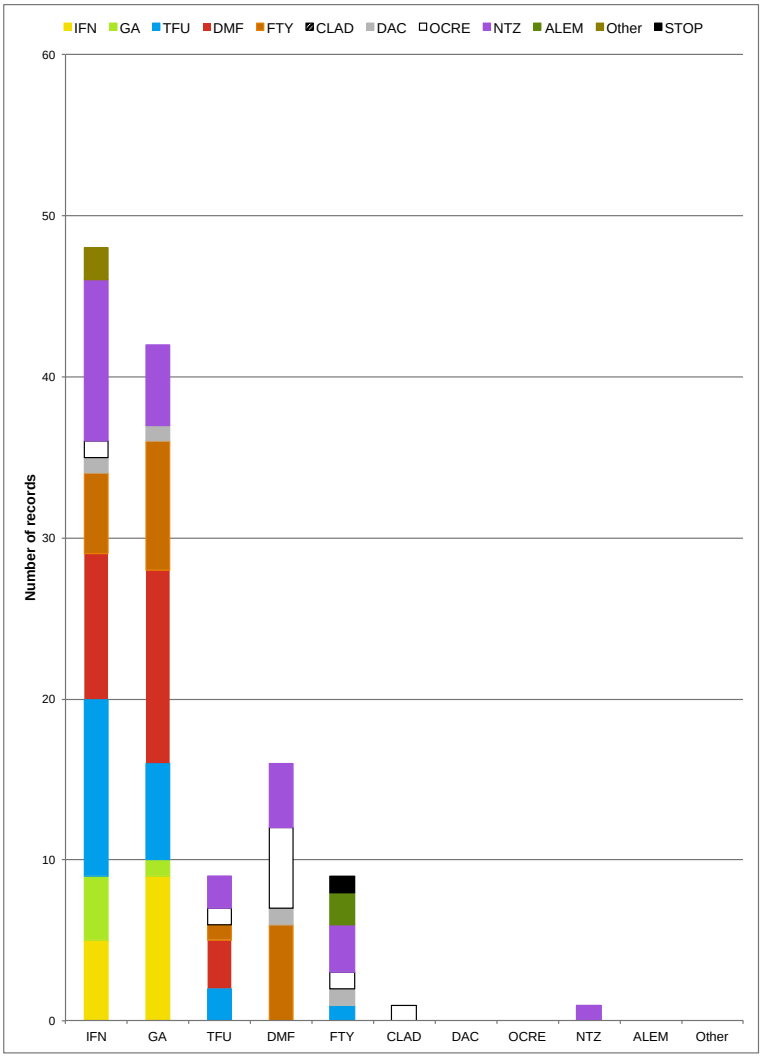

Figure 9: Switch FROM analyse within switchers due to radiological MS activity. The bar graph represents the DMT switches from first DMT, which is reported on x-axes to another DMT, which is reported on y-axes. Of note, there are some cases of switch from IFN to IFN and from GA to GA, that is

because there are 4 different MS approved formulations of IFN and 2 different MS approved formulations of GA.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

Overall, the most prevalent DMT after the switch due MS radiological activity was natalizumab (20.16%), followed by dimethyl fumarate (19.35%), and fingolimod (16.13%) and teriflunomide (16.13%). Clustering the analysis by the date of fingolimod AIFA approval, the most prevalent DMT was interferon-beta in the pre-approval group and dimethyl fumarate in post-approval group **table 6 and figure 10**.

	Overall	**PRE fingolimod AIFA approval**	**POST fingolimod AIFA approval**
Interferon beta, n(%)	14 (11.29)	7 (41.18)	7 (6.54)
Glatiramer acetate, n(%)	5 (4.03)	3 (17.65)	2 (1.87)
Teriflunomide, n(%)	20 (16.13)	0	20 (18.69)
Dimethyl fumarate, n(%)	24 (19.35)	0	24 (22.43)
Fingolimod, n(%)	20 (16.13)	1 (5.88)	19 (17.76)
Daclizumab, n(%)	4 (3.23)	0	4 (3.74)
Cladribine, n(%)		0	
Ocrelizumab, n(%)	9 (7.26)	0	9 (8.41)
Natalizumab, n(%)	25 (20.16)	4 (23.53)	21 (19.63)
Alemtuzumab, n(%)			
other, n(%)	2 (1.62)	2 (11.76)	
STOP, n(%)	1 (0.81)		1 (0.93)
Total, n	**124**	**17**	**107**

Table 6: DMT type prescriptions after the switch within switchers due to radiological MS activity.

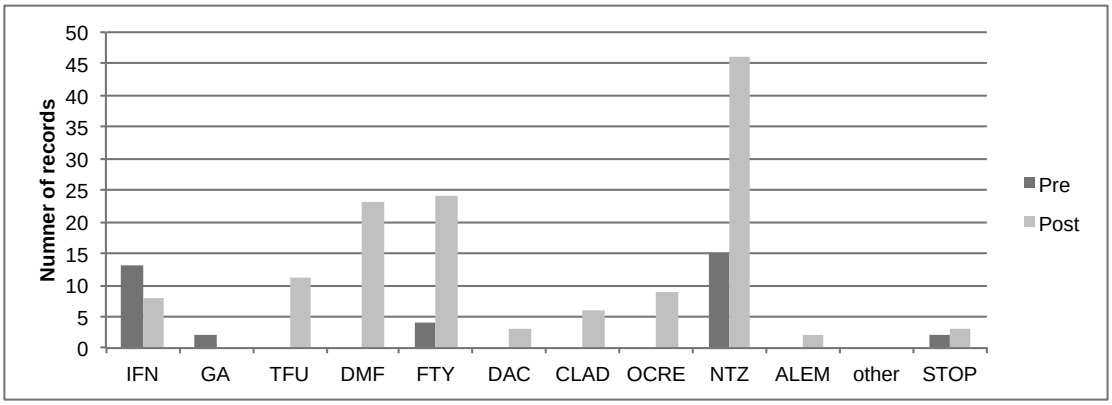

Figure 8: Switch TO analysis within switchers due to radiological MS activity. The bar graph represents the switches or to the new DMT, to DMT withdrawal (i.e. STOP). Different colours have been applied to the switches before (dark grey) and after (light grey) fingolimod AIFA approval. Of note, before AIFA approval, FTY have been used in compassionate study, this explains FTY prescription before AIFA approval.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

3.3.3 Reasons for switching DMT: safety

Eighty MS patients (total of 91 records) switched DMT due to safety reasons. **Table 7** reports their characteristics.

In general, 72.53% of the records were female. At DMT start, the mean age was 29.52 (± 10.02) and 78.31 had a low EDSS score. Before switching, 7.69% of records were on interferon-beta, 2.30 % on glatiramer acetate, 9.89% on teriflunomide, 10.99% on dimethyl fumarate, 6.59% in fingolimod, 12.98% in daclizumab, 47.25% on natalizumab, and only one case was on ocrelizumab, mitoxantrone and alemtuzumab. The percentage of records that already had one or more former immunotherapy switches was 81.32%, while for the remaining 18.68% that was the first switch.

Mean TTD was 2.17 years (± 1.99).

The overall variation of EDSS from DMT start to DMT withdrawal was 0.22 point (± 0.55); in detail the median of the delta was 0 point (-1.0; 2.5) and 0.25 point (0; 2.0) in those records with EDSS score of 0-3.5 and of ≥ 4, respectively.

DMTs before and after the switch are provided in **figure 11**.

Characteristics	**Number of switches**	
Gender, n(%)	91	
Female		66 (72.53)
Male		25 (27.47)
Age at MS onset (yrs), median (min; max)	91	28.55 (11.26; 56.21)
Age at DMT start (yrs), mean (SD)	91	40.33 (10.92)
Age at DMT withdrawal (yrs), mean (SD)	91	42.50 (11.22)

BREMSO, median (min; max)	84	-0.105 (-0.70; 2.85)
Number of switch, n(%)	91	
1		17 (18.68)
2		40 (43.96)
3		20 (21.98)
4		8 (8.79)
5		5 (5.49)
>5		1 (1.10)-
MS duration at DMT start (yrs), median (min; max)	91	8.23 (0.19; 30.13)
DMT (n%)	91	
Interferon		7 (7.69)
Glatiramer acetate		2 (2.20)
Teriflunomide		9 (9.89)
Dimethyl fumarate		10 (10.99)
Fingolimod		6 (6.59)
Daclizumab		11 (12.09)
Cladribine		-
Ocrelizumab		1 (1.10)
Natalizumab		43 (47.25)
Alemtuzumab		-
other		2 (2.20)
AIFA DMT classification	91	
First line, n (%)		28 (30.77
Second line, n(%)		63 (69.23)
EDSS at DMT start, median (min; max)	83	2.0 (0; 7.5)
0-3.5, n (%)		65 (78.31)
>=4, n (%)		18 (21.69)
EDSS at DMT withdrawal, median (min; max)	83	2.0 (0; 7.5)
EDSS Delta, mean (SD)	83	0.22 (0.55)
MSSS at DMT start,	83	2.901 (0.043; 9.092)
TTD (yrs), median (min; max)	91	1.92 (0.38; 8.59)
Pre-baseline		
Relapse free patients, n(%**)**	83	77 (92.77)
Number of clinical relapse, mean (SD)	83	0.09 (0.37)

Time to first clinical relapse, (months), mean (SD)	6	2.02 (1.53)
Time to first radiological activity (months), mean (SD)	1	na
Post-baseline		
Relapse free patients, n(%)	83	76 (91.57)
Number of clinical relapse, mean (SD)	83	0.08 (0.27)
Time to first clinical relapse (months), median (min; max)	7	12.16 (7.26; 39.13)
ARR		0,036
MRI activity free patients, n(%)	83	81 (97.59)
Time to first radiological activity, median (min;max)	2	na

Table 7: Baseline records and disease characteristics of the 80 MS patients (91 records) who switched DMT due to safety reasons.
ARR: annualized relapse rate; BREMSO: Bayesian Risk Estimate for MS at Onset; EDSS: expanded disability status scale; DMT: disease modifying treatment; MRI: magnetic resonance imaging; MSSS: multiple sclerosis severity scale; SD: standard deviation; TTD: time to treatment discontinuation; yrs: years.

Details about switch due to safety concerns were available for 61 out of 91 records, of note they were available for all records that switched from natalizumab and from daclizumab. In the case of the switch from natalizumab, the safety concern was PML in all cases, while for the switch from daclizumab the risk concern was meningoencephalitis and DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) in all cases. The risk linked to ALT increased was the main reason of switch in one record on teriflunomide, while 4 records switched dimethyl fumarate due to lymphocytopenia grade 2. One records switch fingolimod due to COVID-19 risk.

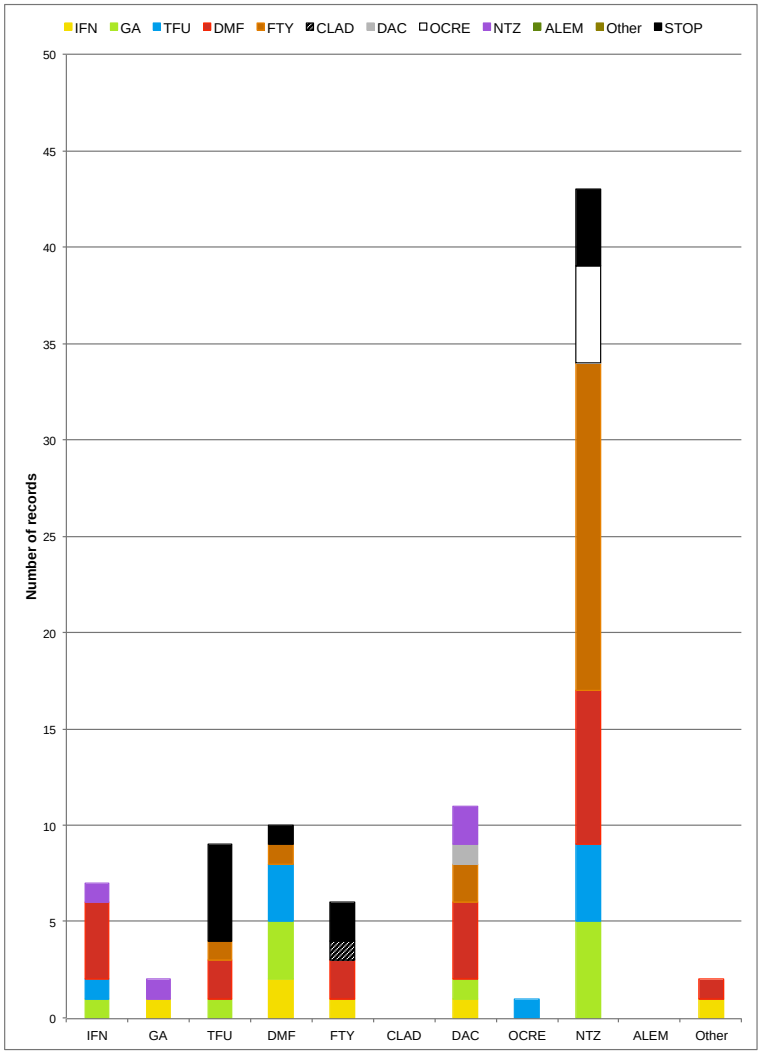

Figure 11: Switch FROM analyse within switchers due to safety reasons. The bar graph represents the DMT switches from first DMT, which is reported on x-axes to another DMT, which is reported on y-axes.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

Overall, the two most prevalent DMTs after the switch due to safety were dimethyl fumarate and fingolimod (23.08%), followed by DMT interruption (13.19%) and glatiramer acetate (12.09%) **table 8 and figure 12**.

	Overall	PRE fingolimod AIFA approval	POST fingolimod AIFA approval
Interferon beta, n(%)	6 (6.59)	2 (20.00)	4 (4.94)
Glatiramer acetate, n(%)	11 (12.09)	2 (20.00)	9 (11.11)
Teriflunomide, n(%)	9 (9.89)	1 (10.00)	8 (9.88)
Dimethyl fumarate, n(%)	21 (23.08)	1 (10.00)	20 (24.69)
Fingolimod, n(%)	21 (23.08)	1 (10.00)	20 (24.69)
Daclizumab, n(%)	1 (1.10)	0	1 (1.23)
Cladribine, n(%)	1 (1.10)	0	1 (1.23)
Ocrelizumab, n(%)	5 (5.49)	0	5 (6.17)
Natalizumab, n(%)	4 (4.40)	1 (10.00)	3 (3.70)
Alemtuzumab, n(%)			
other, n(%)			
STOP, n(%)	12 (13.19)	2 (20.00)	10 (12.35)
Total, n	**91**	**10**	**81**

Table 8: DMT type prescriptions after the switch within switchers due to safety reasons.

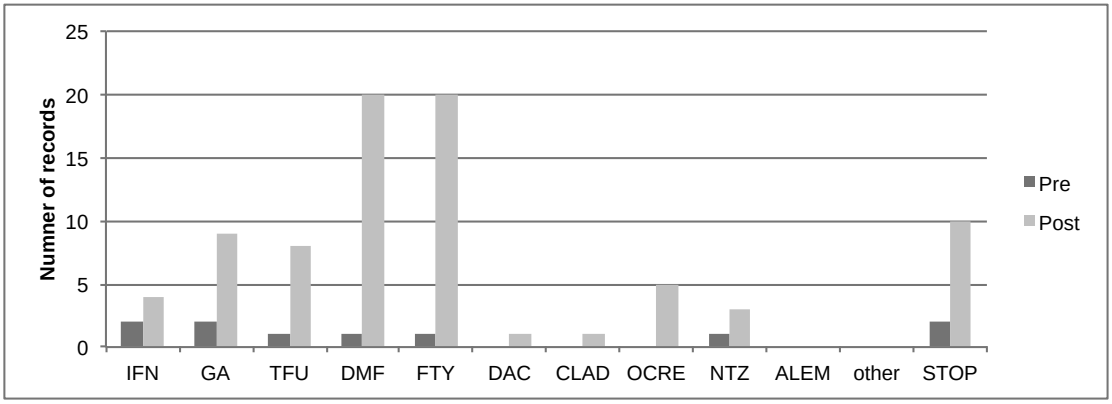

Figure 12: Switch TO analyse within switchers due to safety reasons. The bar graph represents the switches to the new DMT, or to DMT withdrawal (i.e. STOP). Different colours have been applied to the switches before (dark grey) and after (light grey) fingolimod AIFA approval. Of note, before AIFA approval, FTY have been used in compassionate study, this explains FTY prescription before AIFA approval.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

3.3.4 Reasons for switching DMT: patient's wish/tolerability

One hundred and twenty-seven MS patients (total of 173 records) switched DMT due to wish/tolerability reasons. **Table 9** reports their characteristics.

In general, 72.83% of the records were female. At DMT start, the mean age was 29.71 (± 9.56) and 91.52% had a low EDSS score. Before switching, 63.01% of records were on interfone-beta, 17.34 % on glatiramer acetate, 5.78% on teriflunomide, 9.83% on dimethyl fumarate, 2.31% in fingolimod, 1.16% on natalizumab, and only one case was on alemtuzumab. The percentage of records that already had one or more former immunotherapy switches was 45.09%, while for the remaining 54.91% that was the first switch.

Mean TTD was 2.59 years (± 2.77).

The overall variation of EDSS from DMT start to DMT withdrawal was 0.16 point (± 0.55); in detail the median of the delta was 0 point (-1.0; 3.0) and 0 point (-2.0; 1.5) in those records with EDSS score of 0-3.5 and of ≥ 4, respectively.

DMTs before and after the switch are provided in **figure 13**.

Characteristics	**Number of switches**	
Gender, n(%)	173	
Female		126 (72.83)
Male		47 (27.17)
Age at MS onset (yrs), median (min; max)	173	28.28 (11.26; 55.56)
Age at DMT start (yrs), mean (SD)	173	38.26 (9.89)
Age at DMT withdrawal (yrs), mean (SD)	173	42.85 (9.81)
BREMSO, median (min; max)	163	-0.55 (-0.70; 2.85)
Number of switch, n(%)	173	
1		95 (54.91)
2		58 (33.53)
3		17 (9.83)
4		1 (0.58)
5		2 (1.16)
>5		-
MS duration at DMT start (yrs), median (min; max)	173	7.13 (0.05; 33.07)

DMT (n%)	171	
Interferon		109 (63.01)
Glatiramer acetate		30 (17.34)
Teriflunomide		10 (5.78)
Dimethyl fumarate		17 (9.83)
Fingolimod		4 (2.31)
Daclizumab		-
Cladribine		-
Ocrelizumab		-
Natalizumab		2 (1.16)
Alemtuzumab		1 (0.58)
other		-
AIFA DMT classification	173	
First line, n (%)		166 (95.95)
Second line, n(%)		7 (4.05)
EDSS at DMT start, median (min; max)	165	1.0 (0; 6.0)
0-3.5, n (%)		151 (91.52)
>=4, n (%)		14 (8.48)
EDSS at DMT withdrawal, median (min;max)	165	1.5 (0; 6.0)
EDSS Delta, mean (SD)	165	0.16 (0.55)
MSSS at DMT start,	165	1.446 (0.053; 9.586)
TTD (yrs), median (min; max)	173	1.79 (0.01; 14.40)
Pre-baseline		
Relapse free patients, n(%**)**	158	148 (93.67))
Number of clinical relapse, mean (SD)	158	0.06 (0.24)
Time to first clinical relapse, (months), mean (SD)	10	3.10 (1.84)
Time to first radiological activity (months), mean (SD)	5	4.06 (1.87)
Post-baseline		
Relapse free patients, n(%)	158	140 (88.61)
Number of clinical relapse, mean (SD)	158	0.12 (0.34)
Time to first clinical relapse (months), median (min; max)	18	28.33 (7; 94.60)

ARR		0,043
MRI activity free patients, n (%)	158	138 (87.34)
Time to first radiological activity, median (min;max)	20	30.88 (8.7; 84.4)

Table 9: Baseline records and disease characteristics of the 127 MS patients (173 records) who switch DMT due to patient's wish/tolerability.

ARR: annualized relapse rate; BREMSO: Bayesian Risk Estimate for MS at Onset; EDSS: expanded disability status scale; DMT: disease modifying treatment; MRI: magnetic resonance imaging; MSSS: multiple sclerosis severity scale; SD: standard deviation; TTD: time to treatment discontinuation; yrs: years.

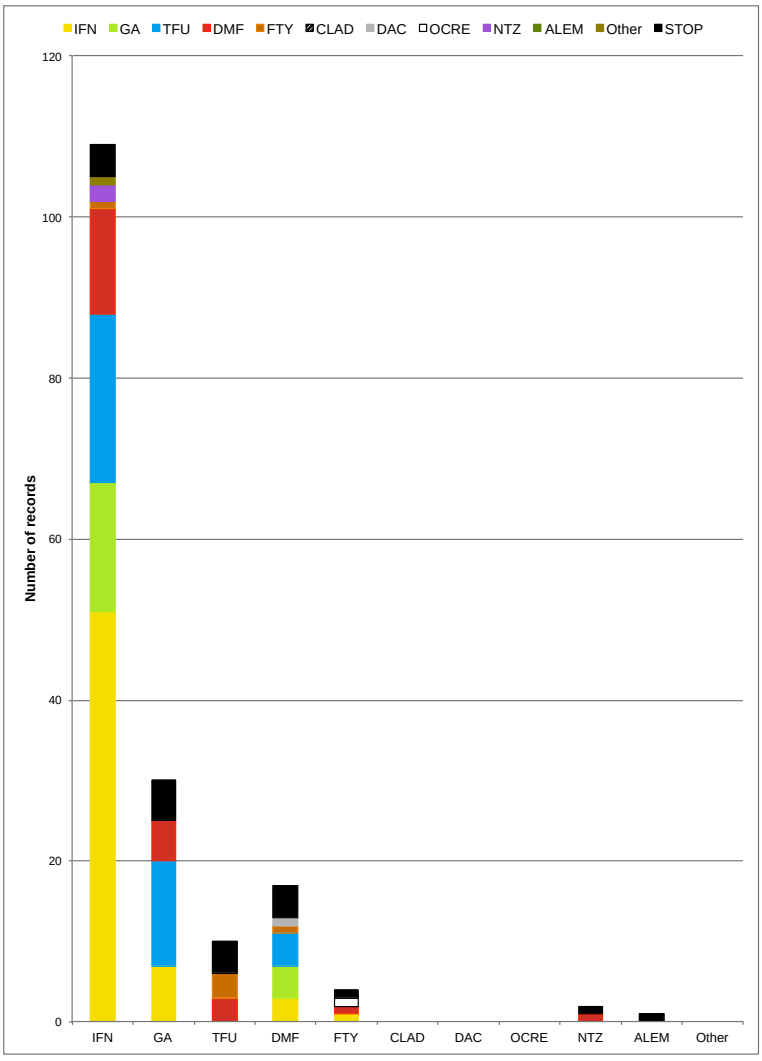

Figure 13: Switch FROM analyse within switchers due to patient's wish/tolerability. The bar graph represents the DMT switches from first DMT, which is reported on x-axes to another DMT, which is reported on y-axes. Of note, there are some cases of switch from IFN to IFN, that is because there are 4 different MS approved formulations of IFN.

Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

Overall, the most prevalent DMTs after the switch due to patient's wish/tolerability was interferon (35.84%), followed by teriflunomide (21.97%) and dimethyl fumarate (13.29%) Clustering the analysis by the date of fingolimod AIFA approval, the most prevalent DMT was glatiramern acetate in the pre-approval group and interferon beta in post-approval group **table 10 and figure 14**.

	Overall	**PRE fingolimod AIFA approval**	**POST fingolimod AIFA approval**
Interferon beta, n(%)	62 (35.84)	9 (37.50)	53 (35.57)
Glatiramer acetate, n(%)	20 (11.56)	12 (50.00)	8 (5.36)
Teriflunomide, n(%)	38 (21.97)	0	38 (25.50)
Dimethyl fumarate, n(%)	23 (13.29)	0	23 (15.43)
Fingolimod, n(%)	5	0	5 (3.32)
Daclizumab, n(%)	1 (0.58)	0	1 (0.67)
Cladribine, n(%)			
Ocrelizumab, n(%)	1 (0.58)	0	1 (0.67)
Natalizumab, n(%)	1 (1.16)	1 (4.16)	1 (0.67)
Alemtuzumab, n(%)			
other, n(%)	1 (0.58)	1 (4.16)	0
STOP, n(%)	20 (11.56)	1 (4.16)	19 (12.75)
Total, n	173	24	149

Table 10: DMT type prescriptions after the switch within switchers due to patient's wish/tolerability.

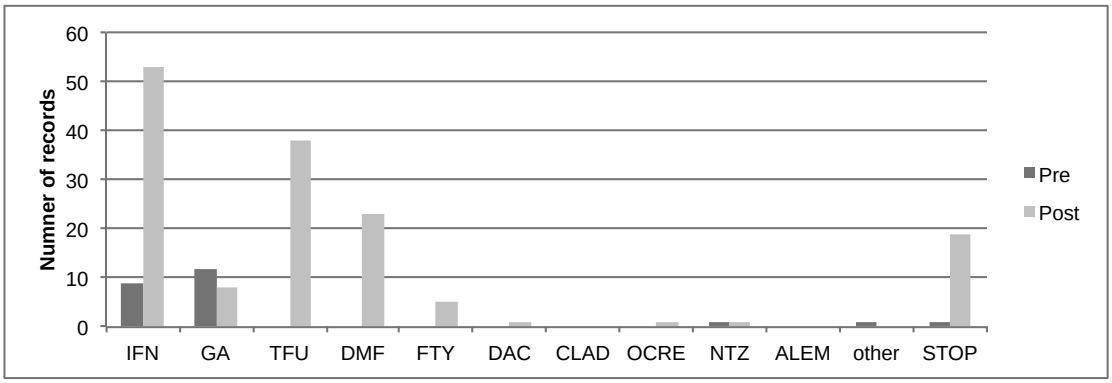

Figure 14: Switch TO analyse within switchers due to patient's wish/tolerability. The bar graph represents the switches to the new DMT, to DMT withdrawal (i.e. STOP). Different colours have been applied to the switches before (dark grey) and after (light grey) fingolimod AIFA approval.
Abbreviation: ALEM: alemtuzumab; CLAD: cladribine; DAC: daclizumab; DMF: dimethyl fumarate; FTY: fingolimod; GA: glatiramer acetate; IFN: interferon; NTZ: natalizumab; OCRE: ocrelizumab; TFU: teriflunomide.

Due to the low sample size, detailed results for the following reasons to DMT switch are not reported: adverse event (42 records), pregnancy planning (23 records) and other reasons (48 records).

3.4 Comparison between the groups on the basis of reason of DMT switch

The baseline characteristics (i.e. sex, age at MS onset and BREMSO) of the 4 groups according the reason of DMT switch did not show statistically significant differences (**table 11).**

Characteristics	Clinical MS activity	Radiological MS activity	Safety	Patient's wish /tolerability	p-value
Female, %	69.01%	66.13%	72.53%	72.83%	0.593*
Age at MS onset (yrs), mean (SD)	28.08 (8.77)	31.04 (8.57)	29.51 (10.02)	29.71 (9.56)	0.054^
BREMSO, mean (SD)	0.03 (0.83)	0.11 (0.77)	0.74 (0.78)	-0.01 (0.73)	0.608^

Table 11: Baseline characteristics grouped by the reason to DMT switch (clinical MS activity, radiological MS activity, safety and patient's wish(tolerability)
^ =one way ANOVA statistical analysis; *=chi –squared analisis
BREMSO: bayesian risk estimate for multiple sclerosis at onset; DMT: disease modifying treatment; MS: multiple sclerosis

Thus, statistical analyses were conducted to determine if variables at DMT start and DMT withdrawal were different across groups with different reasons to DMT switch.
The one-way ANOVA showed that there was a significant difference between groups for the following variables: age at DMT start, MS duration at DMT start, MSSS at DMT start, TTD and the variation of EDSS during the period on DMT (**table 12**). The

Bonferroni *post hoc* test was conducted to reveal the differences across specific groups (**figure 15-18**)

Pearson's Chi-squared analyses showed a significant difference between groups for EDSS at DMT start, type of DMT according to AIFA prescription and for clinical and radiological MS activity groups (**table 12** and **figure 19-23**). Additionally, the analysis showed a significant difference across groups also for the number of switched DMT at DMT start (**figure 24** p<0.0001) for the type of DMT at DMT start (**figure 25** p<0.0001)

Characteristics	Clinical MS activity	Radiological MS activity	Safety	Patient's wish /tolerability	p-value
Age at DMT start (yrs), mean (SD)	35.46 (10.36)	37.95 (8.84)	40.33 (10.92)	38.26 (9.89)	**0.001^**
MS duration at DMT start (yrs), mean (SD)	6.88 (6.99)	6.37 (5.74)	10.27 (7.96)	8.06 (6.50)	**<0.0001^**
EDSS at DMT start *0-3.5, %*	88.96%	91.45%	78.31%	91.52%	**0.011***
TTD (yrs), mean (SD)	3.16 (3.02)	3.34 (2.94)	2.18 (1.99)	2.59 (2.77)	**0.0054^**
AIFA DMT classification *First line, %*	92.40%	92.74%	30.77%	95.95%	**<0.0001***
EDSS Delta, mean (SD)	0.56 (0.80)	0.35 (0.62)	0.23 (0.56)	0.17 (0.55)	**<0.0001^**
MSSS at DMT start, mean (SD)	2.79 (2.06)	2.38 (1.92)	2.90 (2.31)	2.23 (2.22)	**0.035^**
Relapse free pre baseline, %	66.43%	90.60%	92.77%	93.67%	**<0.0001***
Relapse free post baseline, %	29.37%	71.79%	91.57	88.61%	**<0.0001***
MRI activity free post baseline, %	41.26	11.11	97.59	87.34	**<0.0001***

Table 12: Difference of main variables grouped by the reason to DMT switch (clinical MS activity, radiological MS activity, safety and patient's wish/tolerability)

^ =one way ANOVA statistical analysis; *=chi –squared analysis

BREMSO: Bayesian Risk Estimate for multiple sclerosis at Onset; EDSS: expanded disability status scale; DMT: disease modifying treatment; MRI: magnetic resonance imaging; MS: multiple sclerosis, MSSS: multiple sclerosis severity scale; SD: standard deviation; TTD: time to treatment discontinuation; yrs: years.

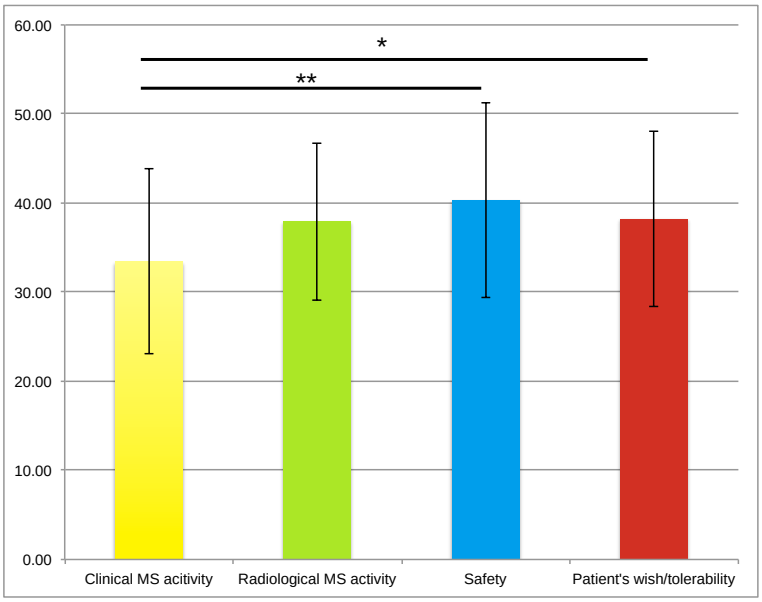

Figure 15: Age at DMT start. A Bonferroni *post-hoc* test shows that mean age at DMT start is lower in the switchers due to Clinical MS activity (yellow) compared to the switchers due to safety (blue) (p= 0.001) and to switchers due to patients' wish/tolerability (red) (p= 0.057)

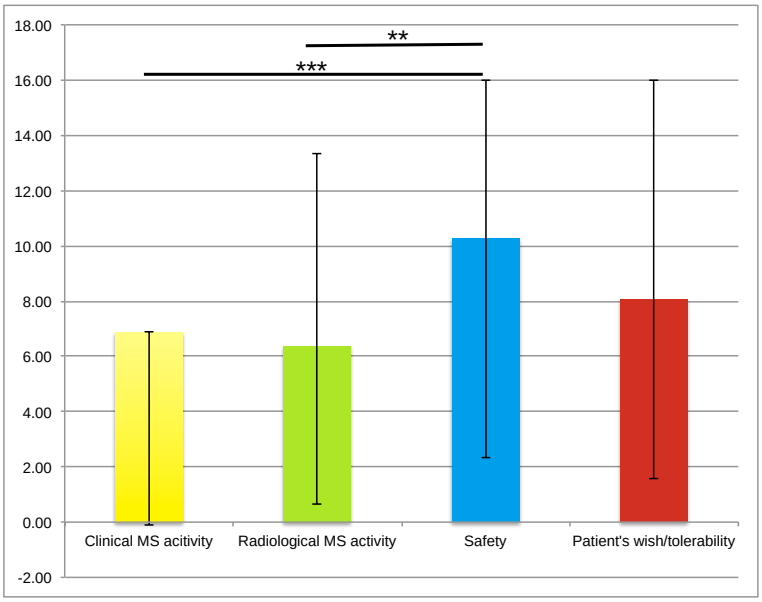

Figure 16: MS duration at DMT start. A Bonferroni *post-hoc* test shows that mean MS duration is higher in the switchers due to safety (blue) compared to the switchers due to clinical MS activity (yellow) (p<0.0001) and to switchers due to patient's wish/tolerability (green) (p=0.001)

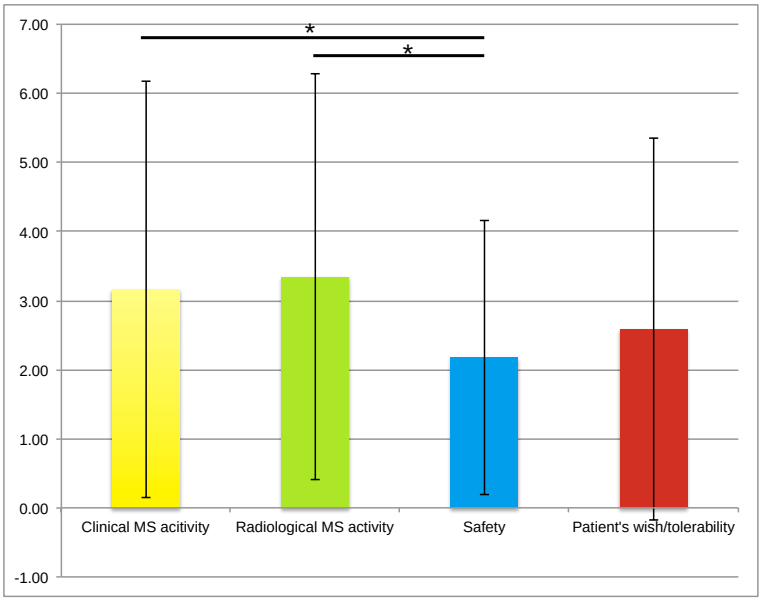

Figure 17: Time to treatment discontinuation (TTD). A Bonferroni *post-hoc* test shows that mean TDD is lower in the switchers due to safety (blue) compared to switchers due radiological MS activity (green) (p=0.016) and to clinical MS activity (yellow) (p=0.038)

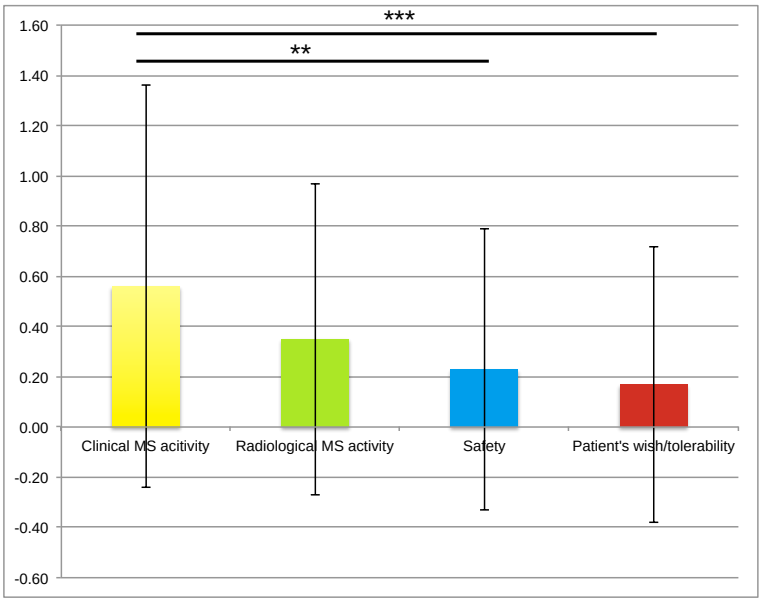

Figure 18: EDSS delta. A Bonferroni *post-hoc* test shows that mean the variation of EDSS between DMT start ad DMT withdrawal is higher in the switchers due to clinical MS activity (yellow) compared to switchers due safety (blue) (p=0.001) and to patients' wish/tolerability (red) (p<0.0001)

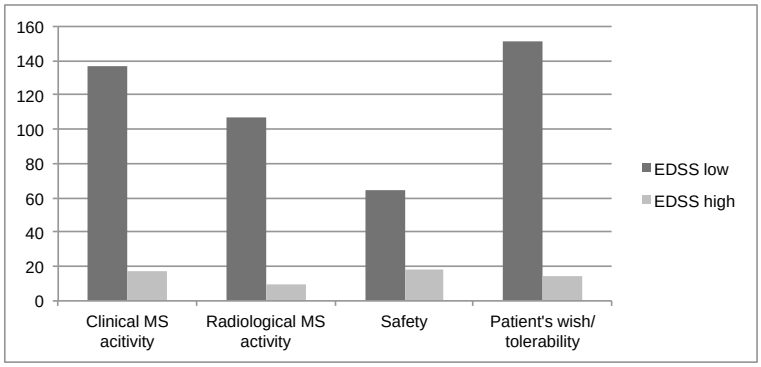

Figure 19: Results of the Pearson Chi-Square test indicating how low EDSS (EDSS ≤ 3.5, dark grey) and high EDSS (> 4.0, light grey) is distributed across the reasons of DMT switch. P=0.011

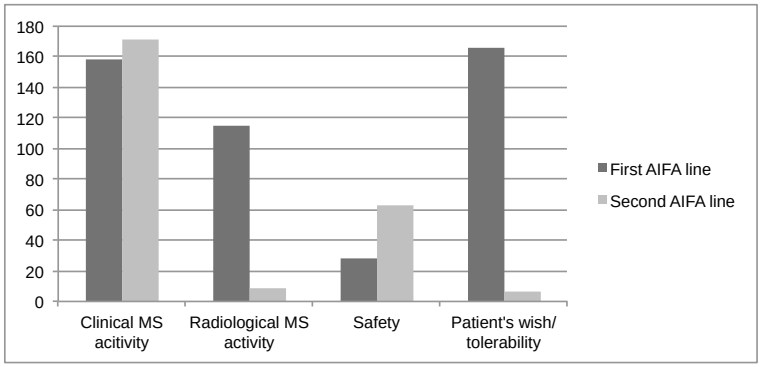

Figure 20: Results of the Pearson Chi-Square test indicating how first line DMTs records according to AIFA prescription (dark grey) and second line DMTs records according to AIFA prescription (light grey) at the time of DMT switch are distributed across the reasons of DMT switch. P<0.0001

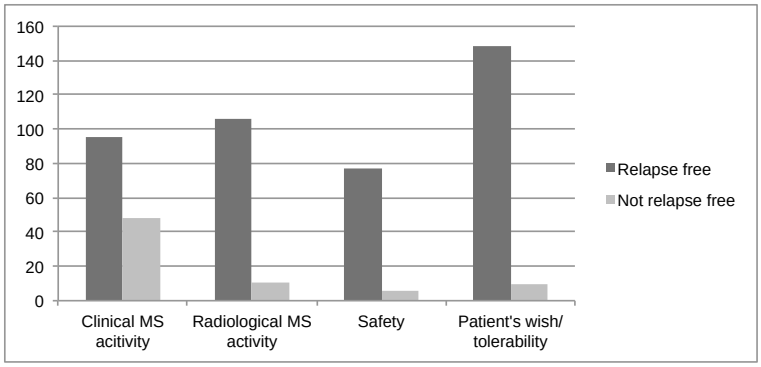

Figure 21: Results of the Pearson Chi-Square test indicating how relapse free records (dark grey) and not relapse free records (light grey) during *pre-rebaseline* are distributed across the reasons of DMT switch. P<0.0001

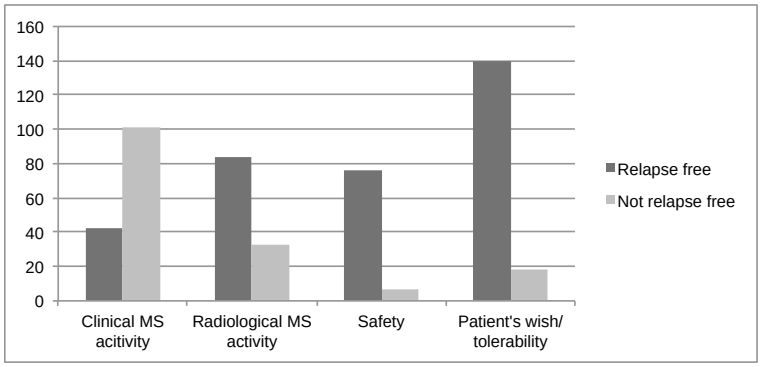

Figure 22: Results of the Pearson Chi-Square test indicating how relapse free records (dark grey) and not relapse free records (light grey) during *post-rebaseline* are distributed across the reasons of DMT switch. P<0.0001

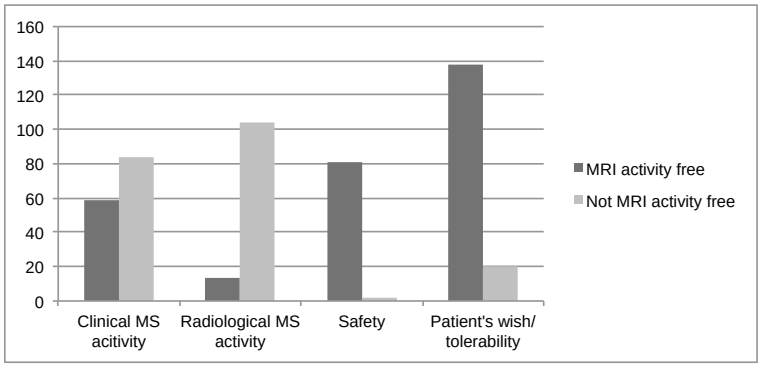

Figure 23: Results of the Pearson Chi-Square test indicating how MRI activity free records (dark grey) and not MRI activity free records (light grey) during *POST-baseline* are distributed across the reasons of DMT switch. P<0.0001

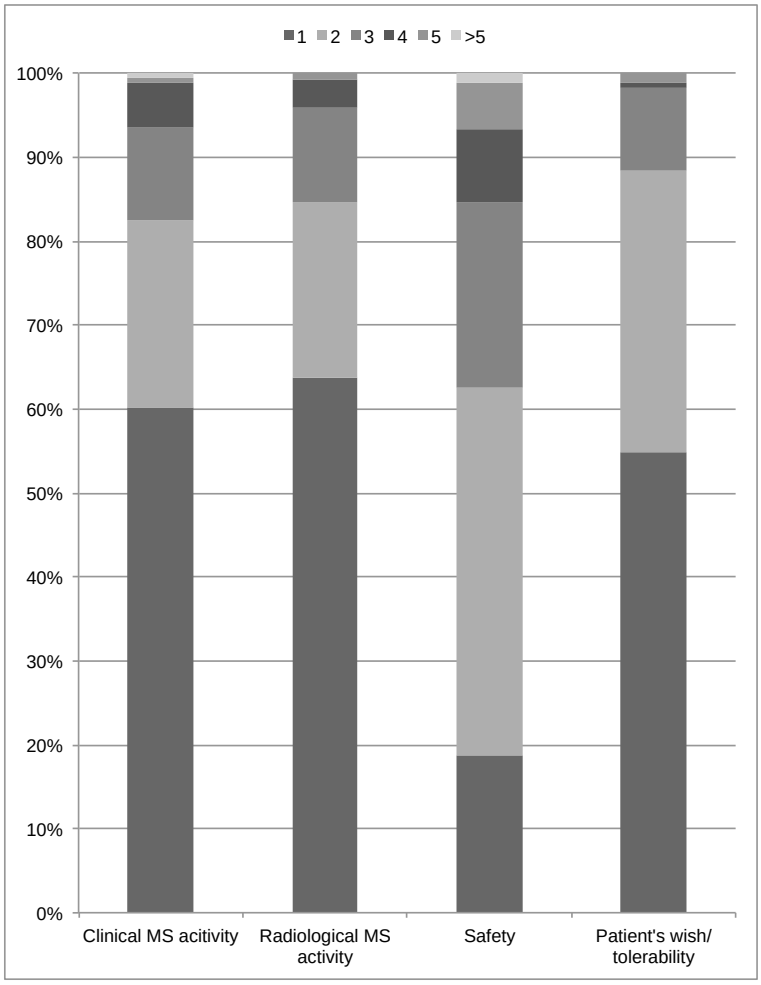

Figure 24: Results of the Pearson Chi-Square test indicating how number of switches distributed across the reasons of DMT switch. P<0.0001

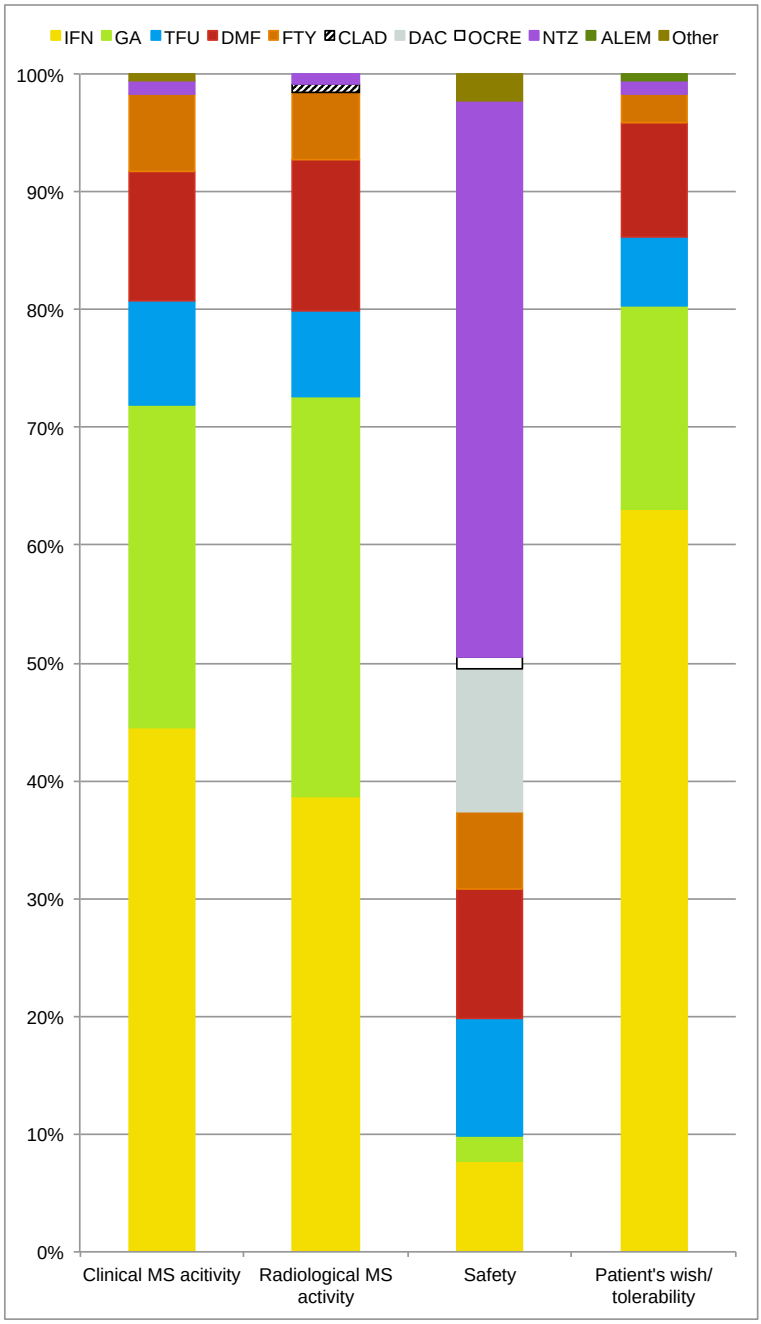

Figure 25: Results of the Pearson Chi-Square test indicating how DMT distributed across the reasons of DMT switch. P<0.0001

4. DISCUSSION

This study presents a systematic outlook and characterization of the reasons for switching DMTs for PwMS in daily clinical practice at the MS Center at the IRCCS Mondino, Pavia, Italy. Presenting DMT switch data from the point of view of "the reason of switch", is a kind of novelty in MS field, as per today only few real-life studies have investigated the reasons for switching DMTs in detail, but more focusing on the "from-to DMT" analysis [44,45], on a single DMT, on short time frame [46] or from patients' perspective [47].

In this study I collected the data of 355 PwMS, who regularly referred to the MS Center at IRCCS Mondino. I matched their clinical data (stored as digital medical records) and their drug prescription data (stored as digital files). I was able to recall data from the last 25 years. During the observational period, a total of 682 switches occurred within the 355 PwMS.

In general, the main reason to DMT switch within the 682 records was treatment failure, defined as the presence of *clinical MS activity (including clinical worsening) or radiological MS activity* (43.32%). Similar observations were made in recent population-based studies: Italian real-life study by Saccà and colleagues[45], reported that switches due to inefficacy were more frequent than switches due to intolerance/safety; Italian real life study by Patti and colleagues[46] reported that the most common first reason for switching was lack of efficacy (58.4%), followed by poor safety and/or tolerability (33.0%); and German real life study by Maurer and colleagues[44] reported that the main reasons to switch DMT were failure of current therapy (53.9%) followed by patient wish (22.4%). However, if clinical and radiological MS activity were not grouped together, the main reason of DMT switch was shared by both *clinical MS activity* (25.07%) and *patient's wish/tolerability* (25.36%). Switched due to *safety* reasons only represented the 13% of cases and in the vast majority of them, they signified "switch due to the risk of progressive multifocal leukoencephalopathy (PML)".

Of note, ⅕ (21.05%) of the records within the clinical MS activity DMT switch displayed the same codes, meaning that some PwMS has switched DMT due to *clinical MS activity* at least 2 times. This rate of "duplicates" reduced to 1/10 (13.70%) when the reason for DMT switching was *radiological MS activity*, but it rose up to ½ (48.55%) for the switches due to *patient's wish/tolerability*.

Results show four main groups according to the reason to switch: *clinical MS activity, radiological MS activity, safety and patient's wish/tolerability*. These four main groups displayed the same BREMSO scores. Briefly, BREMSO score expresses PwMS risk for an unfavorable disease evolution at disease onset and before starting a DMT; BREMSO score ensures indeed a good balance of prognostic correlates at MS onset (baseline) and allows managing observational data in a relatively unbiased way. According to that, as demonstrated and detailed in the following paper "A method to compare prospective and historical cohorts to evaluate drug effects" [43], the main four groups could be compared via statistics.

Despite the differences highlighted between the four groups do not allow to make a clear identikit of the subjects who belong to a specific group, it can be commented that compared to the switches due to DMT failure, DMT switches due to *safety* reasons mainly (about 80%) occurred when PwMS were on second line DMT. Moreover, that those switches due to *safety* concerned primarily represent the second or third switch of a PwMS, and that they mainly verified in PwMS with longer MS duration and with older age at DMT start. Finally, in this type of switch, the time to drug discontinuation is about one year shorter compared to the switches due to DMT failure.

Of the 295 records switched for failure on previous DMTs, 57.28% switched to therapies approved for moderate–highly aggressive MS. Of those, 154 records were previously on first line DMTs and 17 records were on second line DMTs.
Analyzing the pattern of DMT switch according AIFA first *versus* second line DMT, I did not see any major difference within the switch pattern between those PwMS who switched only one time due to DMT failure and those PwMS who switched at least 2 times due to DMT failure.
Moreover, in both cases in which patients were switched to DMTs due to *clinical MS activity* or *radiological MS activity*, natalizumab (55.96% and 43.10% of records respectively) was robustly preferred over fingolimod (25.68% and 34.48% of records respectively) and over other monoclonal antibodies (ocrelizumab 7.33% and 15.51% of the records, respectively; and alemtuzumab 1.83% of the records in clinical activity MS group). Although natalizumab, fingolimod and monoclonal antibodies belong to the very same group according to AIFA, the preference towards natalizumab may be explained by several reasons including the DMT efficacy and effectiveness profiles (monoclonal antibodies including natalizumab are likely more effective in the prevention of clinical relapses and radiological activity) [47–54]; and the long term data about its safety and its effectiveness [56,57]. It will be interesting to see if the gained

experience with the more recent DMTs (e.g. ocrelizumab and cladribine) and the advent of new compounds a in the next future will or will not affect this polarization towards natalizumab.

I also performed the very same analysis within the 119 records, which were related to a switch within the first line DMTs in order to highlight any trend within subgroups of PwMS and/or any trend in DMT prescription.

Similar to what happen within the switch towards a second line DMT, I did not see any major effect on the prescription of a DMT type between those PwMS who switched only one time due to DMT failure and those PwMS who switched at least 2 times due to DMT failure.

Literature reports lower ARR, higher relapse-free survival, and lower incidence of discontinuation due to disease breakthrough on treatment with dimethyl fumarate compared with teriflunomide [58]; longer time to first relapse and lower ARR with DMF compared to matched interferons and glatiramer acetate [59]; and improvement of ARR also in those PwMS who switch from injectable therapies due to tolerability and efficacy issues [60]. Despite those results, dimethyl fumarate was not preferred to the other DMTs even in those patients that had already changed DMT at least two times. Further analysis will be directed to analyze a different (i.e. more recent) time frame in order to highlight the if the treatment approach is changed in accordance with literature data or not.

Of the 173 records switched due to patient's wish/tolerability, 95.95% were on first line DMTs and 11% stop therapy after the switch; of note, 2/3 of those who withdrew therapy had before switched DMT for the same reason at least 2 times.

Despite out of the scope of this project, the broad time interval analyzed in this study gives the possibility to perform detailed analysis of the treatment approach in MS field during the last 20 years (figure 6), which roughly corresponds to the DMT era since its very beginning. In particular it could be analysed how the advent of new compounds has affected this therapeutic approach. Before discussing the single advent of a new DMT, I clarify that as Covid-19 pandemic may have biased the usage of DMTs compared to standard practice, thus, 2020 was not considered for this analysis.

In late 2011, AIFA approved fingolimod as second line treatment. Fingolimod approval was a watershed: fingolimod was indeed not only the very first oral drug approved for MS treatment but it was also a valid therapeutic alternative for those PwMS for whom natalizumab could not be prescribe (mainly due to the risk of PML). Fingolimod approval at the end of 2011 has truly affected MS therapeutic approach. As shown in

figure 6, after fingolimod approval, the percentage of DMT switch due to *safety* (i.e. PML risk) dramatically increased about 4 times. This increase gradually reduced till 2016.

In late 2014 and at the beginning of 2015, AIFA approved teriflunomide and dimethyl fumarate, respectively. They were the first oral DMTs approved for first line treatment. Parallel to the advent of the first line oral DMTs, the percentage of switches due to *patient's wish/tolerability* increased more than 1.5 times, lasting about 3 years. Of note, a little unexpectedly data analysis showed switches from injectable DMTs to oral DMTs but also from oral DMTs to injectable DMTs. The advent of first line oral DMT is also linked with an increase of adverse events, which lasted about 3 years. Improving the monitoring and the management of adverse events [61,62] has likely reduced the switches due to them.

In 2018, cladribine and ocrelizumab were approved as second line DMT. Despite less evident compared to the advent of fingolimod, an increase of the switches due to *safety* (i.e. due to PML risk) can be observed. To date, however limited data on the effects of these two compounds are available due to their recent use in a limited group of patients, probably also hinder by the advent of COVID-19 pandemic.

Alemtuzumab did not seem to have affected treatment approach at MS Center at IRCCS Mondino.

Finally, focusing on the percentage of switches due DMT failure, it can be argued that despite the introduction of more effective DMTs, which also hold a better tolerable profile, there are still switches due to DMT failure and that this trend is not even decreasing. An overall increased in expectation of new DMT effectiveness and safety profile over time likely explains the aforementioned phenomenon.

This study shows a major limitation: patients matching the inclusion criteria, but not switching, were not yet analyzed as a control group; despite we do not expect different findings, this additional analysis may further strengthen present findings hence I will consider such an approach for future researches. Despite the above-mentioned limitation, the method we followed – unique in the recent literature -has to be considered an alternative and complementary approach to standard real-world evidence analysis, typically focusing on single treatment (or treatments) rather than the patient and the very event. This study improved current awareness on these dynamics, better characterizing everyday practice switch trends with the ultimate goal of improving disease management and patient care.

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