Multiple Sclerosis and Related Disorders 42 (2020) 102124

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Clinical and patient determinants of changing therapy in relapsing-remitting multiple sclerosis (SWITCH study)

Francesco Patti[a,#,*], Clara Grazia Chisari[a,#], Emanuele D'Amico[a], Pietro Annovazzi[d], Paola Banfi[e], Roberto Bergamaschi[f], Raffaella Clerici[g], Marta Zaffira Conti[h], Antonio Cortese[i], Roberta Fantozzi[c], Mariano Fischetti[c], Maura Frigo[j], Maurizia Gatto[k], Paolo Immovilli[l], Stefania Leoni[m], Simona Malucchi[n], Giorgia Maniscalco[o], Girolama Alessandra Marfia[p], Damiano Paolicelli[q], Paola Perini[r], Carlo Serrati[s], Patrizia Sola[t], Rocco Totaro[u], Gabriella Turano[v], Paola Valentino[w], Mauro Zaffaroni[d], Cristina Zuliani[x], Diego Centonze[b,c,*]

[a] Department "GF Ingrassia" Section of Neurosciences, University of Catania, Catania, Italy
[b] Laboratory of Synaptic Immunopathology, Department of Systems Medicine, "Tor Vergata" University, Rome, Italy
[c] Unit of Neurology – IRCCS Neuromed, Pozzilli, Isernia, Italy
[d] Multiple Sclerosis Center, Hospital of Gallarate – ASST della Valle Olona, Gallarate, Italy
[e] Operative Unit of Neurology and Stroke Unit, Varese, Italy
[f] Multiple Sclerosis Center, IRCCS Mondino Foundation, Pavia, Italy
[g] Operative Unit of Neurology – Valduce Hospital, Como, Italy
[h] Department of Neurology, ASST Papa Giovanni XXIII, Bergamo, Italy
[i] Department of Human Neurosciences, University of Rome, Sapienza, Italy
[j] Neurology Department, San Gerardo Hospital, Monza, Italy
[k] Department of Neurology, General Regional Hospital "Miulli", Acquaviva delle Fonti, Bari, Italy
[l] Emergency Department, Neurology Unit, G. da Saliceto Hospital, Piacenza, Italy
[m] Unit of Clinical Neurology – AOU Sassari, Italy
[n] SCDO Neurologia-CRESM, University Hospital San Luigi Gonzaga, Orbassano, Turin, Italy
[o] Multiple Sclerosis Center, Cardarelli Hospital, Naples, Italy
[p] Multiple Sclerosis Clinical & Research Center, Department of Systems Medicine, "Tor Vergata" University, Rome, Italy
[q] Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy
[r] Multiple Sclerosis Center, Neurological Clinic, University Hospital of Padua, Italy
[s] Operative Unit of Neurology and Stroke Unit, IRCCS Hospital San Martino, Genoa, Italy
[t] Department of Neuroscience, UO of Neurology, AOU Policlinico OB, Modena, Italy
[u] Demyelinating Disease Center, Department of Neurology, San Salvatore Hospital, L'Aquila, Italy
[v] Department of Neurology, Mondovì General Hospital, Local Health Authority CN1, Mondovì, Cuneo, Italy
[w] Neurology, University Magna Graecia, Catanzaro, Italy
[x] Operative Unit of Neurology, Mirano, Venice, Italy

ARTICLE INFO

Keywords:
Multiple sclerosis
Disease modifying therapies
Switching therapies

ABSTRACT

Background: clinical factors and frequency of disease-modifying therapy (DMT) changes/interruptions in relapsing-remitting multiple sclerosis (RRMS) patients have not been well defined. The aim of this study was to describe reasons of MS treatment modifications in a large cohort of Italian MS patients.

Methods: this multicenter, cross-sectional non interventional study (SWITCH) conducted at 28 Italian MS centers, screened, by visit/telephone contact between June 2016 and June 2017, all RRMS patients receiving stable DMT treatment and enrolled patients with change in DMT treatment.

Results: out of 13,657 recorded in the log, 409 (3%) changed therapy. Of these, 336 (2.5%), met the study criteria and were considered eligible. Among 303 (90.2% of 336) patients switching, the most common reason was "lack of efficacy" (58.4% of 303). Among 30 (8.9%) patients who interrupted treatment temporarily, the most common reason was pregnancy (40.0% of 30). Out of 3 (0.9%) patients who discontinued treatment permanently, 2 (66.7%) had as first reason as "patient decision". Multivariate analysis showed that EDSS was the

* Corresponding authors.
E-mail addresses: patti@unict.it (F. Patti), centonze@uniroma2.it (D. Centonze).
# equally contributed to the manuscript

https://doi.org/10.1016/j.msard.2020.102124
Received 20 August 2019; Received in revised form 14 March 2020; Accepted 29 March 2020

only variable with statistically significant effect on changing treatments (r = 8.33; p-value of Type III Sum of Squares = 0.016).
Conclusion: in our study, 303 (90.2% of eligible patients) switched treatment, 30 (8.9%) interrupted treatment temporarily, and 3 (0.9%) discontinued treatment permanently. Efficacy remains the main driving force behind switching behavior, as the primary aim of treatment is to be disease free or reduce disease activity.

1. Introduction

The introduction of highly effective treatments has considerably changed the therapeutic scenario for people suffering from relapsing remitting multiple sclerosis (RRMS). The number of available MS treatment options has increased considerably over the past 20 years, but so far no definitive cure exists (Guarnera et al., 2017).

The most frequently used treatment approach in RRMS is based on early initiation of a therapeutic regimen with a disease modifying treatment (DMT), in the attempt to reduce inflammation, delay neurodegeneration, and consequently reduce disability (Noyes and Weinstock-Guttman, 2013; Ciotti and Cross, 2018).

In this regard, effective and strategic interventions require prompt treatment optimization, and a switch of therapy in patients with suboptimal response or treatment failure with their current MS treatment (Ziemssen et al., 2016; D'Amico et al., 2018).

How and when to switch therapy has been debated frequently, but increasing evidence showed that there is a limited window of opportunity to intervene effectively in RRMS management (Ziemssen et al., 2016; Meuth et al., 2010; Kieseier et al., 2008; Girouard and Theoret, 2008). Moreover, a change of treatment may be necessary for lack of tolerability, safety, or convenience, thereby complicating a switch decision (Weber et al., 2012). The availability of several therapeutic options has increased the possibility of tailoring the DMT to the individual patient but, so far, no universal guidelines exist to encompass all the scenarios a physician may encounter, nor address patient perspectives (Meuth et al., 2010). Lack of treatment efficacy and adverse events remain the main driving force behind a therapeutic switch. Meeting patients' goals requires a continuous and concordant relationship between the neurologist and the patient (Weber et al., 2012).

In this study (SWITCH), we aimed to investigate the reasons, related or unrelated to therapy and/or to the disease, that brought about modification of treatment, with reference to the three therapeutic change modalities: switch, temporary interruption, or permanent discontinuation.

2. Materials and methods

This was a multicenter, cross-sectional non-interventional study conducted at 28 Italian centers authorized for the diagnosis and treatment of MS; 12 (42.9%) located in the north, 9 (32.1%) in the center, and 7 (25%) in the south of the country. To faithfully represent the Italian MS population, study centers were distributed geographically by region according to epidemiological data collected by the Italian Association for MS. The study was carried out between June 2016 and June 2017.

A patient tracking log (named log-book) was used to track all RRMS patients seen by each investigator (principal or sub-investigator) conducting the study at each participating centers. Each patient was counted only once in the log (a patient needing to modify treatment more than once over the study period was counted and enrolled only once, as was a patient having more than one visit over the study period).

Those patients who fulfilled the following eligibility criteria were asked for their informed consent and were enrolled in the study.

Inclusion criteria:

1 Patients of both genders aged ≥ 18 years.
2 Patients with RRMS according to 2010 revised McDonald criteria (Polman et al., 2011).
3 Patients receiving stable DMT treatment with at least 80% of therapy administered in the 3 months preceding the visit/telephone contact during which treatment modification was decided.
4 The adherence rate to the treatment was collected retrospectively according to medical records.
5 Signed written informed consent.

Exclusion criteria:

1 Patients with primary-progressive MS (PPMS) or secondary-progressive MS (SPMS).
2 Patients unable to participate for various reasons (e.g. unable to understand the aim of the study).
3 Patients participating in another clinical study with an investigational product.
4 Patients switching to another DMT with the same mechanism of action as the previous drug.

A change in MS treatment consisted of one of the following:

Switch: a change for any reasons from one DMT to another that did not have the same mechanism of action. The wash-out period between the two drugs could be no longer than 4 months.

Temporary interruption: an interruption of more than 4 months before resuming therapy with the same drug or changing to a different one. The interruption may have been due to causes related to treatment (e.g. side effects) or unrelated (e.g. pregnancy, concomitant diseases, surgery).

Permanent discontinuation: no MS treatment was planned once the current drug was stopped. This applied, for example, to patients who developed SPMS or to those who had been clinically and radiologically stable for several years.

All enrolled patients' data were uploaded in an electronic case report form (e-CRF) specifically designed for this study. Site data quality controls were performed by the Sponsor through site monitoring and/or phone calls, and appropriate consecutive corrective actions were carried out where needed.

Only data from the single visit were collected and no follow-up was done. Enrolment for each center lasted 6 months.

2.1. Data collection and management

The following data were collected for each enrolled patient **and recorded in the eCRF:** demographic and historical clinical data; clinical data: date of onset of MS symptoms and date of diagnosis, number of relapses in the last two years, date of onset and severity of last/current relapse/exacerbation; previous and current Expanded Disability Status Scale (EDSS), if available; presence of new T2 lesions in the most recent MRI (within 6 months) in comparison with previous MRI and previous and current DMT.

We also recorded reasons for modifying treatment with the three therapeutic change modalities (investigators had to indicate from one to three reasons per modality): reasons related and/or unrelated to treatment to be interrupted temporarily or discontinued (e.g. side effects, pregnancy, concomitant disease, surgery); reasons related and/or unrelated to the disease (e.g. transition to SPMS, clinical and

radiological stability); reasons related to treatment to be changed in case of switch (lack of efficacy, poor safety and/or tolerability, convenience, other); reasons related to treatment to be started, in case of switch or temporary interruption (better route of administration, better perceived efficacy, better perceived safety, other).

2.2. Statistical analysis

All tables, figures, listings, and statistical analyses were generated using SAS® for Windows release 9.4 (64-bit) on eligible patients. All tables were quality controlled. Double programming was performed for the critical tables (e.g. tables on primary endpoints). Simple re-programming activities or SAS® code checks were performed for all the other tables.

Continuous data are summarized by number of observations, mean, standard deviation (SD), median, 1st and 3rd quartile, minimum and maximum. Categorical data were presented by absolute and relative frequencies (*n* and%) or contingency tables.

The total frequency of RRMS patients requiring treatment modification was calculated on a single-point analysis.

We analyzed the reasons for modifying treatment for each therapeutic change modality (switch, temporary interruption, and permanent discontinuation). Moreover, the frequency and proportion of patients in each therapeutic change modality (switch, temporary interruption, and permanent discontinuation) were also summarized. The correlation between preferred change modalities and the following demographic and clinical information were analyzed using a multinomial logistic regression model and considering the "switch" modality as the reference value: current age, gender, time from MS onset to informed consent signature, number of relapses in the last two years, severity of last or current relapse/exacerbation, EDSS score, presence of new T2 lesions in comparison with previous MRI, size and geographic area of the center. The covariates described above were then selected using a stepwise procedure, in which variables were added one by one to the model and the F statistic for a variable to be added had to be significant at the 0.05 level. After a variable was added, the stepwise method looked at all the variables already included in the model and deleted any variable that did not produce a F statistical significance at the 0.05 level.

Given the epidemiological and cross-sectional non-interventional nature of the study, no formal sample size determination was done.

3. Results

3.1. Demographical and clinical data

Out of 13,657 patients recorded in the log, 409 (3%) changed treatment, 367 (2.7% of 13,657) of whom provided written informed consent and were enrolled in the study. Out of 367 patients, 31 patients (8.4% of 367) reported at least one protocol deviation and were excluded from the data analysis.

Out of 336 eligible patients (mean age 40.7 ± 10.5 years, 70.8% women), 303 (90.2% of 336) switched treatment, 30 (8.9%) interrupted treatment temporarily, and 3 (0.9%) discontinued treatment permanently (Fig. 1). Demographic and clinical characteristics were summarized in Tables 1 and 2.

3.1.1. Geographical distribution of the population

One hundred and twenty-six patients were enrolled in northern Italy (12 sites), 113 in central Italy (9 sites) and 97 in the south (7 sites). Of all the patients recorded in the tracking logs, 6101 were located in the north, 4007 in the center, and 3549 in the south.

3.2. Reasons to modify treatment

Among patients who switched treatment, the most common first reason was consistently related to the treatment to be changed from, and included lack of efficacy (58.4%), poor safety and/or tolerability (33.0%), patient request (3.6%), compliance (2.6%), convenience (1.7%), and other (0.7%) (for other reasons of switching see Fig. 2).

The most common first reason for interrupting treatment temporarily was pregnancy (46.7%, 40.0% for reasons not related to the treatment and 6.7% reason related to the treatment) followed by side effect (23.3%), lack of efficacy (10.0%), and injection fatigue (10.0%) (for other reasons for temporarily interrupting see Fig. 3).

Considering subjects with a permanent discontinuation, 2 of the 3 patients in this group had as their first reason patient decision (66.7%), and the third as transition to SPMS .

Medication to be changed from – medication to be changed to – medication to be interrupted Among the switching cohort, a second line treatment (fingolimod [FTY], natalizumab [NTZ], or alemtuzumab [ALM]) was chosen for 139 (45.9%) of patients.

Specifically, out of 97 patients treated with interferon (IFN) beta-1a (IFNb-1a both intramuscularly [i.m.] and subcutaneously [s.c.] administered), 34 (35.1%) switched to dimethyl-fumarate (DMF), 26 (26.8%) to FTY, 17 (17.5%) to teriflunomide (TFN), and 11 (11.3%) to

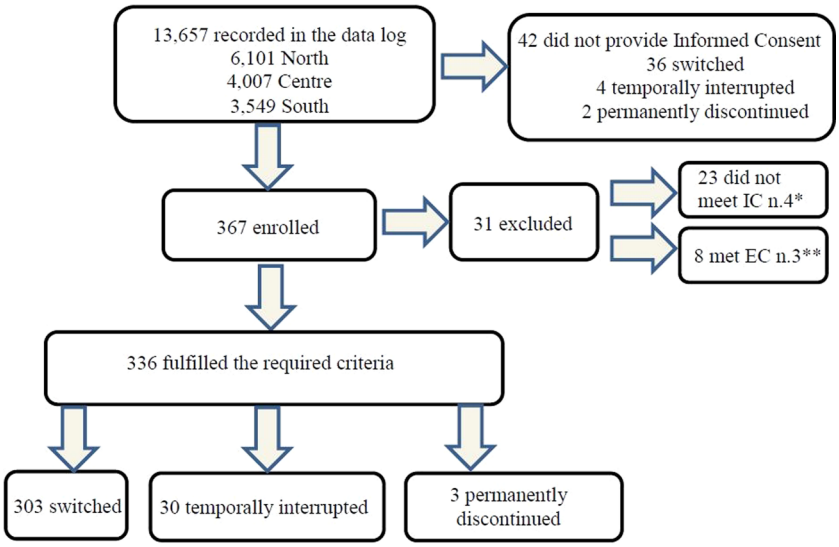

Fig. 1. Patients' selection flow chart.
IC: inclusion criteria; EC: exclusion criteria;
*Inclusion criterion *n.* 4: patients receiving stable DMT treatment with at least 80% of therapy administered in the 3 months preceding the visit/telephone contact during which treatment modification was decided;
** Exclusion criterion n. 3: patients participating in another clinical study with an investigational product.

Table 1
Demographic characteristics of enrolled population (n = 336).

		Switch (303)	Temporary Interruption (30)	Permanent Discontinuation (3)
Gender; n (%)	Women	211 (69.6%)	24 (80%)	3 (100%)
Age; Mean ± SD	years	40.6 ± 10.5	40±10.8	50.3 ± 2.1
Living status; *n* (%)	Alone	40 (13.2%)	4 (13.3%)	1 (33.3%)
	With other adults	253 (83.5%)	26 (86.7%)	2 (67.7%)
	In an institution	1 (0.3%)	0	0
	Not specified	10 (3.3%)	0	0
Educational level; *n* (%)	Primary Education	19 (6.3%)	1 (3.3%)	1 (33.3%)
	Lower secondary education	88 (29%)	6 (20%)	0
	Upper secondary education	136 (44.9%)	15 (50%)	2 (66.7%)
	Higher education	60 (19.8%)	8 (26.7%)	0
Occupational Status; *n* (%)	Student	24 (7.9%)	0	0
	Employed Full Time	142 (46.9%)	19 (63.3%)	0
	Employed Part Time	24 (7.9%)	3 (10%)	0
	Freelance	5 (1.7%)	0	0
	Unemployed	39 (12.9%)	3 (10%)	2 (66.7%)
	Homekeeper	52 (17.2%)	5 (16.7%)	1 (33.3%)
	Retired	5 (1.7%)	0	0
	Unknown	12 (4%)	0	0

SD: standard deviation; ns: not significant.

Table 2
Clinical characteristics of enrolled population (n = 336).

	Switch (303)	Temporary Interruption (30)	Permanent Discontinuation (3)
No of relapses in the previous 2 years; mean ± SD	0.9 ± 0.8	0.9 ± 1	0 ± 0
EDSS before treatment change; mean (SD)	2.2 (1.5)	1.4 (1.0)	3.0 (1.8)
EDSS at time of enrolment; mean (SD)	2.3 (1.6)	1.5 (1.1)	3.3 (2.4)
No new MRI lesions at time of enrolment vs previous MRI; *n* (%)	152 (51.7)	26 (86.7)	3.0 (100)
DMT at time of enrolment; *n* (%)			
Interferon beta 1a*	97 (32%)	9 (30%)	1 (33.3%)
Interferon beta 1b	17 (5.6%)	0	0
Peginterferon beta 1a	18 (5.9%)	0	1 (33.3%)
Glatiramer acetate	57 (18.8%)	8 (26.7%)	0
Teriflunomide	27 (8.9%)	2 (6.7%)	0
Dimethylfumarate	42 (13.9%)	4 (13.3%)	0
Fingolimod	22 (7.3%)	4 (13.3%)	1 (33.3%)
Natalizumab	20 (6.6%)	3 (10%)	0
Others	3 (1%)	0	0

EDSS; expanded disability status scale; DMT: disease modifying therapy; SD: standard deviation; ns: not significant.

* Interferon beta 1a both intramuscularly and subcutaneously administered.

NTZ. Patients treated with IFN beta-1b (IFNb-1b; 17 patients) switched more frequently to DMF (6; 35.3%) followed by TFN (4; 23.5%), and FTY (3; 17.7%). Patients treated with GA (57 patients) most often switched to TFN (17; 29.8%), FTY (16; 28.1%) or DMF (16; 28.1%). Patients treated with peginterferon beta-1a (pIFNb-1a, 18 patients) most often switched to DMF (6; 33.3%) or TFN (5; 27.8%). Out of 27 switching from TFN, 9 patients (33.3%) changed to FTY, followed by DMF (6 patients; 22.2%). For patients switching from DMF (42 patients), 13 (30.9%) changed to FTY, followed by NTZ (10 patients, 23.8%). Patients treated with NTZ (20 patients) most commonly changed to alemtuzumab (7 patients; 35%) or FTY (6 patients, 30%). Fig. 4 shows treatments to be changed from and changed to among patients switching therapy.

Among patients with a temporary interruption, 9 (30.0%) took i.m. and s.c.IFNb-1a, 8 (26.7%) GA, 4 (13.3%) DMF, 4 (13.3%) FTY, 3 (10%) NTZ, and 2 (6.7%) TFN. Patients with a permanent discontinuation were being treated with i.m. and s.c.IFNb-1a (1; 33.3%), pIFNb-1a (1; 33.3%), and FTY (1; 33.3%).

3.3. Multivariate logistic regression

The multivariate logistic regression showed that EDSS score was the only statistically significant variable in the model for switching therapy (r = 8.33; p-value of Type III Sum of Squares = 0.016 with the Wald Chi-square test). Although the presence of new lesions upon MRI showed a p-value <0.05, the quasi-complete separation of data points prevented us from interpreting this result. No reasonable estimate for this variable was detected which was capable of predicting our outcome (Table 3).

4. Discussion

This cross-sectional non-interventional multicenter Italian study showed that 3% of RRMS patients presenting at selected centers and evaluated during a single visit required modification of DMT, and that in the majority of cases the change consisted in a switch of DMT.

The overall low switching rate in our study compared to other pivotal studies may be explained by the cross-sectional nature of the study protocol. Indeed, the decision of switching therapy was made during routine clinical follow-up visits. This means that even those patients with clinically stable diseases were included in the dataset, contributing to make lower the percentage of patients switching because of efficacy. Nevertheless, the lower incidence of patients changing DMT in our study might also reflect high-level expertise in MS management of Italian MS centers participating to the study.

In a recent multicenter Italian study enrolling 3025 patients, the overall switch frequency was 48% after 3 years (11). This value is much higher compared to that found in our cohort and could be explained by the composition of the sample including newly diagnosed RRMS patients likely to present with highly active disease and, therefore, more inclined to change treatment. Conversely, in our study, we excluded those patients participating in clinical trials and those switching to DMTs with the same mechanism of action. Regarding this latter, the rationale of any kind of switch (lateral or escalating) should be moving to a drug with a more pertinent mechanism of action, whether a more potent and effective treatment in case of suboptimal response or a different safer profile in order to resolve or mitigate the risk of adverse events. Thus, even in case of lack of tolerance, changing to drugs with the same mechanism of action (i.e. different dose or delivery schedule of the same agent) could not represent a proper switch. Moreover, the choice to not consider switch as the change within the same class of

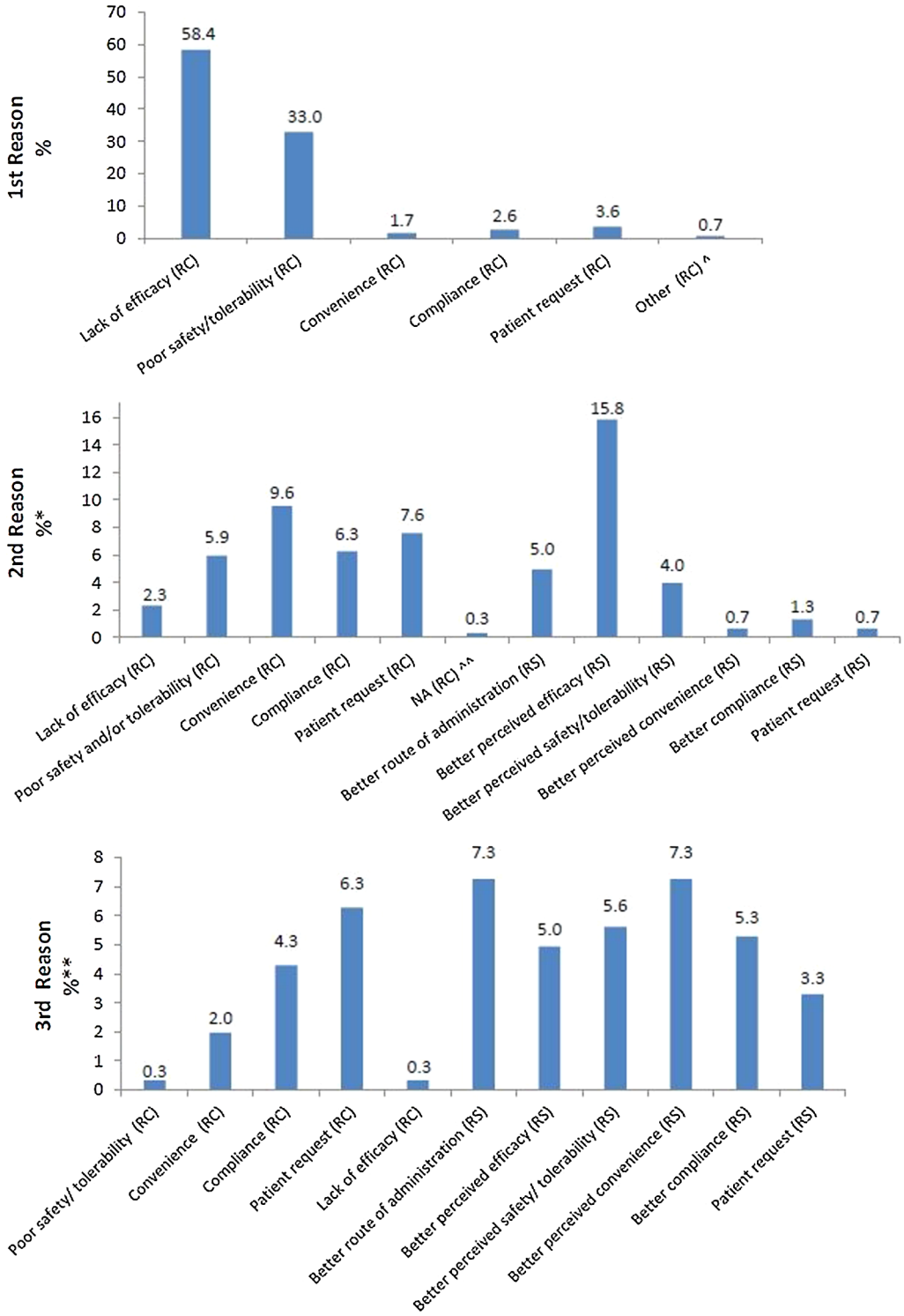

Fig. 2. Reasons for modifying treatments in the switch group (n = 303).
RC: Reason related to treatment to be changed from. RS: Reason related to treatment to be changed to.
*In 40.5% of cases investigators did not indicate a 2nd reason
**In 53.0% of cases investigators did not indicate a 3rd reason
^ 1 JCV+; 1 Negative Benefit/Risk ratio
^^ NA: not applicable; investigators indicated an inappropriate reason (claustrophobia).

injectable agents could be explained by the immunomodulating nature of these classes of drugs (IFNs and GA). Although the mechanism of these drugs is not well defined, their immunomodulatory activity make them similar in terms of effectiveness.

In our study, the most common first reason for switching was lack of efficacy (177; 58.4%), followed by poor safety and/or tolerability (100; 33.0%). Approximately 30% of patients show a suboptimal therapeutic response during the early years of treatment as confirmed in other studies (Coyle, 2013; Miller, 2016), and that rates of discontinuation after 1–3 years of treatment with a DMT have ranged between 30% and

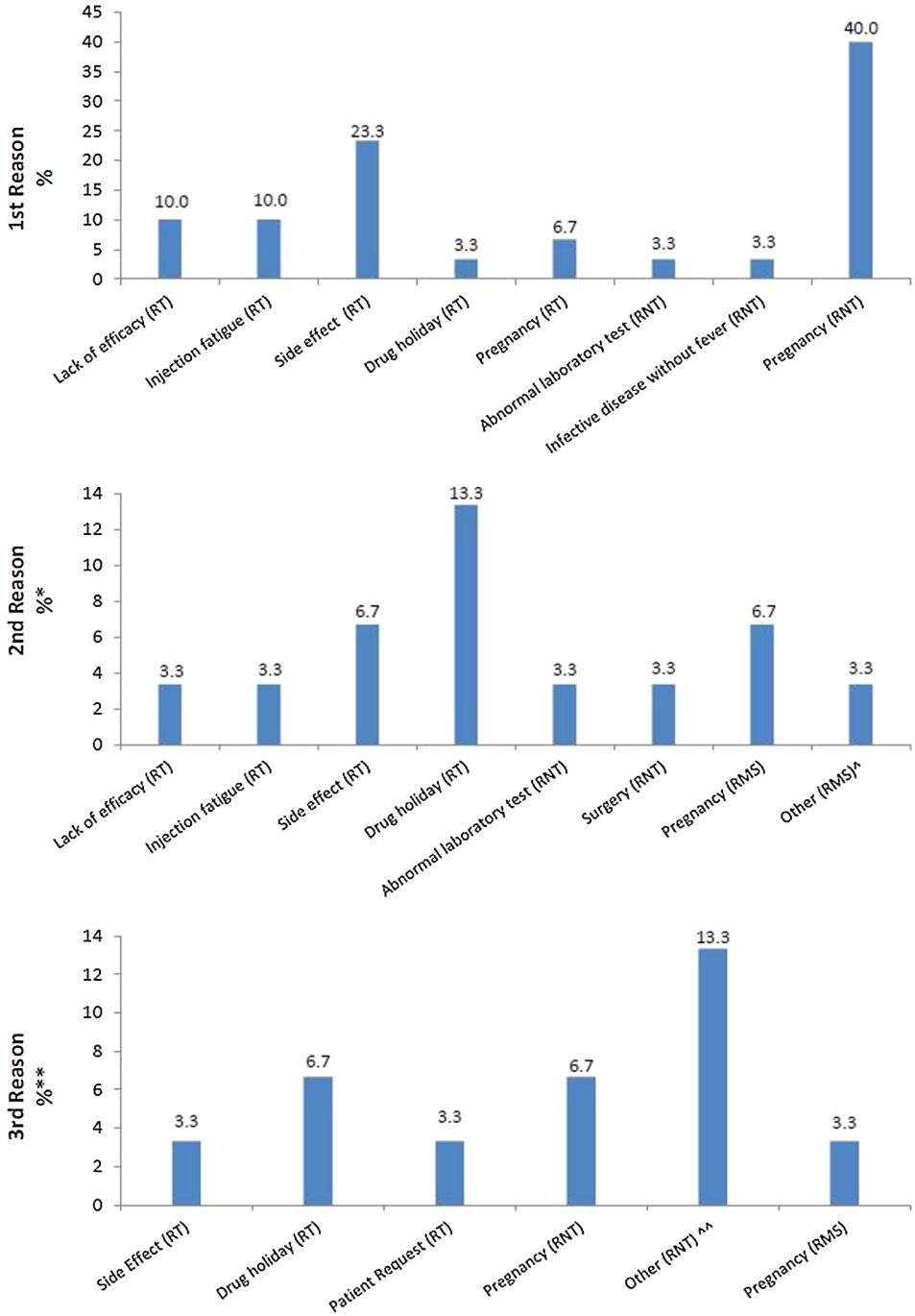

Fig. 3. Reasons for modifying treatments in the temporally interrupted group (n = 30).
RT: Reason related to the treatment. RNT: Reason not related to the treatment nor to MS. RMS: Reason not related to the treatment, but to MS.
*In 56.8% of cases investigators did not indicate a 2nd reason.
**In 63.4% of cases investigators did not indicate a 3rd reason
^ 1 Not specified
^^ 2 Not specified; 1 Surgical reason; 1 Menopause.

40% (Kremenchutzky et al., 2014). Clinical trial data indicate that within 2 years of initiating IFNb or GA therapy, 62% to 79% of patients had relapses and approximately 20% worsen by one point on the EDSS (Teter et al., 2014). In another study, RRMS patients who first received IFNb or GA were classified into three categories, if they changed DMT (for suboptimal response of other reasons) o continued therapy. In this study, out of the 597 patients who initiated first-line DMT, 240 did not change, 155 switched because of treatment failure, and 163 switched for other reasons (roughly half due to intolerance) (Gajofatto et al., 2009).

In our study, switching therapy was found as the most common approach to poor treatment response (Table 1, Fig. 1). This may mean switching between first-line agents (IFNs, GA, DMF, and TFN) or escalating to a second-line agent (FTY, NTZ, and ALM) when prognosis is poor and breakthrough activity is significant. Thus, this result confirmed that there is a consensus, among the various MS centers, to the fact that MS patients experiencing disease activity despite treatment with injectable or oral DMTs (DMF or TFN), may necessitate escalating

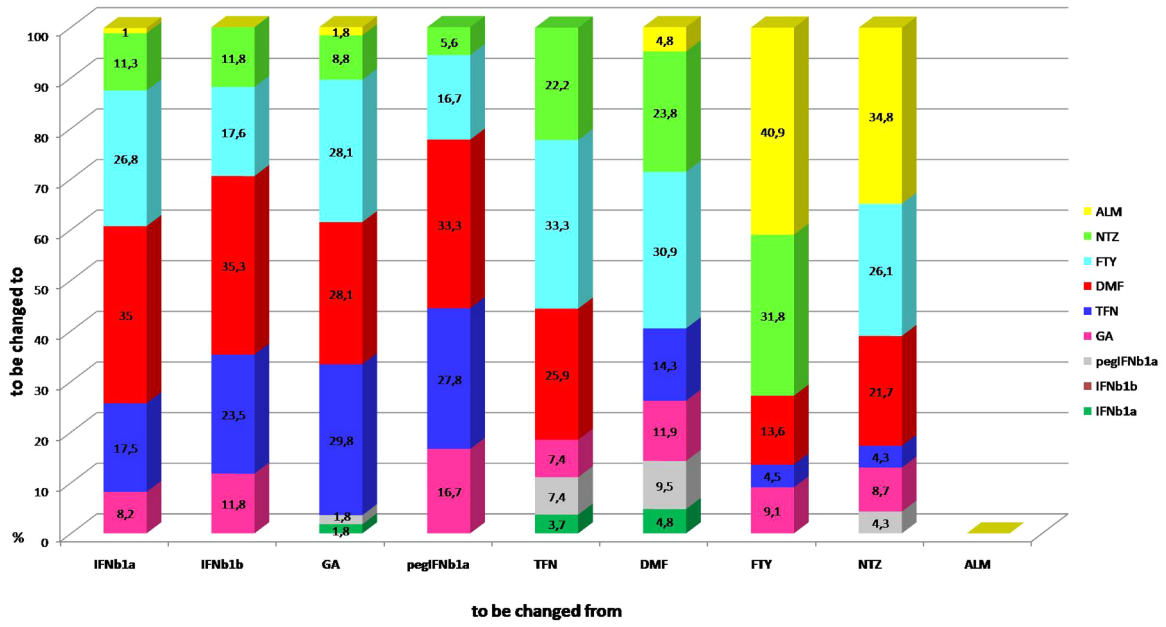

Fig. 4. Treatments to be changed from and to be changed to among switching patients (n = 303).
IFNb1a: interferon beta 1a (both IM and SC), IFNb1b: interferon beta 1b, pegIFNb1a: peginterferon beta-1a; GA: glatiramer acetate; DMF: dimethyl fumarate; TNF: teriflunomide; FTY: fingolimod; NTZ: natalizumab; ALM: alemtuzumab.

Table 3
Multivariate regression analysis.

	Wald Chi-square test	
	Statistic	*P* value
Age (years)	1.39	0.5
Gender	1.35	0.5*
Time from MS onset (years)	2.22	0.4
Number of relapses in the last two years	0.13	0.9*
Severity of last/current relapse/exacerbation	5.57	0.2*
EDSS score at follow-up	8.33	<0.05
Presence of new lesions	10.57	<0.05*
Size of the centre	2.43	0.7
Geographical area of the centre	1.00	0.6

* Quasi-complete separation of data points detected.

to a more potent treatment in order to reduce the risk of accumulation of neurological deficits and, thus, of conversion to secondary progressive MS (Merkel et al., 2017; Montalban et al., 2018).

According to a recent review, although an increased complexity of sequencing MS therapies is apparent, the two primary reasons for discontinuing a DMT were lack of efficacy and occurrence of adverse events (AEs) (Grand'Maison et al., 2018). In case of a suboptimal response due to lack of efficacy, switching to a more powerful DMT with the aim of preventing worsening of disability and long-term irreversible disease progression is the most acceptable strategy (Meuth et al., 2010; Gajofatto and Benedetti, 2015; Montalban et al., 2018; Rae-Grant et al., 2018). Indeed, the Canadian Multiple Sclerosis Working Group proposed an approach for assessing suboptimal response to MS therapy, by assigning three levels of concern (low, medium or high) for three domains of the MS disease status (relapses, disability progression, and MRI). According to these Authors, to change treatment is highly recommended when there is a low level of concern in all domains, a medium level of concern in any two of them, or a high level of concern in just one (Freedman et al., 2013). Furthermore, in order to detect treatment failure in a timely manner, a multi-domains MS decision model was developed by grading the four outcomes: relapse, disability progression, MRI, and neuropsychology (Stangel et al., 2015). Nevertheless, the purpose of our study was not to establish criteria for when clinical and/or MRI activity should trigger a therapeutic change.

In our study, it is worth mentioning that a second-line therapy was preferred for 139 (45.9%) of switching patients. In a recent modeling approach, it was suggested that FTY had a higher probability of no evidence of disease activity (NEDA) than DMF and TFN when phase 3 trial data are compared indirectly (Nixon et al., 2014). Considering another indirect modality to compare DMTs (the evaluation of absolute risk reduction and number needed to treat (NNT), Freedman et al. found that NNTs for each outcomes were similar for DMF and TFN, with marginally lower NNTs observed with FTY (Freedman et al., 2016).

Both NTZ and FTY significantly reduced relapse activity in patients switching therapy from IFNb or GA due to recent disease activity, with similar rates of confirmed progression of disability events post-switch (Kalincik et al., 2015).

Finally, in our cohort, alemtuzumab was used in 6.9% of patients when switching from FTY or NTZ.

Poor safety/tolerability was the most common second reason for changing therapy, and first choice when switching from pIFNb-1a or NTZ. Intra-class switching between first-line drugs prevailed when safety was the main concern with TFN (33.7%) and DMF (32.7%) as the most common drugs to be changed to. The choice of these DMTs over a less frequently administered IFNb to GA products (or vice versa) may be related to oral administration since convenience, compliance, better route of administration, and patient request were quite common as second and third reasons for changing therapy. Accordingly, in our study, oral therapies were commonly chosen for patients switching due to convenience or patient request as in the case of compliance issues. This data supports the notion that suboptimal adherence secondary to administration issues or side effect profiles of platform injectable increases the probability of breakthrough disease (Spelman et al., 2016).

These aspects were recently confirmed by the Teri-PRO, phase 4, multicenter, prospective study results. According to this study, high levels of treatment satisfaction with TFN was reported in those patients switching from another DMT to TFN within 6 months prior to study entry. Authors of this study underlined that the high levels of satisfaction associated with TFN may result in increased treatment adherence which in turns improve clinical outcomes (Coyle et al., 2018).

In addition, a switch to FTY was preferred to injectable DMT for a range of patient- and physician-reported outcomes, in terms of global satisfaction with treatment (Calkwood et al., 2014).

Moreover, a recent real-world retrospective study showed that the frequency of side effects associated were comparable between FTY and DMF, with the odds ratio of experiencing a side effect in favor of FTY over DMF (Wicks et al., 2016).

In our study, EDSS score was the only variable found to have a statistically significant effect on changing treatment. Worsening EDSS may be not considered as a reliable marker of a sub-optimal response to a DMT. However, according to the cross-sectional nature of the study protocol, as the decision-making of changing therapy was set during a clinical practice visits, the finding of the EDSS confirmed progression may have drove the Clinician to switch the current treatment to another more efficacious. This is also in line with several studies demonstrating that poor response to IFN therapy during the first year of treatment is associated to the presence of two or three measures of disease activity (new MRI lesions, relapses, or confirmed 1-point EDSS progression) (Rio et al., 2009). A higher EDSS was associated with a 1.39-fold higher risk of permanent discontinuation versus the risk of switching treatment, and thus linked to the treatment failure leading to the drug discontinuation. In our multilogistic analysis, we also found that the presence of new lesions upon MRI showed a p-value <0.05, although the quasi-complete separation of data points prevented us from interpreting this result.

The current study has several limitations. Firstly, the differences in terms of incidence of eligible patients requiring treatment change among the various sites participating in the study, may reflect the heterogeneity in treatment decision management in Italian MS centers. Although data about any regional variation of clinical practice for switching therapies are not available, MS centers participating to the study protocol were selected from those with higher level of expertise and specialization in MS treatment. Furthermore, all MS centers included in the study took into account the NICE guidelines for MS treatment (33). Secondly, we did not consider pharma-economic data. Thus, further clinical data, including cost-effectiveness analysis, will be needed to understand how treatment costs may influence treatment-decision making processes.Finally, to not consider as switchers those patients moving to drugs with the same mechanism of action may have underestimated the frequency of patients changing therapies.

5. Conclusion

While the availability of various therapeutic options is beneficial to the patient and neurologist, determining which treatment is best for which patient and when to switch therapies remains a major challenge. Consensus papers may provide indications of what is reasonable to warrant a treatment switch, but such papers may neither encompass all the scenarios a physician may encounter, nor address patient perspectives. Despite this, efficacy remains the main driving force behind switching behavior, as the primary aim of MS treatment is to reduce disease activity and slow the disease progression, in order to optimize neurologic reserve, and preserve cognitive and physical functions. However, patient's personal preferences should be carefully considered during treatment decision-making process and the therapy plan, as a concordant relationship between Clinician and Patient is crucial in order to achieve these goals.

Funding

The study was funded by Sanofi

CRediT authorship contribution statement

Francesco Patti: Conceptualization, Methodology, Supervision, Writing - review & editing, Validation. **Clara Grazia Chisari:** Data curation, Writing - original draft. **Emanuele D'Amico:** Writing - review & editing, Validation. **Pietro Annovazzi:** Data curation, Writing - review & editing, Validation. **Paola Banfi:** Data curation, Writing - review & editing, Validation. **Roberto Bergamaschi:** Data curation, Writing - review & editing, Validation. **Raffaella Clerici:** Data curation, Writing - review & editing, Validation. **Marta Zaffira Conti:** Validation. **Antonio Cortese:** Data curation, Writing - review & editing, Validation. **Roberta Fantozzi:** Data curation, Writing - review & editing, Validation. **Mariano Fischetti:** Data curation, Writing - review & editing, Validation. **Maura Frigo:** Data curation, Writing - review & editing, Validation. **Maurizia Gatto:** Data curation, Writing - review & editing, Validation. **Paolo Immovilli:** Data curation, Writing - review & editing, Validation. **Stefania Leoni:** Data curation, Writing - review & editing, Validation. **Simona Malucchi:** Data curation, Writing - review & editing, Validation. **Giorgia Maniscalco:** Data curation, Writing - review & editing, Validation. **Girolama Alessandra Marfia:** Data curation, Writing - review & editing, Validation. **Damiano Paolicelli:** Data curation, Writing - review & editing, Validation. **Paola Perini:** Data curation, Writing - review & editing, Validation. **Carlo Serrati:** Data curation, Writing - review & editing, Validation. **Patrizia Sola:** Data curation, Writing - review & editing, Validation. **Rocco Totaro:** Data curation, Writing - review & editing, Validation. **Gabriella Turano:** Data curation, Writing - review & editing, Validation. **Paola Valentino:** Data curation, Writing - review & editing, Validation. **Mauro Zaffaroni:** Data curation, Writing - review & editing, Validation. **Cristina Zuliani:** Data curation, Writing - review & editing, Validation. **Diego Centonze:** Conceptualization, Methodology, Supervision, Writing - review & editing, Validation.

Declaration of Competing Interest

The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: F.P. has received honoraria for speaking activities by Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; he also served as advisory board member the following companies: Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA; he was also funded by Pfizer and FISM for epidemiological studies; he received grants for congress participation from Almirall, Bayer Shering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. C.G.C. has received grants for congress participation from Almirall, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. E.D'A. has received grants for speaking activities from Bayer Schering, Biogen Idec, Merck Serono, Novartis, TEVA and grants for congress participation from Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. P.A. has received honoraria for lecturing and participation in advisory boards, and/or travel expenses for attending congresses and meetings from Almirall, Biogen Idec, Merck Serono, Mylan, Novartis, Roche, Sanofi Genzyme, and TEVA. P.B. has received support for attendance to scientific meetings from Biogen Idec, Merck Serono, Novartis, and Sanofi Genzyme. R.B: has received honoraria for lectures, travel and registration coverage for attending several national or international congresses or symposia from Almirall, Bayer Shering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Aventis, Sanofi Genzyme, and TEVA. R.C. has received speaker's honoraria, consulting fees, honoraria in advisory boards, support for attendance of scientific meetings from Meck Serono, Novartis, and Sanofi Genzyme. M.C. Author declares there is no conflict of interest. A.C. has received speaker honoraria, travel grants, advisory boards member honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and TEVA. R.F. has received consulting fees and honoraria for advisory boards from Biogen Idec, Merck Serono, Novartis, Roche, and TEVA. M.Fi. Author declares there is no conflict of interest. M.Fr. has received speaker's honoraria and consulting fees, honoraria for advisory boards, support for attendance of scientific meetings from Biogen Idec, Merck Serono, Novartis, TEVA, and Sanofi Genzyme. M.G. Author declares there is no conflict of interest. P.I. has received speaking honoraria,

consulting fees, advisory board honoraria from Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA S.L. Author declares there is no conflict of interest. S.M. has received speaker's honoraria and consulting fees, honoraria in advisory boards from Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and TEVA. G.M. has received honoraria for public speaking and advisory boards from Biogen, Novartis, and Merck Serono. G.A.M. 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. D.P. has received honoraria for consultancy and/or speaking from Almirall, Bayer Shering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. C.S. Author declares there is no conflict of interest. P.P. has received speaker honoraria and consulting fees from Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. P.S. has received speaker's honoraria and consulting fees, honoraria for advisory boards, and travel grants from Biogen Idec, Merck Serono, Novartis, Sanofi genzyme, and TEVA. R.T. has received speaker's honoraria, consulting fee, honoraria for advisory boards, support for attendance of scientific meetings from Alfa Wasserman, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi genzyme, and TEVA. G.T. has received support for attendance to scientific meetings from Almirall, Biogen Idec, Merck Serono, Novartis, and Sanofi Genzyme. P.V. has received speaker's honoraria and consulting fee, honoraria for advisory boards from Biogen Idec, Novartis, Merck Serono, Sanofi Genzyme, and TEVA. M.Z. has received honoraria for lecturing or participating for advisory boards or travel funding from Almirall, Biogen, Merck Serono, Novartis, Sanofi Genzyme, and TEVA. C.Z. has received speaker's honoraria and consulting fees, honoraria for advisory boards, support for attendance of scientific meetings from Almirall, Bayer Shering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA. D.C. is an Advisory Board member of Almirall, Bayer Schering, Biogen Idec, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi Genzyme, and TEVA, and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and TEVA. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi Genzyme, and TEVA. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi Genzyme and TEVA.

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