Journal of Neurology (2019) 266:2440–2446
https://doi.org/10.1007/s00415-019-09424-8

ORIGINAL COMMUNICATION

Outcomes after fingolimod to alemtuzumab treatment shift in relapsing–remitting MS patients: a multicentre cohort study

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Received: 29 April 2019 / Revised: 4 June 2019 / Accepted: 6 June 2019 / Published online: 17 June 2019

Abstract

Background A high reactivation of multiple sclerosis (MS) was reported in patients treated with alemtuzumab after fingolimod. We aimed to understand whether this shift enhanced the risk for reactivation in a real-life cohort.

Methods Subjects with relapsing MS, shifting from fingolimod to alemtuzumab were enrolled. We collected the following data: age, sex, disease duration, relapses after fingolimod withdrawal, new T2/gadolinium (Gd)-enhancing lesions in the last magnetic resonance imaging (MRI) during fingolimod and in the first, while on alemtuzumab, lymphocyte counts at alemtuzumab start, and Expanded Disability Status Scale (EDSS) before and after alemtuzumab.

Results We enrolled 77 patients (women 61 (79%); mean age 36.2 years (SD 9.6), and disease duration 12.3 years (SD 6.8) at fingolimod discontinuation; median washout 1.8 months). The annualised relapse rate was 0.89 during fingolimod, 1.32 during washout, and 0.15 after alemtuzumab ($p=0.001$). The EDSS changed from a median of 3 (IQR 2–4) at the end of fingolimod to 2.5 after alemtuzumab (IQR 1.5–4) ($p=0.013$). The washout length and the lymphocyte count before alemtuzumab were not associated with EDSS change after alemtuzumab ($p=0.59$ and $p=0.33$, respectively). MRI activity decreased after alemtuzumab compared to that during fingolimod ($p=0.001$). At alemtuzumab start, lymphocyte counts were $<0.8\times10^3$/mL in 21 patients.

Conclusions In our cohort, alemtuzumab reduced relapse, new T2/Gd-enhancing lesions, and EDSS score, as compared to the previous periods (fingolimod/washout). These results were not related to washout length or lymphocyte counts. Therefore, a rapid initiation of alemtuzumab after fingolimod does not seem to be a risk factor for MS reactivation.

Keywords Fingolimod · Alemtuzumab · Real life · NEDA

Introduction

During the last decades, many disease-modifying drugs (DMDs) have been approved for the treatment of the relapsing–remitting (RR) course of multiple sclerosis (MS) [1]. These advances in the treatment of MS, as well as the proven benefit of treatment initiation from a very early phase of the disease are able to reduce both the attack rate and transition to the secondary progressive course, with an impact on survival rates [2, 3].

The wide variety of available DMDs and a more empowered and informed patient population results in the personalization of treatment i.e., the selection of "the right drug for the right person at the right time", a crucial issue for disease management [4].

Among the DMDs approved by the European Medicine Agency for the inflammatory aggressive forms of MS, fingolimod and alemtuzumab are available.

Fingolimod is a modulator of sphingosine-1-phosphate receptor, it is able to block its functions, and can reduce the infiltration of lymphocytes in the CNS by trapping them inside

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09424-8) contains supplementary material, which is available to authorized users.

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the lymph nodes [5]. The efficacy of fingolimod in reducing the frequency of relapses, progression of disability, and magnetic resonance imaging (MRI) activity was widely demonstrated in the phase-III clinical trials TRANSFORMS, FREEDOMS, and FREEDOMS II [6–8].

An important issue is the possibility of an MS rebound after fingolimod discontinuation. Many cases have been reported since 2012 [9, 10]; however, the post hoc analysis of the phase-III clinical trials did not identify any difference in the emergence of clinical rebounds between patients treated with fingolimod and placebo [11]. The frequency of rebounds reported in real-life studies ranges between 5 and 10.9% [12, 13].

Alemtuzumab is a monoclonal antibody directed against the CD52 antigen, which is expressed on B and T lymphocytes and causes their rapid and temporary depletion. Compared with interferon beta in phase-III clinical trials, alemtuzumab was effective in decreasing the annualised relapse rate (ARR) and the appearance of MRI lesions in short term, as well as in preserving the long-term absence of disease activity [14, 15].

Recently, many case reports have been described, reporting a severe disease reactivation soon after the initiation of alemtuzumab. To note, some of these subjects had switched from fingolimod to alemtuzumab [16–19]. However, the studies analysing the course of MS in patients receiving alemtuzumab after fingolimod are few and with contrasting results [17, 20]. In particular, a European multicentre observational study described an unexpected high disease activity soon after alemtuzumab initiation in nine patients who shifted from fingolimod [17]. More recently, in a German multicentre observational study, a cohort of 50 RR patients with a history of switch from fingolimod to alemtuzumab was analysed. The shift was highly effective in all but two subjects, and alemtuzumab was considered as rescue therapy in patients with high disease activity during fingolimod [20].

On the basis of our clinical experience, we hypothesised that the possibility of disease activity in patients shifting from fingolimod to alemtuzumab is real but not so frequent, and it is related to the previous inflammatory activity. Moreover, we thought that the duration of washout and the lymphocyte count at alemtuzumab initiation could play a role in the risk of reactivation.

Thus, the aim of our study was to evaluate the course of the inflammatory activity in patients receiving alemtuzumab after fingolimod in a large real-life cohort of RRMS patients.

Methods

Patients

Patients from 11 Italian MS centres were enrolled in the study. We included patients with diagnosis of RRMS according to McDonald criteria [21–23], who shifted directly from fingolimod to alemtuzumab due to inefficacy or partial efficacy, and had a minimum follow-up of 1 year after alemtuzumab administration. All patients provided signed informed consent before their participation in the study, which was approved by the local ethics committee.

All data were retrospectively collected by neurologists with expertise in diagnosis and treatment of MS in electronic or paper-based medical records, according to the typical procedure followed in each centre. Between May 2017 and June 2018, all data were recorded in an electronic case report form by the neurologists involved in the study at each MS centre.

The following data were collected: sex; year of birth; age at first MS symptoms and at diagnosis; dates of start and stop of fingolimod; dates of the last MRI performed during fingolimod and of the first MRI after the initiation of alemtuzumab; presence of new T2 and gadolinium (Gd)-enhancing lesions in the MRI collected; dates of alemtuzumab courses; relapses before and after alemtuzumab start, including those during fingolimod and during the washout period; lymphocyte counts before the initiation of alemtuzumab; Expanded Disability Status Scale (EDSS) scores at start and stop of fingolimod, at alemtuzumab start and during the follow-up after alemtuzumab initiation; duration of the washout periods.

Statistical analyses

Data are reported as mean with standard deviation (SD) or median with interquartile range [IQR]. ARR in the last year of fingolimod, during the washout period and in the first year of alemtuzumab were compared with a non-parametric Wilcoxon signed rank test for paired data. For this comparison, p values were adjusted for multiple comparisons using the false-discovery rate approach. The same test was used to compare the EDSS scores, the new T2 and Gd-enhancing lesions when fingolimod was stopped with those observed at the end of follow-up during alemtuzumab. Kaplan–Meier survival curves were used to analyse the time to the first relapse from when fingolimod was stopped until the start of alemtuzumab and from start of alemtuzumab until the end of follow-up. Cox regression model was used to assess lymphocyte counts before alemtuzumab, age and disease duration when FTY was stopped, ARR during FTY and washout and length of washout on time to first relapse while on alemtuzumab. A linear regression analysis with EDSS score change as the dependent variable was used to test if changes in disability were influenced by washout period lengths or by pre-alemtuzumab lymphocyte counts.

The analysis was adjusted for a centre effect, to limit the potential influence of outcome assessment heterogeneities.

A p value < 0.05 was considered statistically significant. Stata (v.14; StataCorp) was used for the computations.

Results

We enrolled 77 patients meeting the inclusion criteria, in the 11 centres involved. Sixty-one (79%) were women, the mean age at disease onset was 24.3 years (SD 8.7), and the mean age at the time of fingolimod discontinuation was 36.2 years (SD 9.6). The median washout period after fingolimod was stopped was 1.8 months (IQR 0–17). Twenty-eight patients (36.4%) had just one alemtuzumab course at the time of last follow-up, 48 patients (62.4%) had two courses and only 1 patient (1.2%) had three courses. The median follow-up period after the first course of alemtuzumab was 373 days (IQR 342–589). Other clinical features of the cohort are reported in Table 1.

The mean ARR was 0.89 (SD 0.95) during fingolimod, increased to 1.32 (SD 2.33) during the washout period ($p = 0.11$ vs during fingolimod) and it decreased to 0.15 (SD 0.39) after the first course of alemtuzumab ($p = 0.003$ vs during washout and $p = 0.015$ vs during fingolimod). After alemtuzumab start, seven patients experienced one single clinical relapse, and four experienced two relapses. Lymphocyte counts were available for seven of them, and only one subject had grade-3 lymphopenia ($< 0.5 \times 10^3$/mL), whereas the other six had lymphocyte counts higher than 1000×10^3/mL. The main features of these 11 relapsing patients and the comparison with patients who did not experience relapse after alemtuzumab are summarized in Table 2.

The probability to relapse during the washout period after fingolimod was 12.7% during the 1st month, 18.2% after 2 months, and 22.2% after 3 months. After the first alemtuzumab course, the cumulative risk of a relapse was 2.9% during the first 6 months, 10.5% after 9 months, and 20.7% during the first 12 months. We did not record any dropout from alemtuzumab during the 1st year of treatment. Kaplan–Meier curves for time to first relapse during washout and on alemtuzumab are reported in Supplemental Material (Figs. 1S, 2S).

Table 1 Clinical features of the cohort

	$n = 77$ patients
Age at FTY stop, mean (SD)	36.2 (9.6)
Disease duration at FTY stop (years), mean (SD)	12.3 (6.8)
EDSS at FTY stop, mean; median (range)	3.4; 3 (0–7.5)
New T2 lesions at FTY stop, *n* (%)	50/70 (71.4)
Gd at FTY stop, *n* (%)	36/60 (60)

FTY fingolimod, *SD* standard deviation, *Gd* gadolinium

The EDSS scores were significantly reduced from a median of 3 (IQR 2–4) at the end of fingolimod period to a median of 2.5 (IQR 1.5–4) after 1 year of alemtuzumab ($p = 0.013$; Fig. 1). The EDSS scores after alemtuzumab start, available for 60 out of 77 patients (78%), decreased in 24 patients (40%), remained stable in 27 (45%), and increased in 9 patients (15%).

Washout period lengths and lymphocyte counts before alemtuzumab were not associated with the EDSS score changes after alemtuzumab ($p = 0.59$ and $p = 0.33$, respectively). More precisely, before alemtuzumab start, lymphocyte counts available for 56 patients were $< 0.5 \times 10^3$/mL in 9 patients (16%); between 0.5×10^3 and $< 0.8 \times 10^3$/mL in 12 patients (21%); between 0.8×10^3 and 1.0×10^3/mL in 5 patients (9%); and $> 1.0 \times 10^3$/mL in 30 patients (54%) and no association was detected between relapse after alemtuzumab and pre-alemtuzumab lymphocyte counts (Fig. 2).

With regard to imaging assessment, at least 1 MRI scan during fingolimod treatment was available for 65 patients. Of these, 45 had new T2 lesions and 36 had Gd-enhancing lesions. At least 1 MRI scan after alemtuzumab start was available for 56 patients. Eight of them had new T2 lesions and three had Gd-enhancing lesions. The paired comparison between the last MRI scans during fingolimod and the scans after alemtuzumab initiation showed a decrease in new T2 and Gd-enhancing lesions ($p = 0.001$ for both outcomes, Fig. 3).

A detailed description of each enrolled patient is shown in the Supplementary Table 1.

Discussion

We performed a real-life study in a cohort of relapsing MS patients who switched from fingolimod to alemtuzumab. In this study, both the clinical and neuroradiological disease activities were reduced by alemtuzumab as compared to the corresponding activities under fingolimod, and the overall EDSS score improved. We did not detect any case of disease activity rebound after switching to alemtuzumab.

The absence of disease reactivation after fingolimod withdrawal is in contrast with recent studies, reporting a particularly high MS activity in patients switching from fingolimod to alemtuzumab, either in terms of clinical relapses or in terms of new T2 or Gd-enhancing MRI lesions, soon after alemtuzumab initiation [16, 18, 19].

A possible explanation for this is that soon after fingolimod discontinuation, a substantial number of lymphocyte subsets remain segregated in the lymph nodes. Alemtuzumab depletes CD52-expressing immune cells largely in the intravascular compartment and to a lesser extent in lymphoid tissues. If it is administered after a short washout of fingolimod, it might not have the chance to reduce

Table 2 Clinical and demographic features of the patients who experienced at least one relapse in the year after the first course of alemtuzumab

Patient no.	Age at FTY stop	Disease duration at FTY stop	ARR during last year FTY	ARR during washout	Washout (months)	Time to first relapse in alem (days)	EDSS score during relapse	Lymphocyte count at alemtuzumab initiation ($\times 10^3$/mL)
Patients with at least one relapse during alemtuzumab ($n=11$)								
1	45	9	4.04	0	2.9	67	6	–
2	19	3	0	0	1.2	74	2	–
3	38	11	2	2.46	9.9	198	6	1500
4	35	12	1.2	5.80	2.1	235	3	1700
5	46	24	1	0	1.8	237	2.5	1200
6	36	5	0	–	0	256	1	–
7	50	38	0	0	1.7	283	3.5	373
8	33	7	1	5	2.4	315	1.5	1510
9	29	13	3	2.57	4.7	318	5	1090
10	28	8	0	0	3.7	341	1	1200
11	37	19	2	0	2.1	344	2.5	–
Mean (SD)/ median (IQR)	36 (8.9)	13.5 (10.1); 11 (7–19)	1.21 (1.35)	1.49 (2.27)	3 (2.6)	243 (97)	3.1 (1.8)	–
Patients without relapse during alemtuzmab ($n=66$)								
Mean (SD)/ median (IQR)	36.3 (9.9)	11.9 (6.6) 11 (7–17)	0.84 (0.86)	0.93 (2.34)	2.6 (2.8)	–	–	–
p value	0.84	0.41	0.24	0.34	0.99	–	–	–

Comparison between patients who relapsed and who did not relapse after alemtuzumab

FTY fingolimod, *ARR* annualised relapse rate, *alem* alemtuzumab, *IQR* interquartile range, *SD* standard deviation

p values were calculated by Cox regression model on time to first relapse

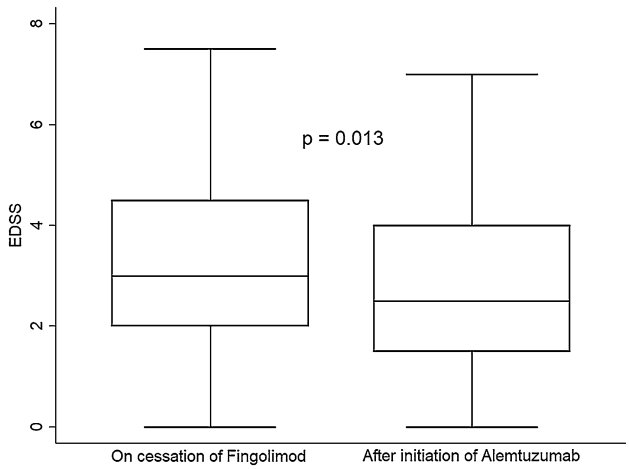

Fig. 1 Joint distribution of the last EDSS score during fingolimod and the last EDSS score after alemtuzumab. The black line represents the 45° line to identify change in EDSS between fingolimod and alemtuzumab. Observation under the line corresponds to patients that decreased EDSS with alemtuzumab

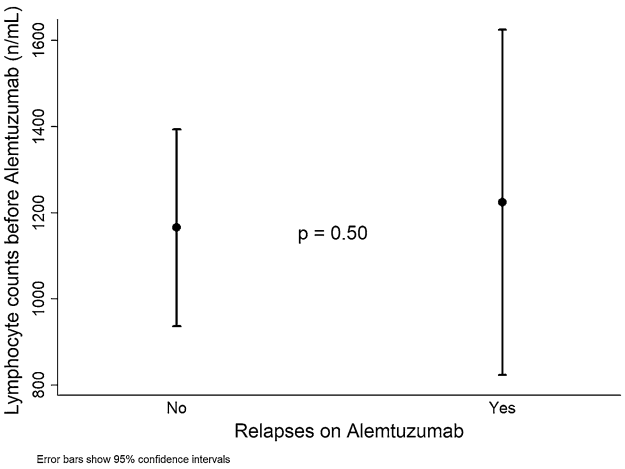

Fig. 2 Relapse during alemtuzumab on the basis of lymphocyte counts when alemtuzumab was started

immunoreactive lymphocytes that could initiate a rebound of the inflammatory activity [17–19]. However, this view was criticised as being too simplistic [24]. Another hypothesis is that the reactivation after alemtuzumab initiation is due to earlier reconstitution of B cells compared with the reconstitution of T cells after the drug course [16]. Nevertheless,

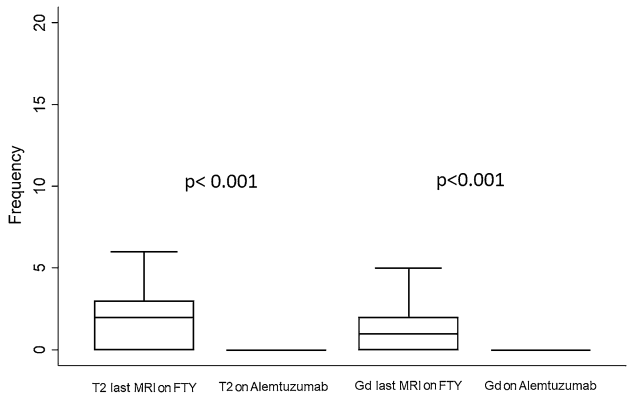

Fig. 3 Comparison between the last MRI during fingolimod and the MRI after alemtuzumab

this view was also criticised, since alemtuzumab is able to alter both quantitatively and qualitatively many cell populations, including adaptive and innate compartments, and it would be too simplistic to ascribe a re-exacerbation only to B cells [25]. Finally, a simple disease rebound secondary to fingolimod discontinuation and not related to the initiation of alemtuzumab could be the cause for MS reactivation [18].

In our opinion, a further explanation can be hypothesised: in the majority of patients, this treatment shift is due to the inefficacy or partial efficacy of fingolimod, as shown by the ARR and the MRI features during fingolimod in our cohort and in other case reports [16, 18, 19]. In patients with disease activity while on a DMD, a continuous activity is expected when the drug is discontinued and the efficacy of a subsequent treatment might be delayed due to the pharmacokinetics of the drug.

Furthermore, four types of response patterns to alemtuzumab were recently described: a complete response with no disease activity, a partial response with reactivation after the second course of alemtuzumab, an incomplete early response with disease activity between the two courses and a control of disease after the second course, and a primary non-response with continuous disease activity [24]. The first outcome is more frequent, being observed in about 50% of patients, but the third outcome is also common in clinical practice and represents about 15% of patients in the CARE-MS I clinical trial [24]. In our cohort, the ARR significantly decreased during the 1st year after alemtuzumab, but we also observed relapse in 11 patients. They had variable ARRs during fingolimod and variable washout durations. Of note, only two of them relapsed during the first 3 months after alemtuzumab, while the other nine relapsed in the second semester after drug initiation.

Until now, only two studies have been performed focusing on this topic comprising a large number of subjects [17, 20], and our cohort was the largest to date analysed. The two previous studies gave contrasting results. In the first study, a high disease reactivation was reported in 9 out of 36 subjects after alemtuzumab start [17], while in the other one, only 2 out of 50 German patients needed a second switch due to inefficacy of alemtuzumab [20]. Moreover, similar to the study of our cohort, in the German study a decrease was found in the ARR and in the appearance of new T2 lesions or Gd-enhancing lesions after alemtuzumab initiation as compared to those during the previous period on fingolimod [20]. The authors hypothesised that lower disease reactivation, detected in their study, was related with a long washout period (mean, 19 weeks). In our population, the median washout period was very short and quite similar to that of the multicentre European cohort (about 7 weeks) [17] and its duration was not associated with a higher risk of reactivation after alemtuzumab.

Notably, in the German cohort, lymphopenia was detected only in four subjects at alemtuzumab initiation [20]. Contrary to a role of basal lymphopenia in the disease reactivation, we did not find any difference in lymphocyte counts between patients who relapsed and patients who did not. Analysing the subjects with at least one relapse during the 1st year after alemtuzumab, only one of them had grade-3 lymphopenia, while the other six had lymphocyte counts higher than 1000×10^3/mL. To note, the lymphocyte count at alemtuzumab initiation was available only for part of the cohort (56/77 patients), and this result needs to be confirmed in a bigger population.

Another important result of our study was the improvement in the EDSS scores that we recorded after alemtuzumab treatment. This result, as well as the reduction of ARR and new T2 or Gd-enhancing lesions on the MRI, was recently reported in a different real-life cohort of Italian patients who switched to alemtuzumab after multiple DMD failures [26]. Similarly, the German study found a stabilization of the EDSS scores [20].

About the occurrence of relapses during the washout period, we found an increasing risk each month after fingolimod discontinuation. It could be due to a gradual reduction of the therapeutic effect of fingolimod.

Nevertheless, our study had the intrinsic limitations of real-life studies, including heterogeneity due to the retrospective analysis of prospectively collected data and heterogeneity in outcome assessments (especially in MRI data), typical for a multicentre setting without centralised assessment. In our support, we accounted for a centre effect during statistical analysis to limit the potential influence of the outcome assessment heterogeneity. Another limitation is the lack of safety data that were available only for few patients and were not complete, thus we did not consider them reliable and we did not include them. However, the research question related to the disease reactivation in patients starting alemtuzumab after fingolimod can only be addressed in a real-life setting. Moreover, the Italian centres involved in

the study are highly specialised in the diagnosis and treatment of MS.

Conclusions

In conclusion, in our cohort alemtuzumab markedly reduced disease activity in patients who did not respond to fingolimod, and we did not observe any rebound of disease activity. The effect of alemtuzumab was clearly exhibited both by relapse reduction, lower MRI activity, and amelioration of disability. Neither the shorter washout periods between the two treatments, nor the low lymphocyte counts before alemtuzumab administration were associated with disease activity when alemtuzumab was given after fingolimod withdrawal.

Therefore, on the basis of our data, early initiation of alemtuzumab soon after fingolimod discontinuation does not seem to increase the risk for MS reactivation. Thus, it may be helpful in preventing disability deterioration in the long run. Other real-life experiences could be helpful in confirming whether our observations were right or not.

Funding This research did not receive any specific Grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflicts of interest Frau J: serves on scientific advisory boards for Biogen and Genzyme, and has received honoraria as a speaker from Merck Serono, Genzyme, Biogen and Teva. Saccà F: received personal compensations for participating in advisory boards and public speaking, or travel grants from Almirall, Biogen Idec, Forward Pharma, Merk Serono, Novartis, Pomona, Roche, Sanofi Genzyme, and Teva. Signori A: has nothing to disclose. Baroncini D: received travel grants from Genzyme, Merck and Biogen for participation in national and international congresses; he received speaking honoraria from Sanofi and Novartis, and personal compensation from Almirall for scientific publication. Fenu G: has received honoraria for consultancy from Novartis and Biogen, and as a speaker from Merck Serono and Teva. Annovazzi P: received honoraria for lecturing and participation in advisory boards, and/or travel expenses for attending congresses and meetings from Merck, Biogen, Teva, Sanofi-Genzyme, Mylan, Almirall, Roche, and Novartis. Capobianco M: received personal compensation for speaking honoraria or participating in advisory boards from: Almirall, Biogen, Merck, Novartis, Roche, Sanofi, and Teva. Signoriello E: received travel funding and speaker honoraria from Biogen, Novartis, Sanofi Genzyme, Bayer, and Teva. Laroni A: received personal compensation from Novartis, Genzyme, Biogen, Merck and TEVA for public speaking and/or advisory boards. La Gioia S: received grants from Novartis. Sartori A: received funding for travel and/or speaker honoraria from Novartis, Teva, Merk, Genzyme, Almirall, and Roche. Maniscalco GT: has served on advisory boards and/or received travel grants and speaker honoraria from Almirall, Biogen, Merck Serono, Novartis and Teva. Bonavita S: received speaker honoraria and advisory board fee from Teva, Genzyme, Biogen, Merck Serono, Novartis, Roche, and Almirall. Clerico M: received personal compensations for participating in advisory boards, public speaking, editorial commitments or travel grants from Biogen Idec, Merck Serono, Fondazione Serono, Novartis, Pomona, Sanofi-Genzyme, and Teva. Russo CV: participated in scientific advisory boards for Merk Serono and Sanofi Genzyme. Gallo A: received travel grants and consulting fees from Biogen, Merck Serono, Roche, Sanofi-Genzyme, and Teva. Lapucci C: has received travel funds from Roche. Carotenuto A: received unrestricted grant from Almirall. Sormani MP: received consulting fees from TEVA, Biogen, Merck, Sanofi Genzyme, Roche, GeNeuro, Novartis, Medday, Actelion, and Celgene. Cocco E: has received honoraria for consultancy or speaking from Bayer, Biogen, Novartis, Sanofi, Genzyme, Merck, and Teva.

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