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Utilization of peginterferon-β-1a in the real-world practice for relapsing-remitting multiple sclerosis

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Abstract. – OBJECTIVE: Peginterferon β-1a (PEG-IFN-β-1a) is the most recent interferon beta formulation approved for treating relapsing-remitting multiple sclerosis (RRMS). We aim to describe the real-world utilization of PEG-IFN-β-1a in RRMS and compare it with other injectable disease-modifying therapies (DMTs).

PATIENTS AND METHODS: In this population-based study, we used 2015-2019 routinely collected healthcare data of the Campania region of Italy from National Health Service DMT prescriptions, inpatient and outpatient clinical records of hospitals in Campania, and the Federico II University MS clinical registry for a subset of patients. We included individuals with RRMS receiving new prescriptions of PEG-IFN-β-1a [n=281; age = 38.8±12.3 years; females=70.5%; disease duration = 8.4±8.3 years; Expanded Disability Status Scale (EDSS) at baseline=2.0 (1.0-6.5)], glatiramer acetate [n=751; age = 46.0±11.4 years; females=67.1%; disease duration = 9.8±8.2 years; EDSS=4.0 (1.5-8.5)], and subcutaneous (SC) IFN-β-1a [n=1,226; age = 39.7±11.7 years; females=66.5%; disease duration = 8.2±6.5 years; EDSS 2.5 (1.5-6.5)]. Adherence [medication possession ratio (MPR)], escalation to more effective DMTs, hospitalization rates and costs were measured. We used mixed-effect linear regression models (for adherence, hospitalization rates and costs) and Cox regression models (for escalation) to assess differences between PEG-IFN-β-1a (statistical reference), glatiramer acetate, and SC IFN-β-1a. All models included age, sex, previous treatment/untreated, year of treatment initiation, treatment duration, and adherence as covariates.

RESULTS: Adherence was lower in glatiramer acetate (MPR = 0.91±0.1; Coeff=-0.11; $p<0.01$), and IFN-β-1a (MPR = 0.92±0.1; Coeff=-0.08; $p<0.01$), compared with PEG-IFN-β-1a (MPR = 1.01±0.1). The probability of escalating to more effective DMTs was higher for glatiramer acetate (14.9%; HR=4.09; $p<0.01$) and IFN-β-1a (9.1%; HR=3.35; $p=0.01$), compared with PEG-IFN-β-1a (4.9%). No differences in annualized hospitalization rates were identified between glatiramer acetate [annualized hospitalization rates (AHR) = 0.05±0.30; Coeff=0.02; $p=0.31$), IFN-β-1a (AHR = 0.02±0.21; Coeff=0.01; $p=0.97$], and PEG-IFN-β-1a (AHR = 0.02±0.24); however, monthly costs for MS admissions were higher for glatiramer acetate (€49.45±€195.27; Coeff=-29.89; $p=0.03$), compared with IFN-β-1a (€29.42±€47.83; Coeff=6.79; $p=0.61$), and PEG-IFN-β-1a (€23.91±€43.90).

CONCLUSIONS: PEG-IFN-β-1a and SC IFN-β-1a were used in relatively similar populations, while glatiramer acetate was preferred in older and more disabled patients. PEG-IFN-β-1a was associated with higher adherence and lower escalation rates toward more effective (and costly) DMTs.

Key Words:
PEG-IFN-β-1a, Relapsing-remitting multiple sclerosis, Real-world practice.

Introduction

Interferons have been a treatment option for relapsing-remitting multiple sclerosis (RRMS)

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for over 20 years. These drugs are considered to offer a favorable benefit-risk profile[1]. Peginterferon-β-1a (PEG-IFN-β-1a), a pegylated form of IFN-β-1a administered subcutaneously every 2 weeks, was approved by the European Medicines Agency (EMA) for treating adult patients with RRMS in July 2014 and by the US FDA for relapsing MS in August 2014[1]. Evidence from the phase III ADVANCE clinical trial[2,3], demonstrating the efficacy of 1 year of treatment with PEG-IFN-β-1a compared with placebo in RRMS on clinical and imaging outcome measures, supported the approval by these regulatory agencies. The ATTAIN extension study[4] confirmed sustained efficacy for over 4 years.

PEGylation is a well-established modification of therapeutic biological compounds introduced to extend drug exposure and prolong dosing intervals. Adding a polyethylene glycol (PEG) moiety increases the molecular mass, inhibits proteolysis, and decreases renal elimination[5,6]. Dosing intervals are prolonged by delaying drug elimination, which should increase treatment adherence, and drug exposure can be more consistent over time[7,8]. PEGylation reduces the risk of poor drug adherence, which is often responsible for the reduced success of treatments for chronic illnesses requiring long-term pharmacotherapy[9]. PEG-IFN-β-1a has a prolonged half-life and increased systemic drug exposure compared to other interferon-based products[7,8]. These characteristics could also help reduce healthcare resource utilization through better adherence compared to other injectable disease-modifying therapies (DMTs) for RRMS[10,11].

This study investigated the use of subcutaneous (SC) PEG-IFN-β-1a and other approved injectable DMTs for treating RRMS in clinical practice in an Italian region, to assess possible differences in population characteristics at baseline, treatment adherence, risk of escalation, and healthcare resource utilization.

Patients and Methods

Study Design

A retrospective population-based study was conducted by analyzing the Administrative Databases of the Campania region and, for a subset of patients, also the clinical registry of the MS unit at Policlinico Federico II University Hospital of Naples. These databases record information on all the patients residing in the Campania region in Southern Italy. More precisely, hospital discharge records, regional prescription data and outpatient records from 2015 to 2019 were analyzed[12].

The study was approved by the Federico II University Ethics Committee [approval code 355/19].

Population

Data was collected between 1 July 2015 and 30 September 2019 (enrollment period), and the observational period was from 1 July 2015 to 31 December 2019. A characterization period was defined from January 1st to June 30, 2015, to identify the presence or absence of previous drug prescriptions for the treatment of RRMS. Patients with new prescriptions of selected DMTs (SC PEG-IFN-β-1a, glatiramer acetate, SC IFN-β-1a) during the study period (January 1st 2015 to December 31st 2019) were were included. The population was stratified as previously treated/untreated with other DMTs (different from SC PEG-IFN-β-1a, glatiramer acetate, SC IFN-β-1a) in the 6 months before the index date (characterization period). The index date (starting treatment) was defined as the date of the first prescription of one of the study drugs during the enrollment period.

Subjects treated with study drugs for less than 3 months, those with incomplete records (age, sex), and those not residing in the Campania region were excluded from the analysis.

Data Extraction

An *ad hoc* query extracted data from hospital discharge records, the regional prescription database, and outpatient records of the Campania region. This procedure allowed the evaluation of all the subjects residing in the Campania region and treated with injectable DMTs between 2015 and 2019, with high sensitivity and low probability of missing cases[12]. For a subset of patients, clinical variables were obtained from the clinical registry of the MS Center at Federico II University of Naples. The data from the different sources were harmonized and combined through a record-linkage process into a single data set suitable for conducting the analyses necessary for the purpose of the study.

Healthcare Resource Utilization, Costs, and Adherence to Treatment

Healthcare resource utilization included MS-related and non-MS-related hospital admissions that were classified based on the main discharge diagnosis. The number of hospital admissions

was reported on an annual basis [annualized hospitalization rates (AHR)][13]. DMT utilization during the study period was used to compute the Medication Possession Ratio (MPR), expressed as the proportion of days of medication supply within the defined time interval between administrations, to measure adherence to treatment[14]. We considered MPR ≥80% as optimal adherence[15,16]. Patients who switched treatment from included DMTs (SC PEG-IFN-β-1a, glatiramer acetate, SC IFN-β-1a) to alemtuzumab, natalizumab or ocrelizumab, were identified to define DMT escalation (first prescription/administration of new DMT was used as censoring date). We specifically decided to include natalizumab, alemtuzumab, and ocrelizumab for the definition of treatment escalation, while we did not consider oral DMTs, where the switch could be related to tolerability issues and not necessarily lack of efficacy.

Direct healthcare costs were derived from regional datasets, referred to corresponding healthcare resource utilization, and inflated to the most recent values (2019) to avoid variations in price per unit of service through different years[13]. Costs are presented in EUR (€1.00 corresponds to about US$1.10)[17].

We further collected age, sex, and, for patients with Hospital Discharge Records, Charlson Comorbidity Index[13]. This latter index assigns different weights to comorbidities reported with ICD codes in Hospital Discharge Records.

Clinical Variables

Age, sex, disease duration (time from reported clinical onset to index date), and disability (only for patients with record linkage with clinical registry) assessed at baseline using the Expanded Disability Status Scale, EDSS[18], were collected.

Statistical Analysis

Demographic and clinical characteristics of patients at index date were reported as frequency (n, %) for categorical variables, and median [min-max] or mean (SD) for continuous variables, as appropriate. Use and type of DMT after a switch was also described as the frequency of use (n, %).

Differences between DMTs (using SC PEG-IFN-β-1a as a reference in the statistical models) were explored using mixed-effect Cox regression models (i.e., risk of DMT escalation to more effective treatment), and linear regression models [i.e., adherence, annualized hospitalization rates (AHR), costs], as appropriate. Covariates were age, sex, year of treatment start, previously treated/untreated patients, treatment duration, and adherence (MPR). Statistical models were used for the subgroup of patients with hospital discharge records, with the addition of the Charlson comorbidity index to the covariates. The proportional hazard assumption was met, as assessed using plots of log (-log survival time) against log survival time and Schoenfeld residuals against survival time; we also used a linear regression of Schoenfeld residuals on time to test for independence between the residuals and the time.

Results were reported as adjusted coefficient (Coeff), adjusted hazard ratio (HR), 95% CIs, and *p*-values, as appropriate. Statistical analyses were performed using Stata 15.0. Results were considered statistically significant for $p<0.05$.

Results

We retrieved 2,643 individual records from the databases, including MS patients with prescriptions of SC PEG-IFN-β-1a, glatiramer acetate, or SC IFN-β-1a. We excluded 475 patients because the treatment period was <3 months, and 16 because of incomplete data recording. Finally, 2,152 patients were included in the analysis (Figure 1).

Demographic and clinical data at baseline are reported in Table I. SC PEG-IFN-β-1a and SC IFN- β-1a were used in populations with similar mean age (38.84±12.35 years and 39.77±11.79 years, respectively), while the mean age of the glatiramer acetate population was higher (46.01±11.41 years).

The EDSS score at baseline and disease duration were available for 553 patients treated at the Federico II MS Center. Median baseline EDSS was higher in patients treated with glatiramer acetate (4.0, range 1.5-8.5), compared to patients receiving SC PEG-IFN-β-1a (2.0, range 1.0-6.5) or SC IFN-β-1a (2.5, range 1.5-6.5). The mean disease duration was longer in the glatiramer acetate population (9.85±8.22 years), compared to SC PEG-IFN-β-1a (8.44±8.34 years) and SC IFN-β-1a (8.22±6.56 years).

Treatment adherence, was significantly higher for SC PEG-IFN-β-1a (MPR = 1.01±0.16), compared to glatiramer acetate (MPR = 0.91±0.19, Coeff=-0.11, 95% CI -0.14 to -0.08; $p<0.01$) and SC IFN-β-1a (MPR = 0.92±0.16, Coeff=-0.08, 95% CI -011 to -0.06; $p<0.01$) (Table II).

Table III shows the switch frequency from each study drug to other DMTs. The majority of switches were dimethyl fumarate, fingolimod, and teriflunomide for all three study DMTs.

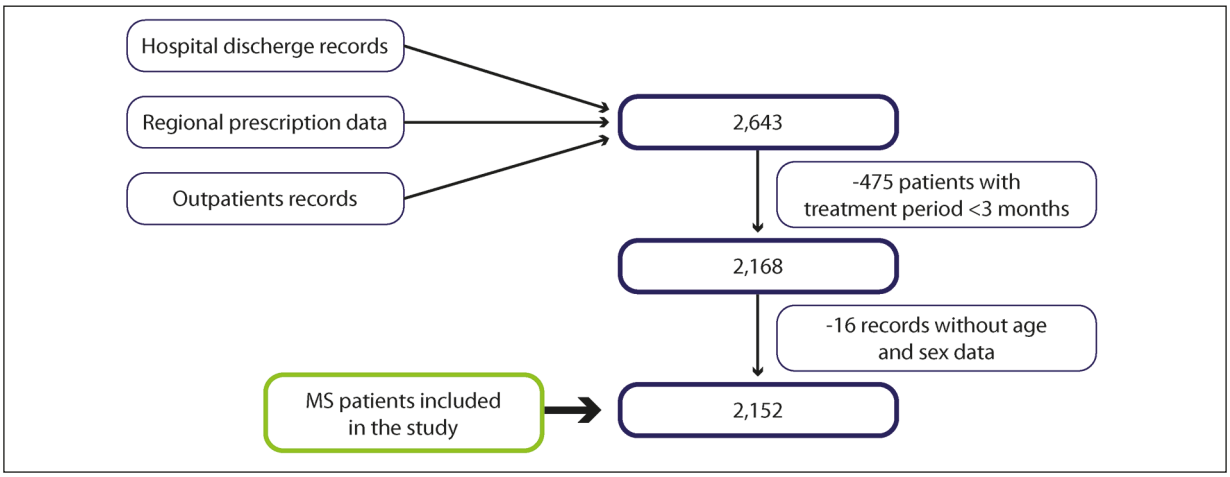

Figure 1. Study flow diagram.

Table I. Demographic and clinical characteristics at index date.

Variable	PEG-IFN-β-1a	SC IFN-β-1a	Glatiramer acetate
N	281	1,226	751
Females, n (%)	198 (70.5)	816 (66.5)	504 (67.1)
Age (years), mean ± SD	38.84 ± 12.35	39.77 ± 11.79	46.01 ± 11.41
No DMT in the previous 6 months (n)	114	1203	650
EDSS* at baseline, mean (range)	2.0 (1-6.5) n = 60	2.5 (1.5-6.5) n = 353	4.0 (1.5-8.5) n = 163
Disease duration* (years), Mean ± SD	8.44 ± 8.34 n = 60	8.22 ± 6.56 n = 353	9.85 ± 8.22 n = 163

*Only for subjects with record linkage with the clinical registry. Peginterferon β-1a (PEG-IFN-β-1a), subcutaneous (SC) interferon beta 1a (IFN-β-1a).

Table II. Healthcare utilization variables and costs.

Variable	PEG-IFN-β-1a	SC IFN-β-1a	Glatiramer acetate
N	281	1,226	751
Mean treatment adherence (MPR) ± SD	1.01 ± 0.1	0.92 ± 0.1 (coeff= -0.08, 95% CI -0.11 to -0.06, $p < 0.01$)	0.91 ± 0.2 (coeff= -0.11, 95% CI -0.14 to -0.08, $p < 0.01$)
Patients with MPR < 80%	8.8%	17.3%	21.2%
Time (months) to escalation (to natalizumab, alemtuzumab or ocrelizumab, mean ± SD	16.15 ± 5.8	22.31 ± 14.2	20.10 ± 14.3
Patients with escalation (to natalizumab, alemtuzumab, or ocrelizumab)	4.9%	9.1% (HR 3.35, 95% CI 1.21-9.20, $p = 0.01$)	14.9% (HR 4.09, 95% CI 1.56-10.74, $p < 0.01$)
Annualized hospitalization rate	0.02 ± 0.24	0.02 ± 0.21 (IRR: 0.01, 95% CI -0.04–0.04, $p = 0.97$)	0.05 ± 0.30 (IRR: 0.02, 95% CI -0.02–0.05, $p = 0.31$)
Costs for hospitalization due to MS (€/month), mean ± SD	23.91 ± 43.9	29.42 ± 47.8 (coeff = 6.79, 95% CI -20.01–33.61, $p = 0.61$)	49.45 ± 195.2 (coeff = 29.89, 95% CI 3.18-56.90, $p = 0.03$)
Costs for hospitalization for any cause (€/month), mean ± SD	30.36 ± 73.83	36.78 ± 68.86 (coeff = 6.88, 95% CI -18.23–31.99, $p = 0.59$)	81.69 ± 257.21 (coeff = 29.9, 95% CI 4.29-53.90, $p = 0.02$)

PEG-IFN-β-1a – reference in the regression models. Peginterferon β-1a (PEG-IFN-β-1a), subcutaneous (SC) interferon beta 1a (IFN-β-1a). €1.00 corresponds to about US$1.10[15].

Table III. Switch from study drug to other DMTs.

	PEG-IFN-β-1a (n = 281), n (%)	SC IFN-β-1a (n = 1,226), n (%)	Glatiramer acetate (n = 751), n (%)
SC PEG-IFN-β-1a	–	51 (4.1)	3 (0.3)
SC IFN-β-1a	8 (2.8)	–	6 (0.6)
SC Glatiramer acetate	11 (3.9)	17 (1.3)	–
IM IFN-β-1a	10 (3.5)	13 (1.0)	1 (0.1)
SC IFN-β-1b	2 (0.7)	1 (0)	3 (0.3)
Os Fingolimod	20 (7.1)	135 (11.0)	54 (7.1)
IV Alemtuzumab	1 (0.3)	4 (0.3)	3 (0.3)
IV Ocrelizumab	2 (0.7)	8 (0.6)	18 (2.3)
Os Teriflunomide	18 (6.4)	57 (4.6)	43 (5.7)
Os Dimethyl fumarate	46 (16.3)	172 (14.0)	56 (7.4)
IV Natalizumab	3 (1.0)	33 (2.6)	8 (1.0)
Total	121 (43.0)	440 (35.8)	195 (25.9)

IM: intramuscular; IV: intravenous; Os: oral; SC: subcutaneous; Peginterferon β-1a (PEG-IFN-β-1a), subcutaneous (SC) interferon beta 1a (IFN-β-1a).

The rate of escalation to more effective DMTs (natalizumab, alemtuzumab, or ocrelizumab) was higher for glatiramer acetate (14.9%; HR=4.09; 95% CI 1.56-10.74; $p<0.01$), and SC IFN-β-1a (9.1%; HR=3.35; 95% CI 1.21-9.20; $p=0.01$), compared to SC PEG-IFN-β-1a (4.9%) (Table II).

AHR was very low in all groups and no difference between treatment groups was observed [SC PEG-IFN-β-1a = 0.02±0.24; glatiramer acetate = 0.05±0.30 (IRR: 0.02, 95% CI -0.02-0.05, $p=0.31$); SC IFN-β-1a = 0.02±0.21 (IRR: 0.01, 95% CI -0.04-0.04, $p=0.97$)]. This result was confirmed after adjusting by the Charlson Comorbidity Index.

Costs for hospitalizations for any cause were higher in patients receiving glatiramer acetate (€81.60±€257.21/month, Coeff=29.9, 95% CI 4.29-53.90, $p=0.02$) than those treated with SC PEG-IFN-β-1a (€30.36±€73.83/month). Similar results were observed for hospitalizations due to MS: costs were 49.45±195.2 (Coeff=29.89, 95% CI 3.18-56.90, $p=0.03$ *vs.* SC PEG-IFN-β-1a) €/month for patient in treatment with glatiramer acetate and €23.91±€43.9/month for SC PEG-IFN-β-1a (Table II). These results were confirmed after adjusting for the Charlson Comorbidity Index.

Discussion

This retrospective population-based study described the utilization of SC PEG-IFN-β-1a, compared to SC IFN-β-1a and glatiramer acetate in the Campania region of Southern Italy. SC PEG-IFN-β-1a, the newest IFN-β-1a formulation approved on the market, demonstrated a favorable profile of adherence, risk of DMT escalation, healthcare resource utilization and related costs when compared to previously approved injectable DMTs (SC IFN-β-1a and glatiramer acetate).

The patient populations in this study were similar in many parameters, but the patients treated with SC PEG-IFN-β-1a and SC IFN-β-1a were younger and had lower disability than patients treated with glatiramer acetate. These results suggest that SC PEG-IFN-β-1a and SC IFN-β-1a are mainly used in the early stages of the disease, which hold greater treatment potential due to higher inflammatory activity and less disability[19]. In contrast, glatiramer acetate was possibly used more often at a later stage of disease when disability has already accumulated beyond compensatory possibilities[19,20], and escalation to more effective treatments was deemed not necessary[21].

Although treatment adherence was high in all groups, MPR was significantly higher in patients receiving SC PEG-IFN-β-1a than in the other groups. It can be hypothesized that this result is related to the prolonged dosing interval, which is expected to facilitate long-term adherence in the treatment of chronic diseases and supports the evidence on the role of pegylation[22-26]. Results from the Platinum, multicenter, open-label, phase IV study[24] conducted in 32 Italian centers suggested that RRMS patients dissatisfied with interferons may find that SC PEG-IFN-β-1a is a viable treatment choice, which is able to improve patient satisfaction, quality of life, and adherence while maintaining comparable clinical efficacy. Coyle et al[27] found better clinical outcomes with SC PEG-IFN-β-1a every 2 weeks than with SC IFN-

β-1a three times per week in matching-adjusted comparisons (annualized relapse rate: 0.256 *vs.* 0.335, respectively; confirmed disability worsening: 6.5% *vs.* 13.2%, respectively), suggesting that higher adherence to treatment could also impact outcomes. A reduction in serious relapse rates (12.4% *vs.* 19.9%, p=0.013) and direct and indirect costs (US$14,095 *vs.* US$16,638, p=0.048) in patients with optimal adherence compared to non-adherent patients was demonstrated by Ivanova et al[16], further highlighting the importance of treatment adherence.

Hospitalization costs for any cause and for MS were higher in patients treated with glatiramer acetate than in the other groups. Since these patients were older than the other groups, the cost difference may be related to older age and the associated burden of comorbidities, shown in the baseline patient characteristics. However, the results were derived from statistical models accounting for age and were confirmed even after adjusting for CCI.

The costs of hospitalization for all causes and for MS are higher in patients treated with SC IFN-β-1a *vs.* SC PEG-IFN-β-1a, but the difference is not statistically significant. These data align with previously reported data[28] supporting that SC PEG-IFN-β-1a compared with SC IFN-β-1a for RRMS treatment in Italy is a cost-saving strategy that moderates healthcare resource use for disability and sick leave costs.

Clinical trial and a phase IV study data support PEG-IFN-β-1a administered subcutaneously every 2 weeks as effective and have a favorable tolerability profile, similar to SC IFN-β-1a, but with significantly less cumulative flu-like syndrome duration[1,2,24,29]. Additionally, PEG-IFN-B-1a is associated with a reduced risk of producing neutralizing antibodies[3,30,31], an established cause of loss of efficacy[32] and higher costs[33]. The results of an economic evaluation[33] suggest the presence of an association between neutralizing antibodies (NAb+) status and increased costs for the management of RRMS in Italy. The cost increase related to the NAb+ status was €3,100 from the Italian societal perspective and €1,111 from the Italian National Healthcare Service perspective.

The risk of escalating to high-efficacy DMTs was higher for glatiramer acetate and SC IFN-β-1a compared to SC PEG-IFN-β-1a. This difference could result in lower costs with SC PEG-IFN-β-1a from the perspective of the Italian National Healthcare Service since the prescription of high-efficacy treatment could lead to a relevant increase in therapeutic costs, being high efficacy options more expensive than injectable platform DMTs. On the other hand, this data could be read as an indirect index of the efficacy of SC PEG-IFN-β-1a compared to SC IFN-β-1a and glatiramer acetate in line with the findings by Reder et al[34] showing SC PEG-IFN-β-1a was associated with lower relapse rate when compared with glatiramer acetate. Additionally, results from separate matching comparisons of phase III clinical trials[35] and extension studies suggested that SC PEG-IFN-β-1a may provide a lower annualized relapse rate and probability of 12-week confirmed disability worsening than glatiramer acetate.

Natalizumab, alemtuzumab, and ocrelizumab were included for the definition of treatment escalation, and oral DMTs were excluded, so as not to confound the reason switching as potentially related to tolerability issues and not lack of efficacy.

Limitations

Limitations of the study include the use of data from a specific geographical area, that may not generalize to other countries[15]. We have had access to clinical variables from a limited sample and have only used them for descriptive purposes; further investigation is warranted using clinical registries as well. Further characterization of the cohort could have included treatment sequencing over the previous years, while we have only accounted for the use of DMTs in the previous 6 months.

Conclusions

SC PEG-IFN-β-1a and SC IFN-β-1a were used in relatively similar populations, while glatiramer acetate was preferred in older and more disabled patients. SC PEG-IFN-β-1a is associated with better adherence to treatment in comparison with SC IFN-β-1a and glatiramer acetate. Increased adherence may improve outcomes, as shown by the reduced risk of treatment escalation, and could be a strategy to reduce direct and indirect costs for RRMS patients.

Conflict of Interest

Marcello Moccia has received research grants from the EC-TRIMS-MAGNIMS, the UK MS Society, and Merck; honoraria from Biogen, Ipsen, Merck, Roche, and Sanofi-Genzyme. Vincenzo Brescia Morra has received research grants from the Italian MS Society, and Roche, and honoraria

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Availability of Data and Materials
All data presented in this article are included in the manuscripts or tables/figures. Further inquiries can be directed to the corresponding author.

Ethics Approval
The study was approved by the Federico II University Ethics Committee (approval code: 355/19).

Informed Consent
All patients signed informed consent authorizing the use of anonymized, routinely collected healthcare data in line with data protection regulations (GDPR EU2016/679).

Authors' Contribution
Study conception and design: MM, LS, RP; collection of data: MM, GA, DC, RL, RP; statistical analysis: RP, MM, VBM; interpretation of data/results: all authors; manuscript drafting: MM, LS, IV; all the authors read and approved the manuscript for submission.

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