Short Communication

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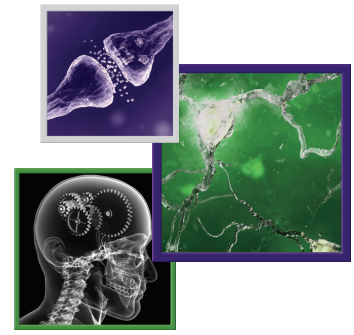
Neurodegenerative Disease Management



Off-Adherence Keeping (OAK) observational study: intentional off-adherence immunomodulatory multiple sclerosis treatment

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Aims: To evaluate how improved treatment adherence with a lower-frequency regimen/treatment of intramuscular (IM) IFNβ-1a impacts therapeutic effectiveness in relapsing-remitting multiple sclerosis (MS) patients switching from a higher-frequency injectable regimen/treatment. **Patients & methods:** Italian patients with relapsing-remitting MS and prior poor adherence to high-frequency injectable treatments (n = 181) were followed for 24 months after starting IM IFNβ-1a. **Results:** During the study, 97.4% of patients were treatment adherent; 22.1% of patients reported a relapse. The estimated probability of remaining relapse-free after 2 years was 78%. A high dropout rate (52.5%) led to small sample size and reduced statistical power. **Conclusion:** Intramuscular IFNβ-1a treatment was associated with high adherence and a low relapse rate. Unfortunately, low patient retention limited the generalizability of these findings.

Plain language summary: Prior research suggests that taking the drug IFNβ-1a through less frequent muscle injections enables more patients to adhere to their prescription than taking other medications. This study included 181 Italian patients with relapsing-remitting multiple sclerosis (MS) who historically did not take medication as often as prescribed. Relapses of MS were counted among patients treated with muscle injections of IFNβ-1a for 2 years; 97.4% of patients followed their prescription and 22.1% experienced a relapse. From these data, 78% of patients were estimated not to experience a relapse during 2 years of IFNβ-1a muscle injections. However, an unusually high number of patients (52.5%) left the study within 2 years, which makes it difficult to draw firm conclusions.

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Keywords: intramuscular interferon beta-1a • multiple sclerosis • quality of life • relapses • treatment adherence

Multiple sclerosis (MS) remains the leading cause of neurological disability in young adults, with about 2.5 million people affected worldwide [1,2]. Due to its chronic progressive evolution and disabling associated symptoms, MS has a dramatic impact on patients' quality of life (QoL) and economic burden [3]. As with any chronic condition, MS requires lifelong treatment and poor adherence to disease-modifying therapy (DMT), which may increase morbidity [4], remains a challenge. Poor adherence to injectable DMTs is reported in up to 46% of patients [5].

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Adherence to treatment depends on the patient's characteristics, beliefs about medication, the timing and frequency of administration and the dosage of the DMT [5,6]. Patients with poor adherence have a higher risk of relapse and hospitalization leading to greater disability, more depression and lower QoL, in addition to higher healthcare costs [7–9]. Forgetting to take injections is the main cause of nonadherence (seen in 50–58% of nonadherent cases), with patients on high-frequency DMTs being more prone to this problem [8–10].

Intramuscular interferon beta-1a (IM IFNβ-1a; Avonex®, Biogen, MA, USA) is administered once a week. In a multicenter observational study lasting 4 weeks, IM IFNβ-1a was associated with better therapeutic adherence than the high-frequency treatment subcutaneous (SC) IFNβ-1a, which is administered three times a week, SC IFNβ-1b, which is administered every other day, and glatiramer acetate, which is administered daily [10]. These findings mirror those reported in a similar study [8]. However, little has been published regarding the effect of adherence to IFNβ-1a on the therapeutic effectiveness of this molecule. This real-world study investigated the effects of better adherence on therapeutic effectiveness in a cohort of Italian patients with a history of noncompliance with treatment for relapsing-remitting MS who switched from high-frequency injectable DMTs to IM IFNβ-1a.

Patients & methods

Study setting & design

This was a prospective, multicenter observational study conducted in Italy at 26 neurological centers across the country. The study was initiated in December 2012 and the total study duration was 42 months. Enrollment lasted 16 months; after inclusion, each patient was followed for 24 months. The last patient was enrolled in April 2014 and the study concluded in May 2016. The study was conducted in line with the principles of the Declaration of Helsinki, and the protocol was approved by local ethics committees. Prior to enrollment, study investigators provided patients with verbal and written explanations of study procedures and the patient's right to withdraw from the study at any time for any reason; all patients signed an informed consent form prior to enrollment.

Patients

Patients ≥18 years of age diagnosed with relapsing-remitting MS who had demonstrated poor adherence to a high-frequency (>1 administration per week) injectable DMT (with poor adherence defined as failure to take the drug at least once in the last 4 weeks before discontinuation) and who had been prescribed IM IFNβ-1a by the treating neurologist for at least 1 week were eligible. Patients who had been treated in the past with IM IFNβ-1a for more than 4 weeks and those enrolled in other clinical studies were excluded. No other inclusion or exclusion criteria were applied. Each enrolled patient could withdraw from the study at any time. Patients were also withdrawn from the study for the following reasons: discontinuation of therapy with IM IFNβ-1a prior to the end of the 24-month follow-up, the onset of adverse events (AEs) or clinical worsening, loss to follow-up or investigator decision.

Assessments

Study visits occurred at enrollment (which included screening for inclusion criteria) and then at 6-month intervals through 24 months. The following assessments were conducted at enrollment and at 6, 12, 18 and 24 months: relapse count, treatment adherence assessment, Visual Analogue Scale (VAS) for injection anxiety, Expanded Disability Status Scale (EDSS) [11], MS QoL (MSQoL-54) [12] and Beck Depression Inventory (BDI–II) [13]. A patient diary for collection of IM IFNβ-1a self-administration dates, which also included reasons for noncompliance and side effect reports, was provided at baseline and completed once a week through the last visit. All patient data, including information on AEs, were recorded through an electronic case report form (eCRF). Information from the clinical charts of all patients was also collected as appropriate.

Outcomes

The main objective of this study was to evaluate the association between relapses (absent/present) and treatment adherence (percentage of drug taken/drug prescribed × 100) over a 24-month observation period, with good adherence defined as adherence ≥80%. Secondary outcomes were as follows: relapse-free time (RFT) defined as the time from enrollment to the first relapse; injection anxiety level evaluated by VAS (100-mm length); disability progression evaluated as the change in EDSS score from enrollment; QoL assessed by the MSQoL-54 questionnaire; and depression evaluated by BDI–II.

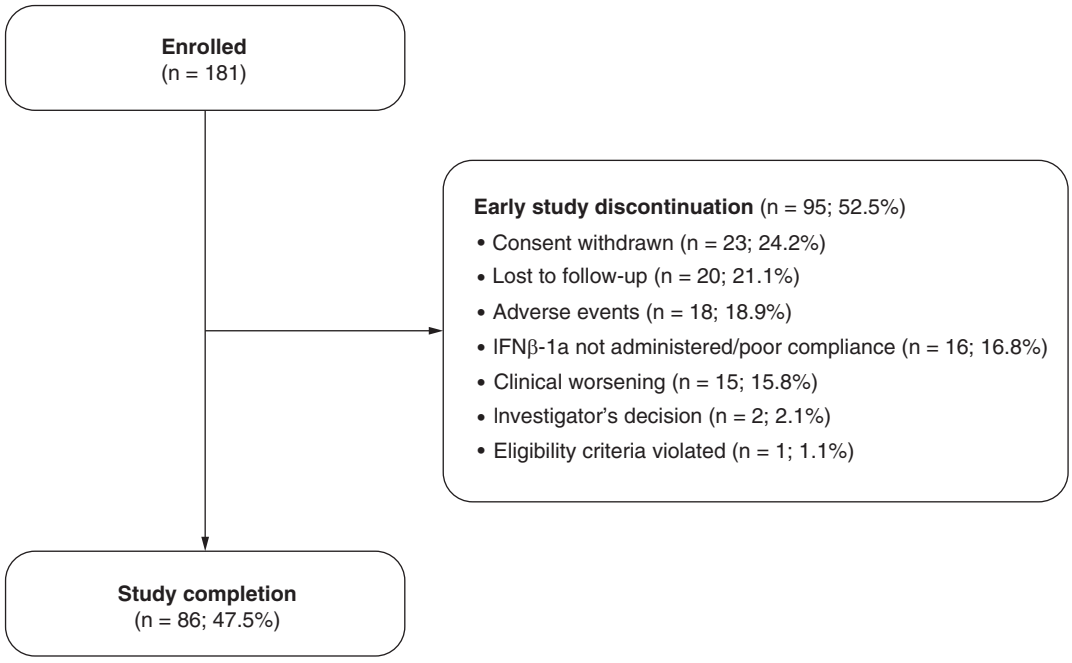

Figure 1. Patient enrollment flowchart including reasons for early discontinuation.

Statistical analysis

All data were analyzed using descriptive statistics. A multivariate logistic regression model was used to determine the relationship between relapses and adherence. In this analysis, the dependent variable, relapse (yes/no), was correlated with the main independent variable (adherence percentage) for each patient. Other adjustment covariates included in the model were age, disease duration, concomitant pathologies, baseline EDSS score, gender and the number of relapses in the year preceding enrollment in the study. Target enrollment was estimated with the logistic regression model under the following assumptions: The multiple correlation coefficient (R^2) between the covariates and the adherence covariate was 0.10 (R^2 = 0.10); and it was hypothesized that the relapse incidence would decrease by at least 30% when the compliance increased by 1 standard deviation (SD), yielding an odds ratio (OR) of 0.64. On this basis, a minimum sample size of 175 enrolled patients would be needed to obtain an OR of 0.64 using $\alpha = 0.05$ and $\beta = 0.20$ (power equal to 80%). The analysis population included all enrolled patients who received ≥1 dose of IM IFNβ-1a. RFT was analyzed by the Kaplan-Meier method. The Cox proportional hazards regression model was used to assess the influence of these baseline covariates on RFT. Comparisons of other parameters at different time points were made using the analysis of variance test for repeated measures. All analyses were performed using SAS System version 9.4 (NC, USA).

Results

Patient population

Figure 1 shows patient disposition throughout the study. In total, 181 patients were enrolled. The mean (SD) age was 40.5 (11.2) years (Table 1). Despite a mean of 7.1 (5.8) years since diagnosis, this population appeared to have relatively mild MS disease activity. Of the 180 patients included in the study, 25 (13.9%) had an MS relapse during the year before enrollment. None of the patients reported relapses between the beginning of IM IFNβ-1a treatment and study enrollment. Among the 170 patients with available EDSS data, the median EDSS score at enrollment was 2.0 (range: 0.0–6.5). Overall, 145 of 170 patients (85.3%) had an EDSS score ≤3.5; 19 of 170 (11.2%) had an EDSS score of 4.0–5.5 and 6 of 170 (3.5%) had an EDSS score ≥6.0.

The mean (SD) duration of prior immunomodulatory high-frequency treatment was 58.3 (51.3) months. Eight of 180 patients (4.4%) received IFNβ prior to the first dose of IM IFNβ-1a and 41 (22.8%) received previous treatments for MS that were not high-frequency immunomodulatory treatments. Overall, the mean duration of prior treatment was 30.6 (33.3) months. In the 180 patients included in the study, the mean number of doses of

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Table 1. Baseline characteristics and disease history of patients with poor adherence to prior disease-modifying therapy for relapsing-remitting multiple sclerosis.

Characteristic	Patients enrolled (n = 180)
Gender, n (%)	
Male	48 (26.7)
Female	132 (73.3)
Age, mean (SD), years	40.5 (11.2)
Ethnicity, n (%)	
Caucasian	179 (99.4)
Asian	1 (0.6)
Concomitant disease, n (%)†	63 (35.0)
Endocrine disorders	17 (9.4)
Gastrointestinal disorders	6 (3.3)
Metabolism and nutrition disorders	7 (3.9)
Musculoskeletal and connective tissue disorders	5 (2.8)
Nervous system disorders	12 (6.7)
Psychiatric disorders	10 (5.6)
Vascular disorders	10 (5.6)
Concomitant medication, n (%)‡	112 (62.2)
Antidepressants	16 (8.9)
Antiepileptics	17 (9.4)
Anti-inflammatories/antirheumatics, nonsteroid	17 (9.4)
Systemic corticosteroids	28 (15.6)
Other analgesics and antipyretics	38 (21.1)
Thyroid preparations	18 (10.0)
Prior disease, n (%)	19 (10.6)
Surgical and medical procedures, n (%)	6 (3.3)
Time since MS diagnosis, mean (SD), years	7.1 (5.8)
EDSS score at MS diagnosis, mean (SD)	2.0 (1.1)
MRI results at MS diagnosis, n (%)§	
Gd+ lesions	71 (93.4)
≥1 T1 Gd+ lesions	36 (47.4)
≥9 T2 hyperintense lesions	32 (42.1)
≥1 infratentorial lesions	43 (56.6)
≥1 subcortical lesions	48 (63.2)
≥3 periventricular lesions	46 (60.5)
Prior MS medications	
High-frequency immunomodulatory treatments, n (%)	180 (100)
Mean duration (SD), months	58.3 (51.3)
IFNβ, n (%)	8 (4.4)
Other previous treatments, n (%)	41 (22.8)
Relapses in the year prior to enrollment, n (%)	25 (13.9)

†Patients could have had >1 concomitant disease.
‡Patients could have received >1 concomitant medication.
§MRI at diagnosis was available for 76 patients. All percentages shown for MRI measures are based on a denominator of 76.
EDSS: Expanded Disability Status Scale; Gd+: Gadolinium-enhancing; MS: Multiple sclerosis; SD: Standard deviation.

previous therapy not received in the last month was 3.4. The most common reasons for noncompliance with other treatments were injection fatigue (reported by 160 patients) and lack of desire (reported by 142 patients; Table 2).

Overall, 86 of 181 enrolled patients (47.5%) completed the study (Figure 1). Out of 181 patients, 95 (52.5%) prematurely discontinued, most commonly because of withdrawal of informed consent (23 of 95; 24.2%), loss to follow-up (20 of 95; 21.1%) and AEs (18 of 95; 18.9%; Figure 1). The numbers of patients who completed the follow-up visit at 6, 12, 18 and 24 months were 149, 124, 99 and 85, respectively; 75 patients completed a dropout

Table 2. Self-reported reasons for noncompliance with prior disease-modifying treatments during the 4 weeks prior to discontinuation.

Reason, n (%)	Frequency (n = 180)		
	Never	Sometimes	Always
Treatment forgotten	74 (42.5)	98 (56.3)	2 (1.1)
Lack of desire	32 (18.4)	92 (52.9)	50 (28.7)
Injection fatigue	14 (8.0)	73 (42.0)	87 (50.0)
Skin reactions at the injection site	43 (24.7)	76 (43.7)	55 (31.6)
Pain at the injection site	47 (27.0)	79 (45.4)	48 (27.6)
Anxiety associated with injection	52 (29.9)	77 (44.3)	45 (25.9)
Absence of someone who helps with drug administration	135 (77.6)	22 (12.6)	17 (9.8)
Other	128 (73.6)	2 (1.1)	4 (2.3)

Table 3. Logistic regression analysis of the interaction between age and time to relapse.

Age range (years)	OR vs age; 18–30 cohort	95% CI	p-value
31–50	0.203	0.075–0.547	0.3312
51–65	0.087	0.016–0.462	0.0508
>65	0.500	0.039–6.351	0.6043

OR: Odds ratio.

Table 4. Adherence to intramuscular IFNβ-1a treatment over 2 years of follow-up.

IM IFNβ-1a exposure and adherence	Patients
Drug exposure, mean (SD), days	533.9 (245.6) (n = 167)
Drug prescribed, mean (SD), days	76.1 (35.1) (n = 167)
Drug taken, mean (SD), days	78.1 (33.0) (n = 155)
Treatment adherence, mean (SD), %	
6 months	98.4 (5.0) (n = 145)
12 months	97.3 (10.0) (n = 114)
18 months	97.4 (6.1) (n = 90)
24 months	97.7 (6.7) (n = 76)

IM: Intramuscular; SD: Standard deviation.

visit before their premature withdrawal from the study. The mean (SD) duration of follow-up for the 180 patients who received at least one dose of IM IFNβ-1a was 1.4 (0.7) years.

Relapse episodes

During the study period, 32 of 145 patients with available data (22.1%) experienced a relapse episode. Using a forward selection method, only age was reported to be a predictor of relapse in the logistic regression model (p = 0.0017). In general, the risk of relapse was lower in the older age groups (Table 3).

Treatment adherence

Of the 155 patients with available data, and irrespective of study completion or early termination, 151 (97.4%) were adherent to IM IFNβ-1a treatment. Overall, adherence remained relatively stable throughout the 24-month study period (Table 4).

Secondary end points

The estimated cumulative probability of remaining relapse free at 2 years of follow-up was 78% (Figure 2). Consistent with the logistic regression model, only age was significantly associated with RFT (Table 5).

Table 6 summarizes the key results reported for secondary end points. In total, 179 patients completed the VAS measurement at baseline, with a mean (SD) value of 46.7 (31.3) mm. This value declined during the 24-month follow-up period (mean [SD] decline: -23.1 [29.0]). Minimal change in EDSS score was observed over the study

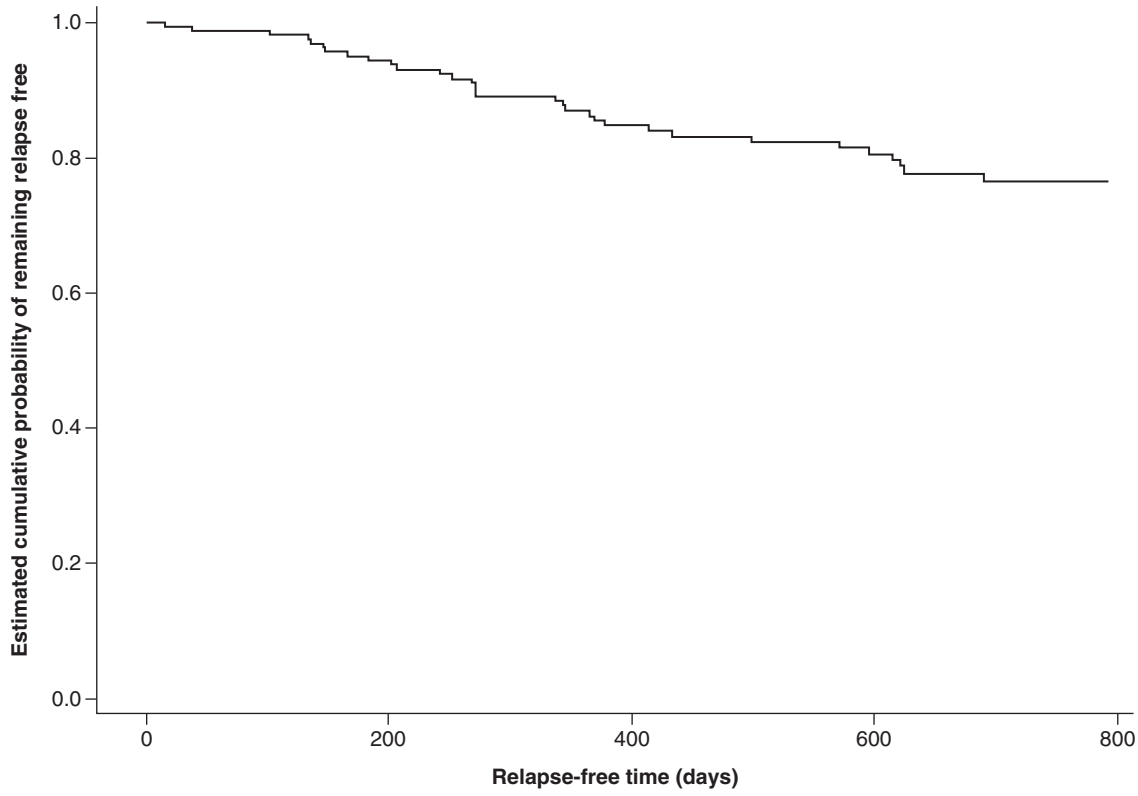

Figure 2. Kaplan-Meier curve depicting the cumulative probability of multiple sclerosis relapse over time after initiating treatment with intramuscular IFNβ-1a.

Table 5. Cox regression analysis of time to relapse by treatment adherence and other covariates.

Variable	Hazard ratio	p-value
Treatment adherence, <80% vs ≥80%	0.000	0.9920
Age cohort		
31–50 years vs 18–30 years	0.269	0.0037
51–65 years vs 18–30 years	0.058	0.0023
>65 years vs 18–30 years	0.271	0.2843
Disease duration, ≤3 years vs >3 years	0.568	0.1999
Presence of concomitant pathologies, no vs yes	1.183	0.6931
EDSS score at enrollment		
4.0–5.5 vs <4.0	1.874	0.2984
6.0–6.5 vs <4.0	4.907	0.1787
Gender, female vs male	1.055	0.8980
Relapses in the previous year (n), 0 vs ≥1	0.688	0.4842

EDSS: Expanded Disability Status Scale.

period, with mean EDSS scores at visits 1–5 being 2.1 (1.4), 2.0 (1.4), 2.0 (1.4), 2.3 (1.5) and 2.1 (1.3), respectively. A statistically significant decline from enrollment to month 18 (-0.12; 95% CI: -0.22 to -0.02) was reported.

The overall mean (SD) MSQoL-54 score at baseline was 66.1 (17.5). The mean (SD) physical health composite was 61.2 (16.5) and the mental health composite was 63.3 (21.3). The overall mean score did not change over the study period. However, there was a statistically significant decrease (improvement) from enrollment to month 24 in the physical composite score (-2.34; 95% CI: -4.54 to -0.14; p = 0.0373) and from enrollment to month 12 in the mental composite score (-3.13; 95% CI: -6.00 to -0.29; p = 0.0310). The mean BDI–II score at enrollment

Table 6. Changes in anxiety, depression and quality of life over time.

Secondary end point	Level (SD) at enrollment	At 6 months		At 12 months		At 18 months		At 24 months	
		Change vs enrollment	p-value	Change vs enrollment	p-value	Change vs enrollment	p-value	Change vs enrollment	p-value
Injection anxiety level (VAS)	46.7 (31.3)	-18.6	NA	-21.4	NA	-25.3	NA	-23.1	NA
EDSS score	2.1 (1.4)	-0.00007	0.9987	-0.02450	0.6040	-0.1231	0.0183†	-0.06158	0.2586
MSQoL-54 – physical health	61.2 (16.5)	-0.3085	0.7261	-1.4729	0.1277	-1.4334	0.1841	-2.3385	0.0373†
MSQoL-54 – mental health	63.3 (21.3)	-1.4251	0.2802	-3.1287	0.0310†	-2.3300	0.1442	-2.6567	0.1116
MSQoL-54 – overall QoL	66.1 (17.5)	-0.08456	0.9438	-0.5707	0.6620	-0.9681	0.4984	0.3240	0.8305
BDI–II	10.0 (8.9)	1.0441	0.0603	1.1758	0.0519	0.9973	0.1339	0.7335	0.2954

†$p < 0.05$.
BDI–II: Beck Depression Inventory; EDSS: Expanded Disability Status Scale; MSQoL-54: Multiple Sclerosis Quality of Life-54; NA: Not analyzed; QoL: Quality of life; SD: Standard deviation; VAS: Visual Analogue Scale.

Table 7. Adverse events observed during treatment with intramuscular IFNβ-1a.

Event, n (%)	n = 180
Any AE	138 (76.7)
General disorder or administration site condition	116 (64.4)
Influenza-like illness	104 (57.8)
Injection site pain	23 (12.8)
Injection site reaction	46 (25.6)
Musculoskeletal or connective tissue disorder	14 (7.8)
Nervous system disorders	111 (61.7)
Headache	96 (53.3)
MS relapse	35 (19.4)
Adverse drug reaction	123 (68.3)
Serious AE	7 (3.9)
Premature discontinuation	24 (13.3)
AE leading to hospitalization	6 (3.3)

AE: Adverse event; MS: Multiple sclerosis.

was 10.0 (8.9). This parameter decreased slightly over the 24-month follow-up period (an increase of 0.734 from baseline to month 24), although statistical significance versus baseline was not reached at any time point.

Safety

In total, 138 of 180 patients (76.7%) reported at least one AE, with 123 experiencing an AE related to IM IFNβ-1a (Table 7). Eight patients (4.4%) reported at least one severe AE, none of which were considered to be related to IM IFNβ-1a. These included three cases of MS relapse and one case each of asthenia, radius fracture, major depression, endometrial adenocarcinoma and central nervous system metastases. The most commonly reported AEs were general disorders and administration site conditions (n = 116; 64.4%). Among these, influenza-like illness was reported by the highest number of patients (n = 104; 57.8%) followed by injection site reactions (n = 46; 25.6%).

A total of 24 out of 180 patients (13.3%) discontinued the study treatment due to AEs and six (3.3%) were hospitalized for serious AEs. No fatal AEs were reported.

Discussion

The results of this study suggest that patients who were not adherent to high-frequency injectable therapies can demonstrate high adherence to the weekly administration schedule of IM IFNβ-1a, potentially leading to better MS disease control. However, these findings should be interpreted with caution, as several additional factors may have influenced the results. A variety of factors have been shown to influence treatment adherence, including memory issues, tolerability, treatment satisfaction, comorbidities and even participation in a clinical trial [14–17].

As the current study was a single-arm observational study, the impact of any given factor on adherence, including reduced injection frequency, could not be isolated.

The study population was fairly representative of the MS patient population in terms of sex, age and ethnicity. However, this population seemed to be healthier and have less active disease in terms of comorbidities, history of relapses and disability worsening than the average MS population included in real-world studies, which could have influenced reported outcomes, as more stable patients are more likely to discontinue treatment and less likely to have relapses [18]. Additionally, this patient population had a wide range of time since diagnosis, with some having switched medications shortly after diagnosis and others having switched later in their treatment course, which may have increased variability in outcomes.

The primary objective of the study was to evaluate the relationship between relapses and treatment adherence over a 24-month observation period. Thirty two of 145 patients with available data (22.1%) had a relapse episode during the study, yielding an annual relapse rate of 0.111. While this rate was ostensibly lower than the rate of relapse in the year prior to the study, it may have been higher if data from patients who discontinued the study were also included.

Adherence to treatment was high (97%) among patients with available data in the eCRF; reasons for nonadherence could not be analyzed due to a lack of data. While the lower frequency of injections associated with IM IFNβ-1a may be partially responsible for this outcome, additional factors likely also contributed to a high rate of adherence. Sixteen patients (16.8% of early discontinuations) withdrew from the study because of poor compliance, indicating that early discontinuation at least partially augmented the adherence rate. The use of a weekly patient diary to track injections in this study could also have encouraged adherence in the patients who remained in the study. However, prior research suggests such monitoring does not affect adherence, even when patients themselves report that it does [19]. Mean treatment adherence, disability status, overall QoL and depression levels remained relatively stable throughout the study period. However, we could not assess the potential relationship between this stability and IM IFNβ-1a treatment because of low statistical power.

Safety data collected during the study did not reveal any new safety concerns, suggesting that the overall safety profile of IM IFNβ-1a in the real-world context is consistent with that observed in clinical trials [20,21]. Thirteen percent of the patients prematurely discontinued the study due to ≥1 AE; the most common AEs were influenza-like illness (57.8%) and headache (53.3%), in line with those reported in the prescribing information for IM IFNβ-1a. Of note, the frequency of injection site reactions was higher in this real-world study (25.6%) than in placebo-controlled studies (3%) [21].

The main limitations of the study were the high dropout rate (52.5%) and the large amount of missing data, which yielded a significantly smaller sample size at the end of the study, with reduced statistical power. The high dropout rate observed, which far exceeds any other dropout rate described in similar studies [22,23], may be related to the inclusion and withdrawal criteria and the approval of new oral drugs and SC peginterferon beta-1a for the treatment of MS during the course of the study. The patient population consisted of those with a history of nonadherence to treatment. These patients may believe that medication is less necessary and even harmful compared to adherent patients [6], which could have influenced patient-related decisions to withdraw from the study. Almost half of the patients who discontinued early left because of withdrawn consent or being lost to follow-up and roughly one-third of patients who withdrew did so within the first 6 months of the trial. This early spike in dropout rate may have also been related to the strict withdrawal criteria imposed by the study, requiring withdrawal of patients after missing one of four postbaseline visits. It is important to note that clinical worsening only accounted for 15.8% of withdrawn patients, similar to the relapse rate observed in the retained patient population. This suggests that the large dropout rate did not directly bias the relapse rate in the final analysis.

As there was no comparator group in this study, no conclusions could be made about any direct relationship between IFNβ-1a administration and adherence, safety or efficacy outcomes. Another key limitation of the study was the use of patient questionnaires, which may have led to the high frequency of missing data. Finally, the inclusion criteria defined nonadherence to a previous therapy as simply missing at least one dose in a 4-week period. As this included several therapies with different administration frequencies, the corresponding degree of nonadherence prior to the study would vary. For instance, in a month, a patient could have missed 1 dose out of 30 for a daily medication or 1 dose out of 12 for a thrice-weekly medication.

Overall, only 85 of 180 enrolled patients (47.2%) completed the study and attended the last visit at 24 months. We were not able to assess differences between patients who withdrew from the study and those who completed it, as dropout visit information was scarce (only 4 out of 95 discontinued patients allowed collection of dropout

visit test results) and no additional analyses comparing the two groups were performed. Complete data on the reasons for the high rate of IM IFNβ-1a discontinuation would have been valuable, especially given that early discontinuation is usually associated with disease complexity or worsening. Patients who dropped out may have suffered more relapses and experienced more difficulties in taking the drug and attending visits to the neurological center. Conversely, patients who completed the study may have been those with fewer relapses and better adherence to treatment.

Conclusion

This single-arm observational study, in the context of prior research, suggests that prescribing a lower-frequency treatment such as weekly IM IFNβ-1a may improve adherence and reduce relapse risk. A Cox regression analysis identified only age as a significant risk factor for relapse over 2 years of IM IFNβ-1a treatment. While adherence was consistently high throughout the study (97% overall), conclusions about the relationship between the treatment, adherence and disease outcomes are limited because of the 54.5% early discontinuation rate. Further studies are required to evaluate the relationship between adherence to IM IFNβ-1a treatment and relapse and progression of the disease in larger, more representative populations.

Summary points

- Patients with multiple sclerosis (MS) frequently report poor adherence to disease-modifying therapy, which may result in a higher risk of relapse and hospitalization and a consequent reduction in quality of life.
- The weekly injections required for intramuscular (IM) IFNβ-1a are less frequent than the multiple injections per week required for other therapies, which could improve adherence.
- This real-world, prospective, multicenter observational study evaluated the relationship between treatment adherence and therapeutic effectiveness in relapsing-remitting MS patients switching from a higher- to a lower-frequency regimen/treatment (i.e., IM IFNβ-1a).
- A total of 97.4% of patients were adherent to treatment during the study and adherence remained relatively stable throughout the study period; however, this value likely overestimates real-world adherence because a large proportion of patients withdrew early, including 16 (8.9%) who withdrew because of poor adherence.
- Overall, 22.1% of patients experienced a relapse episode and the estimated probability of remaining relapse-free after 2 years was 78%.
- In the context of prior research, the results of this study suggest that the weekly administration schedule of IM IFNβ-1a can encourage high levels of adherence in patients who were previously not adherent to high-frequency injectable therapies.
- This study was limited by a high dropout rate (52.5%), which may be explained by the inclusion and withdrawal criteria, as well as by the availability of alternative therapies approved during the course of the study.
- Additional studies are needed to evaluate adherence to IM IFNβ-1a treatment and its relationship to relapse and progression of the disease in larger, more representative populations.

Author contributions

M Peresson and L Prosperini: conception, design and coordination of the study and acquisition and interpretation of data. S Cottone, VB Morra, G Salemi, A Gallo and P Valentino: study conduct and acquisition and interpretation of data. All authors discussed the results and provided critical revisions to the article.

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Ethical conduct of research

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol was approved by local ethics committees. Informed consent was obtained from all participants included in the study.

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