








Interferon-Beta-Induced Headache in Patients with Multiple Sclerosis: Frequency and Characterization

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Background: Studies have shown that interferon-beta (IFN- β) treatment is associated with headaches in patients with multiple sclerosis (MS). Headaches can affect quality of life and overall function of patients with MS. We examined the frequency, relationships, patterns, and characteristics of headaches in response to IFN- β in patients with relapsing-remitting multiple sclerosis (RRMS).

Patients and Methods: This study was a prospective, longitudinal analysis with 1-year follow-up. The study comprised 796 patients with RRMS treated with IFN- β (mean age 30.84 ± 8.98 years) at 5 tertiary referral center outpatient clinics in Egypt between January 2015 and December 2017. Headaches were diagnosed according to the International Classification of Headache Disorders ICHD-3 (beta version), and data were collected through an interviewer-administered Arabic-language-validated questionnaire with an addendum specifically designed to investigate the temporal relationship between commencement of interferon treatment, and headache onset and characteristics.

Results: Two hundred seventy-six patients had pre-existing headaches, and 356 experienced de novo headaches. Of 122 patients who experienced headaches before IFN- β treatment, 55 reported headaches that worsened following onset of IFN- β treatment. In patients with post-IFN- β headaches, 329 had headaches that persisted for >3 months, 51 had chronic headaches, and 278 had episodic headaches, and 216 of these patients required preventive therapies. Univariate analysis showed a >6 - and an approximately 5-fold increased risk of headache among those treated with intramuscular (IM) INF- β -1a (OR 6.51; 95% CI: 3.73–10.01; P-value <0.0001) and 44 μ g of SC INF- β -1a (OR 5.44; 95% CI: 3.15–9.37; P-value <0.0001), respectively, compared with that in patients who received 22 μ g of SC INF- β -1a.

Conclusion: Interferon- β therapy aggravated pre-existing headaches and caused primary headaches in patients with MS. Headache risk was greater following treatment with IM INF- β -1a and 44 μ g SC INF- β -1a.

Keywords: headache, interferon-beta, multiple sclerosis

Introduction

Interferon-beta (IFN- β) is recommended as a first-line disease-modifying treatment (DMT) for relapsing-remitting multiple sclerosis (RRMS) in over 90 countries.¹ Therapeutic options for MS have expanded, but clinical trials have generated a wealth of data on the long-term efficacy and safety of IFN- β for treatment of patients with MS (PwMS).^{2,3} Formulary restrictions by insurance systems, particularly in low- and middle-income countries, may result in exclusion of expensive drugs in favor of relatively less expensive options. In the largest Egyptian registry published in 2017, more than 50% of patients were treated with IFN- β .⁴

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The most frequently reported adverse effects associated with IFN- β treatment worldwide are flu-like symptoms, injection site reactions, fatigue, and transient laboratory abnormalities.^{5,6} Although the original pivotal trials did not systemically investigate headache as a reported side effect of IFN- β -treatment,^{7–11} a significant relative risk for headaches with different types of IFN (beta 1b and 1a) treatments has been reported.¹² In addition, previous studies showed a relationship between headaches and IFN- β , but without precise classification or characterization of headache type.^{13–16}

The purpose of this study was to determine the frequency and characteristics of headaches in PwMS treated with IFN- β , and to classify common headache types experienced by these patients according to the International Headache Society (IHS) criteria.¹⁷

Methods

Study Design and Participant Characteristics

All treatment-naïve patients with RRMS who started IFN- β while attending the outpatient clinics of 5 tertiary referral centers in Cairo, Egypt in the period from November 2014 to December 2017 were invited to participate in this prospective, longitudinal study. A total of 977 consecutive patients with RRMS diagnosed according to McDonald 2010 criteria¹⁸ were screened for eligibility criteria and for compliance with 1-year follow-up visits. At the end of the study observation period, data from 796 patients were analyzed, of whom 283 were men and 513 were women, with ages ranging from 18 to 49 (30.84 ± 8.98) years. Patients were evaluated for the presence of headaches (before or after initiation of IFN- β) using a binary question. Subjects who responded “no” were asked to respond to the demographic and general medical questions only. Patients with reported headaches were asked to recall their headache characteristics and patterns using an interviewer-administered Arabic-language-structured validated questionnaire with an excellent intraclass correlation coefficient (ICC) of 0.903 (95% CI: 0.875–0.925) and overall Cronbach’s coefficient of 0.775 (95% CI: 0.682–0.837).¹⁹ An addendum was added to this validated questionnaire to determine the temporal relationship between commencement of interferon treatment and headache onset and characteristics. Patients were asked whether their headaches were pre-existing or appeared de novo, and had worsened or improved (in terms of frequency and intensity). In

addition, the patients were asked to describe the outcomes of their headaches. Patients were excluded if they had secondary headaches (headache attributed to head and/or neck trauma, cranial and/or cervical vascular disorders, other non-vascular intracranial disorders, infections, headache or facial pain attributed to disorders of the cranium, facial or cervical structure, disorders of homeostasis, or metabolic diseases or psychiatric disorders).

Patient Allocation and Follow-Up Protocol

The patients were divided into 3 groups, including patients with pre-existing headaches, patients with de novo headaches, and patients without headaches (Figure 1). All patients who attended our centers prior to receiving IFN- β treatment were followed-up monthly to monitor treatment efficacy. The first interview regarding headaches was scheduled prior starting IFN- β treatment.

To obtain the most reliable data, patients with headaches were provided with headache diary recordings in which they were asked to map out the frequency, duration, and severity of headaches, the temporal relationship between headaches and each IFN- β injection, other triggers and response to treatments for headaches.

Patients with headaches who experienced relief from preventive therapies with sustained benefits were advised to continue these therapies. Patients who required initiation or alteration of prophylactic treatments for headaches were managed per the KAHDU (Kasr Al-Ainy Headache Disorders Unit) guidelines according to Bendtsen et al²⁰ and patient preference. Patients were also informed that flu-like symptoms could be managed using analgesics, if necessary.

Case Definitions and Diagnostic Criteria

Diagnoses of previous and present headaches were made according to the diagnostic criteria of the International Classification of Headache Disorders ICHD-3 (beta version).¹⁷ “De novo” headache was defined as a new headache occurring for the first time in close temporal relation to either the onset of MS and/or within 4 weeks of commencement of IFN- β treatment. The latter was coded as secondary headache attributed to IFN- β exposure. “Worsening pre-existing” headache was defined as a significant increase (>50%) in mean frequency or duration of headaches per month, and/or an increase in intensity of more than 3/10 on the Visual Analogue Scale (VAS).¹⁵ “De novo” and “worsening pre-existing” headaches with a close temporal relationship

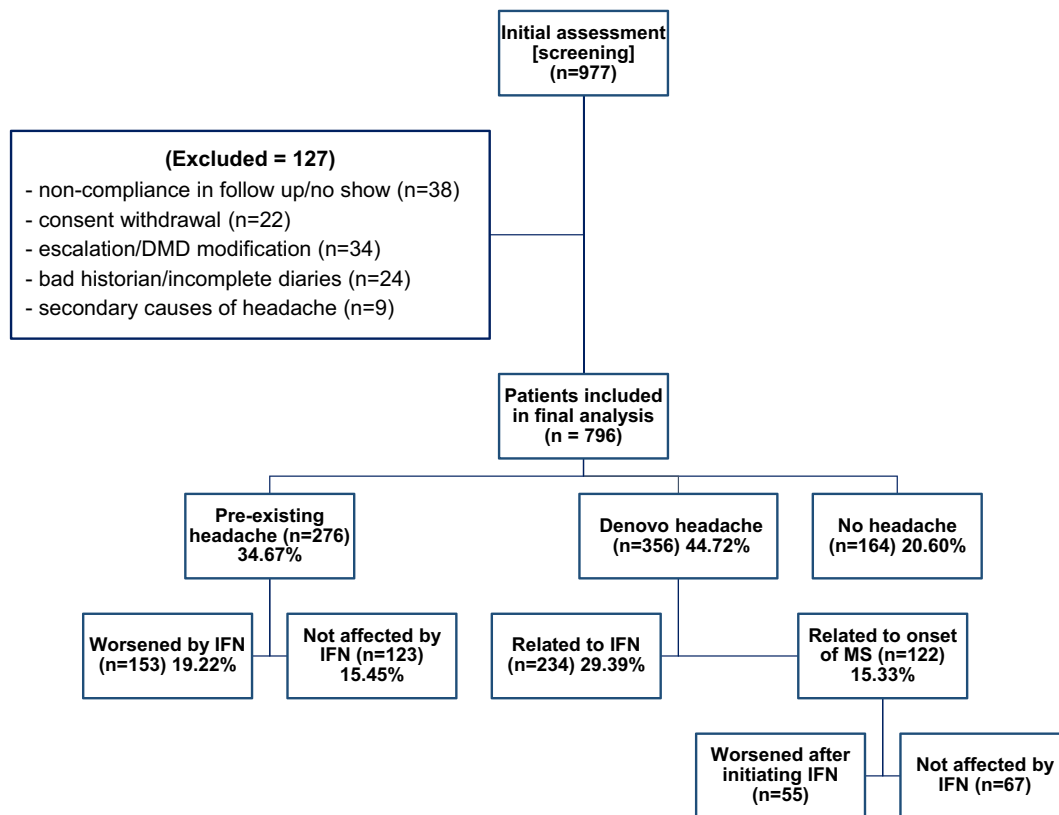


Figure 1 Patient enrollment and disposition.

between headache onset and commencement of IFN- β were labelled as “post-IFN- β headaches.”

Ethical Clearance

This study was designed according to the recommendations of IHS and was approved by the Neurology Department Review Board of Cairo University. A written informed consent was obtained from each study participant for use of data and for publication prior to administration of questionnaires. All participants had the choice to refuse participation in the study.

Statistics

All statistical analyses were performed using IBM SPSS statistics software (Version 21.0 for Windows, SPSS Inc., NY, USA). The Shapiro–Wilk test was used to determine the normality of distributions. Baseline characteristics of the cohorts were summarized as frequencies (%) or medians with interquartile ranges (IQR) for non-normally distributed parameters, or as means \pm SD for normally distributed variables. Analysis of variance (ANOVA) was used to determine differences in demographic and clinical characteristics among the IFN types. Comparison between the two

independent groups (patients with post-IFN- β headaches, and those without post-IFN- β headaches) was performed using Student’s *t*-test. Univariate logistic regression analyses were conducted to calculate the odds ratio (OR) and 95% confidence intervals (CI) of the impacts of different IFN- β preparations on headache occurrence.

Results

Clinical Characteristics

The mean age of the patients who completed the study period (n=796) was 30.84 ± 8.98 years (range: 18–49 years) with a female:male ratio of 1.81:1. Among these patients, 223 (28.02%) were treated with IM-IFN- β -1a (Avonex[®]), 89 (11.18%) were treated with SC-IFN- β -1a (Rebif[®], 22 μ g), 259 (32.53%) were treated with SC-IFN- β -1a (Rebif[®], 44 μ g), and 225 (28.27%) were treated with IFN- β -1b (Betaferon[®]). The socio-demographic and major clinical characteristics of the participants did not significantly differ among the treatment groups (Table 1).

Headache History

Pre-existing headache was reported by 276 patients (34.67%), among whom 153 (55.43%) had worsening

Table 1 Demographic and Clinical Data of Patient in Different Treatment Groups

		Total	IFN β 1-a IM (n=223, 28.02%)	IFN β 1-a SC 22 μ g (n=89, 11.18%)	IFN β 1-a SC 44 μ g (n=259, 32.53%)	IFN β 1-b SC (n=225, 28.27%)	P value
Age at disease onset (range, mean \pm SD)		16–47.5, 29.06 \pm 8.92	16–47.5, 29.23 \pm 8.90	16–47.5, 29.21 \pm 9.69	16–47.5, 29.21 \pm 8.99	16–47.5, 28.66 \pm 8.58	0.890
Sex (F)		513 (64.45%)	140 (62.78%)	66 (74.16%)	170 (65.64%)	137 (60.89%)	0.149
Occupation (n,%)	Professional	103 (12.94%)	29 (13.01%)	15 (16.85%)	38 (14.67%)	21 (9.33%)	0.171
	Managerial and technical	85 (10.68%)	23 (10.31%)	9 (10.11%)	27 (10.42%)	26 (11.56%)	
	Skilled (manual and non-manual)	138 (17.33%)	39 (17.49%)	16 (17.98%)	43 (16.60%)	40 (17.78%)	
	Unskilled	172 (21.61%)	47 (21.08%)	18 (20.22%)	53 (20.46%)	54 (24%)	
	Student	124 (15.58%)	37 (16.59%)	14 (15.73%)	42 (16.21%)	31 (13.78%)	
	Unemployed	174 (21.86%)	48 (21.52%)	17 (19.10%)	56 (21.62%)	53 (23.56%)	
Marriage (n,%)	Yes	424 (53.27%)	121	43	129	131	0.31
	No	372 (46.73%)	102	46	130	94	
Contraceptive pills/injection or HRT (n,%) (n=513)		67/513 (13.06%)	18/140 (12.86%)	8/66 (12.12%)	22/170 (12.94%)	19/137 (13.87%)	0.482
Disease duration at end of data collection (months) (Range, mean \pm SD)		15–48 (21.36 \pm 7.21)	15–48 (21.44 \pm 7.08)	15–48 (21.57 \pm 8.05)	15–48 (21.41 \pm 6.89)	15–48 (21.23 \pm 7.22)	0.982
Initial EDSS (Range, median, IQR)		0.5–5.5, 2.5 (2–4)	0.5–5.5, 3 (2–4)	0.5–5.5, 2.5, (2–3.5)	0.5–5.5, 3 (2.5–4)	0.5–5.5, 2.5 (2–4)	0.288
Time from disease onset to IFN- β commencement (months)		4–36 (9.39 \pm 7.22)	4–36 (9.44 \pm 7.08)	4–36 (9.57 \pm 7.92)	4–36 (9.41 \pm 6.98)	4–36 (9.24 \pm 7.22)	0.974

Abbreviations: EDSS, expanded disability status scale; HRT, hormone replacement therapy; IM, intramuscular; IFN- β , interferon-beta; SC, subcutaneous; SD, Standard Deviation; IQR, interquartile range.

headache patterns within 4 weeks of initiation of IFN- β . Worsening headache included increased frequency in 85 patients (55.56%), increased intensity in 91 patients (59.48%), and increased duration in 53 patients (34.64%).

De novo headaches after onset of multiple sclerosis occurred in 356 patients (44.72%), among whom 122 (34.27%) suffered from headaches prior to IFN- β treatment and 234 (65.73%) experienced onset of headache within 4 weeks of treatment initiation. Among patients who experienced headache prior to IFN- β treatment (n=122), 55 (45.08%) reported worsening of headaches after initiation of IFN- β treatment. This worsening included increased duration (n=39) or intensity (n=26), and each of these patients experienced “tension-type characteristics”.

Pattern Identification

Post-interferon headaches included “worsened pre-existing” (n=153), “de novo headaches related to IFN- β ” (n=234), and “de novo headaches related to MS onset that worsened after commencement of IFN- β ” (n=55) (442 patients total; 55.53%). The remaining patients (n=354) were categorized as “without post-IFN- β headaches.” There were no statistically significant differences between the groups in terms of age, gender, disease duration, type of MS, or family history of headaches (Table 2).

Two distinct headache categories were recognized. Headaches with remission (or regression to pre-IFN status) within \leq 3 months were labelled as “interim headache” (n=113). Eighty-two of these patients had migraine headaches, and 6 had unclassified headaches. Headaches that

Table 2 Headache Patterns of Patient in Different Treatment Groups

			IFNβ1-a IM (n=223, 28.02%)	IFNβ1-a SC 22 μg (n=89, 11.18%)	IFNβ1-a SC 44 μg (n=259, 32.53%)	IFNβ1-b SC (n=225, 28.27%)	Total (n=796)
Pre-existing headache not worsened by IFN-β	Number		13	11	25	74	123 (15.45%)
	Characters	Migraine	9	7	17	51	84
		Tension type	3	4	6	20	33
		Others	1	0	2	3	6
Pre-existing headache worsened by IFN-β	Number		55	14	61	23	153 (19.22%)
	Characters	Migraine	17	5	19	12	53
		Tension type	36	8	40	9	93
		Others/ unclassified	2	1	2	2	7
Denovo headache not related to IFN-β			18	18	31	55	122 (15.33%)
Denovo headache related to IFN-β commencement	Number		97	8	105	24	234 (29.39%)
	Character	Migraine	21/97	1/8	18/105	6/24	46/234
		Tension	74/97	7/8	83/105	18/24	182/234
		Others/ unclassified	2/97	0	4/105	0	6/234
No headache (n=165)			40	38	37	49	164 (20.60%)

Abbreviations: IM, intramuscular; IFN-β, interferon-beta; SC, subcutaneous.

persisted (or worsened) for >3 months (n=329) were categorized as “persistent headaches,” which were further subdivided into chronic or intermittent (episodic) patterns based on number of headache days/month (Figure 2). Of patients with “persistent headaches” (n=329), 216 (65.65%) required prophylactic headache medications. Medications administered included topiramate (n=56), valproate (n=43), BTX-A (n=9), venlafaxine (n=39), amitriptyline (n=62), mirtazapine (n=21), propranolol (n=49), and selective serotonin reuptake inhibitors (SSRIs) (n=91). Twenty-four patients were diagnosed with Medication overuse headache (MOH) (7.29%). These patients underwent an outpatient regimen for detox and management.

Impact of different IFN-β preparations on headache. Logistic regression was performed using SC-IFNβ-1a 22 μg as reference group. Univariate analysis showed more than 6-fold increased risk of headache for patients treated with IM-IFN-β-1a (OR 6.51; 95% CI 3.73–10.01; P-value <0.0001) and about 5-fold increased risk of headache

among those treated with SC-IFNβ-1a 44μg (OR 5.44; 95% CI 3.15–9.37; P-value <0.0001) (Figure 3). ORs adjusted by sex and age were similar to those obtained by univariate analysis.

Discussion

In this prospective study, treatment with IFN-β significantly worsened pre-existing headaches and headaches that occurred concurrently with onset of MS in more than half of patients with histories of headaches that preceded commencement of IFN-β treatment. Treatment with IFN-β also triggered de novo headaches in about one-third of those who did not report having headaches prior to treatment. These three categories of patients accounted for more than half of our cohort (n=442/796, 55.53%). According to ICHD-3,¹⁷ these types were coded as “headache attributed to use of or exposure to a substance (code 8.1).” The presence of a causative substance and a close temporal relationship between onset of headache and onset of the presumed causative disorder was sufficient to establish

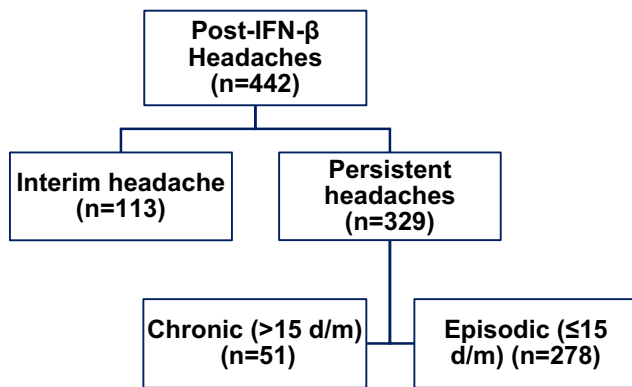


Figure 2 Post-interferon headache patterns.

causation in cases where the symptoms were not better explained by another ICHD-3 diagnosis.

In our study, 29.39% (234/796) of patients developed de novo headaches within 4 weeks of initiation of IFN-β treatment. Interferon-beta pivotal trials⁷⁻¹¹ and post-market evidence^{21,22} underestimated the prevalence of headaches as

an adverse effect. In these studies, headaches were either not included among adverse events,^{7,8} or may have been considered flu-like symptoms.^{13,15,22} However, headache is one of the most common adverse events associated with IFN-β treatment,¹⁴⁻¹⁶ with a reported prevalence from 13.1% to 58% (Table 3). Smith et al²¹ reported a more precise definition of headache incidence rates (IRs) per 100 person-years. This calculation incorporated headaches that occurred after initiation of therapy that were not present in the 90-day pre-index period, which resulted in a rate of 6.94 per 100 person-years (95% CI = 6.52-7.38). Moreover, headaches associated with IFN-β treatment were a significant reason for treatment withdrawal in a previous study.⁷ Furthermore, headaches were included as a flu-like symptom in other trials,²²⁻²⁴ but these studies did not specify which flu-like symptoms were responsible for withdrawal.

Previous studies have rarely addressed worsening (aggravation) of pre-existing headaches following commencement of IFN-β treatment.^{13,15,16} La Mantia et al¹³

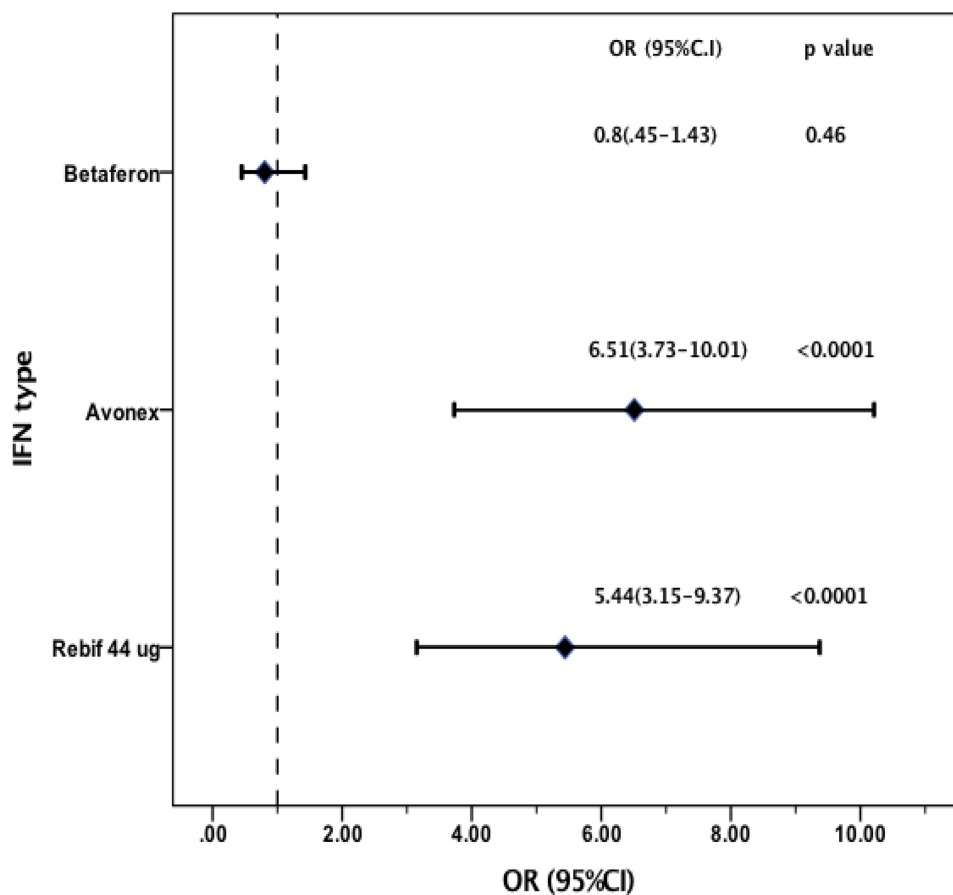


Figure 3 Impact of different IFN-β preparations on headache occurrence. **Abbreviations:** OR, odds ratio; CI, 95% confidence interval.

Table 3 Comparative Analysis of Multiple Sclerosis Studies Potentially Addressing Headache in IFN- β Receivers

Study	Type of IFN- β	No of Patients on IFN- β	Study Duration	Study Design and IFN- β Type	Headache Frequency
OWIMS 1999 ¹²	SC-IFN- β -1a 22 μ g QW	95	48 weeks	Randomized, double-blind study of IFN- β -1a 22 μ g, 44 μ g, or placebo administered once weekly SC injection.	46 (48%)
	SC-IFN- β -1a 44 μ g QW	98	48 weeks		49 (50%)
EVIDENCE 2002 ²³	IFN- β -1a 44 μ g SC t.i.w	339	24 weeks	Randomized trial compared IFN- β -1a 44 μ g SC t.i.w, and IFN- β -1a 30 μ g IM QW	143 (42%)
	IFN- β -1a 30 μ g QW	337			165 (49%)
Herndon et al ²⁵	IM IFN- β -1a QW	279	8 years	Open-label extension study of the phase III trial of IM IFN- β -1a	58%
BENEFIT ²⁶	250 μ g IFN- β -1b	292	24 months	Randomized, double-blind trial of IFN- β -1b 250 μ g SC EOD vs placebo	78 (26.7%)
REGARD ²⁷	IFN- β -1a 44 μ g SC t.i.w	381	96 weeks	Open label, randomized trial of 44 μ g SC t.i.w IFN- β -1a vs daily SC 20 mg GA.	74 (19.4%)
BEYOND ²⁸	500 μ g IFN- β -1b	887	Filling of the triangle design (2–3.5 years)	Randomized trial assigned 2:2:1 to receive one of two doses of IFN- β -1b (250 μ g or 500 μ g) SC, EOD vs daily SC 20 mg GA	293 (33%)
	250 μ g IFN- β -1b	888			280 (32%)
RNF ²⁴	IFN- β -1a (RNF) 44 μ g SC t.i.w	260	96 weeks	Single-arm, Phase IIIb, open-label study to evaluate RNF, 44 μ g SC t.i.w.	98 (37.7%)
16-year LTF ²⁹	IFN- β -1b	69 (within past 2 years)	LTF visit (Past 2 years)	Multi-center, observational study through a structured questionnaire	19 (27.5%)
ADVANCE ³⁰	Peginterferon β -1a 125 μ g every 2 weeks	512	2 years	Randomized, double-blind, placebo-controlled, phase III study to receive placebo or SC peg-IFN- β -1a 125 μ g every 2 weeks or every 4 weeks	224 (44%)
	Peginterferon β -1a 125 μ g every 4 weeks	500			204 (41%)
Smith et al ²¹	IFN- β -1a 44 μ g SC t.i.w	8,107	6 years (eligible subjects)	Observational, retrospective Post-marketing study of IFN- β -1a SC tiw	IRs/100 person-years 6.94 (6.52–7.38)
REFLEXION ³¹	SC IFN- β -1a tiw	99	60 months	Extension trial of the phase III REFLEX study ³²	16(16.2%)
	SC IFN- β -1a QW	117			19(16.2%)
	Delayed treatment	84			11(13.1%)

Abbreviations: ADVANCE, pegylated interferon β -1a for relapsing-remitting multiple sclerosis; BENEFIT, Betaferon[®]/Betaseron[®] in Newly Emerging Multiple Sclerosis for Initial Treatment; BEYOND, Betaferon[®]/Betaseron[®] Efficacy Yielding Outcomes of a New Dose; EOD, every other day; EVIDENCE, Evidence of Interferon Dose-Response: European North American Comparative Efficacy; GA, Glatiramer acetate; IM, intramuscular; IFN- β , interferon-beta; IM, intramuscular; IRs, incidence rates; LTF, long term follow-up; OWIMS, The Once Weekly Interferon for MS Study Group; QW, once a week; REFLEX, REbif FLEXible dosing in early MS; REFLEXION, REbif FLEXible dosing in early MS extension; REGARD, the REbif vs Glatiramer Acetate in Relapsing MS Disease; RNF, Rebif[®] New Formulation; SC, subcutaneous; t.i.w, three times a week.

reported changes in pre-existing headache characteristics following initiation of IFN- β treatment that led to changes in headache diagnoses from tension-type headaches to migraines without aura. Previous studies have also evaluated the underlying mechanisms of headache aggravation, and attributed this phenomenon to neuronal hyperexcitability induced by IFN- β , or the effects of inflammatory mediators.^{13,33,34}

In the current study, post-IFN- β headaches were pressing in character in 330/442 (~75%) patients, and persistent for the one-year study duration in 329/442

(~75%) patients. However, migraine characteristics were detected in only 99 patients (22.4%), most whom (82/99) experienced headache improvement after 3 months following initiation of IFN- β treatment. In contrast, the primary headaches in the study by La Mantia et al¹³ were migraine without aura, migraine not fulfilling all criteria, and tension-type headache without significant differences. This study included 150 patients, interferons were compared with other DMTs, and patients underwent a semi-structured interview to retrospectively recall their headache history. D'Amico et al³⁵

reported that about half of patients with de novo headaches following commencement of IFN- β treatment developed migraines, and the other half developed tension-type headaches (TTH). However, the mechanisms underlying tension-type headaches remain unclear, and the exact relationship between IFN- β and development of headaches has been a topic of debate. Another point of contention is whether there is a clear-cut separation of migraine as a vascular headache and TTH as a consequence of muscle contraction.³⁶ It is possible that TTH and migraines share a common pathophysiology.³⁷ Furthermore, the relationship among IFN- β , depression, and development of TTH has been demonstrated. However, in our study, about 85% of patients had episodic headaches (278/329) rather than the chronic pattern that is classically associated with higher levels of anxiety and depression.^{38,39} Few studies have directly addressed stress levels and TTH in MS.⁴⁰

In our study, higher doses of SC-IFN β -1a and IM-IFN- β -1a were more frequently associated with headaches than either SC-IFN β -1b or lower doses of SC-IFN β -1a, which agreed with findings in a study performed by Patti et al.¹⁶ Differences in the effects of IFNs on cytokine profiles (especially IL-4 and IL-10) could partially explain some of the differences in cephalalgia spectrum and headache profiles induced by the various forms of IFN.^{1,4,16} This study was the first to evaluate the relationship among various IFN- β preparations and headache occurrence, and represents the largest MS study aimed at evaluating the characteristics and patterns of post-IFN- β treatment and headache. However, our study was limited by lack of a control group comprised untreated patients with MS, and lack of other DMTs for comparison with IFN- β . Despite these limitations, we achieved our primary goal of characterization and identification of features of post-IFN- β headaches.

In conclusion, the current study showed that aggravation of pre-existing headaches, or onset of de novo primary headaches, should be considered common IFN- β adverse effects, as headaches can significantly affect quality of life and function of PwMS. Prospective monitoring of IFN- β -related headaches might facilitate development of appropriate treatment strategies to enhance IFN- β therapy adherence.

Disclosure

The authors report no conflicts of interest in this work.

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