Skin Complications Associated with Interferon-β Treatment in Patients with Multiple Sclerosis, Tehran in 2021 - 2

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Abstract

Background: Interferons are generally prescribed in multiple sclerosis (MS) treatment. This study was done to investigate the severity and type of skin side effects of interferon beta (IFNβ) in patients with MS.

Methods: This was a cross-sectional descriptive study on the patients with MS taking IFNβ medication referred to Baqiyatullah Hospital in 2021 - 22. The sample size was 322, and the sampling method was census. Data were documented in a checklist, and analyses were performed by SPSS software version 24 at a significance level of 0.05.

Result: About 46% of patients had no skin complications. The erythema at the injection site was the commonest skin complication (45.2%). The hair loss severity after treatment had a statistically significant increase than before ($P < 0.001$). If the severity of the patient's current disease was moderate, the estimated odds of developing the erythema compared to no complication was 2.60 times higher than the patient with mild current severity of the disease ($P = 0.003$), and if the severity of the current disease was moderate, the estimated odds of developing erythema + eczema than no complications was 7.70 times higher than the patient with the current severity of the mild disease ($P = 0.001$).

Conclusions: The most important skin complications MS patients experience following the use of IFNβ are injection site skin reactions and erythema. Hair loss increased in MS patients after IFNβ treatment. Prospective studies on the procedure of hair loss after treatment with IFNβ in MS patients are recommended.

Keywords: Multiple Sclerosis, Interferon-beta, Skin, Complication

1. Background

Multiple sclerosis (MS) is one of the most common causes of neurological disability in young adults, which is characterized by inflammatory demyelination of the central nervous system (CNS) by activated immune cells in the CNS and causes inflammation, neurodegeneration, and tissue damage (1).

A total of 2.8 million people are estimated to live with MS worldwide (35.9 per 100,000 population). It is three times more common in females, and the most prevalent affected regions are in northern Europe, North America, Australia, and New Zealand (2).

MS symptoms are usually unpredictable and unclear. Because the disease can affect any area of the CNS, it can cause almost any neurological symptom. Common presentations of MS are unilateral optic neuritis characterized by gradual onset monocular visual loss, pain on moving the eye, and altered color vision. The partial myelitis in the spinal cord that presents with sensory and motor symptoms of the limbs and brainstem syndromes can cause diplopia, facial sensory loss, vertigo, and dysarthria (1).

Disease-modifying drugs (DMDs) may delay the progression of disability over time; however, there is no known cure for the disease. Interferons are a class of DMDs,

and many patients benefit from interferon therapy and experience reduced relapse rates and delayed disability (3). A large body of evidence supports the long-term efficacy and safety of interferons in reducing the relapse rate, slowing disability worsening, and decreasing the number of CNS lesions (4). The mechanism of action of interferon beta (IFNβ) in MS is multifactorial and incompletely understood. IFNβ can increase the expression of anti-inflammatory cytokines (e.g., interleukin [IL]-4, IL-5, IL-10, IL-13, IL-27, and transforming growth factor beta) and decrease the expression of proinflammatory cytokines (e.g., IL-17, IFNγ, and tumor necrosis factor-alpha), which helps stabilize dysregulated CNS inflammation (5).

Interferons are generally safe with good medication compliance (6), which makes them the most commonly used drug in MS treatment (7). Relatively frequent side effects include flu-like symptoms, transient laboratory abnormalities, menstrual disorders, and increased spasticity (8). The most common cutaneous adverse events in MS patients using interferons are local injection site reactions, such as erythema, stiffness, swelling, and pain (9). Moreover, persistent and systemic local skin effects may also occur (10). More severe or persistent side effects, such as lipoatrophy, skin necrosis, and ulceration (11), and inflammatory skin diseases, such as psoriasis and vasculitis, may also occur (12). More severe cutaneous reactions, such as deep wounds, skin infections, or necrosis, are the least known skin complications (1 - 3%) (13). Although interferons have increased the overall quality of life in MS patients, studies have shown that mental health has not increased, which could be related to the side effects of the drug (14).

2. Objectives

Due to the discrepancies between published studies and the lack of studies in this field, this study was done to investigate the severity and type of skin side effects of beta interferon in patients with MS.

3. Methods

This cross-sectional descriptive study was conducted on the patients suffering from MS who were referred to Baqiyatallah Hospital between March 2021 and March 2022 in Tehran and entered the study after completing the informed consent form. The sample size was 322 using the prevalence rate of 30% (10), alpha error of 5%, and beta of 20%. The sampling method was a census, and all the

patients who met the study inclusion criteria and signed the consent form were included.

The inclusion criteria were (A) MS diagnosis, (B) the use of IFNβ for at least one year, and (C) the age between 15 and 65 years. The exclusion criteria were the lack of consent to participate in the study and the patient or the physician changing and stopping the drug. Demographic information of people, including age, gender, marital status, education (illiterate, less than a diploma, diploma, and academic), as well as information, including current disease severity (mild, moderate, and severe), hair loss severity before and after the treatment (mild, moderate, and severe), skin complications (erythema, erythema+eczema, and eczema/hives/skin rash/others), medications (none, contraception, beta-blockers, anti-depression, combination, etc.), anemia history, thyroid problem/hormonal disorders, comorbidities (none and cardiovascular disease (CVD)/debates mellitus/hypertension (HTN)/etc.) and type of treatment (Rabif/Resin/Actoserc/Avonex and Betaferon/Betaseron/Actoferon treatment), and known cutaneous side effects of interferon mentioned in the dermatology text of Bolognia, were recorded (15).

First, a neurologist selected the patients according to the inclusion criteria. All confirmed MS patients receiving interferon treatment for at least one year were included. The drugs included rabif, resin, actoserc, avonex, betaferon, betaseron, and actoferon. All the drugs have been used as the first-line treatment, and Betaserone, Betaferon, and Aoctoferon were injected subcutaneously in patients with mild disease or in the early stages. Rabif and resin were used every other day and subcutaneously. Actoserc and Avonex were used intramuscularly weekly in patients with mild attacks and low brain plaques without spinal cord involvement. The necessary explanations about the study were given to the patients. The dermatologist visited and examined the patients. She asked about the complications listed in the checklist, examined the patient's skin lesions, followed the checklist, and assessed the hair loss by asking and examining using the hair pull test. Patients were also treated in case of complications. All patients' information remained confidential. This study received the code of ethics from the ethics committee of Baqiyatullah Hospital.

Statistical analysis: Quantitative normal variables were reported as mean ± standard deviation (SD). Categorical variables were also expressed as frequency (percent). In an attempt to deal with the multiple collinearities, pairwise independence of variables was evaluated. The

independence of categorical variables was assessed using an independent chi-square test (if test-related defaults are established) or Fisher's exact test (if the chi-square test defaults are not established).

In order to compare quantitative variables with the levels of categorical variables with more than two levels, the one-way analysis of variance (ANOVA) or its non-parametric equivalent, the Kruskal-Wallis test, was used. Friedman's non-parametric test was also used to investigate differences between three or more dependent groups. This test is the non-parametric equivalent of one-way ANOVA with repeated measures. Multinomial logistic regression was used to investigate the effect of one or more independent variables on nominal variables. The effect of one or more independent variables on ordinal variables was investigated using ordinal logistic regression. Analyses were performed by SPSS software version 24 at a significance level of 0.05.

4. Results

A total of 328 eligible MS patients with a mean age of 35.1 + 11.3 years were included in this study, of whom 218 cases (66.5%) were female and 110 cases (33.5%) were male. The majority of patients were married (75.3%). About 46% of patients had no skin complications. No patient had serious or life-threatening skin complications. The erythema at the injection site was the commonest skin complication (45.2%), and other complications were eczema (4%) and urticaria (3.3%).

In order to study skin complications and the severity of hair loss after treatment, first, the homogeneity of underlying variables between the levels of hair loss status after treatment and skin complications were investigated. The gender was not related to the severity of hair loss (P = 0.704) and skin complications (P = 0. 868) after treatment. Also, education was independent of hair loss severity after treatment (P = 0.599) and skin complication (P = 0.072). In addition, the mean age of patients showed no significant effect on hair loss severity levels (P = 0.144) and skin complication levels (P = 0.544) after treatment. The marital status of patients was independent of hair loss severity (P = 0.287) and skin complications (P = 286.0). Therefore, the underlying variables were homogeneous between the levels of skin complications and the hair loss severity of the patients after treatment.

Anemia, thyroid /hormonal disorders, and CVD/DM/HTN/others were observed in 65%, 18%, and 17% of studied patients, respectively. The most common

disease was anemia in the studied population. It should be noted that the variables of suffering from anemia, thyroid problems/hormonal disorders, and CVD/DM/HTN/others were considered three separate variables, and a subject could suffer from all these diseases or two of them at the same time.

The most common medication used by the studied patients was beta-blockers; furthermore, 31.7% of patients received vitamin D regularly.

Friedman's non-parametric test showed a significant difference in hair loss severity (none, mild, moderate, and severe) before the onset of the disease, before the treatment, and after treatment (P < 0.001).

In other words, the disease onset or the treatment onset affected the hair loss severity. The mild hair loss, which was about 29 - 30% before the disease onset or before the treatment onset, reached a value of about 73% after treatment.

The disease severity at the diagnosis time was associated with the current disease severity (P < 0.001). Comorbidities (P < 0.001) or a history of thyroid /hormonal disorders (P < 0.001) were related to medication use. Anemia was related to co-morbidities (P = 0.029) and the current disease severity (P < 0.001). The facial acne history was related to anemia (P < 0.001) and comorbidities (P = 0.004). Anxiety and stress during the day were related to comorbidities (P = 0.015); vitamin D intake was not homogeneously distributed in any treatment type (P = 0.012). Therefore, the variables of treatment completion, the current disease severity, comorbidities, and treatment type were candidates to enter the regression model. Based on the clinical expert's opinion, to investigate the effect of these variables together, these four variables were entered into the model simultaneously.

As can be seen in Table 1, in the path of no hair loss to severe hair loss, only the current disease severity variable was effective in the hair loss status after the treatment (P = 0.001).

The estimated odds of hair loss status for an MS patient with the current moderate disease in the path of no hair loss to severe hair loss was 2.96 times higher than an MS patient with the current mild disease.

As can be noticed in Table 2, only the current disease severity variable was effective in skin complications after the treatment. If the severity of the patient's current disease was moderate, in the presence of other variables in the model, the estimated odds of developing the erythema than no complication was 2.60 times higher than in

Table 1. Effect of the Specified Independent Variables on Hair Loss Severity After Treatment Using Multinomial Logistic Regression with Ordinal Response

Independent Variables	No Hair Loss vs. Severe Hair Loss, OR (95% CI)	P-Value
Incomplete treatment vs. complete treatment	1.36 (0.68 - 2.70)	0.382
Suffering from CVD/DM/HTN/others vs. not suffering from thyroid disorders	1.96 (0.85 - 4.47)	0.112
Rabif/Resin/Actoserc/Avonex treatment vs. betaferon/betaseron/actoferon	0.83 (0.48 - 1.45)	0.518
Moderate current disease severity vs. mild severity	2.96 (1.56 - 5.61)	0.001 [a]

Abbreviation: OR, odds ratio.
[a] Significant at the $\alpha = 0.05$

Table 2. Effect of Specified Independent Variables on Skin Complications After Treatment Using the Multinomial Logistic Regression Model [a]

Independent Variables	Skin Complications				Eczema/Hives/Skin Rash/Other vs. No Complication, OR (95% CI)	P-Value
	Erythema vs. No Complication		Erythema + Eczema vs. No Complication			
	OR (95% CI)	P-Value	OR (95% CI)	P-Value		
Incomplete treatment vs. complete treatment	1.55 (0.80 - 3.01)	0.195	-	-	2.16 (0.26,17.83)	0.474
Suffering from CVD/DM/HTN/others vs. not suffering from thyroid disorders	0.60 (0.27 - 1.33)	0.207	0.46 (0.05 - 4.06)	0.485	0.65 (0.08 - 5.46)	0.691
Rabif/resin/actoserc/avonex treatment vs. betaferon/betaseron/actoferon	0.77 (0.45 - 1.31)	0.330	0.27 (0.05 - 1.34)	0.108	1.23 (0.33 - 4.53)	0.757
moderate current disease severity vs. mild severity	2.60 (1.40 - 4.58)	0.003 [b]	7.70 (2.22 - 26.78)	0.001 [b]	1.48 (0.29 - 7.55)	0.637

Abbreviation: OR, odds ratio.
[a] Due to the non-availability of data in this category, P-value is incalculable.
[b] Significant at the $\alpha = 0.05$.

patients with the current mild disease (P = 0.003).

In addition, if the severity of the current disease was moderate, in the presence of other variables in the model, the estimated odds of developing erythema+eczema than no complications was 7.70 times higher than in a patient with the current mild f disease (P = 0.001).

5. Discussion

Interferons are generally safe and play an important role as standard and first-line treatment for MS ([16], [17]). Frequent side effects include flu-like symptoms, transient laboratory abnormalities, menstrual disorders, and increased spasticity ([18]).

In the current study, the most common skin complications were erythema and eczema, with more skin complications reported in patients with subcutaneous interferon treatment. In a study by Balak et al., the prevalence of cutaneous adverse events was also higher for subcutaneous DMDs (75 – 82%) compared to intramuscular DMDs (41%) (P < 0.001). Erythema and lipoatrophy were the most common skin reactions observed in 156 (68%) and 45

(20%) patients, respectively ([10]). In 2015, Kolb-Maurer et al. revealed that the most common cutaneous adverse events in MS patients using interferons were local injection site skin reactions ([19]), which was consistent with the results of this study. Rommer and Zettl reported that the most important cutaneous side effects of IFNβ were lipoatrophy and the possibility of local injection site reactions ([20]). This was contrary to the results of a recent study, which indicated lipoatrophy as the most common implication ([21]). More severe skin reactions, such as deep ulcers, skin infections, or necrosis (1 - 3%), are rare ([12]). In the present study, no cases of necrosis and infection were observed. More severe skin reactions, such as deep ulcers and skin necrosis, were reported in 1 - 3% of cases ([22]). No cases of necrosis and infection were reported in our study. In this study, disease severity was the only effective variable in skin complications after the treatment.

Mild hair loss increased from 29 - 30% before treatment to 73% after treatment with interferon. Hair loss is not a symptom of MS, but it can be a side effect of various MS treatments ([23]). In vitro, studies have shown that IFNβ in the dermal papilla cells negatively regulates the growth of

outer root sheath cells of the hair and possibly can have a negative effect on hair growth.

In a study by Porwal et al., mild alopecia was reported in 4% of patients as a possible side effect within prescription instructions for IFNβ, but they did not report the level of hair loss before the treatment. Besides, at the injection site, alopecia areata has been reported as a complication (24). Various factors can cause hair loss, which was considered as a confounding factor. In this study, we observed increased hair loss after IFNβ consumption, which suggests the negative effect of IFNβ on hair growth. The rate of hair loss after interferon treatment should be investigated in future prospective studies to understand the effect of intervening factors.

Skin symptoms following the treatment of MS may reduce the degree of treatment compliance (25), which can disrupt the treatment process in patients. On the other hand, these adverse events can affect the quality of life of MS patients due to the long-term use of these drugs. Therefore, physicians' awareness and early diagnosis and treatment of the skin complications caused by interferon treatment can be helpful for MS patients.

The strength of this study was the patients' interest in the study topic, their cooperation with the researcher, and their satisfaction with the dermatologist visit. The limitation of the study was the multiplicity of drugs and the difficulty of interpreting the drugs separately. It is suggested to investigate drugs separately in subsequent studies.

5.1. Conclusions

The most important skin complications that MS patients experience following the use of IFNβ are injection site skin reactions and erythema. Hair loss increased in MS patients after IFNβ treatment. The complications were not associated with gender and demographic factors. Prospective studies on the procedure of hair loss after treatment with IFNβ in MS patients are recommended.

Footnotes

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