Iranian Journal of Pharmaceutical Sciences
Summer 2005: 1(3): 177-182
www.ijps.ir

Original Article

Side Effects of β-Interferon: A Comparative Study Among Avonex, Betaseron and Rebif

Masoud Etemadifar[a,*], Keyvan Basiri[a], Naser Tavakoli[b]

[a]*Department of Neurology, Al-zahra Hospital,*
[b]*Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran*

Abstract

The administration of β-interferon is a recognized treatment for multiple sclerosis. The frequency of side effects is an important factor in drug or product selection. In this study, the side effects of three available β-interferon products are compared in 122 multiple sclerosis patients who were treated with β-interferon products for at least three months and had the Expanded Disability Status Scale (EDSS) between 1 and 6. The frequencies of side effects were determined for each group and the collected information were compared in the three treated groups. Fever, chills, headache, malaise and asthenia were the most frequent observed complications. Necrosis at the injection site was seen only in Betaseron group. Somnolence was more frequent with the administration of Avonex. Gastro-intestinal disturbances were less frequent in patients treated with Rebif. Weight gain was more frequent in patients treated with Avonex, and seizure and migraine were observed only in this group.Urticaria and hypersensitivity skin reactions were less frequent with the administration of Avonex. Rebif may be a better choice for patients with gastro-intestinal disturbances, suicidal attempts and chronic fatigue syndrome. Avonex may be better tolerated in patients with a history of urticaria and hypersensitivity skin reactions, but it is less recommended for patients with a history of seizure, migraine and syncope. Betaseron may be a better choice in patients with a history of chest pain and hypertension.

Keywords: β-Interferon; Multiple Sclerosis; Side effects.
Received: January 12, 2005; *Accepted:* May 15, 2005

1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the brain and spinal cord. The T cell reaction against myelin basic protein (MBP) and proteolipid protein is the fundamental process in the formation of MS plaques.

β-Interferon is a specific drug that alters the natural history of the disease towards a more favorable outcome, and it is recommended by National Multiple Sclerosis Society (NMSS) for all of the patients with

*Corresponding author: Masoud Etemadifar, Department of Neurology, Al-Zahra Hospital, Sofe Avenue, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel (+98) 311-2678999, Fax (+98) 311- 6613492
E-mail: etemadifar@med.mui.ac.ir

clinically definite exacerbating disease [1]. β-Interferon is a recognized treatment for relapsing MS, and it may delay the onset of definite MS in patients with the first clinical demylinating episode [2].

Frequently reported side effects of β-interferon are flue like reactions, transient alteration of transaminases and increase in spasticity [3-5]. Local reaction at the injection site is another frequent complication [6]. Urticarial IgE-mediated reaction has also been reported [7, 8]. Focal neuropathy associated with cutaneous necrosis may occur at the injection site [9]. Necrotizing vasculopathic skin lesions, local erythematous reactions and fasciitis are also reported in drug recipients [10, 11]. Also, severe Raynaund's phenomenon, livedo-reticularis and digital necrosis have been reported [12]. Pneumonia may occur after injection of β-interferon [13]. Rhabdomyolysis and nephritic syndrome have also been reported in β-interferon recipients [14-16].

Arthritis is a potential side effect [17], and seizure has been reported in a 21 years old male patient after the administration of β-la-interferon [18]. Retinopathy and Type-1 diabetes mellitus are also among the reported complications [19, 20]. Autoimmune diseases including hypothyroidism, systemic lupus erythematous (SLE), and hemolytic anemia have been reported to be induced by the administration of β-interferon [21-23]. Other reported complications are acute delirium, delusions, depression, and suicidal ideation [24-26]. Capillary leak syndrome, anaphylactic shock, thrombotic thrombocytopenic purpura (TTP), insomnia, headaches, alopecia and mild anemia are among other reported side effects [2, 3].

In clinical practice, side effect is an important factor in drug selection; therefore, complications of three available β-interferon products are compared in this article.

2. Materials and methods

One hundred twenty two MS patients (32 male and 90 female) who were treated with β-interferon for at least 3 months (3-15 months, mean=7.3) were studied with cross sectional design (Table 1). Forty three patients were treated with Avonex (from Biogen Idec) and 35 and 44 patients were treated with Betaseron (from Berlex Laboratories) and Rebif (from Serono Inc.), respectively (Table 1).

Study populations were clinically definite MS patients (with history of at least two attacks and involvement of at least two neurological systems in physical examination) who were consulted in Noor hospital specialty clinic or in Isfahan MS society. At first clinically definite MS patients who were treated with β-interferon for at least three months or patients in whom administration of drug were resulted in serious side effects, severe enough to discontinue the drug, were evaluated. Clinical course and MRI findings were reviewed by a competent neurologist and Expanded Disability Status Scale (EDSS) was determined for each patient, separately. Only patients with clinically definite relapsing remitting MS and EDSS between 1 and 6 were enrolled in the study. Patients with EDSS below 1 or above 6, and patients who were treated for less than three months were excluded from the study. Avonex was administrated 80 mcg, i.m., once weekly; Betaseron 0.25 mg, s.c., every other day; and Rebif 4.4 mcg, s.c., every 60 hours. For evaluation of the side effects, a questionnaire was prepared and completed for each patient by the same neurologist. At last, the frequencies of the side effects were determined for each group, and the collected information was compared in the three treated groups.

3. Results

The administration of β-interferon induced

Table 1. Demographic characteristics of 122 patients included in the study.

	Male	Female	Total
Avonex	11	32	43
Betaseron	7	28	35
Rebif	14	30	44

serious side effects in 15 patients (6 with Avonex; 4 with Betaseron; 5 with Rebif) that resulted in discontinuation of the drug administration. In four patients, the administration of Avonex resulted in exacerbation of the disease and escalation of the EDSS; in one of them hospital admission and pulse therapy was needed for the control of the attack. In two patients, the administration of Avonex was followed by tonic clonic seizure. Betaseron was discontinued in four patients, in three of them because of the exacerbation of the disease and escalation of EDSS, and in the other one for induction of serious chills and fever that was intolerable for the patients. The administration of Rebif was discontinued in five patients as a result of drug-induced exacerbation of the disease activity (Table 2).

The most prevalent observed side effects are summarized in Table 3. Fever, chills, headache, malaise and asthenia were the most frequent observed complications, and were not statistically different in three groups. Flu-like reaction was observed in 44% and 40% of the patients who were treated with Avonex and Betaseron, respectively, but was less frequent with the administration of Rebif (27%). Ecchymosis at the injection site was observed frequently in all three groups, but the injection site necrosis was seen only in the Betaseron group. Myalgia, muscular weakness, arthralgia, lightheadedness, anxiety and restlessness were other frequent complications. Somnolence was observed in 14% of Avonex and Rebif groups but was twice more frequent with the Betaseron administration (28%).

Peripheral vasodilatation, palpitation, anorexia and sweating were other frequent complications with little difference in the three treated groups. Less frequent complications are depicted in Table 4. Suicidal attempts were observed in 5% and 3% of Avonex and Betaseron groups, respectively, but were not observed with the administration of Rebif. Syncope was more frequent with the Avonex administration (7%) than with the Betaseron or Rebif administration (3% and 2%, respectively). Hypertension (>140/90 mmHg) occurred in 5% of the Avonex group and 2% of the Rebif group, but it was not observed with the administration of Betaseron. Also the frequency of chest pain was lower in patients treated with Betaseron (3%) than in patients treated with Avonex or Rebif (12% and 9%, respectively). In gastrointestinal system, the frequency of constipation was lower with the administration of Betaseron (6%) than with the administration of Avonex or Rebif (19% and 16%, respectively), but the frequency of nausea and vomiting was higher in patients treated with Betaseron (20%) than in patients treated with Avonex or Rebif (9% and 2%, respectively). Weight gain was more frequent in patients treated with Avonex (16%), and seizure (5%) and migraine (5%) were observed only with the administration of Avonex. In the genitourinary system, dysmenorrhea was observed in 21% and 10% of the patients treated with Betaseron and Rebif, respectively, but it was not observed

Table 2. Complications that resulted in discontinuation of β-interferon.

Side effect	Exacerbation of disease	Seizure	Severe chills & fever	Total
Avonex	4	2	-	6
Betaseron	3	-	1	4
Rebif	5	-	-	5

Table 3. The most frequent side effects of β-interferon.

Side effect	Avonex	Betaseron	Rebif
Inflammation of injection site	46%	48%	48%
Fever	46%	57%	61%
Chills	49%	48%	54%
Malaise	37%	26%	25%
Asthenia	46%	37%	39%
Injection site echymosis	25%	28%	25%
Injection site necrosis	-	14%	-
Headache	44%	40%	41%
Flue like reaction	44%	40%	27%
Myalgia	30%	23%	25%
Muscular weakness	35%	23%	27%
Arthralgia	19%	14%	11%
Light headedness	16%	23%	23%
Anxiety	16%	20%	16%
Restlessness	19%	20%	11%
Somnolence	14%	28%	14%
Peripheral vasodilatation	14%	11%	23%
Palpitation	12%	14%	18%
Anorexia	21%	20%	25%
Perspiration	16%	20%	25%

with Avonex. On the other hand, dysfunctional uterine bleeding was observed in 6% and 3% of the Avonex and Betaseron groups, respectively, but it was not observed with the administration of Rebif. The frequency of urticaria and hypersensitivity skin reaction in the patients treated with Avonex (2%) was well below the frequency of this complication in the other two groups (14% in each group). Other less frequently observed complications were, gastro-esophageal reflux, diarrhea, dyspnea, alopecia, nevus, conjunctivitis, mastalgia, urinary frequency, sinusitis, upper respiratory tract infection, herpes-zoster skin lesions, herpes-simplex skin lesions, hearing loss, visual loss, otitis media, urinary tract infection, ovarian cyst and vaginitis.

4. Discussion

The most frequently observed side effects (fever, chills, headache, malaise, asthenia, and flu-like reaction) were not statistically different in the three treated groups. Cutaneous necrosis at the site of β-interferon injection has been reported by Creange et al. [9]. In our patients, the injection site necrosis was seen only in the Betaseron group (p<0.002). Also, somnolence was more frequent in this group than in other groups but was not statistically significant (p<0.160). Suicidal attempts were not observed in patients treated with Rebif, and also nausea and vomiting were less frequent in this group (p<0.031). Dubisar et al. [18] reported a case of seizure after the administration of β-interferon-la. In our patients, seizure and migraine were observed only with the administration of Avonex. Urticaria has been reported with the administration of β-interferon-la-lb [7, 8]. However, in this study, hypersensitivity skin reaction and urticaria were less frequent in the patients treated with Avonex (p<0.127). Hypertension was not observed with the Betaseron administration and also the incidence of chest pain was lower in this group (p<0.338).

The results of this study indicate that: Rebif may be a better choice for the patients with GI disturbances, suicidal attempts and chronic fatigue syndrome.

Avonex may be better tolerated in patients with a history of dysmenorrheal, but is less

Table 4. Less frequent side effects of β-interferon.

Side effect	Avonex	Betaseron	Rebif
Generalized edema	5%	8%	4%
Suicidal attempts	5%	3%	-
Syncope	7%	3%	2%
HTN	5%	-	2%
Chest pain	12%	3%	9%
Diarrhea	-	3%	2%
Constipation	19%	6%	16%
Nausea & vomiting	9%	20%	2%
Abdominal pain	5%	6%	2%
GE reflux	9%	11%	7%
Weight gain	16%	8%	4%
Weight loss	5%	14%	11%
Seizure	5%	-	-
Migraine	5%	-	-
Dyspnea	14%	14%	11%
Alopecia	14%	8%	18%
Nevus	5%	11%	9%
Conjunctivitis	9%	17%	14%
Dysmenorrhea	-	21%	10%
Mastalgia	6%	3%	13%
DUB	6%	3%	-
Urinary frequency	12%	14%	7%
Urticaria	2%	14%	14%

recommended for patients with a history of seizure and migraine.

Betaseron may be a better choice in patients with a history of hypertention, but the injection site necrosis may limit its use.

In conclusion, although the administration of Avonex is more comfortable for the patients (once weekly), but Rebif and Betaseron may be better tolerated because of less frequent side effects.

References

[1] Miller JR. Multiple sclerosis. In: Rowland P, (editor). *Merritt's neurology*. 10th ed. Philadelphia: Lipincott Williams & Wilkins, 2000; p. 773-92.

[2] Aslam AK, Singh T. Aplastic anemia associated with interferon b-1a. *Am J Ther* 2002; 9: 522-3.

[3] Zivadinov R, Zorzon M, Tommasi MA, Nasuelli D, Bernardi M, Monti-Bragadin L, Cazzato G. A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-la. *J Neurol Sci* 2003; 216: 113-8.

[4] Montalban X, Duran I, Rio J, Saez-Torres I, Tintore M, Martinez- caceres EM. Can we predict flu-like symptoms in patients with multiple sclerosis treated with interferon-beta? *J Neurol* 2000; 247: 259-62.

[5] Lofits JM, Hauser P. The phenomenology and treatment of interferon-induced depression. *J Affect Disord* 2004; 82:175-90.

[6] Garcia-F-Villalta M, Dauden E, Sanchez J, Fraga J, Ramo C, Garcia- Diez A. Local reactions associated with subcataneus injections of beta-interferon. *Acta Derm Venereol* 2001; 81: 152.

[7] Brown DL, Login IS, Borish L, Powers PL. An urticarial IgE-mediated reaction to interferon beta-1b. *Neurology* 2001; 56: 1416-7.

[8] Mazzeo L, Ricciardi L, Fazio MC, Fogliani O, Fedele R, Ferlazzo E, Isola S. Severe urticaria due to recombinant interferon beta-1a. *Br J Dermatol* 2003; 148: 172.

[9] Creange A, Lefaucheur JP. Focal neuropathy associated with cutaneus necrosis at the site of interferon-beta injection for multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000; 68: 395.

[10] Casoni F, Merelli E, Bedin R, Martella A, Casinaro A, Bertolotto A. Necrotizing skin lesions and NABs development in a multiple sclerosis patient treated with IFNbeta 1b. *Mult Sclor* 2003; 9: 420-3.

[11] Cooper CL, Gerstein R, Kaita K. Fascitis complicating subcutaneous injection of interferon beta. *Can J Gastroenterol* 2000; 14: 81B- 2B.

[12] Cruz BA, Queiroz ED, Nunes SV, Cruz A, Campos GB, Monteiro EL, Grivellari H. Severe Raynaud's phenomenon associated with interferon beta therapy for multiple sclerosis: a case report. *Arq Neuropsiquiatr* 2000; 58: 556-9.

[13] Kourakata H, Tanabe Y, Mikami O, Sato K, Suzuki E. A case of interferon beta-induced pneumonia. *Nihon Kokyuki Gakkai Zasshi* 2000; 38: 687-91.

[14] Lunemann JD, Schwarzenberger B, Kasim N, Zschenderlein R, Zipp F. Rhabdomyolysis during interferon–beta 1a treatment. *J Neurol Neurosurg Psychiatry* 2002; 72: 274.

[15] Tola MR, Caniatti IM, Graganiello J, Russo M, Stabellini M, Granieri E. Recurrent nephritic syndrome in patients with multiple sclerosis treated with interferon beta 1a. *J Neurol* 2003; 250: 768-9.

[16] Gotsman L, Elhallel-Darnitski M, Friedlander Z, Haviv YS. Beta-interferon-induced nephritic syndrome in a patient with multiple sclerosis. *Clin Nephrol* 2000; 54: 425-6.

[17] Altintas A, Alici Y, Melikoglu M, Sira A. Arthritis during interferon beta-1b treatment in multiple sclerosis. *Mult Scler* 2002; 8: 534-6.

[18] Dubisar BM, Stoner SC, Khan R, Farrar CD. Seizures and extra pyramidal symptoms in a patient with Tourett's syndrome, Asperger syndrome, and multiple sclerosis treated with interferon beta-1a and clomipramine. *Pharmacol* 2002; 22: 1504-7.

[19] Sommer S, Sablon JC, Zaouri M, Rozot P, Hosni A. Interferon beta-1b retinopathy during a treatment for multiple sclerosis. *J Fr Ophtalmol* 2001; 24: 509-12.

[20] McDonald ND, Pender MP. Autoimmune hypothyroidism associated with interferon beta-1b treatment in two patients with multiple sclerosis. *Aust N Z J Med* 2000; 30: 278-9.

[21] Kado S, Miyamoto J, Komatsu N, Iwaki Y, Ozaki H, Tagnchi H, Kure M, Sarashina G, Watanabe T, Katsura Y, Nemoto Y, Noritake M, Matsuoka T. Type 1 diabetes mellitus caused by treatment with interferon-beta. *Intern Med* 2000; 39: 146-9.

[22] Watts RA. Musculuskeletal and systemic reactions to biological therapeutic agents. *Curr Opin Rheumatol* 2000; 12: 49-52.

[23] Kazuta Y, Watanabe N, Sagawa K, Kobayashi H, Kojima T, Funabashi H, Moritoh T, Kasukawa R. A case of autoimmune hemolytic anemia induced by IFN-beta therapy for Type-C chronic hepatitis. *Fukushima J Med Sci* 1995; 41: 43-9.

[24] Goeb JL, Cailleau A, Laine P, Etcharry-Bouyx F, Mangin D, Duverger P, Gohier B, Rannou-Dubas K, Dubas F, Garre JB. Acute delirium, delusion, and depression during IFN-beta-1a therapy for Multiple sclerosis. *Clin Neuropharmacol* 2003; 26: 5-7.

[25] Pandya R, Patten S. Depression in multiple sclerosis associated with interferon-beta-1a. *Can J Psychiatry* 2002; 47: 686.

[26] Lana-Peixoto MA, Teixeira AL, Haase VG. Interferon-beta-1a-induced depression and suicidal ideation in multiple sclerosis. *Arg Neuropsiquiatr* 2002; 60: 721-4.