Original Article: Comparing the Safety and Efficacy of Ziferon and Betaferon in Patients With Remitting-Relapsing Multiple Sclerosis

Mohammad Reza Gheini[1], Mohammad Ali Sahraian[1], Amir Reza Azimi[1], Naser Mmoghadasi[1], Mahmud Abdoli[1], Gelareh Rahimi[2], Monir Ghazaeian[3*]

1. Sina MS Research Center, Neuroscience Institute, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.
2. Bio Statistician Research Institute, Baylor Scott & White Health, Dallas, Texas, United States of America.
3. Department of Clinical Pharmacy, Faculty of pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

*** Corresponding Author:**
Monir Ghazaeian, PhD.
Address: Department of Clinical Pharmacy, Faculty of pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
Phone: +98 (911) 3732940
E-mail: ghazaeianm@gmail.com

Article info:
Received: 05 Aug 2019
Accepted: 22 Oct 2019

Keywords:
Interferon-beta (INF-β)1b, Relapsing-Remitting Multiple Sclerosis (RRMS), Outcome measure

ABSTRACT

Background: The present study aimed to compare the clinical efficacy and safety profile of Ziferon and Betaferon.

Objectives: In total, 41 consecutive patients with relapsing forms of Multiple Sclerosis (MS) were selected from the MS outpatient clinic affiliated to Tehran University of Medical Sciences. The patients were randomly assigned into two groups.

Methods: Each group either received Ziferon 250 mcg Subcutaneously (SC) in alternate days or Betaferon 250 mcg SC on alternate days. Clinical and para-clinical outcomes, such as mean relapse rate/year score, mean Expanded Disability Status Scale (EDSS)/year score, the cumulative number, and the volume of gadolinium-enhancing lesions, in addition to the cumulative number of new T2 lesions and safety profile were evaluated for each group during the years of treatment.

Results: There were no significant differences in Magnetic Resonance Imaging (MRI) outcomes (change in total lesion volume, new lesion per T2-weighted scan, and gadolinium-enhancing lesions per T1-weighted scan from baseline; P=0.236, P=0.56, & P=0.496, respectively was observed). There was no significant difference in the relapse rate between Ziferon and Betaferon treated groups (P=0.56). There were no unexpected safety events. The number of patients who discontinued the study due to adverse events occurrence was similar between the two groups.

Conclusion: Evidence demonstrates the non-inferiority and bio-similarity of Ziferon (interferon beta-1b) to Betaferon in terms of efficacy and safety profile.

Citation Gheini MR, Sahraian MA, Azimi AR, Mmoghadasi N, Abdoli M, Rahimi G, Ghazaeian M. Comparing the Safety and Efficacy of Ziferon and Betaferon in Patients With Remitting-Relapsing Multiple Sclerosis. Pharmaceutical and Biomedical Research. 2019; 5(4):21-26.
DOI: http://dx.doi.org/10.18502/pbr.v5i4.2393

Introduction

Interferon-beta (INF-β) is among the most critical immunomodulatory agents used for treating the Relapsing-Remitting (RR) form of Multiple Sclerosis (MS) disease [1, 2]. This natural polypeptide product is mainly created by fibroblasts. The inhibition of T-lymphocyte proliferation, conversion of inflammatory response to an anti-inflammatory response of cytokines, and decreased permeability of inflammatory cells to the blood-brain barrier are assumed to be the significant anti-inflammatory effects of INF-β. The recombinant types of INF-β, namely interferon β-1a or interferon β-1b, are available and applied for treating RRMS [3-6].

INF β-1b is administered at a dose of 250 mcg subcutaneously every other day. The INF-β efficacy can be determined based on the rate and severity of clinical relapses, or Magnetic Resonance Imaging (MRI) changes, as markers of disease activity [7, 8]. Clinical relapses are usually associated with, and more often occur prior to the signs of disease activity, in MRI data, including hyper-intense lesions on T1-weighted post-gadolinium (Gd) scan series; new enlarging or extending old T2 lesions; or new T1 hypo-intense lesions pre-Gd scan series [9].

Ziferon (INF-β-1b) is made by Zistdaru Danesh Biopharmaceutical Company. Ziferon belongs to a group of natural proteins produced by eukaryotic cells in response to viral infection and other biologic agents. According to the Food and Drug Administration (FDA) recommendation, a comparative clinical study is necessary for manufacturers to support bio-similarity between the proposed product and the reference product [10].

Ziferon demonstrated reduced clinical exacerbation rates in patients with a relapsing form or those who have experienced a first clinical episode of MS. The present study aimed to evaluate the safety and efficacy of Ziferon as a Betaferon bio-similar product in patients with relapsing MS to indicate the non-inferiority of this product.

Patients and Methods

This prospective, randomized, double-blind, comparative trial was conducted on the patients recruited from Sina Center of Tehran University of Medical Sciences. After the screening phase, eligible patients were randomly assigned into two groups (in a 1:1 ratio) to receive either Ziferon or Betaferon for 96 weeks. Randomization was performed by employing a permuted-block randomization schedule with stratification based on the treatment product type. During the study, the investigators and sponsor agreed to maintain the confidentiality of the data.

Eligible patients were aged 18–50 years and had relapsing MS meeting 2005 McDonald criteria, with or without underlying progression, with an Expanded Disability Status Scale (EDSS) score of ≤5.5, who had a history of at least two relapses in the last two years, and no relapse within past 30 days before randomization.

Patients were excluded if they had other relevant diseases, and were pregnant, breastfeeding, or planned to conceive during the study, or if they previously or concomitantly had received cytotoxic therapy, other INF-β therapy, or Glatiramer acetate within the six months of randomization, or ever used Natalizumab or other immunosuppressive agents and clinically relevant cardiovascular, hepatic (except Gilbert syndrome), neurological (except RRMS), renal (Serum creatinine >1.1) or other major systemic diseases, significantly impaired bone marrow function or significant anemia, leukopenia or thrombocytopenia, a history of allergic or hypersensitivity reaction to other INFs products, a history of suicidal ideation or attempts, or any recorded condition or circumstance interfering with the investigator's opinion, compliance, or completion of the study.

We determined two primary efficacy outcomes, including Annualized Relapse Rate (ARR) and mean EDSS score changes. Additionally, the primary safety outcome was the occurrence of adverse effects. MRI outcomes, including changes in the total lesion volume, new lesion per T2-weighted scan, and gadolinium-enhancing lesions per T1-weighted scan from baseline, were considered as the secondary result of the study.

In total, 32 patients randomly assigned into each treatment group would have provided 80% power to detect 30% of the changes in EDSS at the two-tailed significance level of α=0.05 and a standard deviation of 0.50. The number of samples considered for data analysis at the end of the study was 41 patients.

An independent, specially trained, and certified examining neurologist determined all EDSS scores and conducted all functional system assessments. Both treating and examining neurologists were unaware of treatment assignments; EDSS scores were determined at the screening time, at baseline visit, every four weeks after baseline visit, and at unscheduled visits when patients referred to the clinic for assessing potential relapse.

MRI scans were obtained based on the study protocol at the baseline and at weeks 24, 48, 72, and 108 of the study; imaging data were collected at MRI facilities and provided to the central MRI Analysis of Sina Center for processing and data extraction. The study patients were requested to contact their treating investigator immediately if becoming suspicious of any relapse. Furthermore, they requested to visit the center within seven days of symptom onset. Suspected and confirmed relapses could be treated by administrating intravenous glucocorticoids for three to five days; after that, oral steroids should be started and tapered for two weeks after the onset of symptoms.

The study patients were requested to visit the study site within 14 days after the trial onset, to being examined by the examining neurologist. Safety was evaluated based on adverse events reported by the study participants or investigators. Laboratory tests were conducted at the time of screening, at baseline, every week of the first month of study, every two weeks for the second month, and monthly until the study completion.

Physical and neurologic examinations were performed weekly in the first month, followed by every four weeks. Clinical and para-clinical data and safety profiles were compared between the two groups using the Chi-squared test. Fisher's exact P-value was calculated as needed. Marginal models with Generalized Estimating Equations (GEE) were used to compare between-group MRI lesion volume measurements. Moreover, considering identity link function and Auto-Regressive (AR1) working correlation matrix, $P<0.05$ was set as statistically significant. SPSS was used for data analysis.

Results

In total, 41 patients were randomly assigned into two treatment groups from January 2011 to April 2015; 20(49%) and 21(51%) of them were exposed to Betaferon and Ziferon medications, respectively. Figure 1 illustrates a flow chart of patients' assignments, including the number of patients who were randomized and completed the study, and those who discontinued their participation (with their reasons). A majority of studied patients were female [37(90%) of 41 patients], and 4(10%) of them were male. All included patients had Iranian nationality without any racial differences.

In both INF-β-1b groups, the relapse rate decreased, and no difference was found between the two study groups (P=0.56). Mean changes from baseline to endpoint time in total EDSS score did not significantly differ between the two study groups (P=0.81). hanges in total lesion volume, new lesion per T2-weighted scan, and gadolinium-enhancing lesions per T1-weighted scan from baseline, did not significantly differ between the two study groups (P=0.236, P=0.56, and P=0.496, respectively).

Due to group differences in lesion volume at baseline, lesion volume changes were periodically (every 6 months) assessed and analyzed. No difference was found between the two groups in this regard (P=0.58) (Table 1). In total, 7 patients discontinued consuming the prescribed medicine, in Betaferon and Ziferon groups. Major reasons were adverse events occurrence, unavailable follow-up data, and disease progression, respectively. No differences were found in the proportion of dropouts among the treatment groups at various time points.

The minimum duration of exposure to the treatment dose was 5 weeks. The majority of included patients completed more than half (90%) of planned follow-up visits. Moreover, 41 of them completed the study period (24 months). Patients who were enrolled in the trial received the same dose of INF-β-1-b as 250 mcg (both products). All studied patients who received at least one dose of each product were considered in safety analysis.

Similar proportions of patients in both INF groups experienced Adverse Events (AEs) (70% and 71.4% for Betaferon and Ziferon, respectively). In addition, the frequency of adverse events leading to the discontinuation of consuming study medication was the same between the 2 groups (15% and 14.3%). The most frequent adverse events (≥10% in each group) were flu-like syndrome, injection site reaction, liver test abnormalities, headache, and depression. Overall, the occurrence of common AEs was similar in both treatment groups (Table 2). No deaths were reported.

A similar incidence of serious AEs was noted across the groups. Injection site reaction was the most frequent cause of treatment discontinuation (28.6%). No significant AEs leading to permanent treatment discontinuation, significant additional concomitant therapy, or deaths were observed, other than the serious reported AEs.

For all common AEs with INF-βeta-1-b, reported cases were generally resolved with continued treatment, and discontinuation rates were low. The study medications' effects on laboratory evaluations, such as liver enzymes and hematological variables, were similar.

PBR
Pharmaceutical & Biomedical Research

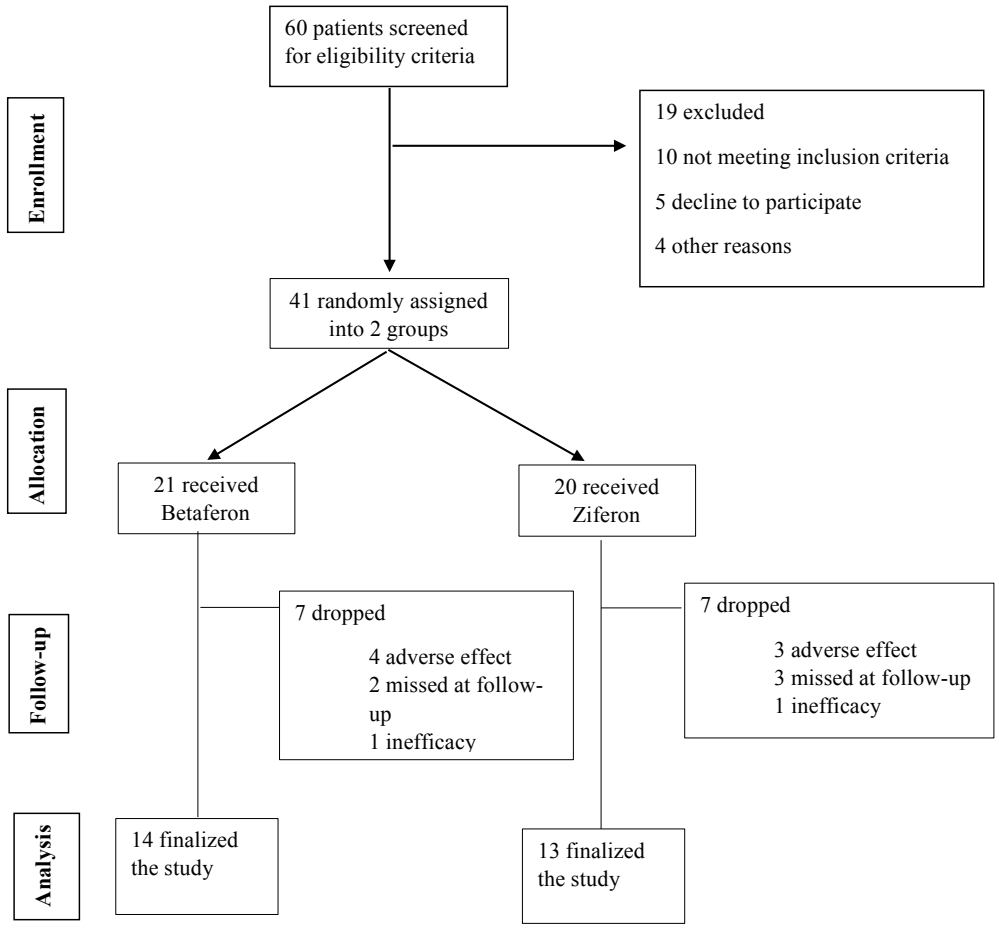

Figure 1. Patient flow chart

Discussion

Biosimilars are described as biological products with high similarity to the reference product and minor alterations; they have no clinical differences regarding efficacy, purity, and safety concerns. Because of intrinsic structural complexity and immunogenicity differences between biosimilar and innovator products, comparative clinical data are required to support their interchangeability [11, 12]. Therefore, the present study aimed to determine the non-inferiority of Ziferon, as the biosimilar product, and Betaferon, as the reference product.

The obtained data suggested no significant difference in primary and secondary endpoints between Ziferon and Betaferon treated groups. Significant findings of the

Table 1. Comparing MRI lesion volume measurements

Volume	Mean± Std Error		P *
	Betaferon	Ziferon	
Baseline	8992.65±1240.00	12867.40±3291.49	
6th Month	8903.91±1221.07	13059.10±2761.29	
12th Month	7044.62±834.62	11194.59±3111.93	0.236
18th Month	6102.22±712.79	12247.00±3879.84	
24th Month	6190.20±807.01	17680.73±12730.55	

*Based on the marginal model for the comparison of the two groups

Table 2. Overview of the most common adverse events of INF-β-1b in two study groups*

Adverse events	No. (%)		P *
	Betaferon	Ziferon	
Flu-like symptoms	13 (65%)	11 (52.4%)	0.91
Injection Site Reaction	14 (65%)	14 (66.7%)	0.70
Liver test abnormalities	1 (5%)	3 (14.3%)	0.31
Headache	8 (40%)	6 (28.6%)	0.38
Depression	4 (20%)	4 (19%)	0.32

* Statistical test used for comparison was the Chi-squared test.

PBR

study were similar in terms of decreased relapse rate. MRI is an acceptable marker for treatment monitoring in clinical trials [9, 13, 14]. Based on MRI findings, treatment with Ziferon also reduced active inflammatory lesions. Similar benefits were observed in patients receiving the experimental product (Ziferon) and initial treatment (Betaferon) in MRI follow-up data.

The trial results demonstrated no significant difference in efficacy and safety parameters between Ziferon and Betaferon treated groups. The same reduction found in the relapse rate provided some clinical insights into the relative efficacy of the experimental products (Ziferon).

The mean total EDSS score changes between the two study groups was not statistically significant at 24-month follow-up. The disability progression trend, along with EDSS changes, remained steady in both groups. This finding can indicate the non-inferiority of Ziferon to Betaferon in terms of efficacy outcomes; as MRI lesions and EDSS progression in RRMS patients by considering lower cost of biosimilar product treatment. These results are compatible with the previous study findings [15, 16].

Treatment with INF-β is associated with safety concerns. Its most commonly reported adverse effects are the following: injection site reactions and flu-like symptoms, including myalgia, fevers, chills, and fatigue [17, 18]. Regarding the observed side effects, the safety profile of both INF-β-1-b products was consistent with previous trials. The most common adverse effects of Ziferon in terms of safety and tolerability profiles regard the treatment selection, depending on patients' characteristics and potential comorbidities.

The frequency of AEs concerning severity was similar between the study groups. These AEs were partly related to injection site reactions. At least 70% of patients in each group reported one case of injection site reaction and both groups showed similar rates in this respect.

Conclusion

The obtained data suggested that Ziferon, as a biosimilar recombinant product, has the equivalent efficacy and safety profile to Betaferon. It is an effective alternative for treating RRMS patients with an acceptable safety profile and efficacy results.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Code: 764/425). The study was registered in the Iranian Registry of Clinical Trials (registration date: Nov 13, 2015; No.: IRCT138806102397N1).

Funding

This study was financially supported by Zistdaru Danesh Company.

Authors' contributions

All authors contributed equally in preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Goodin DS, Reder AT, Ebers GC, Cutter M, Kremenchutzky M, Orger J, et al. Survival in MS, A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. Neurol. 2012; 78(17):1315-22. [DOI:10.1212/WNL.0b013e3182535cf6] [PMID] [PMCID]

[2] Reder AT, Ebers GC, Traboulsee A, Li D, Langdon D, Goodin DS, et al. Cross-sectional study assessing long-term safety of interferon-β-1b for relapsing-remitting MS. Neurol. 2010; 74(23):1877-85. [DOI:10.1212/WNL.0b013e3181e240d0] [PMID]

[3] Durelli L, Conti L, Clerico M, Boselli D, Contessa G, Ripellino P, et al. T-helper 17 cells expand in multiple sclerosis and are inhibited by interferon-β. Ann Neurol. 2009; 65(5):499-509. [DOI:10.1002/ana.21652] [PMID]

[4] Tao Y, Zhang X, Chorpa M, Kim MJ, Buch KR, Kong D, et al. The role of endogenous IFN-β in the regulation of Th17 responses in patients with relapsing-remitting multiple sclerosis. J Immunol . 2014; 192(12):5610-7. [DOI:10.4049/jimmunol.1302580] [PMID]

[5] Dhib-Jalbut S. Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis. Neurol. 2002. 58(8 suppl 4):S3-9. [DOI:10.1212/WNL.58.8_suppl_4.S3] [PMID]

[6] Weber F, Janovskaja J, Polak T, Poser S, Rieckmann P. Effect of interferon β on human myelin basic protein-specific T-cell lines: Comparison of IFNβ-1a and IFNβ-1b. Neurol. 1999; 52(5):1069. [DOI:10.1212/WNL.52.5.1069] [PMID]

[7] Edan G, Kappos L, Montalban X, Polman CH, Freedman MS, Hartung HP, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. J Neurol, Neurosurg & Psychiatry. 2013; 85(11):1183-9. [DOI:10.1136/jnnp-2013-306222] [PMID] [PMCID]

[8] Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. The Lancet Neurol. 2009. 8(11):987-97. [DOI:10.1016/S1474-4422(09)70237-6]

[9] Paty DW, Li DKB. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurol. 1993; 43(4):662. [DOI:10.1212/WNL.43.4.662] [PMID]

[10] Olech E. Biosimilars: Rationale and current regulatory landscape. Semin Arthritis Rheum. 2016; 45(5 Suppl):S1-10. [DOI:10.1016/j.semarthrit.2016.01.001] [PMID]

[11] Schellekens H. Biosimilar therapeutics-what do we need to consider? NDT Plus. 2009; 2(suppl 1):i27-36. [DOI:10.1093/ndtplus/sfn177] [PMID] [PMCID]

[12] Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: guidance for industry [Internet]. 2019 [Updated 2019 May]. Available from: https://www.fda.gov/media/124907/download

[13] Ebers GC. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. The Lancet. 1998; 352(9139):1498-1504. [DOI:10.1016/S0140-6736(98)03334-0]

[14] Jacobs LD, Jacobs MD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996; 39(3):285-94. [DOI:10.1002/ana.410390304] [PMID]

[15] Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Conner P, et al. Randomized, comparative study of interferon β-1a treatment regimens in MS: The EVIDENCE trial. Neurol. 2002; 59(10):1496-506. [DOI:10.1212/01.WNL.0000034080.43681.DA] [PMID]

[16] Milanese C, Mantia LL, Palumbo R, Martinelli V, Murialdo A, Zaffaroni M, et al., A post-marketing study on interferon β 1b and 1a treatment in relapsing-remitting multiple sclerosis: Different response in drop-outs and treated patients. J Neurol, Neurosurg & Psychiatry. 2003; 74(12):1689-92. [DOI:10.1136/jnnp.74.12.1689] [PMID] [PMCID]

[17] Gross R, Corboy J. Monitoring, Switching, and Stopping Multiple Sclerosis Disease-Modifying Therapies. Continuum: Lifelong Learn in Neurol. 2019; 25(3):715-35. [DOI:10.1212/CON.0000000000000738] [PMID]

[18] de Jong HJI, Kingwell E, Shirani A, Willem Cohen Tervaert J, Hupperts R, Zhao Y, et al. Evaluating the safety of β-interferons in MS. A series of nested case-control studies. Neurol. 2017 88(24):2310-20. [DOI:10.1212/WNL.0000000000004037] [PMID] [PMCID]