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Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: A double blind randomized clinical trial

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ABSTRACT

Objective: We compared the efficacy and safety of two biosimilar forms of interferon beta-1a in the treatment of multiple sclerosis: Avonex (Biogen Idec, USA) and CinnoVex (CinnaGen, Iran).
Methods: In a double blind randomized clinical trial study 84 patients with relapsing remitting multiple sclerosis (RRMS) with Expanded Disability Status Scale (EDSS) score of 0–5.5 were randomly allocated to two groups of 42 subjects.
Results: Twenty-four patients lost to follow-up. Finally, 31 patients (mean ± SD of age = 33.7 ± 7.0; 7 males and 24 females) in the Avonex and 29 patients (mean ± SD of age = 32.2 ± 9.2; 8 males and 21 females) in the CinnoVex group completed full 24 months of study period. Decrease in EDSS was 1.05 ± 0.24, $p = 0.62$ in the Avonex and 0.16 ± 0.88, $p = 1.0$ in the CinnoVex group after 12 months and 0.27 ± 1.05, $p = 0.46$ in the Avonex and 0.16 ± 1.06, $p = 1.0$ in the CinnoVex group after 24 months. There was no statistically significant difference in attack number between two groups (1.0 ± 1.2 in Avonex and 1.2 ± 1.3 in CinnoVex; $p = 0.46$). Volume of T2-weighted lesions on MRI showed a progressive significant increase in the 12th month (28056 ± 23693) in Avonex treated patients compared with first image (16353 ± 11172) ($p = 0.01$). But number of gadolinium-enhancing lesions in CinnoVex showed statistically significant decrease after 12 months (0.08 ± 0.28 vs. 1.00 ± 1.22; $p = 0.03$). However, there were no significant differences between groups after 24 months. There were no significant differences between 2 groups regarding frequency and duration of most considerable side effects, as well. Neutralizing antibodies were not positive in any patients.
Conclusion: CinnoVex can be used as a safe and effective alternative to Avonex in treatment of RRMS.

1. Introduction

Multiple sclerosis (MS) is potentially the most common disabling neurological disease of the young adults [1,2]. As a result, MS treatment should be initiated as soon as possible to prevent disability. The therapeutic approaches to the various forms of MS have been changed dramatically during the past decade and various disease modifier agents have been introduced and marketed successfully [3–5]. Interferon beta (IFNβ) is the first line treatment for RRMS. Various formulations of this medication have been studied in multicentric; randomized, placebo-controlled trials [6–8]. Treatment with IFNβ would reduce disease exacerbations and magnetic resonance imaging (MRI) burden [9].

INFβ-1a is produced recombinantly in a Chinese hamster ovary cell line and has been successfully marketed as Avonex® (Biogen Idec, USA) and Rebif® (Merck Serono, Switzerland) in many countries.

Prescription of IFNs for the patients with MS at the earliest possible time is closely related with better economic outcome and availability of the drug. Recently, biosimilar interferon formulations have been produced as an appropriate solution in some countries like Iran. Currently, for the approval of biosimilars, no legal guidance documents exist in the United States and the Food and Drug Administration does not have a framework in this case. The European Medicines Agency has provided a valuable base for

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EU legislation to evolve from [10]. According to findings with brand products, it is advised to support manufacturing of recombinant proteins by stringent controls. The biosimilar manufacturers must ensure safety and consistency in their production.

CinnoVex is a biosimilar form of intramuscular (i.m.) IFNβ-1a manufactured by CinnaGen Co., Iran. It is produced in CHO cells, the same cell line that produce Avonex. The process of production and purification are also similar. Previously, quality studies including in vitro assays, impurity profiling, and clinical pharmacokinetic and pharmacodynamic studies were performed to demonstrate the physicochemical identical compound of CinnoVex to the original drug branded by Biogen Idec, Iran. We undertook a double blind, randomized clinical trial study in relapsing remitting multiple sclerosis (RRMS) to compare the effects of Avonex with CinnoVex.

2. Material and methods

2.1. Patients

In this double blind, randomized clinical trial, 84 patients with RRMS were enrolled in a 24 months study period. They were recruited from August 2006 to August 2007 from all MS clinics affiliated to main three medical universities in Tehran, Iran. Patients were randomly assigned into two groups receiving weekly i.m. injections of CinnoVex (42 patients) or Avonex (42 patients). The randomization list was stratified by a conducting center. All patients signed a written informed consent form that was approved by the Ministry of Health of Iran before treatment initiation.

Eligible subjects were patients aged 18–50 years who had clinically definite RRMS according to Mc Donald's criteria. They were enrolled if they have had at least two relapses in the preceding 2 years with clinical disability index of 0–5.5 according to the Expanded Disability Status Scale (EDSS).

Exclusion criteria were: pregnancy or willing for pregnancy, major depression, suicidal attempts, allergy or sensitivity to the administered drug, plasma exchange or using intravenous immunoglobulin, indication for prescription of cytotoxic agents during the study, raise in liver enzymes (AST/ALT) more than 3 times of the baseline, any evidence for leucopenia and discontinuing IFN administration for any reason more than 4 weeks. Also changing to secondary progressive type and a sustained increase of at least 1 point in EDSS caused the patients to be excluded.

2.2. Design

After assignment, patients were categorized in two groups randomly. Baseline lab tests including AST/ALT, CBC and renal function tests were checked. All patients were examined by a neurologist to evaluate EDSS. The neurologist was responsible for neurological assessments and follow-up of relapses and overall medical management of the patient, including treatment of any side-effects. Neurological assessment was performed every week for the first month and then monthly to the end of study for all patients. A comprehensive form was filled in for each of the patients for registration of the data in the first and monthly visits. Additional assessments were done facing relapses or unpredicted side effects. All adverse events during treatment containing depression, seizures, cardiac events, and injection-site reactions, or flu-like symptoms, whether or not they were serious, were recorded by physicians. Side effects were controlled by a 60 items checklist and occurrence and duration of each side effect was recorded.

The study drug was packed and delivered to the center without any label to prevent study neurologist, nurses, patients and staff from knowing which medication was received. Intramuscular injections of IFNβ-1a once per week were administered by trained nurses. Half of the dose was prescribed for the first injection and the full dose (i.e., 30 μg of active protein which is equal to 6 million international unit of activity) was given for the remaining sessions, to lessen possible side-effects.

All patients underwent proton density T2-weighted scans and gadolinium-enhanced scans at the entrance time and every six months. Scans were analyzed centrally by the MS/MRI Analysis Research Group and treatment allocation was concealed from outcome assessors.

Serum was assayed for the presence of neutralizing antibodies (NAbs) every six months. The incidence of titers greater than or equal to 1:20 LU/ML was reported positive. Briefly, heat inactivated sera was preincubated with 10 LU/mL IFN and added to cells transformed with a luciferase reporter gene for 6–16, an interferon stimulated gene. Each serum sample was tested against both CinnoVex® and Avonex® as antigens. Titers were reported in TRU/ml and considered positive when they were >20 TRU/ml.

2.3. Statistical analysis

Data were analyzed using Mann–Whitney, paired *t*-test, independent *t*-test and Chi-square tests. Values are given as mean ± standard deviation (SD). A p value less than 0.05 was considered as statistically significant.

3. Results

3.1. Patients

Of total 84 recruited patients, 24 subjects were lost to follow-up: 2 subjects due to pregnancy, 5 patients refused to continue, 1 due to chemotherapy, 1 due to moving to another city, and 12 patients did not return for follow-up. There was no statistically significant difference in the number of withdrawals between two groups ($p = 0.09$). In addition 3 patients (1 in the Avonex and 2 in CinnoVex group) were excluded due to increase in EDSS and presence of side effects ($p = 0.61$).

Finally, 31 patients (mean ± SD of age = 33.7 ± 7.0; 7 males and 24 females) in the Avonex and 29 patients (mean ± SD of age = 32.2 ± 9.2; 8 males and 21 females) in the CinnoVex group completed full 24 months of study period. Comparison of age and sex showed no statistically significant difference between two groups ($p = 0.45$ for age and $p = 0.65$ for sex).

3.2. Side effects

During the 24 months, there were no significant differences between 2 groups regarding side effects. The most prevalent side effect was flu-like syndrome which was repeated 6.35 ± 6.93 in patients in the Avonex and 5.55 ± 4.45 in the CinnoVex group ($p = 0.59$). Headache (4.61 ± 4.72 in Avonex; 1.59 ± 2.26 in CinnoVex; $p = 0.003$), myalgia (1.97 ± 2.54 in Avonex vs. 1.38 ± 2.71 in CinnoVex; $p = 0.38$), and fatigue (1.35 ± 1.89 in Avonex vs. 1.55 ± 2.37 in CinnoVex; $p = 0.72$) were placed in next order of prevalence. Duration and frequency of any adverse events are shown in supplements 1 and 2, respectively. Frequency and duration of arthralgia, oral ulcer, headache and SGOT/SGPT increase were reported to be higher in the Avonex group than the CinnoVex ($p < 0.05$).

Neutralizing antibodies were not found in any of the patients during 24 months study period.

3.3. Disability and relapses

Treatment effects were noted by decrease in EDSS mean over 2 years within 2 groups which were 2.03 ± 1.67 vs. 2.64 ± 1.12 at baseline ($p > 0.05$), 1.79 ± 1.50 vs. 2.48 ± 1.44 at 12th month and

Table 1
Number of relapses during the 2 years of the study for the patients who had completed 24 months of study period.

Attacks number	Avonex	CinnoVex	*p*-Value
0	14 (45.2%)	12 (41.4%)	0.83
1	9 (29.0%)	7 (24.1%)	
2	5 (16.1%)	4 (13.8%)	
3	2 (6.5%)	4 (13.8%)	
More	1 (3.2%)	2 (6.9%)	

1.76 ± 1.62 vs. 2.48 ± 1.58 at the 24th month in the Avonex and CinnoVex groups, respectively. Based on repeated measure ANOVA within group, changes in the first, 12th and 24th month EDSS were not statistically significant ($p = 0.37$ for Avonex and $p = 0.64$ for CinnoVex). Also there was a slight decrease in EDSS in two groups during 24 months without statistically significant difference. Decreases in EDSS were 1.05 ± 0.24, $p = 0.62$ in the Avonex and 0.16 ± 0.88, $p = 1.0$ in the CinnoVex group after 12 months and 0.27 ± 1.05, $p = 0.46$ in the Avonex and 0.16 ± 1.06, $p = 1.0$ in the CinnoVex group after 24 months. Six (19.3%) patients in the Avonex and 3 (10.3%) patients in the CinnoVex group showed sustained disability according to EDSS during 24 months ($p = 0.47$). There was no statistically significant difference between attacks number of two groups (1.0 ± 1.2 in Avonex and 1.2 ± 1.3 in CinnoVex; $p = 0.46$). Seventeen patients (54.8%) in the Avonex and 17 patients (58.6%) in the CinnoVex group developed new attack during 24 months ($p = 0.76$). Totally 30 attacks in the Avonex and 35 attacks in the CinnoVex group were recorded ($p = 0.83$). Details of number of relapses are shown in Table 1.

3.4. MRI scans findings

Repeated measure ANOVA that was adjusted for multiple comparisons using Bonferroni method was performed between two groups for number of gadolinium-enhancing lesions, lesion volume and number of lesion. Follow-up of accumulation of disease burden as measured by the volume of T2-weighted lesions on MRI showed a progressive significant increase in the 12th month in Avonex treated patients compared with the first image ($28{,}056 \pm 23{,}693$ vs. $16{,}353 \pm 11{,}172$; $p = 0.01$). But number of gadolinium-enhancing lesions in CinnoVex showed statistically significant decrease after 12 months (0.08 ± 0.28 vs. 1.00 ± 1.22; $p = 0.03$). However, there were no significant differences between groups after 24 months. More details are shown in the supplement 3.

4. Discussion

The results of our study showed that there were no significant differences between the CinnoVex and Avonex in four major outcomes i.e., relapse, MRI lesion changes impairment in function and disability. Desirable effects of intramuscular administration of IFNβ-1a were seen in both of CinnoVex and Avonex treated groups. Relapse control is one of the main achievements when IFNs are used and is highly valued. The relapse rates of both groups were similar to the results of a previous study which used weekly i.m. IFNβ-1a [11], and more than that was seen with using subcutaneous IFNβ-1a (Rebif®), reported in PRISM study [12]. Also this rate is greater than the relapse rate showed in subcutaneous IFNβ-1b [13].

Comparing the EDSS of the patients in a multi-stage pattern showed clinical-based similarity between Avonex and CinnoVex. In other words, disability was well controlled according to delay in progressive increase of EDSS score within either CinnoVex or Avonex treated groups. Disability which is measured by EDSS was better investigated in this study compared with those that their end points were the development of clinically definite MS or changes in findings of brain MRI like CHAMPS study [14]. Also in our study we had an acceptable time to follow the patients after initiation of IFNβ-1a. It means that we begun with definite MS patients compared with the studies which ended in definite MS [14].

PRISM study group showed the same findings in their clinical trial in which integrated disability status scale (IDSS) showed significant therapeutic effects on groups treated with various doses of subcutaneous IFNβ-1a. The IDSS is a summary measure of disability used to quantify both temporary and unremitting disability during the study period in PRISM study [12]. Keeping the ability of doing their own personal life without dependency in most of the patients is an important achievement. Moreover, social and professional performance would be continued as well.

Brain MRI scans findings in our study also support the clinically observed effectiveness objectively such as decrease in relapse rate and control of disability in both groups. In other studies, it was confirmed by comparing weekly IFNβ-1a to the high dose high frequent ones, but in our study we compared low dose IFNβ-1a between two groups. Other studies showed a stronger dose-effect on MRI lesions in term of using 44 micro gram subcutaneous IFNβ-1a weekly [11,15].

NAbs can develop during long-term administration of IFNβ products. The effect of NAbs on IFNβ therapy remains as a topic of controversy [16]. But many believe that sustained high-titers of NAbs are associated with a reduction in the therapeutic effects of INFβ [17]. The incidence of NAbs is reported in 28–47% of patients who develop NAbs to INF β-1b, 12–28% to INFβ-1a subcutaneous (Rebif®) and 2–6% to INFβ.1a i.m. (Avonex®) [18]. However, difference between dose, frequency and route of administration, structural drug characteristics, level of homology to the natural human IFN, differences in manufacturing, purification, and formulation processes, all contribute to the variable immunogenicity of compounds [16]. It is of note that there were no NAbs positive patients in our study. Although, most studies had follow-up for 2 years, this period of follow-up is considered as relative short timeframe to evaluate the significant effects of NAbs on both clinical and paraclinical parameters [19].

Therapy with IFNβ may be associated with a number of adverse reactions. Common side effects associated with these protein-based therapeutics are flu-like symptoms, transient laboratory abnormalities such as lymphopenia, neutropenia, leucopenia, and raised liver aminotransferase values, muscle weakness and headache [20–22]. In the Avonex-treated patients, arthralgia and headache were more frequent than in CinnoVex-treated patients but vice versa for skin rash and sensory loss. The duration of depression was longer in Avonex-treated patients whereas ataxia in CinnoVex-treated patients, although the statistical analysis did not reach a significant difference. These results showed that during 24 months follow-up there were no severe side effects. CinnoVex was well tolerated, with no serious treatment-related adverse effects and the safety profile was not different from Avonex. Flu-like syndrome was the most prevalent side effect in both groups. Headache, myalgia and fatigue were other reported side effects in both groups.

In summary, CinnoVex as a biosimilar recombinant protein had comparable clinical safety and efficacy profile to Avonex. Post Marketing Surveillance Trial is an essential component in tracking rare but serious adverse events. It is highly recommended to follow CinnoVex clinical safety and efficacy by designation of appropriate post-marketing studies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clineuro.2012.02.039.

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