A Therapeutic Trial of Bioequivalence Between Two Interferons Beta – 1a for Treating Relapsing – Remitting Multiple Sclerosis

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Abstract

In order to appropriately support the equivalence between a biosimilar and the referenced biopharmaceutical it is essential to carry out equivalence or non-inferiority clinical studies. The objective of this paper was to study the therapeutic bioequivalence of IFN β-1A biosimilar vs. IFN β-1A innovator. The efficacy and safety of these drugs was assessed in Mexican patients under treatment for relapsing-remitting multiple sclerosis (RRMS). A parallel, multicenter, prospective and comparative study was carried out. Fifty patients with confirmed RRMS were studied. The following parameters were considered for the diagnosis of confirmed RRMS: Magnetic Resonance Imaging (MRI) demonstrating demyelinating lesions; expanded disability status scale (EDSS) scores between 0 – 5.5; and McDonald’s criteria compatible with MS. Patients were randomly divided into 2 groups of 25 patients each. Patients from the first group were treated with Avonex®, 30 mg-per-week. Patients from the second group were treated with Axuareb® at the same dose. All patients were followed for a period of 24 months. Forty-five patients (90%) out of the initially recruited 50 patients completed the follow-up period. Annual relapse rates were 11% and 8% for Avonex and Axuareb, respectively. The proportions of relapse-free, improvement and detriment showed non-significant differences (p>0.05) between groups. The incidence of side effects showed a non-significant difference (p>0.05) between groups. SF-36 data of physical and mental status demonstrated non-significant differences between groups after the follow-up period. Although, MRI findings demonstrated a significant increase (p<0.05) in the number of demyelinating lesions after the follow-up period in both groups of patients, the group of patients treated with Axuareb demonstrated a significantly reduced mean number of lesions after the follow-up period. In conclusion, both drugs showed similar effectiveness and safety. Thus, from the results of this clinical trial, it seems that Axuareb, a biosimilar IFN is a safe and reliable alternative for treating patients with MS.

Keywords: Interferon β-1A; Multiple Sclerosis; Safety; Biosimilar; Treatment

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease characterized by an autoimmune disorder. The demyelination is considered a disorder of T and B cells which cause axonal damage. MS is a non-curable disease. Its natural history can be modified using medical treatments including Interferons (IFN), Glatiramer acetate, and some immunomodulators. Approximately, thirty to forty-percent of the patients with MS respond well to treatment with Interferon β. The rest of the patients show only partial improvement or no improvement at all [1,2].

It has been reported that the incidence of MS in Mexico ranges from 1.6 / 100 000 to 16/100 000. However, the frequency seems to have been increasing in the last 10 years [3,4].

In Mexico, as well as in other Latin American countries, limited social – economical resources significantly reduce the possibility to use high-quality biologic compounds. The use of biosimilar products decreases the cost of these treatments. Thus, the Ministry of Health of Mexico has emitted a regulatory pathway for the approval of these products.

Biosimilar drugs are characterized by their chemical and therapeutic equivalence with original biopharmaceuticals with expired patents.

Biogenerics are biological products which are replicas of their biopharmaceuticals [5]. In order to develop a biosimilar, a manufacturer must demonstrate adequate quality, safety and efficacy. Moreover, the drug must be biosimilar to the reference product. Thus, the key for the development of a biosimilar is to demonstrate a high-degree of molecular similarity.

Also, adequate safety and efficacy have to be demonstrated through a clinical trial before commercial viability can be achieved. Biosimilar manufacturers usually submit applications to the regulatory authorities based upon safety and efficacy reliable data of the equivalent product.

It is necessary to demonstrate that the pharmacokinetics of the same molar dose of the product is within acceptable predefined parameters. This proof of bioequivalence is an important issue affecting both generic and original drugs [6].

Actually, a biosimilar drug must be supported by its own clinical data including bioavailability, efficacy and safety. Biosimilars represent new challenges for the health care authorities as compared with...
conventional generic drugs. Hence, the marketing approval of a biosimilar is usually more complicated.

The complexity of biopharmaceuticals creates difficulties for avoiding heterogeneity between batches from the same manufacturing process, as well as between the same proteins from different manufacturers [7]. Furthermore, it is difficult if not impossible to establish therapeutic equivalence of biosimilars with reference products without clinical trials [8-10].

Safety of a biosimilar is a critical factor. An important difference between biopharmaceuticals and conventional drugs with regard to safety is the significant potential to induce an immune response (immunogenicity) [11,12].

The purpose of this study is to evaluate the therapeutic bioequivalence and safety of a biosimilar IFN (Axuareb®), as compared with an innovator IFN (Avonex®) in patients with MS.

Materials and Methods

A total of 62 patients diagnosed with MS with a relapsing-remitting clinical course were recruited. Patients were recruited at the Hospital Angeles Metropolitano and Hospital Angeles del Pedregal in Mexico City, and the Hospital Regional de Alta Especialidad in Veracruz, Mexico.

All patients signed an informed consent form. The study was approved by the Internal Review Board (IRB) of each Hospital and was certified by the Ministry of Health of Mexico. All patients had a baseline neurological evaluation. The extended disability status score (EDSS) was used. Also, all patients underwent brain Magnetic Resonance Imaging (MRI). All patients included in the initial study group tested negative for anti-interferon anti-bodies (NAB).

Patients from both sexes were included. Ages ranged from 8 to 50 years. All patients presented with a clinically defined MS according to the McDonald Criteria (MC) (13).

All patients showed EDSS scores of 0 – 5.5 and they all had had at least 2 relapses in the preceding year. Patients with any of the following were excluded: (a) Sensitivity to IFN; (b) major depression with suicidal ideas; (c) Epilepsy; (d) History of heart disease; (e) History of liver disease; (f) Cancer; (g) Pregnancy; (h) Breastfeeding; (i) Liver enzyme levels beyond 3 times reference values.

Patients were divided into 2 groups. Group 1 included those patients who were treated with Avonex® (Stendhal, Vetter Pharma-Fertigung, Ravensburg, Germany), 30 mg-per-week by subcutaneous way. Group 2 was assembled with patients who were treated with a biosimilar IFN – Axuareb® (Laboratorios PiSA, Guadalajara, Mexico) at the same dose – Axuareb ® (Laboratorios PiSA, Guadalajara, Mexico) at the same dose to safety is the significant potential to induce an immune response (immunogenicity) [11,12].

Results

Twelve patients showed one or more of the exclusion criteria mentioned herein and were not included in the study. Fifty patients were finally included in the clinical trial and they were randomly divided into the 2 study groups.

Out of 50 patients, forty-five (90%) patients completed the follow-up period. Two patients from group 1 (Avonex) withdrew from the study prematurely due to personal reasons. Three patients from group 2 (Axuareb – Biosimilar IFN) withdrew from the study before completing the follow-up period. From these 3 cases, two of them withdrew due to adverse effects of the medication and one because of severe disability progression. Demographic data from both groups of patients are displayed in Table 1.

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The EDSS scores of patients treated with Biosimilar IFN were as follows: 2.26 ± 0.192 (baseline); 1.98 ± 0.412 (12 months); 2.072 ± 0.86 (24 months). In other words, as assessed by the EDSS scores, the proportion of patients who improved remained stable or deteriorated were similar across groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Avonex</th>
<th>Axuareb</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
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<td>25</td>
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<tr>
<td>Age</td>
<td>31.47 ± 6.5 years</td>
<td>32.88 ± 3.6 years</td>
</tr>
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<td>Sex</td>
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<td></td>
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<tr>
<td>Weight</td>
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<td>72.6 ± 5.2 kg</td>
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<tr>
<td>Height</td>
<td>157.2 ± 16.2 mts</td>
<td>164.84 ± 14.9 mts</td>
</tr>
<tr>
<td>Previous therapy with IFNs</td>
<td>5 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Previous therapy with steroids</td>
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Table 1: Demographic data.
Annualized relapse rates were 11% in patients treated with Avonex (Group 1) and 8% in patients from group 2. A non-significant relationship was demonstrated between these rates (p>0.05). It should be pointed out that all relapses were confirmed by the attending neurologist. Moreover, all patients with confirmed relapses were placed on a steroid regimen. The severity of the events was similar across groups. (Table 2)

The SF-36 scale data of physical, and mental component, are summarized in table 4. The mean physical health data were 65.17 versus 59.21 at treatment onset; 74.65 versus 73.02 at 12 months; and 73.85 versus 75.39 at 24 months in groups 1 and 2 respectively (p values <0.05 at 12 and 24 months as compared with onset. The mean mental health data for both groups were 61.12 versus 58.95 at onset; 76.15 versus 77.35 at 12 month; and 74.98 versus 76.36 at 24 months (p <0.05). (Table 3)

The results from the four components of physical (physical function, physical role, body pain, and general health) and mental (mental health, emotional role, social function, and vitality) revealed non-significant differences (p > 0.05) between groups.

The numbers of demyelinating lesions detected by MRI were dispersed through all assessments. However, the mean number of lesions at onset was significantly reduced in patients from group 2 (treated with Axuareb – biosimilar IFN) (63.04; SD=57.90 versus 77.09; SD=6.05; p< 0.05). The mean number of lesions was significantly increased (p < 0.05) at the end of the follow-up period (24 months) in both groups of patients. As should be expected, the mean number of lesions persisted significantly reduced in patients of group 2. Nonetheless, although the mean number of lesions significantly increased in both groups of patients, patients of group 2 showed a relatively minor increase (group 1: Onset = 77.09; End = 96.54; versus group 2: Onset = 63.04; End = 77.95).

NABs were measured in 45 patients (23 from group 1 and 22 from group 2). It should be emphasized that at treatment onset, none of the patients were NAB positive. NABs were detected in 3 patients from group 1 and 4 patients from group 2. Disability progression and annualized relapse rate were similar in patients NAB+ patients and NAB–patients. Furthermore, the detection of NAB was not associated with increased number of demyelinating lesions as assessed by MRI. No effects on clinical outcomes could be discerned either.

Flu-like symptoms occurred in 38.5% of patients from group 1 and...
in 47.4% of patients from group 2. Local reactions were detected in 20% and 25% of the patients from groups 1 and 2 respectively. Depression symptoms were detected in 15% of patients from group 1 and 11% of patients from group 2. Myalgia was reported in 15% and 18% of the patients from groups 1 and 2 respectively.

Treatment had to be discontinued in 2 patients from group 2 and 2 patients from group 2 because of drug related dermatitis. It should be pointed out that these 5 patients were referred to a dermatologist for treatment and follow-up. None of the patients showed abnormal laboratory data associated with either one of the IFN’s.

Discussion

Clinical benefits of IFN β – 1A, as measured by the EDSS score, annualized relapse rate and MRI findings in patients with RRMS have been well documented by several reports. The results of this clinical trial support these findings. Moreover, the results of this trial which was carried out under normal clinical practice conditions, demonstrated that both IFN’s studied herein (Axuareb – Biosimilar and Avonex – Original) are comparable safe and reliable treatment options. Both products showed similarly significant beneficial impacts on disease activity [14-17].

EDSS scores revealed non-significant differences between both treatment groups during the follow-up period of 24 months. A sustained decreased disability progression was similarly observed in both groups of patients. These results are in agreement with previous reports [18,19].

MRI findings including data of brain parenchymal fraction, T1 lesion volume, T2 lesion volume, number of new and/or enlarged T2 lesions and gadolinium enhanced lesion volume and count are similar to a previous report [20].

NAB data was similar in both groups of patients. Furthermore, no relationships were found between the presence of NAB and disability progression, new or enlarged T2 lesions and gadolinium lesions after the 24-month follow-up period. These data suggest that the relationship between NAB and long – term MS outcome in patients treated with IFN – β – 1A is quite complex.

Both drugs studied in this trial showed comparable tolerability. However, fewer patients receiving the biosimilar IFN showed side effects such as injection site reactions and flu-like symptoms.

Although one of the limitations of this study is the reduced number of patients included in the study groups, no significant differences were found in the efficacy and safety of both IFN’s.

In contrast with other chronic neurological diseases, several reports support the statement that MS exerts the most significant effects on health related quality of life (HRQOL) [21,22]. Physical dysfunction and social limitations severely disrupt HRQOL of patients with MS. The results of this study showed an improvement in overall HRQL of all patients after the 24-month treatment period. Furthermore, improvement was non-significantly different between groups.

Biosimilars can have a major impact on affordability and availability of important biologic products in the health care systems of countries with limited economic and social resources. Approval of biosimilars will lower cost and hence enhance patient accessibility to these drugs. However, quality of biosimilar products must be demonstrated in formal clinical trials.

A biosimilar product is defined as highly similar to the reference product notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety and potency of the product [23].

The complex high-molecular weight and 3-D structures of biopharmaceutical products, as well as their dependence to be produced in living cells, makes them different from conventional chemical drugs. Thus, verification of the similarity of biosimilars with innovated biopharmaceutical products is still a key challenge. Moreover, a critical safety issue, such as the immunogenicity of biopharmaceutical products has received a lot of attention in recent years. Such attention is confirming the need for comprehensive immunogenicity testing prior to approval and extended post – marketing surveillance. Bottom line is that only clinical trials and post – authorization pharmacological surveillance for monitoring potential immunogenicity will be able to provide definitive evidence for product comparison concerning safety and efficacy [10,24]. It seems that biosimilars present a whole new set of challenges for health care regulatory authorities.

The results of this trial demonstrated that safety and efficacy of the biosimilar IFN under study were significantly similar than the original IFN. The use of the biosimilar IFN slowed progression of the disease and decreased the frequency of relapses. In sum, the results of this trial confirm safety and beneficial effects of the biosimilar IFN (Axuareb) for treating patients with RRMS.

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References


