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PHARMACOKINETIC AND PHARMACODYNAMIC BIOCOMPARABILITY OF TWO r-hGH (INNOVATOR AND BIOSIMILAR) FORMULATIONS AFTER SUBCUTANEOUS ADMINISTRATION IN HEALTHY VOLUNTEERS

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ABSTRACT

Biosimilars are biological products that are the replica of their innovator biopharmaceuticals. Growth hormone is used to treat growth deficiency in children and another disorder. The objective of this study was to assess the relative pharmacokinetic and pharmacodynamics biocomparability of r-hGH biosimilar versus r-hGH reference. The study was performed in 23 healthy volunteers who underwent pituitary somatotrope cell down-regulation using octreotide, according to a randomized, two-period, and two sequence crossover design. Following subcutaneous administration of r-hGH (biosimilar or reference) pharmacokinetic and pharmacodynamics parameters were analyzed. Geometric mean values for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24}$ and $t_{½}$ were similar between the two r-hHG and the 95% confidence interval, all within the specified acceptance range (80-125%). There were no significative differences for IGF-I and IGFBP-III biomarkers, and also for the IGF-I/IGFBP-III molar ratio. Results demonstrate de biosimilarity of the r-hGH biosimilar with r-hGH reference in healthy volunteers.

Keywords: Biosimilars, Biocomparability, r-hGH, Pharmacokinetic, Pharmacodynamic.

INTRODUCTION

Biopharmaceuticals are medications, predominantly proteins that are manufactured using live organisms. These include blood and plasma products, non-recombinant proteins purified from natural sources, recombinant proteins and monoclonal antibodies produced in cell cultured. Follow-on protein products are those manufactured using biotechnology or derived from natural sources that are intended to be sufficiently similar to a biopharmaceutical product already approved by a regulatory agency [1]. These are called biosimilars and also have been referred to as a biogenerics or biosimilar. A biosimilar product is defined as a 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 [2].

Biosimilars, unlike conventional generic drugs, require more quality data and therefore must demonstrate full comparability, to the reference product.

Growth hormone deficiency (GHD) affects both children and adults, and clinical manifestations vary depending on the age of onset [2]. Children with short stature and low growth rate [3], while adults have altered body composition and metabolism with reduced physical performance [4]. At all ages, quality of life is impaired [5,6].

For many years, replacement therapy using exogenous human growth hormone (GH) has been used successfully to treat children with GHD [7], and has more recently benefited adult patients with GHD [8]. GH is now produced using recombinant DNA technology [9] and is also used to treat growth failure due to a number of other

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children disorders including Turner's syndrome [10-12] and chronic renal failure [13], and in children with born small for gestational age [14].

Different brands and biosimilars r-hGH have been approved for varying indications in different countries.

Xerendip^{R} is a biosimilar r-hGH formulation developed in two concentrations 4 and 16 IU. This trial is the first comparison in Mexico of the pharmacokinetic (PK) and pharmacodynamics (PD) characteristics the biosimilar r-hGH versus innovator r-hGH formulation in healthy volunteers.

The objective of the present study was to assess the bioequivalence of a biosimilar r-hGH formulation versus the reference r-hGH formulation since the pharmacokinetic and pharmacodynamics point of view.

METHODS

The study enrolled 23 healthy male and female volunteers. Eligible subjects were required to be age 18-55 years; have a body weight greater than 48.5 kg and a body mass index (BMI) of > 19 and ≤ 26.4 kg/m^2; have vital signs within the normal range; and to be non-smokers. Females were also required to have a negative serum pregnancy test within 3 weeks of the trial start and negative urine pregnancy test at the day before dosing. The following exclusion criteria were applied: a history or presence of diabetes, tumors in the pituitary gland or hypothalamus, any serious allergy, positive serological test for hepatitis B or C and HIV, hypertension or other significant cardiovascular abnormality. Subjects were also excluded if they had a significant history or clinical evidence of auto-immune, gastrointestinal, hematological, hepatic, neurological, pancreatic or renal disease, or had positive drug or alcohol test or chronic use of medication.
The single center trial Axis Clinical Latinamerica, carried out a clinical pharmacology research center in Mexico had an open, randomized, two-way crossover design. Treatment with r-hGH (Xerendip; Laboratorios PiSA, Mexico) biosimilar or r-hGH (Genotropin C; Pfizer, Mexico) innovator started within 30 days of screening. Each volunteer received two treatments: r-hHG biosimilar or r-hGH reference. The two treatments were administered as a single subcutaneous dose of 1.3 mg/ml (4 IU), to allow proper determination of the PK and PD parameters. The dose was administered in a randomized sequence with a 1-week wash-out period between each administration. The doses were injected into the right arm, using a needle and syringe.

Additionally, intravenous octreotide 0.1 mg (Infatalidina, Laboratorios PiSA) was administered by subcutaneous way 1 hour before the administration of r-hGH. This pituitary down-regulation was necessary to suppress endogenous GH secretion in the healthy volunteers to allow reliable calculation of PK and PD parameters.

For each r-hGH administration, the subject attended the clinical unit on the day before the study drug administration (days -1, 7 and 14) and stayed in the unit until 24 hours after drug administration (days 2, 8 and 15). Blood samples for PK, -1.0, -0.5, 0.0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, and 24 hours were taken post-dosing for both treatments. For PD analysis the samples were taken -1.0, -0.5, 0.0. 12.0 and 24 hours post-dose. Vital signs, safety and tolerability were assessed before and 24 hours after each dose and after the last dose.

The trial was conducted in compliance under Good Clinical Practice and COFEPRIS (Regulatory Agency in Mexico) directives for proper conduct of clinical drugs trials. The protocol was approved by the local ethics committee of Axis and the informed consent was obtained before star the trial.

The primary PK endpoints were the area under the serum concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-24}); area under the serum concentration-time curve extrapolated to infinity (AUC_{0-inf}), peak serum concentration (C_{max}); time of peak serum concentration (t_{max}); and elimination half-life ($t_{1/2}$). Determination of r-hGH in serum samples was performing using a chemiluminescent immunometric assay. (Siemens immulite/immulite 1000 GH, USA). Serum concentrations of r-hGH were analyzed for each subject by non-compartmental methods using WinNonLin Professional 4.1 (Pharsight, USA).

The primary PD endpoints were the serum concentrations of insulin-like growth factor-I (IGF-I) and insulin-like growth factor-III (IGFBP-III). For determination of IGF-I in serum samples was performed using the chemiluminescent immunoassay sandwich type method (Dia Sorin LIASON IGF-1, USA) and the quantification of IGFBP-III was performed with chemiluminescent immunometric test (SIEMENS Immulite/Immulite 1000 IFGBP-3, USA).

The PK endpoints were the levels of IGF-I and IGFBP-III. Analysis of the PD endpoints IGF-I and IGFBP-III was performed on the standard deviation values. Change from baseline to steady-state for all PD endpoints was analyzed between subject groups by an ANOVA, including subject group as fixed effect and the baseline assessment as covariate.

RESULTS

Trial subjects were recruited between November 2012 and April 2013. Of the 23 subjects (11 male and 12 female) allocated to treatment, all completed the trial. There were no major protocol deviations. The mean age of the volunteers was 31.91 years (range 18-55 years). At the pre-study examination, the mean weight was 62.53 kg (48.5 to 78.6), BMI was 23.64 (19.0 to 26.4) and height was 1.63 (1.41 to 1.85). The characteristics of subjects were similar through the treatment sequences. The PK and PD population comprised 23 subjects, and all 23 subjects

received the two doses of trial medication, and were included for PK, PD and safety evaluation.

The ANOVA model assumptions were met satisfactorily and there was no significant sequence effect (p=0.980). The mean ± SD serum concentrations vs time profiles for r-hGH following administration of 1.3 mg of r-hGH by either the biosimilar or innovator were generally similar throughout the blood monitoring period (Figure 1). Geometric mean values for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and $t_{½}$ were similar between the two r-hHG (Figure 1) The maximum serum r-hHG concentration (C_{max}) were 12.996 (SD ± 6.63) and 15.054 (SD ± 7.12) for biosimilar and reference, respectively (Table 1).

The 95% CIs for the ratio of biosimilar to reference r-hHG expressed as a percentage for $AUC_{0\text{-}24}$ (94.6, 116.8), $AUC_{0\text{-inf}}$ (95.9, 115.1), t_{max} (92.7, 111.4) and C_{max} (98.3, 118.5) were all within the specified acceptance range (80-125%) for average bioequivalence (Table 1).

The median t_{max} following dosing with the biosimilar r-hHG was 4.174 hours, compared with 4.913 hours following dosing using the reference r-hHG (Figure 2) and the Friedman testing showed no difference statistically significant (p>0.000) between both drugs.

The mean PD data are showing are presented in figure 3 and 4. The IGF-I and IGFBP-III values between both groups not showed a significant difference (p>0.05) between the healthy subjects. IGF-I SD score, and to a lesser extent IGFBP-III SD score, increased in both groups compared with baseline. The IGF-I/IGFBP-III molar ratio increased slightly for both groups, but there was no significant difference between groups. It should be noted that data for biomarkers, were highly variable, as depicted in the SDs.

No serious or life-threating adverse events (AEs) were observed, and no subject was withdrawn due to AEs. The majority of AEs were mild intensity and short duration, most frequently headache, nausea of mild severity. Although there was a higher incidence of local redness in subjects after use of both formulations, this was generally mild and was not associated with any significant difference in pain, bruising, swelling, and induration or itching.

Table 1. Primary and secondary pharmacokinetics efficacy endpoints in healthy volunteers

PK	Reference			Biosimilar		
	Mean	SD	Standard Error	Mean	SD	Standard Error
$T_{máx}$	4.913	1.411	0.294	4.174	1.337	0.279
$C_{máx}$	15.054	7.127	1.486	12.996	6.632	1.383
$ABC_{0\text{-}t}$	111.225	37.038	7.723	100.025	31.478	6.564
$ABC_{0\text{-inf}}$	116.629	40.139	8.370	104.482	32.107	6.695
$t_{1/2}$	4.764	3.292	0.686	4.901	2.007	0.418

Figure 1. Mean r-hGH serum concentration vs time profiles following subcutaneous administration of 1.3 mg r-hGH/subject using reference or biosimilar

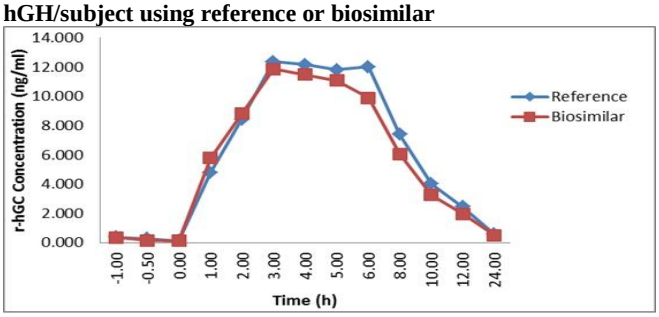


Figure 2. The median t_{max} following dosing with the biosimilar or reference r-hHG

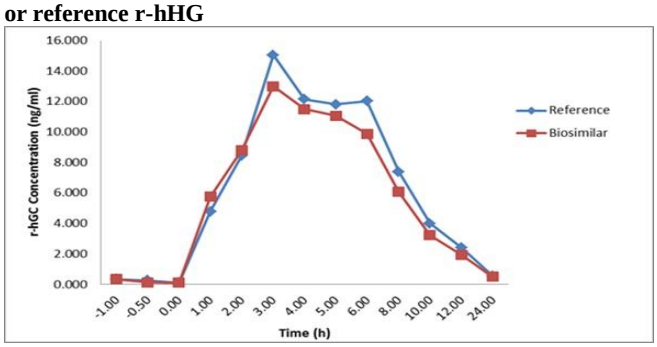


Figure 3. Pharmacodynamic efficacy end points for IGF-1

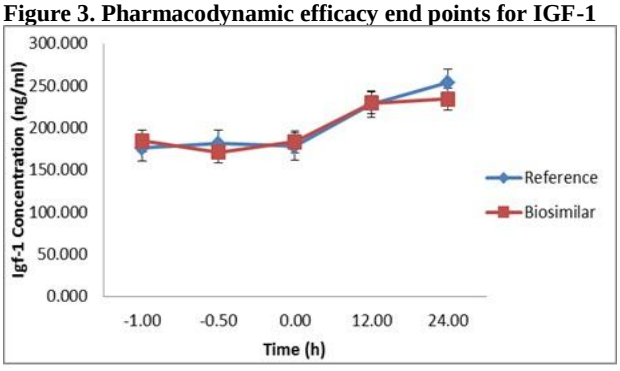
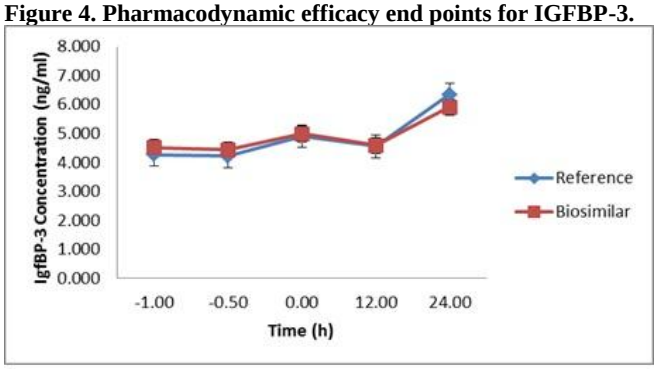


Figure 4. Pharmacodynamic efficacy end points for IGFBP-3.



DISCUSION

Biopharmaceutical drugs have become an essential part of modern pharmacology. These comprise proteins derived from recombinant DNA technology and monoclonal antibodies. Living organisms such as animal cells, bacteria, viruses and yearst are employed for the production of biopharmaceuticals. Biopharmaceuticals have the potential to reach up to 50% share in global pharmaceutical market in the next few years [15].

In the standard pharmaceutical sector, competition from cost-effective medicines is encouraged for many years now to stimulate innovation and to free up health care budget resources [16].

Follow-on protein products are those manufactured using biotechnology or derived from natural sources that are intended to be sufficiently similar to a biopharmaceutical product or products already approved by a regulatory agency [1].

Biosimilars, unlike conventional generic drugs, require more quality data and therefore must demonstrate full comparability (including pharmacokinetic and pharmacodynamics data), to the innovator product. The manufacturer must prove the quality of the generic product and, since the safety and efficacy of the active substance are already well known, the generic has to demonstrate its therapeutic equivalence with the original product through what are called bioequivalence studies [17].

This study has shown that the r-hGH biosimilar formulation was bioequivalent to the r-hGH innovator formulation in healthy volunteers with pituitary somatrope cell down-regulation. There were no apparent differences between the two formulations of r-hGH in the rate and extent of drug exposure, AUC_{0-24}, AUC_{0-inf}, C_{max}, t_{max}, and half-life, and IGF-I and IGFBP-III concentrations. In addition, variability in the PK or PD parameters was low through the two treatments.

Demonstration of bioequivalence of different formulations is not assumed to be significantly influenced by characteristics of the study population. Because of this, data from healthy volunteers can be extrapolated to adults as well as children patients.

The results of this bioequivalence study demonstrate that the concentration-time profile of r-hGH following subcutaneous delivery of r-hGH using biosimilar is comparable to the concentration-time profile of the same dose or r-hGH innovator. Regulatory guidance stipulates that 90% CIs for the ratios (test to reference) of the areas under the serum concentrations vs time curves (AUC ratio) and the maximum plasma drug concentration (C_{max} ratio) must fall between 80% and 125% [17], and this study shows that both rate and extent of exposure of r-hGH meet the accepted criteria for bioequivalence. These criteria have been used for many years, and there are the same for all drugs and routes of administration.

With respect to standard GH biomarkers IGF-I and IGFBP-III showed no significant difference between both groups in healthy volunteers after treatment were observed.

Our results are in agreement with previous pharmacokinetics and pharmacodynamics studies [19-21]. In these studies the 90% CIs around the ration of injection were 95.9-115.1% for area under curve to infinity. GH has a known metabolic half-life 20-30 min while the observed terminal half-lifes were 2-4 hours. Times of maximum concentrations, terminal half-lives and lag times to start of absorption appeared to be similar to results obtained in this study with both r-hGH. The previous and present studies were associated with a significant and similar rise in IGF-I and IGFBP-III. The plasma levels of IGF-I and IGFBP-III obtained by Houdijk EC et al [22] in children and adolescents were also similar our results.

It has been argued [23] that the safety of biosimilars is not “one a par” with the knowledge gained through the previous approval processes for GH, this is not correct [24]. Although no statistical analysis was performed to compare AEs, both treatments were tolerated in the study in terms of both AEs and local tolerability and pain assessment. Local redness, generally mild, was the most commonly observed reaction after administration or r-hGH biosimilar or reference.

Our conclusion is the two r-hGH, biosimilar and innovator formulations are pharmacokinetic and pharmacodynamic bioequivalent and both are well tolerated. In this case the r-hGH biosimilar is defined as being interchangeable with the reference product because is biosimilar to that product and can be expected to produce the same clinical result as that product in any given patient and there is no greater risk of safety or diminished efficacy when alternating or switching between the biosimilar and innovator products.

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