Growth Hormone & IGF Research 30–31 (2016) 31–36

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Comparative pharmacokinetic and pharmacodynamic evaluation between a new biosimilar and reference recombinant human growth hormone

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ARTICLE INFO

Article history:
Received 11 April 2016
Received in revised form 13 September 2016
Accepted 16 September 2016
Available online 16 September 2016

Keywords:
Human growth hormone
r-hGH
Biosimilar
Genotropin
Bioequivalence

ABSTRACT

Objective: To extend available dosing options in the treatment of growth hormone deficiency, a comparative pharmacokinetic and pharmacodynamic phase-1 clinical study involving subcutaneous administration of growth hormone was conducted.
Design: The test formulation (biosimilar recombinant human growth hormone; r-hGH; Somatotropin) and reference formulation (Genotropin®) were tested in 38 adult healthy subjects after their subcutaneous administration of 12.8 IU in an open label, single dose, randomized, two period cross over study separated with a washout period of 11 days. Endogenous growth hormone release was suppressed by a continuous Octreotide infusion up to 24 h after r-hGH administration. All the subjects were evaluated for local tolerance using Wong-Baker Faces pain rating scale and an injection site reaction (ISR) score. Detection of serum levels of r-hGH, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) was done by suitable validated bio-analytical methods. Assessment of bioequivalence for pharmacokinetic parameters was done using log-transformed area under the curve (AUC) and maximum concentration (C_{max}) for r-hGH. The pharmacodynamic assessment was done by comparing the area under the effect-time curve (AUEClast) and maximum measured effect concentration (E_{max}) of IGF-1 and IGFBP-3.
Results: The biosimilar formulation of recombinant human growth hormone fulfilled the predefined bioequivalence criteria for pharmacokinetic and pharmacodynamic parameters.
Conclusion: The new biosimilar recombinant human growth hormone bears the potential to become an alternative option for the treatment of growth hormone deficiency.

1. Introduction

Growth hormone deficiency (GHD) arises as a consequence of decreased secretion of growth hormone from the anterior pituitary. Decreased physical and psychological well-being and quality of life are recognized as particularly important and, from the patients' perspective, have become the major indication for replacement therapy [1]. GHD has been treated with growth hormone replacement since 1958. The usage of cadaveric growth hormone to treat severe GHD in children was the mainstay of treatment until 1985. Availability of recombinant human growth hormone (r-hGH) due to technological advances has allowed an expansion in its uses due to a greater availability, greater biological safety and significant refinements regarding dosage and administration frequency of this hormone [2]. The usage of r-hGH in children suffering from GHD, chronic kidney disease, Turner Syndrome and Prader–Willi Syndrome dates back to year 1985, 1993, 1997 and 2000 respectively. The usage of growth hormone in growth hormone deficient adults was approved in 1996. Improvement in body composition, bone health, cardiovascular risk factors, and quality of life indicators has been reported after growth hormone treatment in growth hormone deficient adults [3,4].

High costs of r-hGH treatment, however, cause a considerable burden for individuals and health systems, or even exclude patients from their required treatment. Unfortunately, this cost has been escalating through the coming years resulting in rise in overall healthcare costs. Considerable attention needs to be given to bring down the growth hormone replacement therapy cost without compromising with the quality of life.

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http://dx.doi.org/10.1016/j.ghir.2016.09.003
1096-6374/

Alternate treatment strategies such as increased duration of growth hormone treatment and high pubertal dosing of growth hormone did not substantially improve the cost-effectiveness ratio [2].

A major strategy for lowering the cost of growth hormone therapy has been the introduction of equivalents of the innovator drug, Genotropin® in global markets and hence there is considerable public interest in the availability of affordable r-hGH products, especially after the patent of the originator r-hGH product, Genotropin® has expired [2,5–7].

For small molecules, the standard bioequivalence approach has been developed and applied successfully for decades to assess therapeutic interchangeability of two preparations with one chemically identical active component. Similarly, in case of large molecules, the concept of 'biosimilarity' was introduced indicating that the products are considered to be similar in terms of quality, safety, and efficacy. Biosimilar in the case of recombinant proteins generally means that preparations contain the same protein backbone according to the amino acid sequence, have similar biological, pharmacokinetic and pharmacodynamic properties, exhibit a similar safety profile and similar therapeutic efficacy tested in accurate clinical studies, and therefore, might be considered a substitute to the reference product [8]. The biosimilars aim is to achieve a reduction in costs that greatly contribute to the sustainability of health systems. Cristália Produtos Químicos Farmacêuticos Ltda, Brazil has developed recombinant human growth hormone (r-hGH) as a biosimilar substitute to the corresponding innovator product Genotropin® of Laboratórios Pfizer Ltda. The present phase I clinical study was conducted to assess the bioequivalence between these two products. All physiochemical and biological attributes of both products were extensively compared before entering in to this phase 1 clinical study. This study was conducted as per the European Medicines Agency (EMA) guidelines effective at the time of study conduction and the International Conference on Harmonization for Good Clinical Practice (ICH GCP) guidelines [9,10].

2. Materials and methods

The present study compared the pharmacokinetic and pharmacodynamic parameters of subcutaneous dose of recombinant human growth hormone (r-hGH) of Cristália Produtos Químicos Farmacêuticos Ltda [each mL containing 5.33 mg of somatropin equivalent to 16 International Units (IU)] with Genotropin® of Laboratórios Pfizer Ltda [each mL containing 5.33 mg of somatropin (16 IU)].

2.1. Study population

A total of 38 (19 male and 19 female) normal, healthy, adult, human subjects were included in the study. The demographic and anthropometric assessment included measurement of age, height, weight, body mass index and waist measurement of the study population. The waist circumference measurement was done for obesity evaluation. The health of the subjects was determined by the medical history, physical examination,12-lead electrocardiogram (ECG), vital signs, oral glucose tolerance test, laboratory examinations such as hemogram, biochemistry (including fasting blood glucose, serum triglyceride and High Density Lipid (HDL) cholesterol etc.), serum fasting insulin, serology tests, breath alcohol test and urinalysis. The post-study evaluation was done by repeating these examinations and laboratory investigations at the end of study in each subject.

2.2. Clinical interventions and their timings

The study was performed with a randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design in normal, healthy, adult, male and female human subjects under fed condition. The study protocol was approved by the Independent Ethics Committee before the start of the study. A written approval to conduct the present phase I study in Indian subjects was obtained from the Drug Controller General of India Office. The study was conducted in accordance with the Declaration of Helsinki. The subjects were informed about all aspects of the study and signed consent was obtained before any study related procedure.

The subjects were confined in Clinical Pharmacological Unit for at least 12 h prior to drug administration till 24 h post-dose in each study period. Subjects taking any over the counter (OTC) product or enzyme modifying drug within 28 days of study initiation were excluded from the study. The female subjects taking oral contraceptive pills or any other hormonal contraceptive preparation were excluded from the study. The inclusion of female subjects was done irrespective of the phase of menstrual cycle in both periods of the study. Thus, the possibility of female subjects having different phases of menstrual cycle during the period of study conduction was not ruled out. Except for continuous intravenous infusion of Octreotide (40 μg/h), no other concomitant medication was allowed in the study. The subjects requiring medication for the treatment of adverse events were to be withdrawn from the study. The female subjects were not allowed to take any hormonal contraceptive medication until the completion of the study. As Octreotide injection has been routinely employed in r-hGH bioequivalence studies in healthy volunteers for suppression of endogenous GH secretion, all subjects in each period were administered with Octreotide infusion (40 μg/h) starting 1 h before and up to 24 h after the r-hGH administration [11]. The study was conducted in fed state as usage of Octreotide is associated with abdominal discomfort and hypoglycemia secondary to inhibition of Glucagon. A high-fat and high calorie breakfast was provided to the subjects 30 min before administration of r-hGH.

A tuberculin syringe having capacity of 1 mL was used for the administration of each treatment. The composition of test product (after reconstitution of the lyophilized powder) and reference product (preconstituted solution) was 5.33 mg/mL corresponding to 16 IU/mL. Keeping in mind the possibility of not having 1 mL reconstituted or pre-constituted solution accurately in the syringe after complete removal of air bubbles from it, decision to administer 0.80 mL of the study treatments was taken a priori. Thus, single subcutaneous dose of 0.80 mL of either of the treatments (corresponding to 12.8 IU) was given just below the groin at upper inner thigh as per the randomization in each study period.

Three baseline venous blood samples at −1, −0.50 and 0 h prior to growth hormone dosing and adequate number of blood samples up to 24 h after dosing were taken for the pharmacokinetic (PK) assessment of r-hGH. For pharmacodynamic (PD) assessment of Insulin like growth factor-1 (IGF-1) and Insulin like growth factor binding protein-3 (IGFBP-3), the venous blood samples were extended up to 96 h post-dose. The collection of whole blood was done in a gel tube having clotting accelerator in it for the measurement of PK and PD parameters. Without shaking, the tubes were kept in a standing position up to 20–30 min at room temperature (25 °C ± 5 °C). Thereafter, the tubes were centrifuged at 3500 RPM at 4° ± 2 °C for 10 min to obtain the serum. The serum samples collected for r-hGH were stored in deep freezer maintained at −20 °C ± 5 °C while remaining samples were placed in deep freezer maintained at −70 °C ± 10 °C.

The vital sign measurement, ECG recording, well-being assessment physical examination and clinical laboratory tests were done frequently before and after the administration of r-hGH. The subjects were monitored for adverse events, and serious adverse events.

Evaluation of local tolerance at the site of injection was done by the subjects using Wong-Baker Faces pain rating scale which included various scores such as zero (no hurt), 2 (hurts little bit), 4 (hurts little more), 6 (hurts even more), 8 (hurts whole lot) and 10 (hurts worst). Local tolerance was also evaluated by the treatment blinded assessor using an injection site reaction (ISR) score (grading from 0 = no reaction to 3 = severe reaction) at different time points. This was done by assessing the diameter of injection-site redness, injection-site swelling, bruising, and consideration of subject-reported itching.