CLINICAL STUDY

Bioequivalence between novel ready-to-use liquid formulations of the recombinant human GH Omnitrope and the original lyophilized formulations for reconstitution of Omnitrope and Genotropin

Uwe Fuhr, Daniel Tuculanu¹, Alexander Berghout², Sigrid Balser², Arnd Schwebig² and Paul Saenger³

Clinical Pharmacology Unit, Department of Pharmacology, Hospital of the University of Cologne, D-50931 Cologne, Germany, ¹Fourth Medical Clinic, Timisoara University of Medicine and Pharmacy, RO-300173 Timisoara, Romania, ²Sandoz Biopharmaceutical Development, Industriestrasse 25, D-83607 Holzkirchen, Germany and ³Endocrinology, Albert Einstein College of Medicine, Bronx, NY-10467 New Jersey, USA

(Correspondence should be addressed to A Berghout; Email: alexander.berghout@sandoz.com)

Abstract

Objective: Two strengths of a novel ready-to-use liquid preparation of the recombinant human GH (rhGH) Omnitrope were developed to increase the convenience for the patients.

Design: Omnitrope 3.3 mg/ml solution or Omnitrope 6.7 mg/ml solution was compared to Omnitrope 5 mg/ml powder and Genotropin 5 mg/ml powder in terms of pharmacokinetics, pharmacodynamics, safety, and local tolerance after a single s.c. dose of 5 mg.

Methods: Two randomized, double-blind, single-dose, three-way crossover studies were carried out in 36 young healthy volunteers each. Endogenous GH secretion was suppressed with a 25-h continuous i.v. infusion of octreotide (40 µg/h) starting 1 h before rhGH administration.

Results: Pharmacokinetic parameters were similar for the three treatments in both studies respectively. Bioequivalence criteria were met for area under the concentration–time curve (AUC) and C_{max} . Likewise, the pharmacodynamic parameters for IGF1, IGF-binding protein 3, and non-esterified fatty acid were similar for all preparations. No differences in adverse events were observed between groups.

Conclusions: Omnitrope 3.3 mg/ml solution, 6.7 mg/ml solution, and 5 mg/ml powder, and Genotropin 5 mg/ml powder are bioequivalent, have similar pharmacokinetic and pharmacodynamic profiles, and are equally safe. Overall, the products can be considered to be therapeutically interchangeable.

European Journal of Endocrinology 162 1051–1058

Introduction

Prior to the introduction of recombinant human GHs (rhGHs) in the 1980s, extracts from human pituitary glands (pithGH) have been used to treat GH deficiency, mainly in pituitary dwarfism. Availability, purification, standardization, immunogenicity, microbial safety, and especially the cumulative appearance of Creutzfeldt–Jakob disease were the major limitations of this approach (1, 2). Therefore, the development of rhGH preparations and their first use in 1981 were major therapeutic advances, and also enabled the broader use of rhGH in other diseases with deficient endogenous GH production, in insulin-like growth factor 1 (IGF1) resistance (e.g. Turner syndrome), and in growth disturbances due to other diseases (3, 4).

High costs of rhGH treatment, however, cause a considerable burden for individuals and health systems, or even exclude patients from their required treatment. Thus, there is considerable public interest in the availability of affordable rhGH products, especially

after the patent of the originator rhGH products has expired, with the new products being tailored for the individual use (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 (8). Since biopharmaceuticals differ from small-molecule drugs in complexity and proof of essential similarity cannot be achieved in such products (9), the bioequivalence approach was modified for biopharmaceuticals, and the concept of ‘biosimilarity’ was introduced indicating that the products are considered to be similar in terms of quality, safety, and efficacy (10–12). Biosimilar in the case of recombinant proteins generally means that preparations contain the same protein backbone according to the amino acid sequence, have similar pharmacokinetic and pharmacodynamic properties, exhibit a similar safety profile and similar therapeutic efficacy tested in accurate clinical studies, and therefore, can be considered interchangeable (11, 13).

The products still may have subtle structural and physicochemical differences attributable e.g. to post-translational modification, complex formation, or degradation resulting in different distribution of (micro) heterogeneity of the individual preparations (11, 12). To define acceptance criteria, the European Medicines Agency (EMA) developed general guidelines on biosimilar drugs (14–16) as well as specific guidelines for individual biosimilar substances including rhGH (17, 18).

The rhGH products studied here, i.e. Omnitrope and Genotropin, have the same amino acid sequence which is identical to that of natural hGH. The therapeutic effects of GH are mediated by IGF1 (19). IGF1-binding proteins (IGFBPs) play important regulatory roles in controlling the bioavailability and action of IGF1, and are regulated by various factors including GH (20, 21). About 90% of IGF1 is bound to IGFBP3. Because rhGH preparations induce significant increases in IGF1, IGFBP3, and non-esterified fatty acid (NEFA) (22) related to GH mechanism of action, these molecules are accepted as pharmacodynamic (PD) parameters for GH activity; however, the spurious relationship between serum IGF1 levels and growth response precludes the use of IGF1 as a surrogate marker for efficacy (17).

Omnitrope has been developed as a similar biological medicinal product (biosimilar) with Genotropin as the reference product, based on a concise clinical program consisting of phase I studies and phase III studies according to the respective guidelines. In 2006, marketing authorization for Omnitrope 5 mg/ml powder for solution for injection (Omnitrope 5 P) was granted by both the EMA and the FDA. To extend the usability of Omnitrope and to increase the convenience for patients, a ready-to-use Omnitrope 3.3 mg/ml solution for injection (Omnitrope 3.3 S) and also a higher concentrated liquid preparation of Omnitrope containing 6.7 mg of rhGH per ml (Omnitrope 6.7 S) were developed. Equivalent therapeutic efficacy and clinical comparability in terms of safety and immunogenicity of Omnitrope 5 P with Genotropin 5 mg/ml powder (Genotropin 5 P) and Omnitrope 3.3 S have already been reported in a limited set of clinical studies (23). The purpose of the present two studies was to demonstrate the bioequivalence of the two novel rhGH liquid preparations, Omnitrope 3.3 S and Omnitrope 6.7 S, with the commercial powder preparations Omnitrope 5 P and Genotropin 5 P, and to demonstrate the comparability in terms of pharmacokinetic (PK), PD, safety, and local tolerance after a single s.c. dose of 5 mg of each product in healthy subjects.

Methods

Study design

For each of the two novel Omnitrope liquid preparations – Omnitrope 3.3 S and Omnitrope 6.7 S – a separate randomized, double-blind, single-dose, three-way

crossover study was carried out in 36 healthy volunteers (studies A and B respectively). In both studies, in addition to the respective novel preparation, both marketed Omnitrope and Genotropin 5 mg/ml powder preparations were included as references. The studies were conducted in healthy, young, non-smoking, Caucasian male or female subjects. Both studies were conducted according to the revised Declaration of Helsinki and GCP guidelines, and were approved by the pertinent ethics committee and the regulatory authorities. All individuals examined during the study gave their written informed consent. Eligibility was based on extensive examinations including physical examination, clinical chemistry, urinalysis, electrocardiogram (ECG) recording, vital signs, tests for substance abuse, and pregnancy. For both studies, study procedures were the same in each of the three treatment periods, which were separated by a 7-day washout period between the rhGH administrations. Subjects underwent a full physical and safety examination with standard clinical laboratory evaluation, urinalysis, ECG, virology, toxicology, and alcohol screening, and in addition, a pregnancy test was done for female subjects at the screening examination and also 14 days after the last dosing. Healthy male and female volunteers who met the inclusion/exclusion criteria were randomized to one of the six possible treatment sequences. The subjects were confined to the study center from the evening prior to each treatment period until blood sampling 24 h after rhGH administration, which was done after overnight fasting. Upon admission to the ward, a baseline evaluation was done including eligibility, concomitant medications, safety, toxicology, and alcohol screening, and again, a pregnancy test was done for female subjects in addition to that described above. One hour before the administration of rhGH, a 25-h continuous i.v. infusion of octreotide (40 µg/h; a somatostatin analog, Sandostatin, Novartis Pharma AG, Basel, Switzerland) was started. This schedule is effective to almost completely suppress endogenous GH secretion (Sandoz GmbH, Kundl, Austria, data on file).

Blood sampling for hGH and NEFA analyses was performed at –1.0, –0.5, 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 h relative to rhGH administration, while samples for IGF1 and IGFBP3 analyses were drawn at –1.0, –0.5, 0, 12, 16, 24, 48, 72, and 96 h. Vital signs were measured repeatedly during the sampling period, and further safety checks were done 96 h after dosing. Nutrition was standardized during the in-house period. Adverse events and use of any concomitant medications were recorded at 12, 24, 48, 72, and 96 h relative to rhGH administration, and at the final follow-up visit. In each treatment period, local tolerance was assessed 5 min and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h after dosing. Local tolerance was evaluated by the subjects using a 100-mm visual analogue scale (VAS) for pain, and by the assessor using an injection site reaction (ISR) score (grading from 0 = no reaction to 3 = severe harm).

Study medication

The intended dose of rhGH in all cases was 5.00 mg. Omnitrope 5 mg/ml powder preparations (5 P) and Omnitrope ready-to-use solution preparations (3.3 S and 6.7 S) were manufactured by Sandoz GmbH. Genotropin 5 mg/ml powder preparation (5 P) was purchased from Pfizer Pharma GmbH, Karlsruhe, Germany. The ready-to-use solutions were administered as such, while the powder preparations were reconstituted prior to administration according to the respective method as registered. Accordingly, scheduled volumes for administration were 1.50 ml for Omnitrope 3.3 S, 0.75 ml for Omnitrope 6.7 S, and 1.00 ml for the reconstituted powder preparations of Omnitrope 5 P and Genotropin 5 P (given in both studies). Administration was via the s.c. route to the lower abdomen. Syringes used in the studies were weighed before and after administration to detect potential differences between the intended and the actually administered dose possibly caused by slight variations in drug reconstitution and administration technique. For those individuals included in the analyses, the actual mean (s.d.) administered dose of Omnitrope 3.3 S was 4.76 (0.06) mg and of Omnitrope 6.7 S was 4.90 (0.68) mg. For the Omnitrope 5 P and Genotropin 5 P preparations, the real administered doses were 4.76 (0.23) mg and 4.95 (0.14) mg in study A, and 4.86 (0.25) mg and 4.97 (0.11) mg in study B respectively.

Sample size and study populations

The sample size was calculated using the standard bioequivalence methods and boundaries (80–125% for 90% confidence interval (CI) of AUC_{last} and C_{max} ratios). Based on a previous bioequivalence study, intra-subject coefficients of variation of 20% for C_{max} and 10% for AUC_{last} and a true ratio of means between 95 and 105% were assumed. A total sample size of 30 subjects was thus considered sufficient to show bioequivalence between all three pairs of treatments simultaneously, with an overall power of at least 80% including adjustment for the multiple testing. Anticipating a drop-out rate of up to 20%, a total number of 36 subjects were dosed for each study.

In study A, 30 male and 6 female volunteers were included. The mean (s.d.) age was 27.4 (5.1) years, body weight 70.6 (11.1) kg, body height 174 (8) cm, and body mass index (BMI) 23.1 (2.5) kg/m². One of the 36 randomized subjects was prematurely withdrawn from the study for not appearing for the second treatment period. Thus, 35 subjects were included in the PK/PD evaluations (per-protocol-population). In study B also, 30 male and 6 female volunteers were included. The mean (s.d.) age was 27.1 (5.1) years, body weight 69.1 (9.2) kg, body height 174 (7) cm, and BMI 22.7 (2.1) kg/m². Two of the subjects withdrew from the study prematurely after period 1 for personal reasons,

and for two subjects, deviations of the syringe weights of more than ± 3 s.d. of the mean weights were observed, leading to an exclusion of four subjects from the per-protocol-population.

Analytical methods

Blood samples were allowed to clot at room temperature. Serum was obtained by centrifugation, and stored at ≤ -20 °C until analysis. The concentrations of hGH, IGF1, and IGFBP3 in serum were measured using the respective commercially available and fully validated chemiluminescent immunometric assay kits of the Immulite 2000 series with the Immulite 2000 Analyzer (DPC Biermann GmbH, Bad Nauheim, Germany). The lower limit of quantification (LLOQ) was 0.2 ng/ml for GH, 25 ng/ml for IGF1, and 500 ng/ml for IGFBP3. The concentration of NEFA in serum was measured using a commercially available and fully validated assay kit obtained from Wako Chemicals GmbH (Neuss, Germany). The LLOQ was 100 nmol/ml. The assays were additionally validated according to the requirements of the FDA guideline for bioanalytical method validation (24). Within the validation, the accuracy and precision (intra- and inter-assay), linearity, LLOQ, and stability of the different parameters (freeze thaw, short term (room temperature and 2–8 °C up to 4 h), and long term for up to 3 months) were tested. All validation parameters fulfilled the acceptance criteria based on the guideline.

Calculation of PK and PD parameters and statistical evaluation

Parameters were calculated from the serum concentration versus actual sampling time profiles of GH (PK parameters) and of IGF1, IGFBP3, and NEFA (PD parameters) by standard non-compartmental methods using the WinNonlin software (version 4.1, Pharsight

Figure 1 Study A: GH serum levels (mean $\pm$ s.d.) after a single s.c. injection of Genotropin 5 mg/ml powder (black boxes), Omnitrope 5 mg/ml powder (white triangles), and Omnitrope 3.3 mg/ml solution (white circles).

Figure 2 Study B: GH serum levels (mean $\pm$ s.d.) after a single s.c. injection of Genotropin 5 mg/ml powder (black boxes), Omnitrope 5 mg/ml powder (white triangles), and Omnitrope 6.7 mg/ml solution (white circles).

Corporation, Mountain View, CA, USA). No corrections for positive baseline values were carried out for any of the calculations. AUC calculations were done using the linear trapezoidal rule. PK parameters included the area under the concentration–time curve from time zero to the time of the last concentration (AUC_{last}), AUC_{last} extrapolated to infinity ($AUC_{0 \rightarrow \infty}$), maximum serum concentration (C_{max}), time to reach C_{max} (t_{max}), and elimination half-time associated with the terminal slope (λ_z) of the semilogarithmic concentration–time curve ($t_{1/2}$). PD variables included area under the effect–time curve ($AUEC_{last}$), maximum measured effect

concentration (E_{max}), and time of E_{max} ($t_{max,E}$). PK and PD parameters were summarized by standard descriptive procedures. For the comparison of treatments, testing for bioequivalence was done based on ANOVA, including sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect, on the ln-transformed PK parameters AUC and C_{max} . For these parameters, 90% CIs were derived from the ANOVA (25), whereas non-parametric analyses were performed to compare t_{max} and $t_{1/2}$. Comparison was confirmatory for AUC_{last} and C_{max} , and descriptive for the remaining parameters. Similarly, 95% CIs were derived from the ANOVA to compare the PD parameters $AUEC_{last}$ and E_{max} , while $t_{max,E}$ was compared based on non-parametric CIs.

Results

Individual GH serum concentration versus time profiles (Figs 1 and 2) and the derived PK parameters (Table 1) were found to be very similar for the three rhGH preparations within each of the two studies. Standard bioequivalence criteria were met for AUC and C_{max} , i.e. the respective 90% CIs for the ratios of the means were within the 0.80–1.25 range for each of the pairwise comparisons (Table 2). In study A, albeit within the bioequivalence range, concentrations and derived PK parameters were significantly ($\alpha=10\%$) higher for the Genotropin preparation, as could be expected from

Table 1 Pharmacokinetic parameters of GH after a single s.c. administration of 5 mg of Omnitrope 3.3 mg/ml solution or Omnitrope 6.7 mg/ml solution respectively in comparison to Omnitrope 5 mg/ml powder and Genotropin 5 mg/ml powder (PP populations). Results are presented as mean (s.d.).

	Preparation		
	Omnitrope 3.3 S	Omnitrope 5 P	Genotropin 5 P
Study A ($n=35$)			
AUC_{last} (h μ g/l)	542 (141)	559 (148)	588 (133)
$AUC_{0 \rightarrow \infty}$ (h μ g/l)	546 (140)	566 (147)	592 (131)
C_{max} (μ g/l)	72 (28)	71 (24)	78 (27)
t_{max} (h) ^a	4.0 (2.0–6.0)	4.0 (2.0–8.0)	4.0 (2.0–8.0)
$t_{1/2}$ (h)	2.8 (0.7)	3.2 (0.7)	2.6 (0.7)
V_d (l)	41 (23)	44 (19)	34 (18)
k_{el} (1/h)	0.26 (0.06)	0.23 (0.06)	0.29 (0.07)
CL/F (l/h)	9.9 (3.4)	9.5 (2.8)	8.9 (2.3)
	Preparation		
	Omnitrope 6.7 S	Omnitrope 5 P	Genotropin 5 P
Study B ($n=32$)			
AUC_{last} (h μ g/l)	558 (115)	550 (96)	537 (110)
$AUC_{0 \rightarrow \infty}$ (h μ g/l)	561 (114)	555 (96)	540 (110)
C_{max} (μ g/l)	74 (22)	69 (16)	73 (20)
t_{max} (h) ^a	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)
$t_{1/2}$ (h)	2.5 (0.7)	2.9 (0.5)	2.5 (0.7)
V_d (l)	35 (18)	39 (11)	36 (17)
k_{el} (1/h)	0.30 (0.07)	0.24 (0.05)	0.29 (0.06)
CL/F (l/h)	9.3 (2.1)	9.3 (1.8)	9.7 (2.3)

^aMedian value (min–max).

Table 2 Results of confirmative comparisons for primary pharmacokinetic parameters AUC_{last} and C_{max} (PP populations).

	AUC _{last} ratio of LS-means (90% CI)	C _{max} ratio of LS-means (90% CI)
Study A (n=35)		
Omnitrope 3.3 S versus Omnitrope 5 P	0.965 (0.922, 1.012)	0.978 (0.903, 1.060)
Omnitrope 3.3 S versus Genotropin 5 P	0.909 (0.868, 0.953)	0.896 (0.827, 0.971)
Omnitrope 5 P versus Genotropin 5 P	0.942 (0.899, 0.987)	0.916 (0.845, 0.992)
Study B (n=32)		
Omnitrope 6.7 S versus Omnitrope 5 P	1.007 (0.975, 1.041)	1.042 (0.989, 1.096)
Omnitrope 6.7 S versus Genotropin 5 P	1.038 (1.004, 1.073)	1.008 (0.958, 1.061)
Omnitrope 5 P versus Genotropin 5 P	1.031 (0.997, 1.065)	0.968 (0.920, 1.019)

the higher mean real administered dose (Genotropin 5 P: 4.95 mg, and Omnitrope 3.3 S and Omnitrope 5 P: 4.76 mg). When corrected for the individually applied real doses, these differences disappeared.

The PD profiles (Table 3) of the secondary parameters IGF1, IGFBP3, and NEFA of the three rhGH preparations were also found to be comparable, based on the corresponding 95% CIs for the ratios of the respective parameters (Table 4).

Local tolerability did not provide any surprising results for a s.c. injection of rhGH. As expected, the results for pain rating by the subjects at the site of the rhGH administration were clustered near the far left-hand side of the 100 mm VAS (no pain). The highest reported pain ratings were immediately following injection. The mean rating in study A (results of study B given in parentheses)

was 9.5 ± 9.3 mm following Omnitrope 3.3 S injection (9.0 ± 8.1 mm following Omnitrope 6.7 S injection), 6.8 ± 5.6 mm (5.3 ± 5.9 mm) following Omnitrope 5 P injection, and 17.3 ± 14.7 mm (11.3 ± 10.2 mm) following Genotropin 5 P injection. The mean pain rating was below 1.0 mm for all three treatments by 2 h (study A) and by 30 min (study B) after the rhGH administration. ISR scores determined by the investigator at the same time points were none or mild for all treatments with no discernable difference between the products. Most reactions were reported within the first 30 min of injection.

The most frequently reported adverse events were abdominal pain (experienced by 50.0% of subjects in study A and by 38.9% subjects in study B), headache (28.3/33.3%), diarrhea (19/25.0%),

Table 3 Pharmacodynamic parameters after a single s.c. administration of 5 mg of Omnitrope 3.3 mg/ml solution or Omnitrope 6.7 mg/ml solution respectively in comparison to Omnitrope 5 mg/ml powder and Genotropin 5 mg/ml powder (PP populations). Results are presented as mean (s.d.).

	Preparation		
	Omnitrope 3.3 S	Omnitrope 5 P	Genotropin 5 P
Study A (n=35)			
IGF1 AUEC _{last} (h µg/l)	16 298 (3664)	16 745 (3795)	15 962 (3557)
IGF1 E _{max} (µg/l)	213 (49)	218 (55)	209 (49)
IGF1 t _{max,E} (h) ^a	24 (12–48)	24 (12–48)	24 (12–48)
IGFBP3 AUEC _{last} (h mg/l)	427 (56)	430 (61)	424 (57)
IGFBP3 E _{max} (mg/l)	4.9 (0.6)	4.9 (0.7)	4.9 (0.7)
IGFBP3 t _{max,E} (h) ^a	48 (12–96)	48 (24–96)	48 (16–72)
NEFA AUEC _{last} (h mmol/l)	14.8 (3.8)	15.2 (4.9)	16.2 (4.9)
NEFA E _{max} (mmol/l)	1.2 (0.3)	1.3 (0.4)	1.3 (0.3)
NEFA t _{max,E} (h) ^a	2 (1–24)	2 (0–16)	3 (1–16)
	Preparation		
	Omnitrope 6.7 S	Omnitrope 5 P	Genotropin 5 P
Study B (n=32)			
IGF1 AUEC _{last} (h µg/l)	19 829 (5107)	20 355 (5067)	19 126 (5072)
IGF1 E _{max} (µg/l)	265 (68)	267 (64)	252 (67)
IGF1 t _{max,E} (h) ^a	24 (16–24)	24 (16–48)	24 (12–24)
IGFBP3 AUEC _{last} (h mg/l)	468 (67)	471 (70)	459 (66)
IGFBP3 E _{max} (mg/l)	5.4 (0.8)	5.4 (0.8)	5.3 (0.7)
IGFBP3 t _{max,E} (h) ^a	48 (0–72)	48 (16–96)	48 (24–72)
NEFA AUEC _{last} (h mmol/l)	12.8 (3.7)	13.1 (3.8)	12.0 (4.2)
NEFA E _{max} (mmol/l)	1.1 (0.3)	1.1 (0.3)	1.0 (0.3)
NEFA t _{max,E} (h) ^a	3 (2–16)	3 (1–16)	3 (1–20)

^aMedian value (min–max).

Table 4 Results of descriptive comparisons for pharmacodynamic parameters.

	AUEC_{last} ratio of LS-means (95% CI)	E_{max} ratio of LS-means (95% CI)
IGF1 study A		
Omnitrope 3.3 S versus Omnitrope 5 P	0.978 (0.942, 1.013)	0.982 (0.937, 1.029)
Omnitrope 3.3 S versus Genotropin 5 P	1.021 (0.985, 1.059)	1.022 (0.975, 1.071)
Omnitrope 5 P versus Genotropin 5 P	1.045 (1.008, 1.084)	1.041 (0.993, 1.090)
IGF1 study B		
Omnitrope 6.7 S versus Omnitrope 5 P	0.974 (0.942, 1.008)	0.994 (0.953, 1.036)
Omnitrope 6.7 S versus Genotropin 5 P	1.042 (1.008, 1.077)	1.057 (1.014, 1.102)
Omnitrope 5 P versus Genotropin 5 P	1.069 (1.034, 1.105)	1.064 (1.020, 1.109)
IGFBP3 study A		
Omnitrope 3.3 S versus Omnitrope 5 P	0.995 (0.978, 1.013)	0.994 (0.968, 1.021)
Omnitrope 3.3 S versus Genotropin 5 P	1.007 (0.989, 1.025)	1.005 (0.979, 1.033)
Omnitrope 5 P versus Genotropin 5 P	1.012 (0.995, 1.030)	1.011 (0.984, 1.039)
IGFBP3 study B		
Omnitrope 6.7 S versus Omnitrope 5 P	0.995 (0.974, 1.017)	0.999 (0.971, 1.029)
Omnitrope 6.7 S versus Genotropin 5 P	1.021 (0.999, 1.043)	1.024 (0.995, 1.055)
Omnitrope 5 P versus Genotropin 5 P	1.025 (1.003, 1.048)	1.025 (0.995, 1.055)
NEFA study A		
Omnitrope 3.3 S versus Omnitrope 5 P	0.981 (0.888, 1.084)	0.975 (0.898, 1.057)
Omnitrope 3.3 S versus Genotropin 5 P	0.922 (0.835, 1.019)	0.928 (0.856, 1.007)
Omnitrope 5 P versus Genotropin 5 P	0.940 (0.851, 1.039)	0.953 (0.879, 1.033)
NEFA study B		
Omnitrope 6.7 S versus Omnitrope 5 P	0.976 (0.894, 1.066)	1.018 (0.927, 1.118)
Omnitrope 6.7 S versus Genotropin 5 P	1.077 (0.986, 1.176)	1.120 (1.020, 1.231)
Omnitrope 5 P versus Genotropin 5 P	1.104 (1.011, 1.206)	1.100 (1.002, 1.209)

flatulence (14.2/11.1%), nausea (8.5/19.4%), vomiting (6.6/13.9%), hypotension (4.7% in study A), dizziness (19.4% in study B), upper abdominal pain (8.3% in study B), and asthenia (8.3% in study B). The causal relationship of these adverse events (AEs) was rated as being unlikely or unrelated in more than 95% of the events in both studies. Intensity of the AEs was rated as mild in roughly 60% of the cases and as severe in less than 5%. Of the eight severe AEs, five were episodes of headache, one was an episode of nasopharyngitis, one was an episode of abdominal pain, and one was a urinary tract infection. All treatment groups were similar in the number, type, and intensity of adverse events. None of the observed AEs was unexpected.

Discussion

Omnitrope 5 mg/ml lyophilized powder for reconstitution received market authorization in Europe on the basis of the first ever biosimilar approval in 2006. The reference product is Genotropin 5 mg/ml lyophilized powder for reconstitution. Two strengths of a novel ready-to-use liquid preparation of Omnitrope were developed to simplify the handling for the patients, and to make the injection procedure less time-consuming. It also represents the first-line extension of a biosimilar product, and illustrates how biosimilar development may stimulate further innovation of biological product development.

Pharmacokinetics

The present studies demonstrate the bioequivalence of the two novel liquid rhGH preparations Omnitrope 3.3 mg/ml solution and Omnitrope 6.7 mg/l solution to the marketed Omnitrope 5 mg/ml powder and Genotropin 5 mg/ml powder preparations, and confirm the bioequivalence of the latter two original preparations. The study design is in agreement with the respective EMEA guideline on GH (17). Single-dose pharmacokinetics, namely AUC, C_{max} , and terminal elimination half-life, are the main criteria to assess similarity with respect to pharmacokinetics and pharmacodynamics. The use of the classical criteria of bioequivalence, i.e. 90% CI for the estimated ratios for AUC and C_{max} within the 80–125% boundaries, is justified on the basis of the known intra-individual variability of 10–20%.

Pharmacodynamics

IGF1 is the preferred pharmacodynamic marker for the activity of somatropin and is, together with IGFBP3, recommended to be used in comparative pharmacodynamic studies (17). The results of the phase I studies demonstrated that s.c. administration of 5 mg of Omnitrope 3.3 mg/ml solution, Omnitrope 6.7 mg/l solution, Omnitrope 5 mg/ml powder, and Genotropin 5 mg/ml powder has similar pharmacokinetic and pharmacodynamic profiles. The sensitivity of the IGF1, IGFBP3, and NEFA parameters has its limitations to detect differences. Although NEFA serum levels show a

significant rise after GH administration, the changes in IGF1 and IGFBP3 serum levels brought about by rhGH at the dose tested are relatively low compared with baseline concentrations (26). The increase in serum levels of IGF1 stayed within the upper normal range, and did not accumulate to reach acromegalic values after the single-dose rhGH administration (27). Furthermore, based on the law of mass action, changes in pharmacodynamic parameters are almost always much less than those in pharmacokinetic parameters. Finally, concentrations of IGF1 and IGFBP3 were taken into account until 96 h after somatropin administration, whereas somatostatin infusion was stopped 24 h post dosing. Nevertheless, the results of the present studies unequivocally show that there are no meaningful differences between the preparations in any respect for all the parameters tested, and that the pharmacodynamic profiles are similar.

Side effects

The most frequently reported adverse events were those affecting the gastrointestinal system, which were mainly considered to be a side effect of octreotide. Therefore, it is difficult to assess whether rhGH treatment might also contribute to these complaints in this setting as described earlier (26, 28). Nevertheless, adverse events were similar regarding the number, type, and intensity in all treatment groups. None of the observed AEs was unexpected.

Conclusions

Two strengths of a novel ready-to-use liquid preparation of Omnitrope were developed to increase the convenience for the patients. Omnitrope 3.3 mg/ml and Omnitrope 6.7 mg/ml ready-to-use solutions fulfill the criteria for bioequivalence compared with the original Omnitrope 5 mg/ml powder and Genotropin 5 mg/ml powder preparations. All products exhibit similar pharmacokinetic and pharmacodynamic profiles, and are equally safe and well tolerated. Together with published data on clinical efficacy (23) and based on current knowledge, these results suggest that the ready-to-use liquid rhGH products are therapeutically interchangeable, while providing a higher level of convenience for the patients.

In the meantime, these products are registered in the European Union, the United States, Canada, Australia, and Japan.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

Dr Fuhr reports that his work was supported by grants from Sandoz. Drs Saenger and Tuculanu report receiving consulting fees from Sandoz. Drs Balser, Berghout, and Schwebig are employees of Sandoz Biopharmaceutical Development/Hexal AG.

Acknowledgements

The authors would like to thank Drs Katherine Brandl and Otto Geisenberger for the initiation and operation management of the studies; Margot Viertlböck-Schudy for reviewing the analytical section; and Drs Jasmin Khan-Boluki, Markus Zabransky, and Michael Münzberg for reviewing the manuscript.

References

- Holmstrom B & Fohlenhag K. Characterization of human growth hormone preparations used for the treatment of pituitary dwarfism: a comparison of concurrently used batches. *Journal of Clinical Endocrinology and Metabolism* 1975 **40** 856–862.
- Swerdlow AJ, Higgins CD, Adlard P, Jones ME & Preece MA. Creutzfeldt–Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003 **61** 783–791.
- Finkelstein BS, Silvers JB, Marrero U, Neuhauser D & Cuttler L. Insurance coverage, physician recommendations, and access to emerging treatments: growth hormone therapy for childhood short stature. *Journal of the American Medical Association* 1998 **279** 663–668.
- Hardin DS, Woo J, Butsch R & Huett B. Current prescribing practices and opinions about growth hormone therapy: results of a nationwide survey of paediatric endocrinologists. *Clinical Endocrinology* 2007 **66** 85–94.
- Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K & Milne R. Clinical effectiveness of growth hormone in children: a systematic review and economic evaluation. *Health Technology Assessment* 2002 **6** 1–168.
- Cook D, Owens G & Jacobs M. Human growth hormone treatment in adults: balancing economics and ethics. *American Journal of Managed Care* 2004 **10** S417–S419.
- Lee JM, Davis MM, Clark SJ, Hofer TP & Kemper AR. Estimated cost–effectiveness of growth hormone therapy for idiopathic short stature. *Archives of Pediatrics & Adolescent Medicine* 2006 **160** 263–269.
- Nation RL & Sansom LN. Bioequivalence requirements for generic products. *Pharmacology and Therapeutics* 1994 **62** 41–55.
- Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal L136*, 30/4/2004, pp 34–57.
- Locatelli F & Roger S. Comparative testing and pharmacovigilance of biosimilars. *Nephrology, Dialysis, Transplantation* 2006 **21** v13–v16.
- Schellekens H. How similar do 'biosimilars' need to be? *Nature Biotechnology* 2004 **22** 1357–1359.
- Crommelin D, Bermejo T, Bissig M, Damiaans J, Krämer I, Rambourg P, Scroccaro G, Strukelj B, Tredree R & Ronco C. Biosimilars, generic versions of the first generation of therapeutic proteins: do they exist? In *Cardiovascular Disorders in Hemodialysis, Contributions to Nephrology*, vol 149, pp 287–294. Eds C Ronco, A Brendolan & NW Levin, Basel: Karger, 2005.
- Hoppe W & Berghout A. Biosimilar somatropin: myths and facts. *Hormone Research* 2008 **69** 29–30.
- Guideline on Similar Biological Medicinal Products (EMEA/CHMP/43704/2005).
- Guideline on Similar Biological Medicinal Products Containing Biotechnological-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005).

- 16 Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMA/CHMP/42832/2005).
 - 17 Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues-guidance on Biosimilar Medicinal Products Containing Somatropin (EMA/CHMP/94528/2005).
 - 18 Pavlovic M, Girardin E, Kapetanovic L, Ho K & Trouvin JH. Similar biological medicinal products containing recombinant human growth hormone: European regulation. *Hormone Research* 2008 **69** 14–21.
 - 19 Ooi GT & Boisclair YR. Molecular biology of the insulin like growth factor binding proteins. In *Contemporary Endocrinology: the IGF System*, ch 6, pp 111–139. Eds R Rosenfeld & C Roberts Jr. Totowa, NJ: Humana Press, 1999.
 - 20 Bier DM. Growth hormone and insulin-like growth factor I: nutritional pathophysiology and therapeutic potential. *Acta Paediatrica Scandinavica* 1991 **374** 119–128.
 - 21 Boisclair YR, Hurst KR, Ueki I, Tremblay ML & Ooi GT. Regulation and role of the acid-labile subunit of the 150-kilodalton insulin-like growth factor complex in the mouse. *Pediatric Nephrology* 2000 **14** 562–566.
 - 22 Hansen TK, Gravholt CH, Ørskov H, Rasmussen MH, Christiansen JS & Jorgensen JO. Dose dependency of the pharmacokinetics and acute lipolytic actions of growth hormone. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 4691–4698.
 - 23 Romer T, Peter F, Saenger P, Starzyk J, Koehler B, Korman E, Walczak M, Wasik R, Ginalska-Malinowska M, Solyom E & Berghout A. Efficacy and safety of a new ready-to-use recombinant human growth hormone solution. *Journal of Endocrinological Investigation* 2007 **30** 578–589.
 - 24 Guidance for Industry: Bioanalytical Method Validation. US Department of Health and Human Services, Food and Drug Administration, CDER, Rockville, USA, May 2001.
 - 25 Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics* 1987 **15** 657–680.
 - 26 Keller A, Wu Z, Kratzsch J, Keller E, Blum WF, Kniess A, Preiss R, Teichert J, Strasburger CJ & Bidlingmaier M. Pharmacokinetics and pharmacodynamics of GH: dependence on route and dosage of administration. *European Journal of Endocrinology* 2007 **156** 647–653.
 - 27 Sata A & Ho KK. Growth hormone measurements in the diagnosis and monitoring of acromegaly. *Pituitary* 2007 **10** 165–172.
 - 28 Jacobsen LV, Rolan P, Christensen MS, Knudsen KM & Rasmussen MH. Bioequivalence between ready-to-use recombinant human growth hormone (rhGH) in liquid formulation and rhGH for reconstitution. *Growth Hormone and IGF Research* 2000 **10** 93–98.
-

Received 26 February 2010

Accepted 22 March 2010