Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 54 (2005) 1276–1281

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Pharmacokinetics and population pharmacodynamic analysis of lanreotide Autogel

Joseph M. Cendros[a], Concepción Peraire[a,*], Iñaki Fernández-Trocóniz[b], Rossend Obach[a]

[a]*Pharmacokinetics and Metabolism Service, Ipsen Pharma S.A., 08980-Saint Feliu Llobregat, Barcelona, Spain*
[b]*Department of Pharmacy, School of Pharmacy, University of Navarra, Pamplona, Spain*

Received 2 November 2004; accepted 26 April 2005

Abstract

Somatostatin analogs are the first-line medical therapy for acromegaly, and the treatment of this disease has been simplified by the development of extended-release formulations of these analogs. Lanreotide is a somatostatin analog that is available either as the microparticle formulation, requiring 7- to 14-day dosing, or as the aqueous Autogel formulation, requiring 28-day dosing. This study investigated the pharmacokinetics and pharmacodynamics of lanreotide. Patients with acromegaly were given 5 injections of lanreotide microparticles, 30 mg, followed by 3 injections of lanreotide Autogel, at doses of 60, 90, or 120 mg every 28 days. The study was extended to a further 12 injections of lanreotide Autogel with dose titration. A total of 144 patients were recruited; 130 received 3 injections of lanreotide Autogel, and 130 completed the extension phase. Average minimum lanreotide concentrations (C_{min}) at steady state were 1.949 ± 0.619, 2.685 ± 0.783, and 3.575 ± 1.271 ng/mL for 60, 90, and 120 mg of lanreotide Autogel, respectively, showing a dose-proportional increase. Population pharmacodynamic analysis showed that the relationship between either formulation of lanreotide and serum growth hormone (GH) concentrations was best described using an inhibitory maximum response (E_{max}) model that allowed for the possibility of an incomplete inhibition of GH. Lanreotide elicited a maximum reduction in GH of 82%. Because patients were already being treated, baseline GH (E_0) was estimated, and the value of 8.63 ng/mL was in agreement with the inclusion criteria of GH 10 ng/mL or less. The effectiveness of treatment was demonstrated by the median serum concentration of lanreotide, 1.13 ng/mL, required to lower GH to 2.5 ng/mL or less. The serum concentration that elicited half of the E_{max} (EC_{50}) was estimated as 0.206 ng/mL, showing a high sensitivity to lanreotide, with a predictably high interpatient variability of 200.75% reflecting the range of dosing regimens needed to control GH.

1. Introduction

Synthetic somatostatin analogs are more potent than the natural compound in inhibiting growth hormone (GH) secretion and are the first-line medical therapy for acromegaly [1,2]. The somatostatin analog lanreotide was initially developed as a prolonged-release (PR) formulation by incorporating the drug into microparticles of biodegradable polymer (lanreotide microparticles). The PR formulation of lanreotide allows control of GH hypersecretion with intramuscular injection every 7 to 14 days and has been shown to have good efficacy and tolerability in the treatment of acromegaly [3-6]. The injection interval has been further extended by the development of a second extended-release formulation of lanreotide that is a mixture of lanreotide acetate and water (lanreotide Autogel, Dreux, France), and is provided in a prefilled syringe for deep subcutaneous (SC) injection every 28 days [7].

The efficacy of lanreotide Autogel and lanreotide microparticles in reducing serum GH concentrations in patients with acromegaly was compared in an open-label study, which was extended so that patients continued to receive lanreotide Autogel for more than 1 year [8,9]. The present study has used this data set to determine the pharmacokinetic profile of lanreotide Autogel after repeated dose administration and to perform a population pharmacodynamic analysis of lanreotide and GH levels after deep SC administration in patients with acromegaly. The primary objective of this analysis was to understand the relationship between the concentration of lanreotide at steady state and that of GH as patients switched from the microparticle formulation lanreotide to the Autogel formulation of lanreotide.

* Corresponding author. Tel.: +34 93 685 8100; fax: +34 93 685 1053.
E-mail address: concepcion.peraire@ipsen.com (C. Peraire).

0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.04.014

2. Methods

2.1. Patients and study design

Data were provided by 2 clinical studies that involved the same patients: the first was an open, multicenter, phase III comparison of lanreotide Autogel with lanreotide microparticles; the second was a follow-up study with lanreotide Autogel [8,9]. Eligible patients were required to have a diagnosis of active acromegaly (basal mean GH level >5 ng/mL or elevated age-normalized insulin-like growth factor 1 [IGF-1], or GH level >2 ng/mL after an oral glucose tolerance test) after their most recent surgery or radiotherapy and within the previous 5 years. Patients were also required to have been receiving treatment with lanreotide microparticles for a minimum of 3 months before inclusion in the first study. All patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

Upon entering the study, patients continued to receive injections of lanreotide microparticles (30 mg), at the same dosing interval as before entry, for a run-in period totaling 5 injections (Fig. 1). A further condition of eligibility for the study was for patients to be responsive to treatment, with a mean plasma GH level 10 ng/mL or less before the fifth injection of lanreotide microparticles. Patients who met these criteria were switched to lanreotide Autogel for a total of 3 injections at 28-day intervals (12 weeks). The lanreotide Autogel dose was determined by each patient's dosing interval for lanreotide microparticles to maintain the same monthly dose with both treatments. If the dosing interval with lanreotide microparticles, 30 mg, was 14 days, patients were switched to lanreotide Autogel, 60 mg every 28 days; if the interval with lanreotide microparticles, 30 mg, was 10 days, patients were switched to lanreotide Autogel, 90 mg every 28 days; and if the interval with lanreotide microparticles, 30 mg, was 7 days, patients were switched to lanreotide Autogel, 120 mg every 28 days. Lanreotide Autogel was given a total of 12 injections. Doses were titrated at entry and after every 4 injections, according to patients' GH and IGF-1 response: the dose was increased in patients receiving 60 or 90 mg with mean GH greater than 2.5 ng/mL; the dose was unchanged with mean GH ≥1 ng/mL and ≤2.5 ng/mL; and the dose was decreased in patients receiving lanreotide at 90 and 120 mg with mean GH less than 1 ng/mL and normal IGF-1. When the dose had been titrated upward, it could not be reduced again during the course of the study.

2.2. Lanreotide and GH serum concentrations

Blood samples for measurement of minimum lanreotide serum levels (C_{min}) were taken before each drug injection. Serum concentrations of lanreotide were determined using a validated radioimmunoassay method, the methodology for which has been reported elsewhere [10]. The limit of quantification for the method was 0.078 ng/mL, and the intra-assay and interassay coefficients of variation were less than 5% and 13.6%, respectively. Blood samples for measurement of GH were taken before the last injection of lanreotide microparticles, before injections 2, 4, 8, and 12 and at the end of treatment with lanreotide Autogel (12, 28, 44, and 60 weeks after the first injection). An average GH level was obtained from 9 samples taken at 30-minute intervals over a 4-hour period before lanreotide injection. GH levels were measured by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, Calif), with a detection limit of 0.02 ng/mL and intra-assay and interassay coefficients of variation of less than 4.2% and 7.2%, respectively.

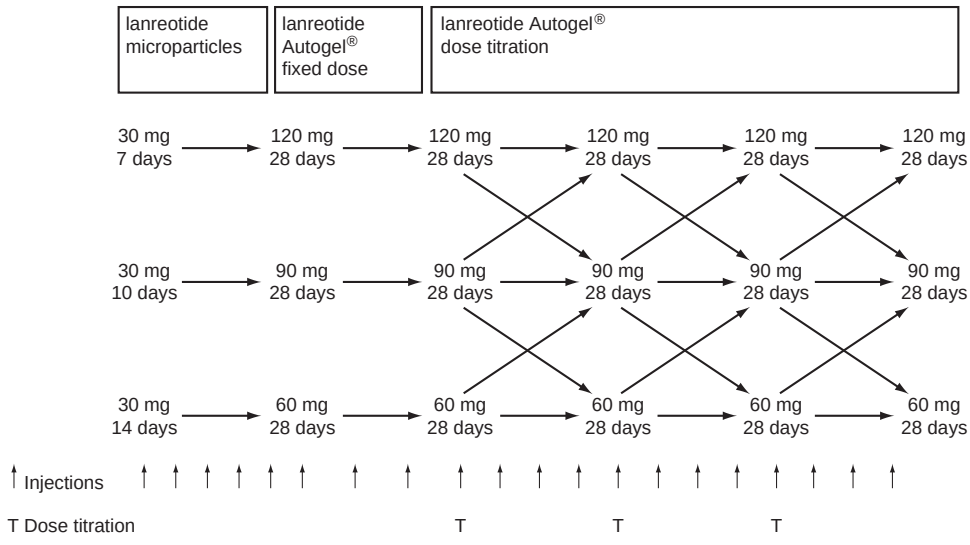

Fig. 1. Study design.

2.3. Pharmacokinetics

Minimum serum steady-state levels of lanreotide ($C_{min,ss}$) were considered to be reached after 4 consecutive injections of the same dose of lanreotide Autogel.

2.4. Population pharmacodynamic modeling

To determine the relationship between lanreotide concentrations and GH levels, a population pharmacodynamic analysis was performed using the NONMEM version V software program and the First-Order Conditional Estimation (FOCE) method with interaction [11], with inhibitory E_{max} type models that allowed exploration of the covariate effects of sex and type of formulation. Patients with at least 1 pair of lanreotide and GH assessments after 3 consecutive injections of the same dose of lanreotide Autogel or at the end of treatment with lanreotide microparticles before switch to lanreotide Autogel were included in the analysis. The population pharmacodynamic analysis was performed in 3 stages: basic model development, covariate selection, and final model selection. Interpatient variability was included in the models exponentially as follows:

$$\theta_{1i} = \theta_{1pop} \cdot e^{\eta_{1i}}$$

where θ_{1i} represents the value of the pharmacodynamic parameter θ_1 in the ith individual, θ_{1pop} is the population value of the parameter θ_1 (and it is common to all individuals in the population), and η_{1i} is the interpatient random effect with mean 0 and variance ω_1^2. The difference between the jth measured value ($E_{obs,ij}$) in the ith patient and its respective prediction ($E_{pred,ij}$) was modeled with a proportional residual error model:

$$E_{obs,ij} = E_{pred,ij} \times (1 + \varepsilon_{ij})$$

where ε_{ij} is an independent random variable with mean 0 and variance σ^2.

Model selection was based on the minimum value of the objective function provided by NONMEM (see below), the precision of the estimates, the visual exploration of the goodness-of-fit plots, and sensitivity of results to initial parameter estimates. The difference in minimum value of the objective function between 2 nested models was compared with a χ^2 distribution in which a difference of 6.63 points was considered significant at the 1% level.

To ensure the robustness of the final model, validation was performed as follows: (i) 100 data sets with the same number of patients, covariates, dosing history, and sampling schedule were simulated, based on the fixed and random-effects parameter estimated from the original data set. The 0.05, 0.5, and 0.95 quantiles were then computed and represented graphically with the corresponding observations, and the agreement between simulations and observations was visually evaluated. (ii) Cross-validation analysis was performed to determine whether parameter estimates and/or a particular covariate model were affected by 1 or more very influential patients. Thirty patients with the highest, medium, and lowest GH levels in the study were deleted from the complete data set, and the new data set was analyzed with the final model. Model parameter estimates were compared with those obtained from the complete (original) data set.

3. Results

3.1. Patients

A total of 144 patients with acromegaly were recruited, and 131 completed the initial study, 130 of the patients entered the dose-titration extension phase, and 123 completed the study. Serum lanreotide levels were determined in 117 patients, who were included in the pharmacokinetic analysis of $C_{min,ss}$; 129 patients (62 men and 67 women) were included in the population pharmacodynamic analysis and supplied 497 paired observations of lanreotide and GH concentration.

3.2. Pharmacokinetics

Patients whose dose remained constant throughout the microparticle and Autogel periods of the study showed lower mean serum levels of lanreotide immediately after the switch between formulations; however, after 3 to 4 injections of lanreotide Autogel, levels of lanreotide increased to those with the microparticle formulation (Fig. 2). Indeed, C_{min} values for lanreotide Autogel at steady state show that serum levels of lanreotide were maintained with the 28-day dosing regimen. $C_{min,ss}$ increased as the administered dose increased. This was shown in both the total pharmacokinetic population (n = 117) and for the subset of patients who received at least 4 consecutive injections of each dose of lanreotide Autogel and for whom calculation of C_{ss} for each of the 3 doses was possible (n = 10, Table 1).

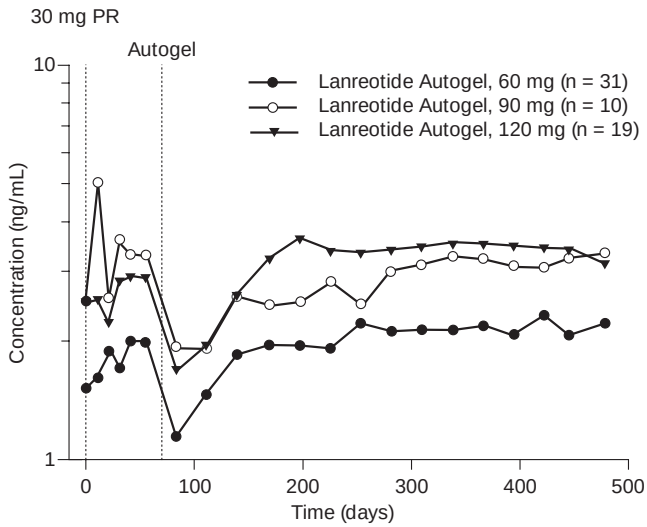

Fig. 2. Mean minimum serum lanreotide levels in patients who received 5 injections of lanreotide microparticles and 15 injections of lanreotide Autogel at the same monthly dose.

Table 1
Minimum serum levels of lanreotide at steady state in patients with acromegaly given lanreotide Autogel every 28 days

Lanreotide $C_{min,ss}$	Dose of lanreotide Autogel (mg)		
	60	90	120
Total population (n = 117)			
Mean ± SD	1.949 ± 0.619	2.685 ± 0.783	3.575 ± 1.271
Coefficient of variation (%)	31.75	29.16	35.55
n per dose	60	56	53
Subset of patients who received at least 4 consecutive injections at each dose (n = 10)			
Mean ± SD	1.602 ± 0.628	2.349 ± 0.701	3.650 ± 1.668
Coefficient of variation (%)	39.19	29.85	45.71
n per dose	10	10	10

3.3. Population pharmacodynamic modeling

Initial analysis of the data indicated that an inhibitory E_{max} model that allows for incomplete inhibition of GH provided the basic model for population pharmacodynamics:

$$E = E_0 \times \left(1 - E_{max} \times \frac{C_{min}}{C_{min} + EC_{50}}\right)$$

where E is the GH serum level in nanograms per milliliter, E_0 is the basal value for GH before starting treatment, E_{max} is the maximum effect (reduction in GH levels from baseline, value constrained between 0 and 1), and EC_{50} is the lanreotide serum level that produces a 50% reduction in the E_{max} GH concentration.

Inclusion of formulation type and patient sex as covariates had no significant effect on the model ($P > .05$). The basic population model was therefore selected as the final population pharmacodynamic model.

Table 2 lists the estimates of the population pharmacodynamic parameters of lanreotide. The typical population estimate of E_{max} was 0.821 with a coefficient of variation (CV%) of 7.53. The corresponding estimates (CV%) of EC_{50} and E_0 were 0.206 (50.0) and 8.63 (31.17) ng/mL, respectively. The degree of interpatient variability in EC_{50} and E_0 was high (200.75% and 67.82%, respectively). Once the typical population parameters were estimated, derived values were then determined. Thus, the typical serum concentration of lanreotide required to reduce serum GH concentration to less than 2.5 ng/mL was 1.13 ng/mL.

Table 2
Population pharmacodynamic parameters of lanreotide

Parameter	Typical population estimate	Interpatient variability
E_{max}	0.821 (7.53)	NE
EC_{50} (ng/mL)	0.206 (50.0)	200.75 (36.48)
E_0 (ng/mL)	8.63 (31.17)	67.82 (13.41)
Residual error (%)	26.89 (10.89)	NA

Model estimates are listed with their corresponding CV% in parentheses. CV% was computed as the ratio between the SE of the parameter and the estimate multiplied by 100. Interpatient variability is also expressed as CV%. NE indicates not estimated in the model; NA, not applicable; E_{max}, maximum reduction in GH that lanreotide is able to elicit; EC_{50}, serum concentration of lanreotide eliciting a half of E_{max} reduction in GH; E_0, baseline GH levels.

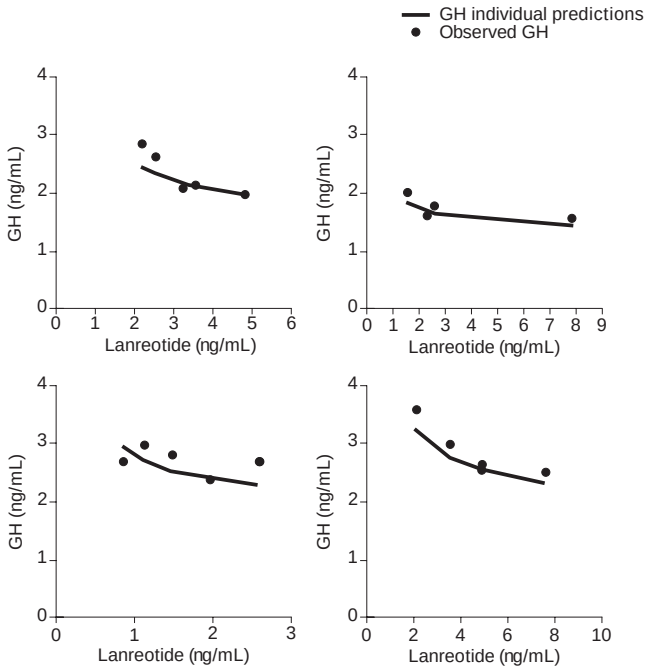

Fig. 3. Predicted and observed GH concentrations vs lanreotide levels in 4 randomly selected patients.

The model described the data well. Fig. 3 shows the individual observed and model-predicted pharmacodynamic profiles for 4 patients chosen at random during the lanreotide microparticles and Autogel phases. Fig. 4 shows the observed GH and C_{min} values with the results from the simulations for each formulation. It can be observed that the

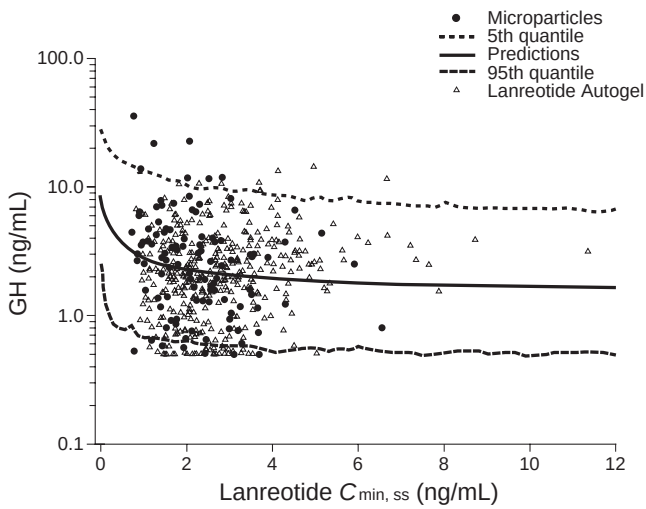

Fig. 4. Observed GH concentrations of all patients and predicted values vs minimum lanreotide concentrations (C_{min}).

median (0.5 quantile) profile describes the overall tendency of the data very well and that the area between the 0.05 and 0.95 quantiles covers most of the observations, indicating that both typical and random estimates of the model are supported by the data.

The parameter estimates of the final model were found to be insensitive to changes in the initial estimates and unaffected by any of the patients involved in the study. Additional validation of the model showed that the values of the median performance errors showed no bias.

4. Discussion

This report describes the pharmacokinetics and the population pharmacodynamics of lanreotide in patients with acromegaly who received multiple intramuscular injections of the microparticle formulation of lanreotide, followed by deep SC injections of the Autogel formulation. The good clinical efficacy and tolerability shown with lanreotide in these studies have been reported elsewhere [8,9].

Comparison of serum lanreotide levels achieved after injection of the microparticle and Autogel formulations demonstrated that the less frequent dosing regimen with the Autogel formulation did not diminish the availability of lanreotide and that serum levels were maintained for at least 28 days. Indeed, patients who remained on a constant dose of lanreotide throughout the study showed an overall trend for higher minimum serum lanreotide levels once steady state was achieved, when receiving Autogel compared with the microparticle formulation. This supports the clinical findings of the study, which demonstrated Autogel to be at least as effective as the microparticle formulation in reducing serum GH and IGF-1 levels [8,9].

Differences between the pharmacokinetic behavior of the 2 formulations of lanreotide did, however, result in lower minimum serum levels of lanreotide after the first administration of lanreotide Autogel compared with the microparticle formulation. This can be explained by the different release profiles of the formulations. Hence, lanreotide is rapidly released from microparticles during an initial burst phase of 1 to 3 days. This is followed by a period of pseudo–zero-order kinetics lasting about 15 days during which time almost constant serum levels of lanreotide are maintained; levels then decline with pseudo–first-order kinetics with a terminal half-life of about 5 days. In contrast, lanreotide is released from the Autogel formulation according to pseudo–first-order kinetics whereby concentrations exponentially decline, leaving a residual level of lanreotide remaining in the body at the end of the dosage interval, 28 days after injection. Upon injection of the next dose, the previous dose is superimposed onto the new dose. Thus, although steady-state concentrations were comparable between both formulations, minimum serum levels of lanreotide were lower after the first injection after switching from microparticles to the Autogel formulation. Four injections of lanreotide Autogel are therefore required to achieve 90% of the steady-state concentrations. The clinical impact of lower lanreotide levels after the first administration after switching was very limited. GH levels increased only slightly, from 2.8 ± 2.0 ng/mL at the end of the microparticle phase to 3.5 ± 2.9 ng/mL after the first Autogel injection, and the duration of the increase was short, with GH reverting to previous levels after the third injection of lanreotide Autogel. There is no evidence that such a small transient increase in GH levels affects acromegaly symptoms.

The steady-state levels of lanreotide after injection of the Autogel formulation suggested dose-proportional behavior in the range of 60, 90, and 120 mg. A slightly less than proportional increase was observed at 90 and 120 mg with respect to the lowest dose, but no statistical differences could be demonstrated between the minimum concentrations obtained at the different dose levels. Comparison of the results from both the maximum number of patients tested and from those who had pharmacokinetic results for each dose of lanreotide Autogel showed ratios of 1.4 and 1.5 for the 90-mg dose compared with the 60-mg dose, and ratios of 1.8 and 2.2 for the 120-mg dose compared with 60 mg. The tendency for a less than proportional increase may be explained by the allocation of doses of lanreotide Autogel. Patients were not randomized to each dose, but their initial dose level was determined by the frequency of administration of lanreotide microparticles. The dose of lanreotide Autogel was subsequently titrated according to the patient's response. It might therefore be expected that patients who received the highest dose of lanreotide Autogel had the highest elimination rate for this drug causing a slight deviation from dose proportionality.

Pharmacodynamic models that describe steady-state conditions were used as the concentration-effect data were obtained in such conditions. Both sigmoidal and simple inhibitory E_{max} models were tested in the population pharmacodynamic analysis, and the best description of the data was provided by an inhibitory E_{max} model with interpatient variability in EC_{50} and E_0. In this model, the covariates of patient sex and type of formulation had no effect on the relationship between lanreotide and GH serum levels. Lanreotide was found to elicit a maximum reduction of serum GH levels of 82%. The model and model estimates are similar to those published previously for the somatostatin analog octreotide, whose pharmacodynamics properties were also described by an inhibitory E_{max} model. An incomplete reduction of GH was also found, as was a high interpatient variability of the estimates [12,13].

In the current study, observed baseline GH concentrations were not obtained because patients were already undergoing treatment with lanreotide; however, the estimated E_0 of 8.63 ng/mL was in agreement with the inclusion criteria of GH levels of 10 ng/mL or less. The value obtained for the median concentration of lanreotide required to decrease the basal value of GH to 2.5 ng/mL or less (1.13 ng/mL) demonstrated the efficacy of the treatment independently of the formulation. The EC_{50} of 0.206

demonstrated the high sensitivity to lanreotide. The high variability in the EC_{50} between patients was expected, as it is consistent with the different dosing regimens needed to reduce GH values in all patients.

In summary, this analysis shows that the 28-day dosing regimen of lanreotide Autogel maintains therapeutic levels of lanreotide in patients with acromegaly, with dose proportionality in the 60-, 90-, and 120-mg dose range. The lower dosing frequency can benefit patients and health care workers alike in helping to lessen the burden of this chronic disease.

References

[1] Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, et al. Guidelines for acromegaly management. J Clin Endocrinol Metab 2002;87:4054-8.

[2] Racine MS, Barkan AL. Medical management of growth hormone-secreting pituitary adenomas. Pituitary 2002;5:67-76.

[3] Cannavò S, Squadrito S, Curtò L, Almoto B, Vieni A, Trimarchi F. Results of a two-year treatment with slow release lanreotide in acromegaly. Horm Metab Res 2000;32:224-9.

[4] Caron P, Morange-Ramos I, Cogne M, Jacquet P. Three year follow-up of acromegalic patients treated with intramuscular slow-release lanreotide. J Clin Endocrinol Metab 1997;82:18-22.

[5] Baldelli R, Colao A, Razzore P, Jaffrain-Rea ML, Marzullo P, Ciccarelli E, et al. Two-year follow-up of acromegalic patients treated with slow release lanreotide (30 mg). J Clin Endocrinol Metab 2000; 85:4099-103.

[6] Giusti M, Gussoni G, Cuttica CM, Giordana G. Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly: six-month report on an Italian multicenter study. Italian Multicenter Slow Release Lanreotide Study Group. J Clin Endocrinol Metab 1996; 81:2089-97.

[7] Lightman S. Somatuline Autogel: an extended release lanreotide formulation. Hosp Med 2002;63:162-5.

[8] Caron P, Beckers A, Cullen DR, Goth MI, Gutt B, Laurberg P, et al. Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in the management of acromegaly. J Clin Endocrinol Metab 2002;87:99-104.

[9] Caron P, Bex M, Cullen DR, Feldt-Rasmussen U, Pico Alfonso AM, Pynka S, et al. One-year follow-up of patients with acromegaly treated with fixed or titrated doses of lanreotide Autogel. Clin Endocrinol 2004;60:734-40.

[10] Barbanoj M, Antonijoan R, Morte A, Grinyo JM, Sola R, Valles J, et al. Pharmacokinetics of the somatostatin analog lanreotide in patients with severe chronic renal insufficiency. Clin Pharmacol Ther 1999;66:485-91.

[11] Beal SL, Sheiner LBS, editors. NONMEM user guides—part V. NONMEM project group. Calif (USA): University of California at San Francisco; 1992. p. 139.

[12] Comets E, Mentré F, Grass P, Kawai R, Marbach P, Vonderscher J. Population pharmacodynamic analysis of octreotide in acromegalic patients. Clin Pharmacol Ther 2003;73:95-106.

[13] Zhou H, Chen T-L, Marino M, Lau H, Miller T, Kalafsky G, et al. Population PK and PK/PD modelling of microencapsulated octreotide acetate in healthy subjects. Br J Clin Pharmacol 2000;50:543-52.