

POPULATION PHARMACODYNAMIC MODELLING OF LANREOTIDE AUTOGEL IN PATIENTS WITH ACROMEGALY

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BACKGROUND

As an analog of endogenous somatostatin, lanreotide acts by inhibiting the secretion of growth hormone (GH). Lanreotide Autogel® (Lan-ATG) is a prolonged release formulation that is given as a deep subcutaneous injection every 28 days. It has been shown to be effective against acromegaly¹ and against the symptoms of carcinoid syndrome associated with neuroendocrine tumours².

OBJECTIVE

To establish the relationship between lanreotide serum levels and pharmacodynamic response (inhibition of growth hormone) in patients with acromegaly.

METHODS

Patients

Patients 18 years old or over with active acromegaly were eligible if their GH levels were over 5 ng/mL. Patients who had been treated with a somatostatin analog or a dopamine agonist within the 3 months prior to study entry were eligible if their GH levels were over 3 ng/mL and had increased more than 100% in a washout period of up to 12 weeks.

Patients were classified with regard to previous acromegalic treatment in two different categories: not pre-treated patients (patients who were never treated with somatostatin analog and dopamine agonists or patients who may have taken some but stopped in the 3 months prior to washout period); and pre-treated patients (patients treated with somatostatin analog and dopamine agonists but stopped prior to washout period).

Study Design

Lan-ATG was injected every 4 weeks for a total of 13 injections. The 52-week study had four phases:

- i) **Washout** (weeks -12-0), for those previously treated
- ii) **Double-blind, placebo-controlled** (weeks 0-4), patients were randomized equally to one injection of Lan-ATG 60, 90, 120 mg or placebo
- iii) **Single-blind, fixed-dose** (weeks 4-20), the same dose was given for the following four injections, and patients on placebo were switched to 60, 90 or 120 mg
- iv) **Open-label dose titration** (weeks 20-52), the final eight injections followed an open-label dose-titration schema that allowed two dose adjustments based on biochemical efficacy [GH and insulin-like factor (IGF-1) levels].

Pharmacodynamic

Lan-ATG has a high apparent terminal half-life (23 to 31 days) with regard to that obtained after i.v. IRF administration (approximately 2 hours). For this reason, the equilibrium of lanreotide levels with the biophase was considered achieved after 24 hours after Lan-ATG administration.

Correlation between lanreotide levels and inhibition of mean serial measurements of GH measured at washout and just before the following injections at weeks 4, 13-16 and 52 was modeled with an inhibitory sigmoid E_{max} model using a population approach (NONMEM):

$$E = E_0 - \frac{E_{max} \cdot C^\gamma}{EC_{50} + C^\gamma}$$

where E is the GH level, E_0 is the concentration of GH in absence of treatment, E_{max} is the maximum GH reduction, C is the lanreotide level, EC_{50} is the lanreotide level that decreased GH by 50% of E_{max} , and γ is the sigmoidicity parameter.

A mixture model was assessed to estimate the probability of the existence of different sub-populations associated to different response to lanreotide (non responders and responders to lanreotide treatment).

RESULTS

- The GH response to lanreotide was adequately described by inhibitory sigmoid E_{max} model.
- Patients treated within the 3 months prior to the first administration of Lan-ATG had a lower E_0 than untreated patients (Table 1).
- A mixture model for EC_{50} , that allows to characterize a priori unidentifiable different subpopulations, was included to account for the variability in response to lanreotide treatment, assuming that the population consisted of two subpopulations: responders (86.3%) and non-responders (13.7%) to drug treatment. EC_{50} was fixed (100 ng/mL) for non-responders and estimated (0.612 ng/mL) for responders (Figure 2).
- PD model was internally (using the posterior predictive check) and externally (with data from another clinical trial) validated. The adequacy of the population PD model is shown in Figure 1, which plot individual GH prediction vs observed GH levels, and Figure 3, that represents the observed and population predicted GH levels vs lanreotide concentration for responders and non-responders based on pre-treatment status.

Parameter	Patient Sub-group	Estimate	IIV	Fraction of population
E_{max}	-	0.823	14%	-
E_0 (ng/mL)	Not pre-treated	15.9	85%	-
	Pre-treated	8.74	-	-
EC_{50} (ng/mL)	Non-responder	100 (fixed)	43%	13.7%
	Responder	0.612	-	86.3%
γ	-	2.63	-	-
Additive (ng/mL)	-	0.116	-	-
Proportional (%)	-	30%	-	-

IIV, inter-subject variability (CV); γ , Sigmoidicity parameter

Table 1. Population PD parameters

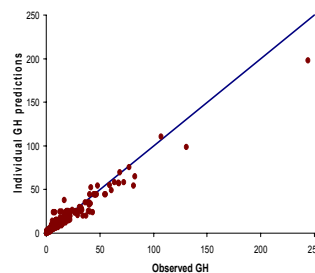


Figure 1. Basic goodness-of-fit plot

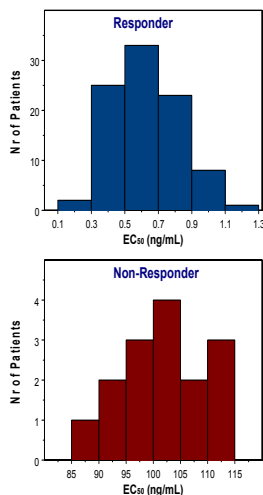


Figure 2. Distribution of EC_{50} according to patient response to lanreotide treatment

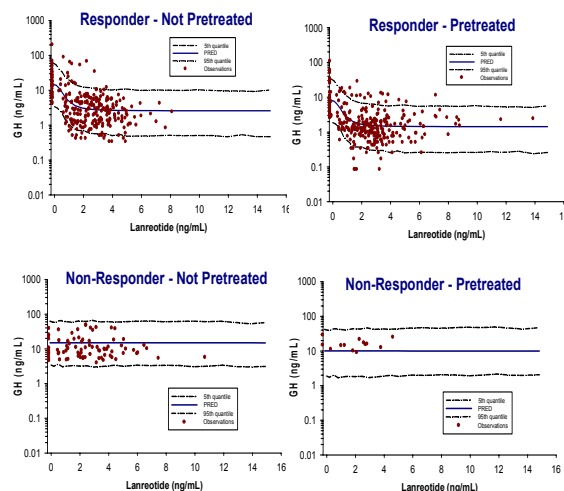


Figure 3. Observed and population predicted GH levels vs lanreotide levels for patients responsive or not responsive to treatment, based on pre-treatment status

CONCLUSIONS

1. PD analysis demonstrated the effectiveness of Lanreotide Autogel® with 28-day dosing.
2. An inhibitory sigmoid E_{max} model adequately described the relationship between lanreotide and GH concentrations with an E_{max} population mean of 82%.
3. Baseline GH level (E_0) was significantly related to pre-treatment status and was estimated as lower for pre-treated patients.
4. The variability in response to lanreotide was explained by the presence of two-subpopulations: non-responders (14%) and responders (86%) to treatment. In responder patients, a lanreotide concentration of 0.612 ng/mL resulted in a 50% decrease in GH levels.

REFERENCES

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2. Ruzsiewicz P, Ish-Shalom, Wiedenmann B *et al.* Gut 2003; 52 (Suppl 6): A145