A multivariable prediction model for pegvisomant dosing: monotherapy and in combination with long-acting somatostatin analogues

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Abstract

Background: Effective treatment of acromegaly with pegvisomant (PEGV), a growth hormone receptor antagonist, requires an appropriate dose titration. PEGV doses vary widely among individual patients, and various covariates may affect its dosing and pharmacokinetics.

Objective: To identify predictors of the PEGV dose required to normalize insulin-like growth factor I (IGF-I) levels during PEGV monotherapy and in combination with long-acting somatostatin analogues (LA-SSAs).

Design: Two retrospective cohorts (Rotterdam + Liège Acromegaly Survey (LAS), total $n = 188$) were meta-analyzed as a form of external replication to study the predictors of PEGV dosing in addition to LA-SSA, the LAS ($n = 83$) was used to study the predictors of PEGV monotherapy dosing. Multivariable regression models were used to identify predictors of the PEGV dose required to normalize IGF-I levels.

Results: For PEGV dosing in combination with LA-SSA, IGF-I levels, weight, height and age, were associated with the PEGV normalization dosage ($P \leq 0.001$, $P \leq 0.001$, $P = 0.028$ and $P = 0.047$ respectively). Taken together, these characteristics predicted the PEGV normalization dose correctly in 63.3% of all patients within a range of ± 60 mg/week (21.3% within a range of ± 20 mg/week). For monotherapy, only weight was associated with the PEGV normalization dose ($P \leq 0.001$) and predicted this dosage correctly in 77.1% of all patients within a range of ± 60 mg/week (31.3% within a range of ± 20 mg/week).

Conclusion: In this study, we show that IGF-I levels, weight, height and age can contribute to define the optimal PEGV dose to normalize IGF-I levels in addition to LA-SSA. For PEGV monotherapy, only the patient's weight was associated with the IGF-I normalization PEGV dosage.

European Journal of
Endocrinology
(2017) 176, 421–431

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Introduction

Acromegaly is a rare disease caused by excessive secretion of growth hormone (GH), and a subsequent increase in IGF-I production (1). The disease is almost exclusively caused by a GH-secreting pituitary adenoma (2). Severity and phenotype of the disease varies among acromegaly patients. Uncontrolled acromegaly is associated with an increase in morbidity and mortality (1). The control of IGF-I levels results in mortality rates similar to the general population (3). Although often unsuccessful in macroadenomas, transsphenoidal surgery generally is considered as the first treatment modality (4, 5). Additional treatment after surgery is necessary when GH and IGF-I levels remain uncontrolled. Long-acting somatostatin analogues (LA-SSAs), as adjuvant medical treatment or as primary medical treatment, are regularly prescribed. Several studies addressed the response of LA-SSA and show that LA-SSA treatment alone reaches control of the disease in about 40% of the patients (6, 7). A highly effective alternative for patients who are not normalized by LA-SSA monotherapy is the addition of pegvisomant (PEGV) to LA-SSA, or PEGV monotherapy, provided that the appropriate PEGV dose is given (8, 9, 10, 11, 12). PEGV is a PEGylated recombinant analogue of GH, which competitively blocks the GH receptor, and thereby reduces the excessive GH actions in the liver and peripheral tissues (13, 14). PEGV is slowly absorbed from the subcutaneous depot ($T_{\max}$ of 33–77 h and $T_{1/2\text{ el}}$ 74–172 h) (15). The mode of PEGV clearance is still not understood. We do not know whether the kidneys and/or the liver metabolize the drug.

The dose of PEGV required to achieve disease control, defined as normalization of IGF-I levels, differs between individual acromegaly patients, both during PEGV monotherapy and in combination with LA-SSA (8, 12). PEGV doses range widely between 20 and 200 mg/weekly during combination treatment with LA-SSA (16). A study by Freda *et al.* observed that patients using PEGV monotherapy in the ACROSTUDY with persistently elevated IGF-I levels needed a higher mean PEGV dosage (17). Defining the optimal starting dose for PEGV is difficult as the pharmacokinetics remain to be elucidated and data on pre-treatment determinants of the PEGV dosage required for biochemical disease control are sparse. Currently, IGF-I levels are most commonly used during PEGV titration, which is in line with a previous study from our group reporting a positive correlation between baseline IGF-I levels and the PEGV dose required for the normalization of IGF-I during combination treatment of

LA-SSA and PEGV (8, 18). Other predictors that have been reported are GH levels, sex, body weight and previous radiotherapy (19, 20). Two studies previously reported about a GH receptor polymorphism lacking exon 3, which seemed to have an influence as well during PEGV dosing (21, 22). However, more recent studies in larger acromegaly cohorts clearly state that this polymorphism has a clinical effect on neither the PEGV response nor the determination of the required PEGV dose (23, 24, 25).

Given the importance of swift biochemical control in acromegaly but the lack of studies investigating pre-treatment predictors, we aimed to develop a multivariate regression model for predicting the required PEGV dose to achieve normalization of IGF-I levels in acromegaly patients.

Subjects and methods

Cohorts description

Patients ($n=271$) were included from two retrospective cohorts: (1) the Rotterdam cohort and (2) the Liège Acromegaly Survey (LAS) cohort (26). The Rotterdam cohort contains data from acromegaly patients using LA-SSA in combination with PEGV ($n=112$) collected in the Pituitary Center Rotterdam between 2004 and 2013, previously published in 2014 (8). The LAS cohort ($n=3194$ from 14 centers) was created using a software tool that enables hospitals throughout Europe to include acromegaly patients and report patient, biochemical and adenoma characteristics (26). For this study, only patients using PEGV monotherapy ($n=83$) or PEGV in combination with LA-SSA ($n=76$) were enrolled from 10 different centers. The inclusion period was between 2010 and 2015.

Rotterdam cohort

Clinical and biochemical data were collected from acromegaly patients with elevated IGF-I levels ($>1.2\times$ upper limit of normal (ULN)), after at least 6 months of the highest dose of LA-SSAs (octreotide LAR 30 mg or lanreotide Autogel 120 mg every 28 days). In this group, 27 acromegaly patients started with 25 mg PEGV weekly as co-treatment, whereas another 18 started with 40 mg PEGV weekly and the last 67 patients started with a variable PEGV dose, guided by their baseline IGF-I levels. This variable PEGV starting dose was based on one of our previous reports (18)). The formula to calculate the PEGV dose is $4 + (\text{IGF-I z-score during treatment with high dose}$

LA-SSA*16) and was deducted from a method described previously (18). This formula can only be used when IGF-I levels are elevated after a period of at least 6 months of LA-SSA treatment. Intervals of dose adaptations were 6–8 weeks until a controlled IGF-I level was achieved on two consecutive occasions. The subjects then visited our outpatient clinic every 16 weeks. When the once-weekly PEGV dose exceeded 80 mg per injection, patients divided the dosage to two weekly injections. With weekly doses over 200 mg, subjects changed administration intervals into daily injections or 5 injections per week. At each visit to our outpatient clinic, standard measurements were performed including assessments of IGF-I levels. Permission from the Institutional Review Board of the Erasmus Medical Center Rotterdam was obtained, and all patients gave their written informed consent.

LAS cohort

Acromegaly patients from the LAS database treated with PEGV were selected and divided in two groups; PEGV in combination with LA-SSA and PEGV monotherapy. From the LAS database, we were able to select 141 potential patients using the combination treatment. We excluded 65 patients, because of two reasons: (1) no IGF-I normalization during LA-SSA+PEGV treatment was achieved ($n=16$) and (2) follow-up data during LA-SSA/PEGV treatment were missing ($n=49$). The remaining patients ($n=76$) were selected for this study. The same exclusion criteria applied for the PEGV monotherapy patients. We were able to select 122 potential patients using PEGV monotherapy. We excluded 39 patients (no IGF-I normalization during PEGV monotherapy was achieved ($n=6$) and follow-up data during PEGV treatment were missing ($n=33$)). The remaining patients ($n=83$) were selected for this study. The medical ethics committee from the Liège University hospital approved the protocol and was covering the other European centers.

Hormone assays

In the Rotterdam cohort, the GH and IGF-I level measurements were assessed with the IMMULITE 2000 assay (DPC Biermann GmbH/Siemens, Fernwald, Germany), a solid-phase, enzyme-labeled chemiluminescent immunometric assay, with an intra-assay variability of 6%, and an inter-assay variability of 5–6% for GH and with an intra-assay variability of 2–5%, and an inter-assay variability of 3–7% for IGF-I. The IGF-I age- and sex-adjusted reference ranges were

used from an article by Elmlinger *et al.* (27). In the LAS cohort, containing acromegaly patients from several European hospitals, the GH and IGF-I level measurements were assessed locally and consequently performed with different assays. Therefore, the IGF-I levels were chosen to be expressed as the upper limit of normal (ULN) of the reference ranges used in the local hospitals. In this study, GH levels were measured as a single random sample and expressed as absolute values.

Candidate predictors

Variables that were considered as possible predictors for PEGV normalization dosage were selected based on the literature (8, 18, 19, 20), biological plausibility and availability of robust data ascertainment in both cohorts and included: age at diagnosis, sex, weight, height, tumor size (micro vs macroadenoma at diagnosis), presence of diabetes mellitus, IGF-I levels (expressed as ULN), random GH levels and previous treatment modalities (transsphenoidal surgery, radiotherapy and the duration of LA-SSA monotherapy before the addition of PEGV). Weight, IGF-I levels (expressed as ULN) and random GH levels were collected between 6 months before and at the time of PEGV addition. Other data were collected at baseline (as indicated), were fixed data in the patient's record or were established during disease process.

Outcome

The outcome used in this study was the PEGV dose (mg/week) needed for the normalization of IGF-I levels either during the addition to LA-SSA (highest tolerable dose) or as PEGV monotherapy.

Statistical analysis

Data are expressed as median (interquartile range). Differences between two subgroups were analyzed using an unpaired *t*-test or the Mann–Whitney *U* test (in case of non-parametric data). Nominal variables were analyzed using Fisher's exact test. For subjects in which PEGV was added to LA-SSA therapy, the distribution of the PEGV dose required for normalization of IGF-I levels was not comparable between the two cohorts; therefore, we meta-analyzed the data as a form of external replication. For all regression models, log-transformation of the outcome variable (required PEGV dose) was performed to normalize

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residuals, and non-linearity was assessed utilizing restricted cubic splines with 3–4 knots. We used univariable linear regression models to assess the association between each candidate predictor and the required PEGV dose. The decision for linear regression models instead of multiple models for the identification of predictors was based on Akaike information criteria and log-likelihood tests comparing multilevel models with random intercepts and/or slope per cohort vs standard linear regression correcting for cohort. To allow for optimal generalizability of effect estimates that predict the required PEGV dose, we performed multivariable multilevel modeling with a random intercept per cohort for the final model. We selected useful predictors using backward selection based on the change in regression coefficients and residual explained variability of the model, with a P value <0.20 as to keep predictors liberally in the model. Other P values are considered statistically significant when lower than 0.05 (two-tailed). For subjects switching from LA-SSA to PEGV monotherapy, we used univariable linear regression models

to assess the association between each potential predictor and the required PEGV dose. We subsequently calculated the predicted normalization dosage for each subject using the outcomes of the final (multivariable) regression models. In addition, we also calculated more conservative and more progressive models to cope with potential under or overtreatment by adding or subtracting the equivalent of 40 mg/week from the outcome of the regression formula. To cope with (differentially) missing values of the candidate predictors, missing data on candidate predictors were multiple imputed (five times). The imputation model included all candidate predictor variables, the outcome variable and several relevant variables descriptive for the study subjects. There was no difference between the original or any of the imputed datasets. All analyses were performed in each of the completed datasets, and final results were pooled. All statistical analyses were performed using Statistical Package of Social Sciences, version 20.0 for Windows (SPSS) or using R statistical software, version 3.2.43 (packages *rms*, *MASS* and *lm4*).

Table 1 Descriptive characteristics of the combination treatment and PEGV monotherapy cohorts. Descriptive characteristics of the three cohorts: Rotterdam cohort using LA-SSA+PEGV, LAS cohort using LA-SSA+PEGV and the LAS cohort using PEGV monotherapy. Missing data were input into the original datasets by multiple imputation. Continuous variables are expressed in median (interquartile range) and categorical variables in percentages.

	Combination treatment (LA-SSA+PEGV)			<i>P</i> value ^a	PEGV monotherapy	
	Total cohort	Rotterdam	LAS		LAS	<i>P</i> value ^b
No. of patients	188	112	76		83	
Patient characteristics						
Age at diagnosis	42.0 (33.0–53.0)	45.5 (36.0–56.0)	39.0 (29.5–47.0)	0.000	41.0 (29.0–51.0)	0.001
Sex (Male (%))	58.0	58.0	57.9	1.000	53.0	0.000
Weight before addition of PEGV (kg)	90.0 (77.0–104.0)	91.5 (79.0–104.0)	89.0 (74.5–105.0)	0.107	83.0 (71.0–93.0)	0.000
Height before addition of PEGV (cm)	175.0 (168.0–182.0)	178.0 (170.0–184.0)	170.0 (166.0–180.0)	0.000	170.0 (163.0–180.0)	0.000
Tumor size (Macro (%))	85.1	81.3	90.8	0.000	83.9	0.276
Diabetes Mellitus (%)	39.4	36.6	43.4	0.025	34.9	0.050
IGF-I xULN before addition of PEGV	2.0 (1.5–2.7)	1.9 (1.5–2.6)	2.1 (1.6–2.8)	0.000	2.1 (1.5–3.2)	0.001
GH before addition of PEGV (μg/L)	7.9 (3.1–17.8)	8.4 (3.2–17.5)	7.5 (2.2–18.6)	0.617	5.9 (2.0–11.0)	0.000
Previous treatment						
Surgery (total (%))	51.0	28.6	84.2	0.000	81.9	0.000
Once debulked (%)	48.6	28.6	78.1		71.1	
Twice debulked (%)	2.4	N/A	6.1		8.4	
>Twice debulked (%)	N/A	N/A	N/A		2.4	
RTx (%)	16.0	10.7	23.7	0.000	40.2	0.000
Duration of LA-SSA before addition of PEGV (months)	16.0 (8.3–39.0)	12.0 (7.2–26.8)	25.0 (11.5–62.0)	0.000	34.4 (13.4–86.4)	0.000
Outcome						
Required PEGV dose (mg weekly)	105.0 (65.0–200)	80.0 (60.0–120.0)	210.0 (105.0–280.0)	0.000	105.0 (105–140)	0.000

^aCombination treatment (Rotterdam) vs combination treatment (LAS); ^bcombination treatment (Rotterdam and LAS) vs PEGV monotherapy (LAS).

cm, centimeter; GH, growth hormone; IGF-I, insulin-like growth factor I; kg, kilogram; LAS, Liège Acromegaly Survey; LA-SSA, long-acting somatostatin analogues; Macro, Macroadenoma; mg, milligram; N/A, not applicable; PEGV, pegvisomant; RTx, radiotherapy.

Results

Cohort characteristics

Patient characteristics and previous treatment modalities of the two combination treatment cohorts and the PEGV monotherapy cohort are depicted in Table 1. Acromegaly patients treated with the combination treatment included in the LAS database are younger (39.0 vs 45.5 years), more likely to be diagnosed with a macroadenoma (90.8% vs 81.3%) and suffered from diabetes mellitus more frequently (43.4% vs 36.6%). Patients from the Rotterdam cohort are taller (178 vs 170 cm). Patients who were included in the LAS database needed higher PEGV doses to achieve normalized IGF-I levels both during combination treatment with LA-SSA and during PEGV monotherapy and had a higher IGF-I level ($\times$ ULN) before the addition of PEGV. Other descriptive data and measurements such as weight, height and biochemical data are depicted in Table 1, as well as comparisons between the combination treatment group and the PEGV monotherapy group. No significant differences were observed in the combination treatment cohort between excluded (all originated from the LAS database) and included patients, except for the percentage of performed surgeries, radiotherapy and height, the excluded patients were smaller in stature. No significant differences were observed in the PEGV monotherapy cohort between excluded and included patients.

Predictors of PEGV dosing required for disease control in combination treatment with LA-SSA

All univariate analyses of the candidate predictors are depicted in Fig. 1. A positive linear association was observed between IGF-I ($\times$ ULN) and the PEGV dosage required for disease control. There was a positive non-linear association of weight with PEGV normalization dosage, suggesting an effect threshold from approximately 100 kg (Fig. 1); results were similar after adjustment for age and height (data not shown). There was a negative linear association of age with PEGV normalization dosage and a positive linear association of height with PEGV normalization dosage. In multivariable analyses, the association of age and height were no longer statistically significant after adjustment for weight; yet, age did meet the pre-specified criteria of being added in the final model. Other potential predictors were not associated with the PEGV normalization dosage (Fig. 1).

Figure 2 depicts the performance of the standard prediction model (X-axis) as compared to the true PEGV normalization dosage (Y-axis) and the difference between the predicted and true normalization PEGV dose for each individual (colored dots are corresponding to the table colors; Fig. 2). The standard prediction formula for PEGV normalization dosage based on multivariable models ($\text{EXP}^{(5.5994 + \text{IGF-I ULN} \times 0.2585 + \text{weight} \times -0.0365 + \text{weight}^2 \times 0.00025 + \text{age} \times -0.0045)}$) (Table 2) predicted the final PEGV normalization dose correctly in 63.3% of all

Figure 1

Identification of potential predictors during combination treatment. Univariate analyses of multiple determinants potential for the prediction of the PEGV dose needed to achieve normalization of IGF-I levels during combination treatment. IGF-I $\times$ ULN, age at diagnosis, weight and height were significantly associated with PEGV dosing during PEGV treatment in combination with LA-SSA. GH, growth hormone; IGF-I, insulin-like growth factor I; macro, macroadenoma; micro, microadenoma; PEGV, pegvisomant; ULN, upper limit of normal.

Figure 2

Association of combined predictive values with the PEGV dose needed for IGF-I normalization. This figure shows the association of the combined predictive values (X-axis, the model) with the PEGV dose needed for IGF-I normalization as obtained in clinical practice (Y-axis). The regression line is represented by the dashed line (gray). The individual data points are colored according to the distance from the regression line (red: distance ≥ 60 mg/week, orange 20–60 mg/week, green < 20 mg/week). Data points in the figure depict the standard model. The conservative and progressive model were defined as the normal model minus or plus 40 mg/week respectively. The table below depicts the n (%) of the different model groups and also display the potential shift between the models.

Model type	Potential overtreatment		Correct treatment	Potential undertreatment	
	Over 60 mg/week	20 – 60 mg/week	between 20 and –20 mg/week	–20 to –60 mg/week	Below –60 mg/week
Conservative (decrease overtreatment)	6 (3.2%)	20 (10.6%)	64 (34.0%)	41 (21.8%)	57 (30.3%)
Standard	27 (14.4%)	63 (33.5%)	40 (21.3%)	16 (8.5%)	42 (22.3%)
Progressive (decrease undertreatment)	90 (47.9%)	41 (21.8%)	16 (8.5%)	14 (7.4%)	27 (14.4%)

patients within a range of ± 60 mg/week and in 21.3% of all patients within a range of ± 20 mg/week (Fig. 2). In addition, a more conservative model (standard prediction model minus 40 mg/week) correctly predicted the PEGV normalization dosage in 66.4% of all patients within a range of ± 60 mg/week and in 34.0% of all patients within a range of ± 20 mg/week (Fig. 2). For a more progressive

model (standard model plus 40 mg/weekly), these numbers were 37.7% and 8.5% respectively (Fig. 2).

Predictors of PEGV dosing required for disease control during PEGV monotherapy

A positive linear association was observed between weight and the PEGV dosage required for disease control ($P \leq 0.001$; Figs 3 and 4). None of the other potential predictors were associated with the PEGV normalization dosage (Fig. 3). Figure 4 depicts the performance of weight (X-axis) as a predictor for PEGV normalization dosage as compared to the true normalization dosage (Y-axis) and the difference between the predicted and true normalization dosage for each individual (colored dots are corresponding to the table colors; Fig. 4). The standard prediction formula for PEGV normalization dosage based on weight ($\text{EXP}^{(4.092 + \text{weight} \times 0.00868)}$) predicted the final PEGV normalization dose correctly in 77.1% of all patients within a range of ± 60 mg/week and in 31.3% of

Table 2 Multivariable analysis of final model to predict optimal PEGV dosing.

Variable	Estimate	SE	P value
Intercept	5.5994	0.9382	< 0.0001
IGF-I ($\times$ ULN)*	0.2585	0.0459	< 0.0001
Weight (kg)*	–0.0365	0.0192	0.0830
Weight ² (kg)*	0.0002	0.0001	0.0038
Age at diagnosis (years)	–0.0045	0.0033	0.1700

As the outcome is not normally distributed, the model should be calculated as: $e^{(\text{final model})}$.

*Before the addition of PEGV to LA-SSA.

IGF-I, insulin-like growth hormone I; PEGV, pegvisomant; SE, standard error; ULN, upper limit of normal.

Figure 3

Identification of potential predictors during PEGV monotherapy. Univariate analyses of multiple determinants potential for the prediction of the PEGV dose needed to achieve normalization of IGF-I levels during PEGV monotherapy. Only weight was significantly associated with PEGV dosing during PEGV monotherapy. GH, growth hormone; IGF-I, insulin-like growth factor I; macro, macroadenoma; micro, microadenoma; PEGV, pegvisomant; ULN, upper limit of normal.

all patients within a range of ± 20 mg/week (Fig. 4). In addition, a more conservative model correctly predicted the PEGV normalization dosage in 67.4% of all patients within a range ± 60 mg/week and in 32.5% of all patients within a range of ± 20 mg/week. For a more progressive model, these numbers were 56.6% and 14.5% respectively.

Discussion

The PEGV dose required for normalization of IGF-I levels in acromegaly is highly variable and a wide inter-individual variation in PEGV serum levels is observed despite identical PEGV dosage (28, 29). Previous studies suggest that this variability depends on disease activity and individual response to the drug (8, 16). Therefore, PEGV titration is a process that requires a tailored approach for each individual. This is the first study that focuses on identifying predictors for PEGV dosing and developing a multivariable model to predict the required PEGV dose to achieve normalization of IGF-I levels in acromegaly patients. The main findings of this study are (1) IGF-I, weight, height and age at diagnosis are associated with the PEGV dose required for normalization of IGF-I levels in patients treated with LA-SSA combined with PEGV and (2) that weight is associated with the PEGV dose required for normalization of IGF-I levels in patients treated with PEGV monotherapy.

To the best of our knowledge, only one previous study has investigated determinants of the PEGV dose needed for IGF-I normalization. Parkinson *et al.* observed that GH and IGF-I levels, sex, weight and previous radiotherapy were associated with the PEGV dose required for disease control in patients treated with PEGV monotherapy ($n=118$) (20). In our study, IGF-I $\times$ ULN was the best predictor for PEGV dosing; yet, GH levels were not associated with the required PEGV dose. The most likely explanation for this difference is the variability of the GH assays. The study by Parkinson *et al.* used a single assay for the measurement of all GH levels, whereas GH levels in our study were measured in several local hospitals and thereby consequently measured by different GH assays. This can lead to measurement errors and a bias. Moreover, single GH has a limited clinical usefulness as it has a short half-life and is pulsatile excreted into the bloodstream. Therefore, random single measurements of GH are less suitable as a biochemical marker for acromegaly in clinical practice. These aspects are less prominent for IGF-I measurements, as they are expressed as the upper limit of normal and are less sensitive to daily variations as compared to GH. Despite the limitations of GH-measurement, we chose to include and analyze these GH levels because of its biological plausibility as a candidate predictor and the intention that our prediction model is going to be used in multiple hospitals and consequently GH measurements will be performed with several different assays.

Model type	Potential overtreatment		Correct treatment	Potential undertreatment	
	over 60 mg/week	20 to 60 mg/week	between 20 and –20 mg/week	–20 to –60 mg/week	below –60 mg/week
Conservative (decrease overtreatment)	1 (1.2%)	3 (3.6%)	27 (32.5%)	26 (31.3%)	26 (31.3%)
Standard	4 (4.8%)	27 (32.5%)	26 (31.3%)	11 (13.3%)	15 (18.1%)
Progressive (decrease undertreatment)	30 (36.1%)	26 (31.3%)	12 (14.5%)	9 (10.8%)	6 (7.2%)

Figure 4

Association of weight with the PEGV dose needed for IGF-I normalization. This figure shows the association of the patient's weight (X-axis) with the PEGV dose needed for disease control as obtained in clinical practice (Y-axis). The regression line is represented by the dashed line (gray). The individual data points are colored according to the distance from the regression line (red: distance = 60 mg/week, orange 20–60 mg/week and green < 20 mg/week). Data points in the figure depict the standard model. The conservative and progressive models were defined as the normal model minus or plus 40 mg/week respectively. The table below depicts the n (%) of the different model groups and also displays the potential shift between the models.

The best predictor during combination treatment, besides IGF-I, is the patients weight before the start of PEGV. Patients with a higher bodyweight, require a higher PEGV dosage, which is a logical and expected phenomenon. However, in our study, a positive non-linear association was observed, suggesting a threshold effect from approximately 100 kg body weight, which remained similar after correction for sex, age and IGF-I levels. A possible explanation for this effect threshold could be that these patients have different disease activity and therefore have a different body composition, possibly more fat mass. Former studies already reported an association between weight and PEGV dose titration

(19, 20, 30). Future studies should investigate whether a clinical assessment of body composition (ratios of lean vs fat mass percentages) may improve the prediction of the PEGV dose required for biochemical normalization.

Female gender is reported to have a better PEGV response with similar PEGV doses during PEGV monotherapy; however, this gender difference was not statically significant anymore when PEGV doses were expressed per kg body weight (19). Another study did observe that women needed a higher average PEGV dose of 0.04 mg/kg/day during PEGV monotherapy (20). It has been speculated that sex differences in PEGV pharmacokinetics may influence absorption, distribution

and/or clearance of the drug as well as the modulation of GH sensitivity by estrogens and fat (31, 32, 33). However, regardless of weight differences, we could not confirm a sex difference in relation to the PEGV normalization dose during our study both in patients treated with PEGV monotherapy and in combination with LA-SSA.

Opposite to patients treated with the combination therapy, we found that IGF-I was not a predictor of PEGV dosing during PEGV monotherapy, despite its biological plausibility. This may be explained by differences in the disease severity of patients in the combination vs monotherapy groups, given that the LAS combination cohort requires a median PEGV dose of 210mg/week on top of the maximum LA-SSA dosage, whereas the LAS cohort treated with PEGV monotherapy required a median dose of 105mg/week. According to the literature, to achieve efficacy rates of more than 90% during PEGV monotherapy, the average expected weekly dose is above 120–130mg (12, 34). Studies about the combination treatment reported PEGV doses that range between 60 and 140mg weekly in addition to LA-SSA (normalization rates range between 67% and 97%) (8, 10, 35). These data show that the LAS monotherapy group contains less severe acromegaly patients, whereas the LAS combination treatment group contains more severe acromegaly patients relative to data from the literature, presumed that the PEGV dose represents disease severity. On the other hand, LA-SSA has a direct and an indirect effect, which results in GH-independent decrease of IGF-I secretion (36, 37). A Danish group observed that PEGV serum levels increase by 20% when combined with LA-SSA (38). Besides dosing difference, it may be expected that the use of two drug modalities is naturally more given to patients with more disease severity. Additionally, IGF-I ($\times$ ULN) levels before the addition of PEGV in both LAS cohorts treated with monotherapy and combination treatment are higher. On the other hand, the differences between the various IGF-I-assays that were used in the different cohorts should be taken into account.

The PEGV doses of the LAS cohort required for IGF-I normalization were strikingly high compared to those of the Rotterdam cohort. The distribution of normalization PEGV dosage was right skewed as opposed to the normally distributed Rotterdam cohort. This most likely reflects the fact that the LAS cohort represents the more severe cases in Europe, whereas the experience with PEGV in Rotterdam has led to a relatively low threshold for prescribing PEGV in addition to LA-SSA. This may not be directly linked to a difference in IGF-I levels before the addition of PEGV in our study; however, LAS patients are younger and are having

more diabetes mellitus, which are the characteristics of more severe acromegaly. Another possible explanation could be the interest of the research group in Liège for genetic disorders causing acromegaly, taking into account that the possible prevalence of a mutation in the aryl hydrocarbon receptor-interacting protein (AIP) gene, X-linked acro gigantism (X-LAG) and/or familial isolated pituitary adenoma (FIPA) patients could be higher in this cohort. Despite these differences, we found that a meta-analysis of both cohorts (as a form of external replication) performed well and also the separate analyses per cohort showed the same effect directions. By combining both cohorts, the results of this study are widely generalizable as this approach has led to a study population that reflects a wide range of acromegaly patient that is eligible to start PEGV treatment.

This study was potentially limited by the retrospective design, which consequently led to missing data. To cope with both differentially and randomly missing data, we used multiple imputation. This study was also limited by the relative small sample size. However, this is expected given the low prevalence of acromegaly as well as the fact that only a subset of acromegaly patients is treated with LA-SSA in combination with PEGV. The Rotterdam cohort harbored exclusively patients who were normalized by LA-SSA in combination with PEGV, as PEGV doses were uptitrated until normalization of IGF-I levels was achieved. The exclusion of patients from the LAS cohort not normalized by LA-SSA and PEGV ($n=16$, 8.5%) or PEGV alone ($n=6$, 7.2%) has remained limited. To overcome these limitations and to replicate our results, prospective studies utilizing a multicenter set-up are required.

This model is designed for patients who are about to start PEGV treatment after failure of LA-SSA monotherapy. Furthermore, this study is not designed to predict PEGV overdosing as PEGV doses were increased until IGF-I levels were normalized. However, this prediction model should be considered as a useful clinical tool during PEGV dose titration, which can be time consuming over multiple outpatient clinic visits, especially when a high PEGV dose is needed to control the disease.

Conclusion

This is the first study that focuses on identifying predictors for the PEGV dose required for disease control in acromegaly and the development of a multivariate prediction model for the required PEGV dose. The model is designed for

Clinical Study	S E Franck and others	Prediction model for pegvisomant dosing	176:4	430
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patients who are about to start PEGV after failure of LA-SSA monotherapy and could be used as a clinical guidance tool during the start of PEGV dose titration. In this study, the PEGV dose needed for normalization of IGF-I levels in addition to LA-SSA is associated with IGF-I levels, weight and age in a multivariate prediction model and predicted the final PEGV normalization dose correctly in 63.3% of all patients within a range of ± 60 mg/week (21.3% within a range of ± 20 mg/week). The required PEGV dose during monotherapy was associated with the patient's weight and predicted the final PEGV normalization dose correctly in 77.1% of all patients within a range of ± 60 mg/week (31.3% within a range of ± 20 mg/week). For an acromegaly patient of age 60 years, weight of 80 kg, height of 1.75 m and a IGF-I level of 1.6 $\times$ the ULN using the maximum dose of LA-SSA, the standard model will calculate 83.3 mg PEGV weekly. In this case, we will recommend to start with 80 mg weekly and titrate up or down guided by the IGF-I level (target 1.0 $\times$ the ULN).

Declaration of interest

A J van der Lely and S J C M M Neggers have received financial support for investigator-initiated research, unrestricted grants and speaker's fees from Novartis, Pfizer and Ipsen. A J van der Lely also received consultancy fees from Novartis and Pfizer. P Petrossians have received consultancy fees from Novartis, Ipsen and Pfizer. P Chanson has received unrestricted research and educational grants from Ipsen, Novartis and Pfizer as Head of the Department of Endocrinology and Reproductive Diseases, Hôpitaux Universitaires Paris-Sud, he has served as investigator (principal or coordinator) for clinical trials funded by Novartis, Pfizer, Ipsen, Italfarmaco and Antisense, he is member of Advisory Boards from Ipsen and Novartis and he gave lectures for Ipsen, Novartis and Pfizer. All the fees and honoraria are paid to his institution. M L Jaffrain-Réa received a consultancy fee from Novartis. T Brue received financial support research grants, consultant or speaker fees from Ipsen, Novartis, Pfizer, Sandoz and Strongbridge. A Colao is a member of the Italian scientific board of Pfizer. C Fajardo has received honoraria from Pfizer as speaker fees. A Beckers has received educational grant funding from Pfizer and Ipsen and Advisory Board Membership for Ipsen. S E Franck, T I M Korevaar, A F Daly, G K Stalla, D Carvalho, V Hana Jr. and B Delemer have nothing to disclose.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. The Liège Acromegaly Survey (LAS) was developed with an unrestricted educational grant from Ipsen to A Beckers.

Acknowledgements

The authors would like to thank all patients for their participation.

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Received 22 November 2016

Revised version received 3 January 2017

Accepted 17 January 2017