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

S.E. Franck[1], T.I.M. Korevaar[1], P. Petrossians[2], A.F. Daly[2], P. Chanson[3], M.L. Jaffrain-Réa[4], T. Brue[5], G.K. Stalla[6], D. Carvalho[7], A. Colao[8], V. Hána Jr.[9], B. Delemer[10], C. Fajardo[11], A.J. van der Lely[1], A. Beckers[2]* and S.J.C.M.M. Neggers[1]*

[1]Department of Internal Medicine, Endocrinology section, Erasmus University Medical Center Rotterdam, The Netherlands.
[2]Department of Internal Medicine, Endocrinology section, Centre Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, Liège, Belgium.
[3]Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Hôpital de Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Le Kremlin Bicêtre, F-94275, France; Inserm 1185, Fac Med Paris Sud, Univ Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, F-94276, France
[4]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila and Neuromed, IRCCS, Pozzilli, Italy.
[5]Aix-Marseille Université, CNRS, CRN2M UMR 7286, 13344 cedex 15, Marseille, and APHM, Hôpital Conception, Service d'Endocrinologie, Diabète et Maladies Métaboliques, Centre de Référence des Maladies Rares d'Origine hypophysaire, Marseille, France.
[6]Clinical Neuroendocrinology, Max-Planck-Institute of Psychiatry, Munich, Germany.
[7]Department of Internal Medicine, Endocrinology, Diabetes and Metabolism section and Instituto de Investigação e Inovação em Saúde, University of Porto, Centro Hospitalar S. João, Alameda Professor Hernâni Monteiro, Porto, Portugal.
[8]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy.
[9]3rdDepartment of Internal Medicine, First Medical Faculty, Charles University, Prague, Czech Republic.
[10]Department of Endocrinology, Diabetes, and Nutrition, University Hospital of Reims, Reims, France.
[11]Servicio de Endocrinología, Hospital Universitario La Ribera, Valencia, Spain.

* A.B. and S.J.C.M.M.N contributed equally and share last authorship

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Corresponding author:
S.E. Franck MD
Department of Internal Medicine, Endocrinology section
Erasmus University Medical Center
PO Box 2040
3000 CA Rotterdam, The Netherlands,
Phone: +31 10 7038692
Fax: +31 10 7036801
Email: s.franck@erasmusmc.nl

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-analysed 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=<0.001, p=<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=<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 in order 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.

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 (8-12). 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 hours, $T_{1/2\ el}$ 74-172 hours) (15). The mode of PEGV-clearance is still not understood. We do not know whether the kidneys and/or the liver metabolizes 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 – 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 is 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 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 no clinical effect on the PEGV response nor the determination of the required PEGV dose (23-25).

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.

Materials & Methods

Cohorts description

Patients (n=271) were included from two retrospective cohorts; 1) the Rotterdam cohort and; 2) the Liége 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 which 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 (>1.2x 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, while 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 (figure 2, (18)). The formula to calculate the PEGV dose is 4 + (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 (8,18-20), 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 was collected at baseline (as indicated), was fixed data in the patient's record, or was 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 analysed using an unpaired t-test or the Mann-Whitney U test (in case of non-parametric data). Nominal variables were analysed 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 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 criterions and log-likelihood tests comparing multilevel models with random intercepts and/or slope per cohort versus standard linear regression correcting for cohort. To allow for optimal generalizability of effect estimates that predict the required PEGV dose, we performed multivariable multilevel modelling 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 Inc. Chicago, IL, USA) or using R statistical software version 3.2.43 (packages *rms*, *MASS* and *lm4*).

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 in order to achieve normalized IGF-I levels both

during combination treatment with LA-SSA and during PEGV monotherapy and had a higher IGF-I level (xULN) 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 figure 1. A positive linear association was observed between IGF-I (xULN) 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 (figure 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 (figure 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; figure 2). The standard prediction formula for PEGV normalization dosage based on multivariable models (EXP^(5.5994 + IGF-1 ULN*0.2585 + weight*-0.0365 + weight^2*0.00025 + age*-0.0045)) (table 2)

predicted the final PEGV normalization dose correctly in 63.3% of all patients within a range of +/- 60 mg/week and in 21.3% of all patients within a range of +/- 20 mg/week (figure 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 (figure 2). For a more progressive model (standard model plus 40 mg/weekly), these numbers were 37.7% and 8.5%, respectively (Figure 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=<0.001; figure 3 and figure 4). None of the other potential predictors were associated with the PEGV normalization dosage (figure 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; figure 4). The standard prediction formula for PEGV normalization dosage based on weight (EXP^(4.092 + weight*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 all patients within a range of +/- 20 mg/week (figure 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 in order 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 xULN 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, while 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 intension that our prediction model is going to be used in multiple hospitals and consequently GH-measurements will be performed with several different assays.

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 (31-33). 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 versus monotherapy groups, given that the LAS combination cohort requires a median PEGV dose of 210 mg/week on top of the maximum LA-SSA dosage, while the LAS cohort treated with PEGV monotherapy required a median dose of 105 mg/week. According to the literature, to achieve efficacy rates of more than 90% during

PEGV monotherapy, the average expected weekly dose is above 120-130 mg (12,34). Studies about the combination treatment reported PEGV doses that range between 60-140 mg weekly in addition to LA-SSA (normalization rates range between 67-97%) (8,10,35). These data show that the LAS-monotherapy group contains less severe acromegaly patients, while 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 (xULN) levels before the addition of PEGV in both LAS cohorts treated with monotherapy and combination treatment are higher. On the other hand, it should be take into account the differences between the various IGF-I-assay's which were used in the different cohorts.

The PEGV doses of the LAS cohort required for IGF-I normalization were strikingly high compared to the Rotterdam cohort. The distribution of normalization PEGV dosage were 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, while the experience with PEGV in Rotterdam has led to a relatively low threshold for prescribing PEGV in addition to LA-SSA. This may not directly be 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 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 acrogigantism (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. In order 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 that were normalized by LA-SSA in combination with PEGV, as PEGV doses were up-titrated until normalization of IGF-I levels were 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. In order 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, since PEGV doses were increased until IGF-I levels were normalized. But 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 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 60 years old, weight of 80 kilograms, height of 1.75 meters, and a IGF-I level of 1.6x 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 1.0x the ULN).

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Tables and figures

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 imputed in the original datasets by multiple imputation. Continues variables are expressed in median [interquartile range] and categorical variables in percentages. LA-SSA: long-acting somatostatin analogues, PEGV: pegvisomant, LAS: Liège acromegaly survey, kg: kilogram, cm: centimeter, Macro: Macroadenoma, IGF-I: insulin-like growth factor I, GH: growth hormone, RTx: radiotherapy, mg: milligram, N/A: not applicable.

a) Combination treatment (Rotterdam) vs. combination treatment (LAS)
b) Combination treatment (Rotterdam and LAS) vs. PEGV monotherapy (LAS)

Figure 1. Identification of potential predictors during combination treatment

Figures are provided separately

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 xULN, age at diagnosis, weight and height were significantly associated with PEGV dosing during PEGV treatment in combination with LA-SSA. PEGV: pegvisomant, IGF-I: insulin-like growth factor I, ULN: upper limit of normal, GH: growth hormone, micro: microadenoma, macro: macroadenoma.

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

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

Figure 2. Association of combined predictive values with the PEGV dose needed for IGF-I normalization

Figures are provided separately

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 (grey). 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.

Figure 3. Identification of potential predictors during PEGV monotherapy

Figures are provided separately

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. PEGV: pegvisomant, IGF-I: insulin-like growth factor I, ULN: upper limit of normal, GH: growth hormone, micro: microadenoma, macro: macroadenoma.

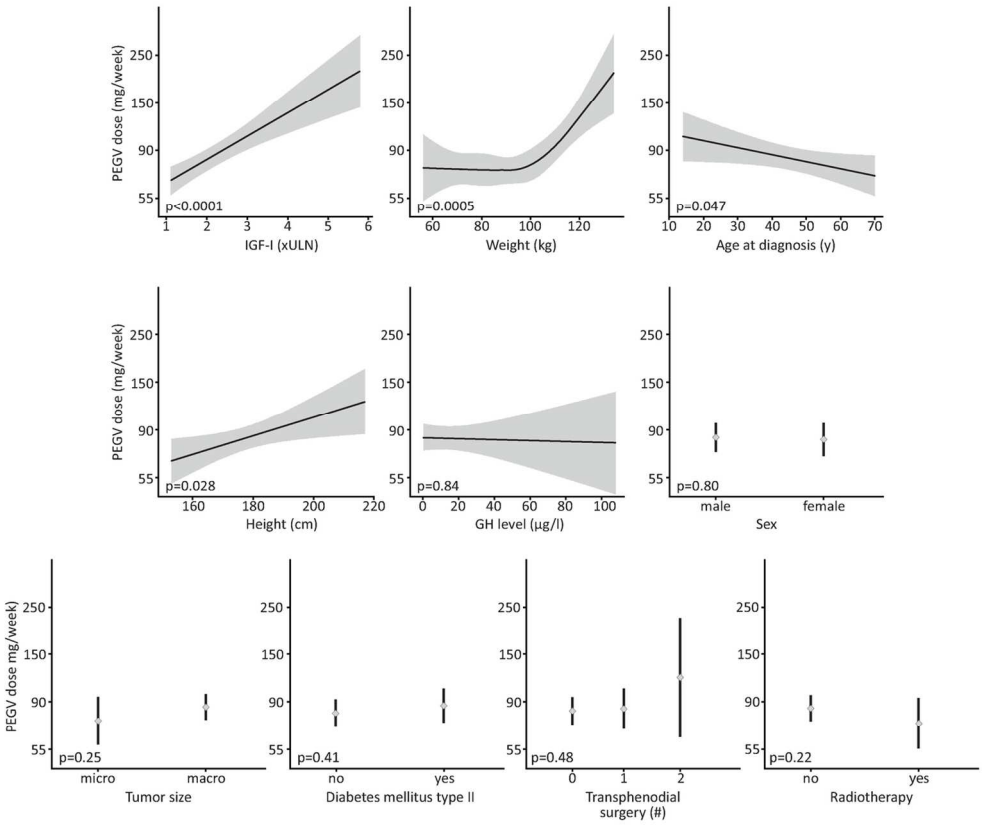
Figure 4. Association of weight with the PEGV dose needed for IGF-I normalization

Figures are provided separately

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 (grey). 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 displays the potential shift between the models.

	Combination treatment LA-SSA + PEGV			p-value[a]	PEGV monotherapy	p-value[b]
	Total cohort	Rotterdam	LAS		LAS	
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

Variable	Estimate	SE	p-value
Intercept	5.5994	0.9382	<0.0001
IGF-I (xULN)*	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



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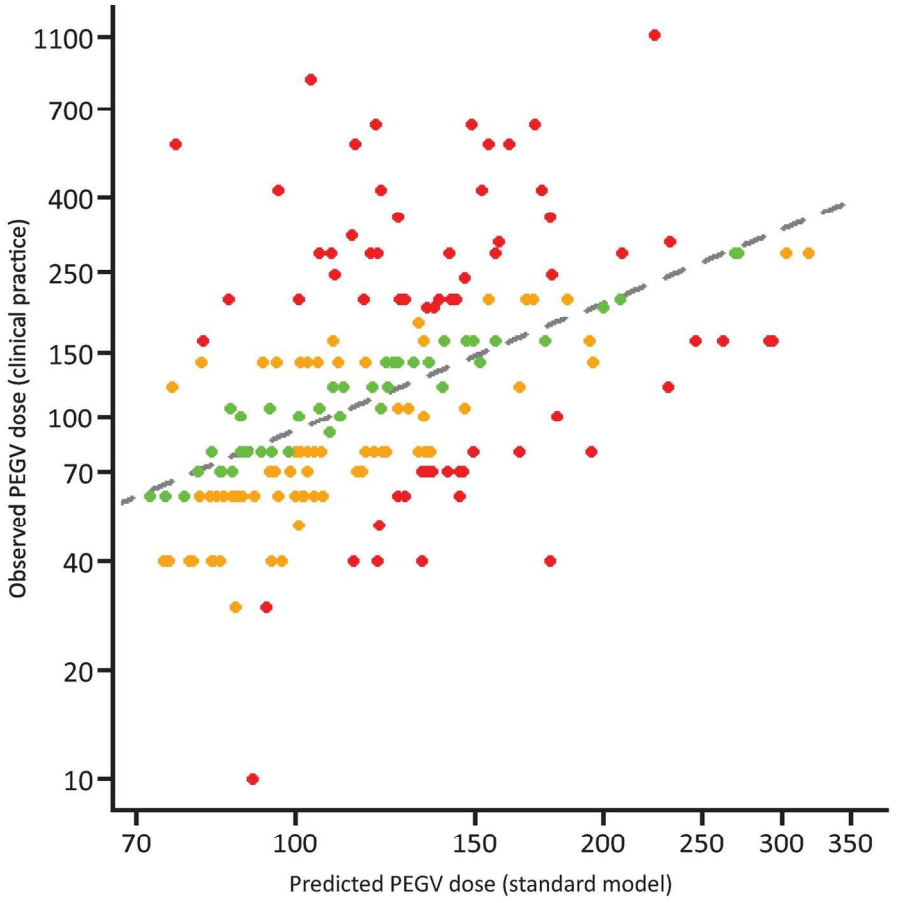

Model type	Potential overtreatment: over 60 mg/week	Potential overtreatment: 20 to 60 mg/week	Correct treatment: between 20 and -20 mg/week	Potential undertreatment: -20 to -60 mg/week	Potential undertreatment: below -60 mg/week
Conservative (decrease overtreatment)	6 (3.2%)	20 (10.6%)	64 (34.0%)	41 (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%)

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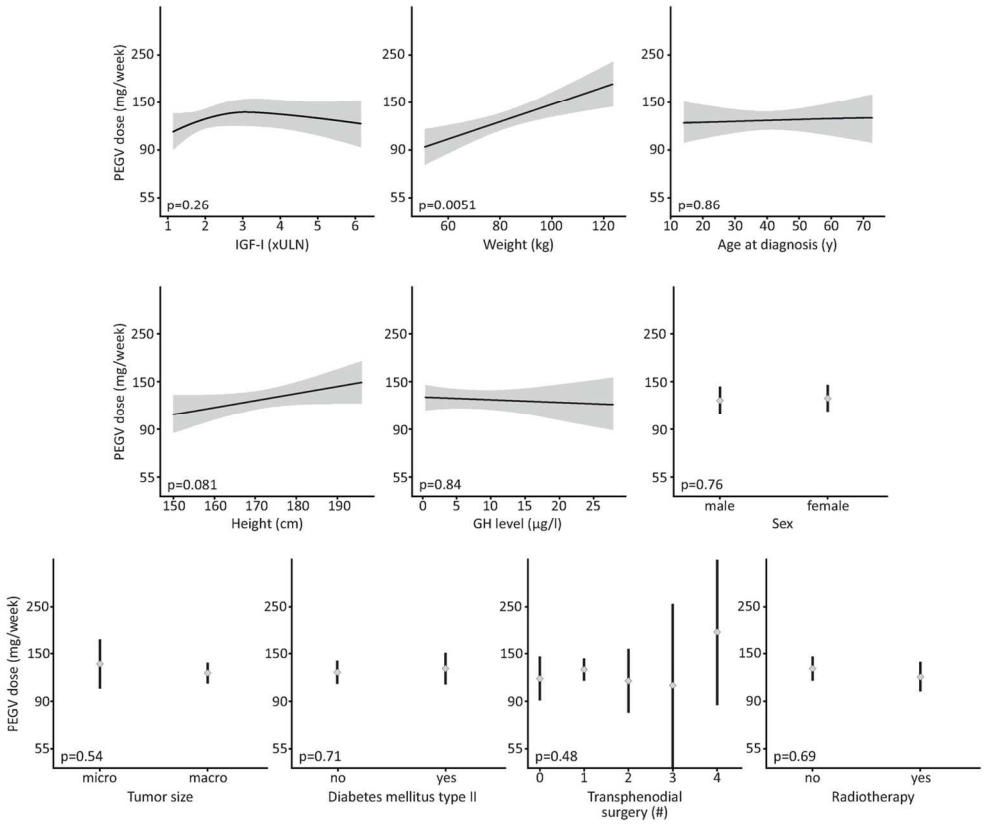

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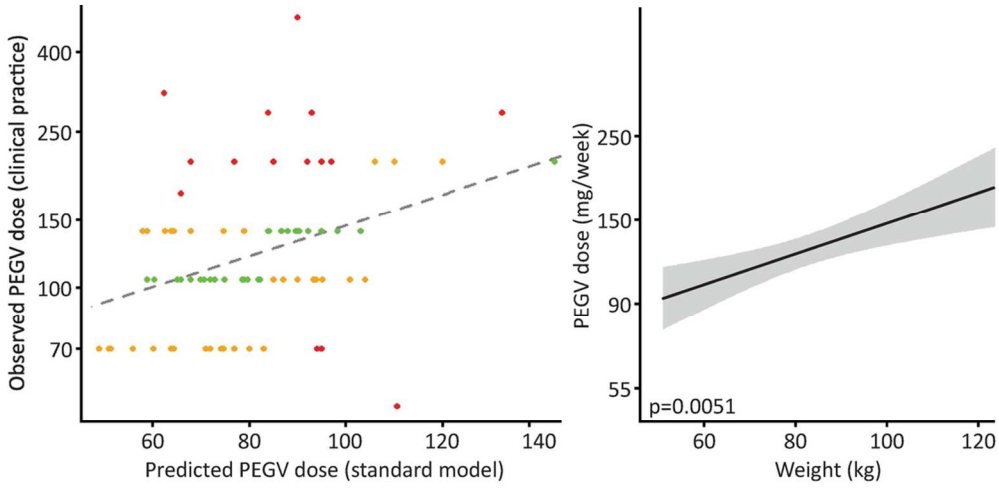

Model type	Potential overtreatment: over 60 mg/week	Potential overtreatment: 20 to 60 mg/week	Correct treatment: between 20 and -20 mg/week	Potential undertreatment: -20 to -60 mg/week	Potential undertreatment: below -60 mg/week
Conservative (decrease overtreatment)	1 (1.2%)	3 (3.6%)	27 (32.5%)	26 (31.3%)	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%)

in the main document

100x72mm (300 x 300 DPI)