Quality of Life in Acromegalic Patients during Long-Term Somatostatin Analog Treatment with and without Pegvisomant

S. J. C. M. M. Neggers, M. O. van Aken, W. W. de Herder, R. A. Feelders, J. A. M. J. L. Janssen, X. Badia, S. M. Webb, and A. J. van der Lely

Department of Internal Medicine (S.J.C.M.M.N., M.O.v.A., W.W.d.H., R.A.F., J.A.M.J.L.J., A.J.v.d.L.), Erasmus University Medical Center Rotterdam, 3000 CA, Rotterdam, The Netherlands; Health Economics and Outcomes Research (X.B.), IMS Health, Centre for Biomedical Research on Rare Diseases (CIBERER Unit 747), 08034 Barcelona, Spain; and Department of Endocrinology (S.M.W.), Hospital Sant Pau, Centre for Biomedical Research on Rare Diseases (CIBERER Unit 747), Autonomous University of Barcelona, 08025 Barcelona, Spain

Objective: The objective of the study was to assess whether weekly administration of 40 mg pegvisomant (PEG-V) improves quality of life (QoL) and metabolic parameters in acromegalic patients with normal age-adjusted IGF-I concentrations during long-acting somatostatin analog (SSA) treatment.

Design: This was a prospective, investigator-initiated, double blind, placebo-controlled, crossover study. Twenty acromegalic subjects received either PEG-V or placebo for two consecutive treatment periods of 16 wk, separated by a washout period of 4 wk. Efficacy was assessed as change between baseline and end of each treatment period. QoL was assessed by the Acromegaly Quality of Life Questionnaire (AcroQoL) and the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ).

Results: The AcroQoL ($P = 0.008$) and AcroQoL physical ($P = 0.002$) improved significantly after PEG-V was added. The addition of PEG-V also significantly improved the PASQ ($P = 0.038$) and the single PASQ questions, perspiration ($P = 0.024$), soft tissue swelling ($P = 0.036$), and overall health status ($P = 0.035$). No significant change in Z-score of IGF-I ($P = 0.34$) was observed during addition of PEG-V. Transient liver enzyme elevations were observed in five subjects (25%).

Conclusion: Improvement in quality of life was observed without significant change in IGF-I after the addition of 40 mg pegvisomant weekly to monthly SSA therapy in acromegalic patients who had normalized IGF-I on SSA monotherapy. These data question the current recommendations in how to assess disease activity in acromegaly. Moreover, the findings question the validity of the current approach of medical treatment in which pegvisomant is used only when SSA therapy has failed to normalize IGF-I. **(*J Clin Endocrinol Metab* 93: 3853–3859, 2008)**

Recent improvement in the medical treatment of acromegaly has resulted in better biochemical disease control in virtually every acromegaly patient (1–4). By normalizing both IGF-I and GH, the elevated long-term mortality will decrease (5–8). However, normalization does not completely relieve patients from their symptoms (9). From the patient's perspective an important parameter of disease control is the quality of life (QoL). Indeed, these residual symptoms result in an impaired QoL (10–13). To quantify the symptoms and QoL in patients with acromegaly, the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) (2, 3) and the Acromegaly Quality of Life Questionnaire (AcroQoL) have been developed (14).

We recently reported that the combination of somatostatin analog (SSA) and (twice) weekly pegvisomant (PEG-V) is an effective treatment for patients in whom the IGF-I remains elevated during SSA monotherapy (1, 4). The rationale for this combined

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2008-0669 Received March 26, 2008. Accepted July 14, 2008.

First Published Online July 22, 2008

Abbreviations: AcroQoL, Acromegaly Quality of Life Questionnaire; GHR, GH receptor; PASQ, Patient-Assessed Acromegaly Symptom Questionnaire; PEG-V, pegvisomant; ΔPEG-V, change between baseline and end of each treatment period with pegvisomant; Δplacebo, change between baseline and end of each treatment period with placebo; QoL, quality of life; SSA, somatostatin analog; TC, total cholesterol; TELET, transient elevated liver enzyme test; ULN, upper limit or normal; V, visit.

treatment is based on the concept that SSA will decrease GH secretion in acromegalic subjects. When there is less endogenous GH to compete for the GH receptor (GHR), less of the GHR antagonist PEG-V is needed. Moreover, *in vitro* data suggest that the inhibition of insulin secretion by SSA in the portal vein results in a reduction of GHR on the cell surface of hepatocytes (15). So when there are fewer hepatic GHRs and less endogenous GH, less PEG-V is necessary. Finally, SSA can also directly inhibit IGF-I production by hepatocytes (16). Therefore, SSA makes the liver less GH sensitive, as the rest of the body might still be slightly acromegalic. If these extrahepatic GH actions could be antagonized by the addition of pegvisomant, one might observe an improvement of QoL.

We therefore performed a randomized, double-blind, placebo-controlled, crossover study in which we assessed QoL, using AcroQoL and PASQ, in acromegalic patients in biochemical remission on long-term SSA monotherapy before and after the addition of a weekly dose of 40 mg PEG-V for a period of 16 wk.

Patients and Methods

Patients

Twenty acromegalic patients, median age 56 (range 39–74) yr, with an IGF-I within the age adjusted normal range during long-term long-acting SSA therapy, were enrolled in this study (17). All subjects were on a stable long-acting monthly SSA treatment for at least 36 months. The single GH levels assessed before the initiation of PEG-V therapy were less than 2.5 μg/liter in all but one subject. Patients' characteristics are presented in Table 1. All patients gave their written informed consent, and the study was approved by the local ethics committee.

Design

The study was a prospective, investigator-initiated, double-blind, placebo-controlled, single-center, crossover study. After enrollment [visit (V)], patients were randomized to receive a single weekly sc injection of 40 mg PEG-V or placebo. QoL assessment and biochemical evaluation were performed at baseline and after 8 (V2) and 16 wk (V3) of combined treatment. After a 4-wk washout period (V4), patients were switched to either placebo or PEG-V for another 16 wk (V5 at 28 wk and V6 at 36 wk).

At all visits efficacy and safety data were assessed including two QoL-questionnaires, IGF-I, glycosylated hemoglobin, fasting glucose, insulin, lipids and homeostasis model assessment insulin resistance. Additional safety including serum alkaline phosphatase, γ-glutamyltranspeptidase, alanine aminotransferase, aspartate aminotransaminase, lactate dehydrogenase, and total bilirubin were measured, and each subject had an electrocardiogram. IGF-I, insulin, and GH concentrations were measured by immunometric assays (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA). For IGF-I the intra- and interassay coefficients of variation are 4.9–6.3 and 3.5–7.5%, respectively (18). IGF-I age-adjusted reference ranges were used to calculate the Z-score of the IGF-I (17).

At baseline and last visit of the study, a magnetic resonance imaging of the pituitary was performed to detect any change in pituitary volume during the study. An independent physician, who did not participate in the study and was unblinded for the medication, evaluated the laboratory findings after each visit to ensure safety and the double-blind set-up of the study. If elevated liver enzyme tests were higher than 4 times the upper limit or normal (ULN) during the treatment periods, the patients were withdrawn from the study.

TABLE 1. Baseline characteristics

	Number[a]	Percent[a]
Patients	20	100
Sex (female)	9	45
Age (yr)		
Mean (SD, range)	55	10.0, 39–74
Diabetes mellitus	3	15
GH at baseline (μg/liter)		
Mean (SD)	1.12	0.7
Median (range)	1.0	0.2–3.1
IGF-I at baseline (nmol/liter)		
Mean (SD)	25.1	5.0
Median (range)	24.6	15.6–35.7
Previous treatment		
TSS	15	75
Both TSS and radiotherapy	6	30
Primary medical therapy	5	25
Pituitary insufficiency		
Panhypopituitarism	5	25
1–2 axis	11	55
No hypopituitarism	4	20
Long-acting SSAs		
Lanreotide	8	40
Octreotide	12	60

TSS, Transsphenoidal surgery.

[a] Unless otherwise specified.

Questionnaires

AcroQoL

AcroQoL comprises 22 questions. Each question has five possible answers scored 1–5, with a total maximum score of 110 and quoted as a percentage. The score of 110 reflects the best possible QoL. The 22 questions are divided into two main categories: physical and psychological function. The psychological dimension is subdivided into appearance and personal relationships (14, 19). The AcroQoL has a good internal consistency (Cronbach's $\alpha > 0.7$) (20).

PASQ

The PASQ is a disease-specific questionnaire, which consists of six questions scoring 0–8 and the seventh question addressing the overall health status, based on the other six questions, scoring 0–10 (2, 3). The first six questions evaluate symptoms as headache, excessive sweating, joint pain, fatigue, soft tissue swelling, and numbness or tingling of the extremities. The maximum score of these six questions is 48 and indicates severe signs and symptoms, with lower scores reflecting improved QoL.

Statistics

For the analysis of QoL questionnaires, the change between baseline and end of each treatment period with pegvisomant (ΔPEG-V) and with placebo (Δplacebo) was calculated. By assessing the change in QoL-questionnaire scores, between baseline and follow-up, possible confounder were taken into account when the paired of these patients were analyzed. The IGF-I results are expressed as Z-score. Therefore, they are reported in SD units. Sample size calculation was made, based on expected PASQ scores, anticipating that SD of each group (assuming they are equal) is 2.5 on the scale of 0–8. When choosing $\alpha = 0.05$, two-tailed, and power = 80%, a number of 20 patients per group will enable detection of differences of 1.82.

The paired data were analyzed with the Wilcoxon's signed rank test. The correlation between the nonparametric data was assessed by the Spearman's rank correlation. Statistical analyses were performed by GraphPad Prism (version 5.00 for Windows; GraphPad Software, San Diego, CA). Statistical significance was accepted at $P < 0.05$ (two tailed). Data are nonparametric and therefore expressed as median $\pm$ SD unless otherwise specified.

TABLE 2. Quantitative changes in QoL in two groups induced by the addition of 40 mg PEG-V once weekly in two different groups of acromegalic patients (PEG-V-placebo, Table 2A, and placebo-PEG-V, Table 2B) with normal IGF-I during long-term treatment with SSAs

A	Baseline [median (range)]	PEG-V [median (range)]	After wash-out [median (range)]	Placebo [median (range)]
PEG-V placebo group				
Z-score of IGF-I	1.50 (1.04–1.73)	1.46 (−0.09 to 1.58)	1.45 (0.89–1.84)	1.64 (1.03–1.99)
Body weight (kg)	83.1 (69.7–107.7)	82.1 (70.3–106.6)	81.6 (70.4–107.3)	83.0 (69.4–106.2)
AcroQoL global(%)	64.2 (44.3–79.5)	69.9 (39.8–87.5)	66.5 (31.8–88.6)	68.2 (30.7–86.0)
AcroQoL physical (%)	51.7 (37.5–92.0)	62.5 (40.6–93.8)	53.1 (31.3–96.9)	59.4 (28.1–87.5)
AcroQoL psychological (%)	65.2 (48.3–87.5)	70.5 (39.3–85.8)	70.5 (32.1–89.3)	72.3 (32.2–85.7)
AcroQoL personal relationships (%)	82.1 (53.6–96.4)	82.1 (46.4–100.0)	80.4 (42.9–100.0)	82.1 (35.7–100.0)
AcroQoL appearance (%)	50.0 (21.4–85.7)	62.5 (28.6–82.1)	64.3 (21.4–82.1)	62.5 (28.6–82.1)
PASQ	14.0 (2.0–21.0)	10.0 (0.0–17.0)	7.5 (0.0–20.0)	10.0 (3.0–22.0)
PASQ headache	1.0 (0.0–3.0)	1.0 (0.0–4.0)	0.0 (0.0–3.0)	1.5 (0.0–4.0)
PASQ excessive sweating	1.0 (0.0–5.0)	0.0 (0.0–3.0)	0.0 (0.0–1.0)	1.0 (0.0–4.0)
PASQ joint pain	4.0 (0.0–6.0)	3.0 (0.0–8.0)	2.5 (0.0–8.0)	3.0 (0.0–7.0)
PASQ fatigue	3.5 (1.0–6.0)	4.0 (0.0–6.0)	2.0 (0.0–6.0)	2.5 (1.0–6.0)
PASQ soft tissue swelling	2.0 (1.0–3.0)	0.5 (0.0–2.0)	0.5 (0.0–3.0)	0.5 (0.0–3.0)
PASQ numbness or tingling	1.5 (0.0–5.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.5 (0.0–3.0)
PASQ overall health status	3.0 (2.0–7.0)	1.5 (0.0–6.0)	1.5 (0.0–6.0)	3.0 (1.0–6.0)
B	**Baseline [median (range)]**	**Placebo [median (range)]**	**After wash-out [median (range)]**	**PEG-V [median (range)]**
Placebo PEG-V group				
Z-score of IGF-I	1.66 (0.82–2.03)	1.52 (0.80–1.92)	1.57 (0.89–1.86)	1.67 (1.26–1.93)
Body weight (kg)	96.8 (69.7–115.8)	95.5 (70.3–117.3)	95.4 (70.4–115.8)	93.7 (69.4–115.1)
AcroQoL global (%)	52.9 (22.7–93.2)	57.4 (22.7–96.6)	54.0 (23.9–95.5)	59.4 (28.4–96.7)
AcroQoL physical (%)	43.9 (18.8–87.5)	40.7 (18.8–90.6)	43.9 (15.6–90.6)	45.3 (34.4–94.4)
AcroQoL psychological (%)	60.7 (21.5–98.2)	69.6 (21.4–100.0)	64.3 (25.0–98.2)	68.8 (25.0–98.0)
AcroQoL personal relationships (%)	71.4 (25.0–100.0)	66.1 (25.0–100.0)	64.3 (25.0–100.0)	71.1 (25.0–100.0)
AcroQoL appearance (%)	55.4 (17.9–96.4)	64.3 (17.9–100.0)	55.3 (25.0–96.4)	64.3 (25.0–96.6)
PASQ	23.5 (9.0–37.0)	26.5 (3.0–39.0)	25.0 (4.0–40.0)	22.0 (5.0–39.0)
PASQ headache	5.0 (0.0–6.0)	3.5 (0.0–7.0)	5.0 (0.0–7.0)	3.0 (0.0–7.0)
PASQ excessive sweating	4.5 (0.0–6.0)	4.5 (0.0–7.0)	3.5 (0.0–7.0)	4.0 (0.0–7.0)
PASQ joint pain	4.5 (2.0–7.0)	5.0 (0.0–8.0)	5.0 (2.0–8.0)	4.5 (0.0–8.0)
PASQ fatigue	4.5 (2.0–8.0)	5.5 (1.0–7.0)	5.0 (0.0–8.0)	5.0 (0.0–7.0)
PASQ soft tissue swelling	1.5 (0.0–6.0)	3.0 (0.0–5.0)	2.5 (0.0–7.0)	3.0 (0.0–5.0)
PASQ numbness or tingling	3.5 (0.0–8.0)	4.0 (0.0–7.0)	3.5 (0.0–7.0)	3.5 (0.0–7.0)
PASQ overall health status	4.5 (1.0–7.0)	4.5 (1.0–8.0)	4.5 (1.0–8.0)	4.5 (0.0–7.0)

Results

All 20 patients completed the study. At baseline, all IGF-I levels were within the age-adjusted normal range and GH was 2.5 μg/liter or less in all except for one subject (GH of 3.1 μg/liter). The QoL scores, parameters of metabolic control, and body weight are presented in Table 2.

AcroQoL

The AcroQoL improved significantly after the addition of PEG-V (ΔPEG-V 6.4 ± 4.25%, Δplacebo −1.1 ± 7.12%, P = 0.008, Fig. 1 and Table 2). PEG-V increased QoL in the AcroQoL physical (ΔPEG-V 8.0 ± 7.88%, Δplacebo 0.0 ± 6.25%, P = 0.002, Fig. 1 and Table 2). However, the AcroQoL psychological (ΔPEG-V 3.6 ± 6.09%, Δplacebo −0.9 ± 9.36%, P = 0.185), AcroQoL appearance (ΔPEG-V 4.0 ± 7.97%, Δplacebo −2.0 ± 12.09%, P = 0.409), and personal relations (ΔPEG-V 0.0 ± 6.14%, Δplacebo −4.0 ± 9.66%, P = 0.109) tended to increase with the addition of PEG-V but failed to reach significance.

PASQ

The PASQ changed significantly (P = 0.038) after cotreatment with PEG-V (ΔPEG-V −2.0 ± 6.60, Δplacebo 1.5 ± 5.02, Fig. 2). In the six questions of the PASQ addressing the different symptoms, a significant decrease in signs and symptoms was observed in the questions soft tissue swelling (ΔPEG-V −0.5 ± 1.37, Δplacebo 0.0 ± 1.28, P = 0.024), excessive sweating (ΔPEG-V 0.0 ± 1.79, Δplacebo 0.5 ± 0.98, P = 0.036), and overall health status (ΔPEG-V −1.0 ± 1.99, Δplacebo 0.5 ± 1.36, P = 0.035, Fig. 2) when PEG-V was added. The joint pain did not improve significantly (ΔPEG-V −1.0 ± 1.47, Δplacebo 0.0 ± 1.49, P = 0.083). In the other parameters, headache (P = 0.899), fatigue (P = 0.662), or numbness or tingling of the extremities (P = 0.175), no significant improvement was observed.

Metabolic parameters

The combined treatment of PEG-V and SSA did not result in a significant change the Z-score of IGF-I (ΔPEG-V −0.064 ± 0.380, Δplacebo 0.102 ± 0. 317, P = 0.341) or in absolute IGF-I concentration (P = 0.444, Fig. 2). The insulin-dependent met-

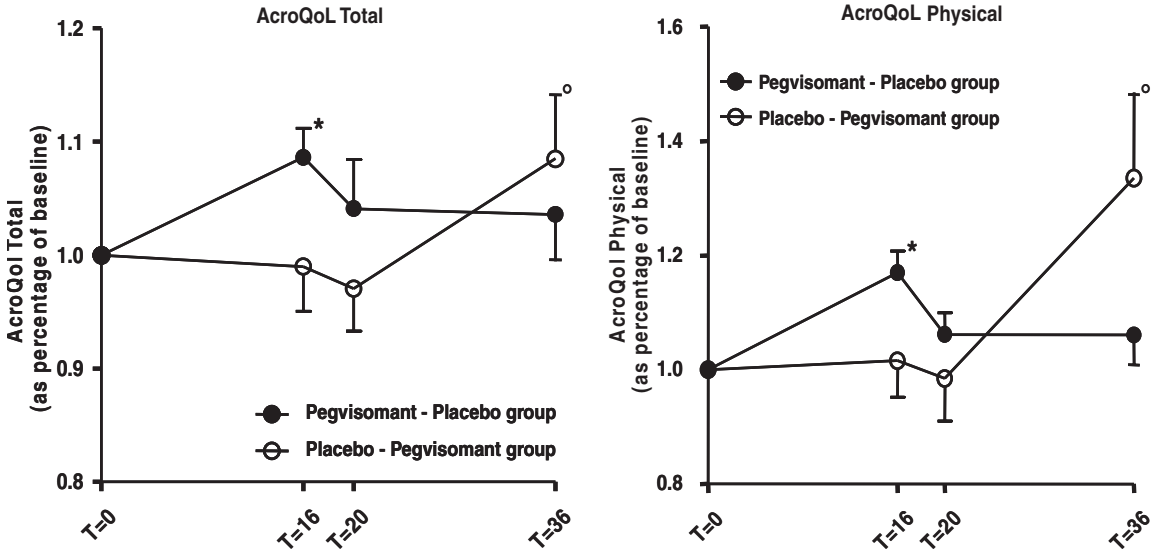

FIG. 1. A, Changes in AcroQoL induced by the addition of 40 mg PEG-V once weekly in two different groups of acromegalic patients (PEG-V-placebo and placebo-PEG-V) with normal IGF-I during long-term treatment with SSAs. *, $P = 0.013$ for T_0 *vs.* T_{16}; °, $P = 0.001$ for T_{20} *vs.* T_{36}. B, Changes in AcroQol physical after the addition of placebo or PEG-V for the two different groups PEG-V-placebo and placebo-PEG-V. *, $P = 0.006$ for T_0 *vs.* T_{16}; °, $P = 0.019$ for T_{20} *vs.* T_{36}. The mean and SEM values are given for each phase of the study. The baseline AcroQoL score is expressed as 1 and the other intervals (T 16, T 20, and T 36 wk) as ratio of baseline QoL.

abolic parameters as homeostasis model assessment insulin resistance ($P = 0.808$, Fig. 3C), glycosylated hemoglobin ($P = 0.241$), and fasting glucose ($P = 0.955$) did not change significantly either. During PEG-V treatment, total cholesterol (TC) and low-density lipoprotein tended to decrease; however, these changes were not significant; TC ΔPEG-V was -0.35 ± 1.04 (median ± SD) and TC Δplacebo was 0.10 ± 1.12 ($P = 0.091$). The low-density lipoprotein ΔPEG-V was -0.19 ± 0.72 and Δplacebo 0.20 ± 0.75 ($P = 0.055$). In the other lipids ($P > 0.05$) and the free fatty acids ($P = 0.231$), no change was observed. We observed no decrease in body weight in the whole group of subjects treated with PEG-V and SSA (ΔPEG-V -0.95 ± 1.70, Δplacebo -0.40 ± 1.60, $P = 0.081$, Fig. 2), although some individuals showed a remarkable decrease in their body weight during their treatment period with both SSA and PEG-V.

Correlations

The correlations between the parameters of QoL and biochemical and phenotypical parameters are presented in Fig. 3. Neither the change in the score of IGF-I nor the baseline GH levels correlated with changes in QoL. Changes in body weight correlated well with the observed improvements in QoL by the AcroQoL physical ($r = -0.449$, $P = 0.047$, Fig. 3) and the PASQ joint pain ($r = 0.489$, $P = 0.029$), excessive sweating, and soft tissue swelling, which are all QoL entities that reflect increased GH actions.

Safety

Transient elevated liver enzyme tests (TELETs) were observed in five patients (25%) but did not necessitate discontinuation of PEG-V treatment. In one patient TELETs up to 9 times the ULN were observed during her last visit of the PEG-V treatment period. Because it was at the end of the treatment period, she was not withdrawn from the study. TELETs up to a maximum of 4 ULN were observed in another four subjects. The duration of TELETs was 8.0 wk median with a SD of ± 5.4. Of these five patients with TELETs, two patients also suffered from diabetes mellitus (40%). As expected, no change in pituitary volume was observed in any of the subjects.

Discussion

Our study has two important messages. The first is that a significant improvement in QoL can be observed without a significant decrease in IGF-I after the addition of 40 mg PEG-V weekly in acromegalic patients with IGF-I concentrations within the age-adjusted range during SSA treatment. This observation questions the current strategy in which PEG-V is used only as monotherapy or in combination with SSA after IGF-I failed to normalize during monotherapy with long-acting SSA. It is noteworthy that the magnitude of the improvement in AcroQoL-score of 6.4% in this study is equal to the observations of Paisley *et al.* (21) [6.8% (−11.4 to 26.1)]. In their study, this change in QoL was observed when elevated IGF-I was reduced to the age adjusted normal range.

Although in some individuals IGF-I levels clearly decreased during PEG-V cotreatment, for the whole group, IGF-I did not decrease significantly. This observation might be explained by an observation by Segev *et al.* (22), who reported that a GH receptor antagonist in rodents was able to block GH actions, in their case in the kidney at lower concentrations than were necessary to decrease serum IGF-I and somatic growth. However, our study was powered to detect a difference in PASQ score and not designed to detect a difference in IGF-I. Therefore, it is possible that studies in larger populations will observe a significant decrease.

The current consensus on the goals of treatment of acromegaly has focused on normalization of IGF-I and GH and thereby reducing long-term morbidity and mortality (23, 24). However, the normalization of levels of total serum IGF-I and GH do not necessarily reflect optimal QoL in acromegalic patients (9–13).

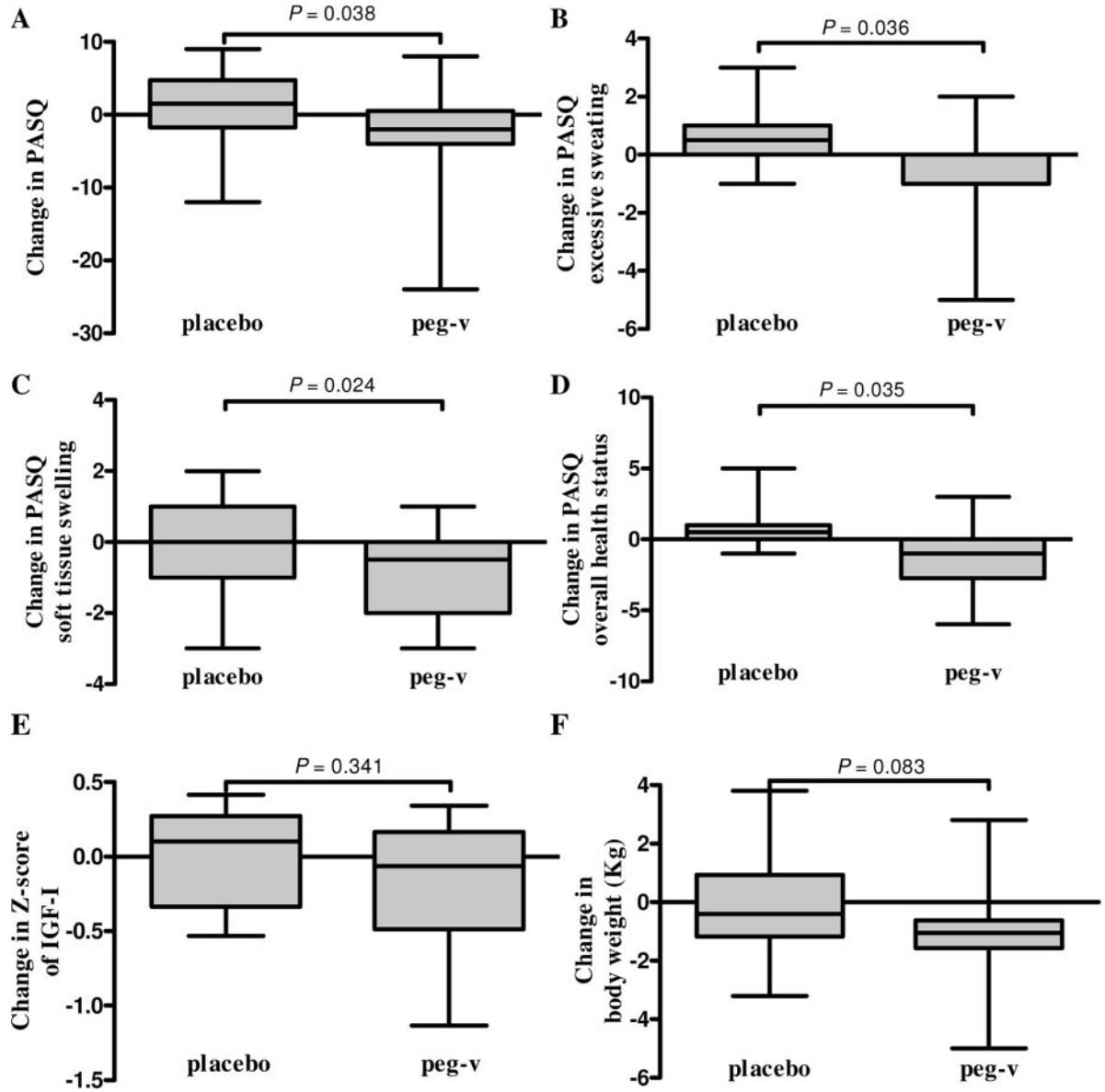

FIG. 2. Change in PASQ and metabolic parameters induced by the addition of 40 mg PEG-V once weekly in two different groups of acromegalic patients (PEG-V-placebo and placebo-PEG-V) with normal IGF-I during long-term treatment with SSAs. A, Total PASQ score. B, PASQ subscore excessive sweating. C, PASQ subscore soft tissue swelling. D, PASQ overall health status. E, Change in Z-score of IGF-I induced by the addition of 40 mg PEG-V once weekly in two different groups of acromegalic patients (PEG-V-placebo and placebo-PEG-V) with normal IGF-I during long-term treatment with SSAs. F, Change in body weight induced by the addition of 40 mg PEG-V once weekly in two different groups of acromegalic patients (PEG-V-placebo and placebo-PEG-V) with normal IGF-I during long-term treatment with somatostatin analogs. Box whisker plots are expressed in minimum, median, and maximum.

The second important message of our study is that total serum IGF-I levels, assessed by the commercially available IGF-I assays, do not correlate well enough with the QoL of the patient to use them for defining proper biochemical control.

In our study the improvement of QoL correlated with other GH-dependent parameters such as loss of body weight, perspiration, soft tissue swelling, and the AcroQoL physical, strongly suggesting that in these patients, integrated GH action is too high, despite normal IGF-I levels. GH action is known to increase extracellular volume (25). GH activates the renin-angiotensin-aldosterone system, which leads to fluid retention when GH concentrations are high (26, 27). These observations could explain the changes we observed in GH dependent parameters. We observed a significant improvement in the physical dimension of the AcroQoL and not in the dimension appearance, which is mostly affected in the chronic phase of acromegaly. This might be explained by the short duration (16 wk) of coadministration of PEG-V, resulting in an acute change that is perceived physically but not as a change in appearance.

The mode of action of SSA might also explain why the addition of PEG-V improves QoL. The effects of SSA analog therapy on GH actions are not only mediated by the reduction of pathological GH secretion by the pituitary adenoma, but SSA also reduces insulin secretion in the portal vein. This mechanism will most likely reduce the available GH receptors on the liver (15). Finally, SSAs are able to directly reduce IGF-I production by hepatocytes (16). These mechanisms are the basis of the concept that the combined use of SSA analogs and pegvisomant should be

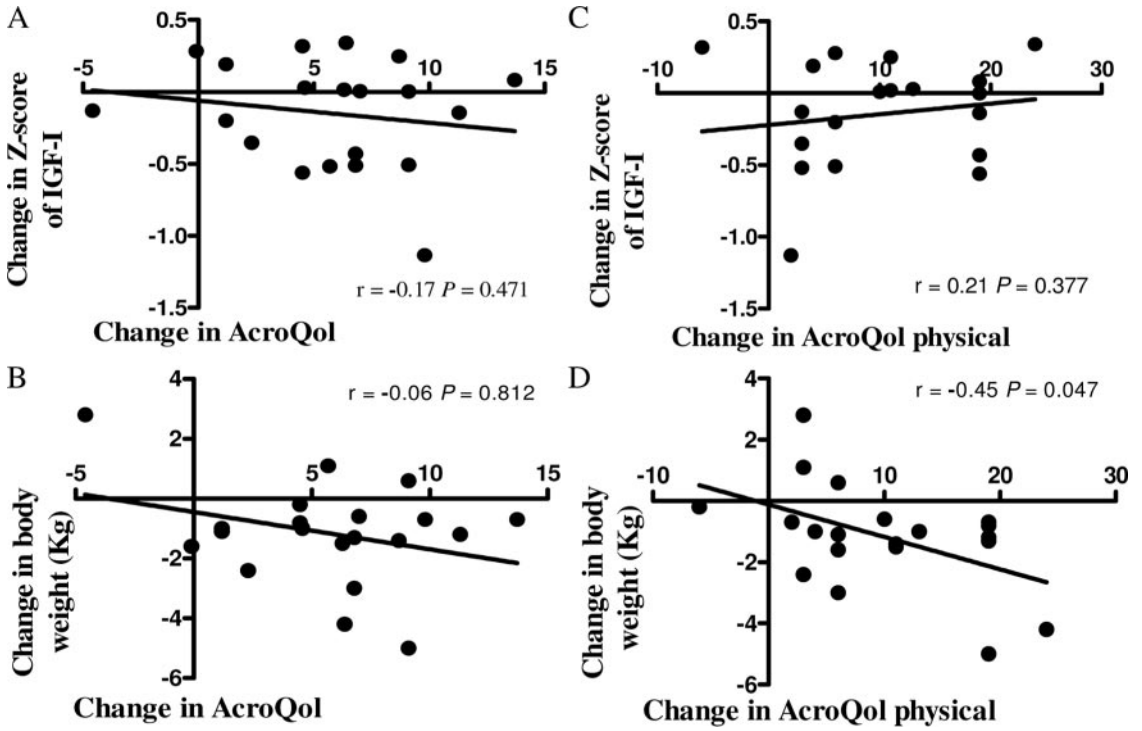

FIG. 3. Correlation between the change in AcroQoL and the Z-score of IGF-I (A) and change in body weight (B). Correlation between the change in AcroQoL, category physical (AcroQoL physical) and the Z-score of IGF-I (C) and change in body weight (D).

able to reduce the dosage and frequency of pegvisomant administration, and indeed they do (1). These mechanisms also suggest that whereas the liver is made relatively GH resistant, the rest of the body is still slightly acromegalic during SSA treatment. One might then expect that the treatment of this extrahepatic acromegaly with low-dose weekly PEG-V administration would therefore improve the GH-dependent signs and symptoms and QoL, and indeed this was observed. The dose of 40 mg of PEG-V per week was pragmatically chosen as being about half the starting dose of PEG-V monotherapy, and the optimal dose has not been determined by this study. Nor do we know whether a further increase in QoL can be achieved by another dose of PEG-V that would decrease serum IGF-I levels.

We believe that our data might be important for treatment of acromegaly when medical treatment is concerned. The available consensus statements aim at just normalizing IGF-I to within the age-adjusted normal range (23, 24). They more or less ignore signs and symptoms of patients the moment IGF-I has become normal. However, from a patient's perspective, just normalization of serum IGF-I levels might not be enough. Our data suggest that most patients seem to know exactly what optimal treatment is, and they favor a combined approach by which both SSA and PEG-V play their specific roles. This suggests that we should abandon the step-up approach and that we should investigate the role of the combined approach in larger series of patients. Apart from the statistical outcome of the study, what really impressed us was the fact that 80% of subjects knew in retrospect which of the two treatment periods was the one in which they had received PEG-V, which is striking in a double-blind study design. They not only recognized the presence of PEG-V but also insisted in getting it back the moment the study was finished.

TELETs were observed in five patients (25%) of which two subjects also suffered from diabetes. Furthermore, as expected in this short study of 4 months of PEG-V exposure, no change in pituitary adenoma size was observed. No change in overall insulin sensitivity or change in lipids in the whole study population was observed. However, this could be due to a type 2 error or to our short treatment period of 16 wk because others have observed improvement (28). One patient had to reduce her oral diabetic medication due to frequent hypoglycemic episodes during PEG-V treatment period. Five weeks after withdrawal of PEG-V, the dose of diabetic medication had to be increased again.

It is internationally accepted that in most studies, a 2-wk period between test and retest is enough to avoid for the memory effect (29, 30). In our study we assessed QoL during a 4-month period so we think that memory could not have any impact on the scores.

In conclusion, QoL in acromegalic patients who normalized serum IGF-I concentrations during long-term treatment with long-acting SSAs can be significantly improved by the addition of a weekly dose of 40 mg pegvisomant. This improvement is not accompanied by a significant decrease in serum IGF-I levels, which questions the importance of total serum IGF-I as a reliable parameter for QoL from a patient's perspective. Our data also question the step-up approach in which patients are treated only with pegvisomant when somatostatin analog monotherapy was not able to normalize IGF-I levels. These findings warrant further investigation on

the efficacy and safety of adding pegvisomant to SSA therapy in most acromegalic patients.

Acknowledgments

Address all correspondence and requests for reprints to: Sebastian J. C. M. M. Neggers, M.D., Erasmus University Medical Center Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: s.neggers@erasmusmc.nl.

This work was not supported by an external funding source or pharmaceutical company; however, Pfizer International kindly provided pegvisomant and placebo.

Disclosure Statement: W.W.d.H., A.J.v.d.L., and S.M.W. are consultants for Novartis Pharma and received travel support from Novartis Pharma and Pfizer International. A.J.v.d.L. is a consultant for Pfizer International and Ipsen Pharma International. The other authors have nothing to disclose.

References

1. **Feenstra J, de Herder WW, ten Have SM, van den Beld AW, Feelders RA, Janssen JA, van der Lely AJ** 2005 Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. Lancet 365:1644–1646
2. **Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF, Davis RJ** 2000 Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342:1171–1177
3. **van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO** 2001 Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754–1759
4. **Neggers SJ, van Aken MO, Janssen JA, Feelders RA, de Herder WW, van der Lely AJ** 2007 Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. J Clin Endocrinol Metab 92:4598–4601
5. **Beauregard C, Truong U, Hardy J, Serri O** 2003 Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 58:86–91
6. **Holdaway IM, Rajasoorya CR, Gamble GD, Stewart AW** 2003 Long-term treatment outcome in acromegaly. Growth Horm IGF Res 13:185–192
7. **Holdaway IM, Rajasoorya RC, Gamble GD** 2004 Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 89:667–674
8. **Swearingen B, Barker FG, 2nd, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N, Black PM, Zervas NT** 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 83:3419–3426
9. **Hua SC, Yan YH, Chang TC** 2006 Associations of remission status and lanreotide treatment with quality of life in patients with treated acromegaly. Eur J Endocrinol 155:831–837
10. **Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F** 2005 Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. J Clin Endocrinol Metab 90:2731–2739
11. **Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA, Roelfsema F** 2004 Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. J Clin Endocrinol Metab 89:5369–5376
12. **Bonapart IE, van Domburg R, ten Have SM, de Herder WW, Erdman RA, Janssen JA, van der Lely AJ** 2005 The 'bio-assay' quality of life might be a better marker of disease activity in acromegalic patients than serum total IGF-I concentrations. Eur J Endocrinol 152:217–224
13. **Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM, Trainer PJ** 2005 Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire. J Clin Endocrinol Metab 90:3337–3341
14. **Webb SM, Prieto L, Badia X, Albareda M, Catala M, Gaztambide S, Lucas T, Paramo C, Pico A, Lucas A, Halperin I, Obiols G, Astorga R** 2002 Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. Clin Endocrinol (Oxf) 57:251–258
15. **Leung KC, Doyle N, Ballesteros M, Waters MJ, Ho KK** 2000 Insulin regulation of human hepatic growth hormone receptors: divergent effects on biosynthesis and surface translocation. J Clin Endocrinol Metab 85:4712–4720
16. **Murray RD, Kim K, Ren SG, Chelly M, Umehara Y, Melmed S** 2004 Central and peripheral actions of somatostatin on the growth hormone-IGF-I axis. J Clin Invest 114:349–356
17. **Elmlinger MW, Kuhnel W, Weber MM, Ranke MB** 2004 Reference ranges for two automated chemiluminescent assays for serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3). Clin Chem Lab Med 42:654–664
18. **Granada ML, Ulied A, Casanueva FF, Pico A, Lucas T, Torres E, Sanmarti A** 2007 Serum IGF-I measured by four different immunoassays in patients with adult GH deficiency or acromegaly and in a control population. Clin Endocrinol (Oxf) 68:942–950
19. **Badia X, Webb SM, Prieto L, Lara N** 2004 Acromegaly Quality of Life Questionnaire (AcroQoL). Health Qual Life Outcomes 2:13
20. **Webb SM** 2006 Quality of life in acromegaly. Neuroendocrinology 83: 224–229
21. **Paisley AN, Rowles SV, Roberts ME, Webb SM, Badia X, Prieto L, Shalet SM, Trainer PJ** 2007 Treatment of acromegaly improves quality of life, measured by AcroQol. Clin Endocrinol (Oxf) 67:358–362
22. **Segev Y, Landau D, Rasch R, Flyvbjerg A, Phillip M** 1999 Growth hormone receptor antagonism prevents early renal changes in nonobese diabetic mice. J Am Soc Nephrol 10:2374–2381
23. **Growth Hormone Research Society, Pituitary Society** 2004 Biochemical assessment and long-term monitoring in patients with acromegaly: statement from a joint consensus conference of the Growth Hormone Research Society and the Pituitary Society. J Clin Endocrinol Metab 89:3099–3102
24. **Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S** 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526–529
25. **Bengtsson BA, Brummer RJ, Eden S, Bosaeus I, Lindstedt G** 1989 Body composition in acromegaly: the effect of treatment. Clin Endocrinol (Oxf) 31:481–490
26. **Hansen TK, Moller J, Thomsen K, Frandsen E, Dall R, Jorgensen JO, Christiansen JS** 2001 Effects of growth hormone on renal tubular handling of sodium in healthy humans. Am J Physiol Endocrinol Metab 281:E1326–E1332
27. **Moller J, Nielsen S, Hansen TK** 1999 Growth hormone and fluid retention. Horm Res 51(Suppl 3):116–120
28. **Jorgensen JO, Feldt-Rasmussen U, Frystyk J, Chen JW, Kristensen LO, Hagen C, Orskov H** 2005 Cotreatment of acromegaly with a somatostatin analog and a growth hormone receptor antagonist. J Clin Endocrinol Metab 90: 5627–5631
29. **Linde L, Sorensen J, Ostergaard M, Horslev-Peterson K, Hetland ML** 2008 Health-related quality of life: validity, reliability, and responsiveness of SF-36, EQ-15D, EQ-5D RAQoL, and HAQ in patients with rheumatoid arthritis. J Rheumatol 35:1528–1537
30. **Keenan AM, McKenna SP, Doward LC, Conaghan PG, Emery P, Tennant A** 2008 Development and validation of a needs-based quality of life instrument for osteoarthritis. Arthritis Rheum 59:841–848