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Quality of life in patients with acromegaly receiving lanreotide autogel: a real-world observational study

Marek Bolanowski[1], Alicja Hubalewska-Dydejczyk[2], Beata Kos-Kudła[3], Marek Ruchała[4], Przemysław Witek[5], Wojciech Zgliczyński[6], Aude Houchard[7], Marta Bartmańska[8]

[1]Department of Endocrinology, Diabetes, and Isotope Therapy, Medical University, Wroclaw, Poland
[2]Department of Endocrinology, Jagiellonian University, Medical College, Krakow, Poland
[3]Department of Endocrinology and Neuroendocrine Tumours, ENETS Centre of Excellence, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland
[4]Department of Endocrinology, Metabolism, and Internal Diseases, University of Medical Sciences, Poznan, Poland
[5]Department of Internal Medicine, Endocrinology, and Diabetes, Medical University of Warsaw, Poland
[6]Department of Endocrinology, Centre of Postgraduate Medical Education, Warsaw, Poland
[7]Ipsen, Boulogne-Billancourt Cedex, France
[8]Ipsen, Warsaw, Poland

Abstract

Introduction: Patients with acromegaly have substantially reduced quality of life (QoL). This study evaluated QoL in patients with acromegaly treated with lanreotide autogel.

Material and methods: This was a prospective, non-interventional, observational, multi-centre study conducted in Poland (NCT02396966). We included patients with acromegaly, who received treatment with lanreotide autogel 120 mg for ≥ 3 months and < 3 years. Patients were assessed approximately every 4–5 months for two years (six visits). QoL was measured with the Acromegaly Quality of Life Questionnaire (AcroQoL).

Results: Of 152 patients enrolled from November 2014 to May 2018 in 37 centres, 24 were excluded due to major protocol deviations. The results are reported for the study population (n = 128). At baseline, the median [95% confidence interval (CI)] time from diagnosis was 3.3 (2.8, 4.2) years, and the median time since lanreotide initiation was 13.4 (9.9, 17.3) months. Symptoms of acromegaly were present at baseline in 86% of patients (headache, 57%; sweating, 58%; joint symptoms, 64%); symptoms remained unchanged at two years in 82% of patients. At baseline, 27% of patients had hormonal control (growth hormone < 2.5 μg/L and insulin-like growth factor-1 within the normal range); hormonal control status did not change during the study period in over 81% of patients. At baseline, 88% of patients were either very satisfied or satisfied with treatment; treatment satisfaction was unchanged in 62% of patients over the study period. Mean (95% CI) AcroQoL scores at baseline were as follows: total, 50.3 (47.3, 53.3); physical dimension, 48.8 (45.2, 52.4); psychological dimension, 51.3 (48.2, 54.4); appearance subdimension, 40.7 (37.5, 43.8); and personal relations subdimension, 62.5 (58.8, 66.2). The psychological appearance subscore improved by 3.8 points (1.2, 6.5) over the two years; scores in the remaining dimensions and subdimensions did not change substantially. The total AcroQoL score remained unchanged over the two years, regardless of prior acromegaly treatment, surgery or radiotherapy, hormonal control, or lanreotide dosing interval. No new safety findings were identified.

Conclusions: AcroQoL total scores and physical and psychological subscores remained stable but impaired among patients with long-lasting acromegaly treated with lanreotide autogel for two years. The psychological appearance subdimension improved numerically.
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Key words: *acromegaly; somatostatin analogue; lanreotide; quality of life; AcroQoL*

Introduction

Acromegaly is caused by an excessive secretion of growth hormone (GH), typically by a pituitary adenoma, with a consequent increase in the production of insulin-like growth factor-1 (IGF-1) [1]. The symptoms and complications of acromegaly include acral enlargement, facial disfiguration, arthralgia and arthritis, headache, sleep apnoea, cardiovascular diseases, and disorders of glucose metabolism [1]. Acromegaly worsens both the physical and emotional well-being of patients, and substantially reduces quality of life (QoL) at all disease stages [2]. Patients with acromegaly have much lower scores on generic questionnaires measuring QoL compared to the general population or patients with other chronic diseases, such as asthma, angina, and osteoarthritis [3–5]. The physical aspect of QoL in acromegaly is substantially affected by pain, weak-

Marta Bartmańska, Medical Advisor Ipsen Poland sp. z o.o., ul. Chmielna 73, Warszawa 00–801, tel: (+48) 505 168 934, (+48) 22 653 68 00; e-mail: marta.bartmanska@ipsen.com

ness, sleep problems, and limitations of daily activities [6]. The psychological aspect of QoL in acromegaly is worsened by a negative perception of one's appearance and difficulties in personal relations [6].

The first-line treatment for most patients with acromegaly is transsphenoidal resection of the adenoma, whereas pharmacological treatment is given to those who have uncontrolled disease after surgery or contraindications to surgery [7, 8]. Long-acting somatostatin analogues (SSAs), such as octreotide or lanreotide, are the most commonly used medications in patients with acromegaly. The current treatment goals in acromegaly are to reduce or control tumour growth, inhibit GH hypersecretion, and normalize IGF-1 levels, which help control disease complications, decrease mortality, and improve QoL [9]. However, the correlation between clinical severity and the impact of the disease perceived by patients is weak; thus, QoL should be used as an additional outcome to incorporate the patient's perspective [10].

Lanreotide autogel is a long-acting, super-saturated, viscous aqueous formulation of lanreotide injected subcutaneously once every 28–56 days [11, 12]. In treatment-naïve patients with acromegaly, lanreotide autogel improved their QoL [13]. In this real-world study, we investigated the effect of lanreotide autogel on QoL among patients who had been on this medication for up to three years. Moreover, we related QoL measures to hormonal and clinical variables.

Material and methods

Study design and setting

This prospective, non-interventional, observational, multi-centre cohort study was conducted at 37 centres in Poland from November 2014 to May 2018. Participants were enrolled over 18 months. After enrolment, participants were followed up for two years at six visits, approximately once every 4–5 months (V1–6). In this non-interventional study, lanreotide autogel 120 mg was administered and managed within routine care.

Participants

We included adult patients (aged > 18 years) with acromegaly, who had received treatment with lanreotide autogel 120 mg for ≥ 3 months and < 3 years. Exclusion criteria were as follows: active participation in any interventional or any other non-interventional acromegaly clinical study or any medical or psychological condition that compromised the ability to give informed consent. Participants were withdrawn if lanreotide autogel 120 mg was stopped or interrupted (i.e. changed for another lanreotide dose or to another SSA). Because this was a non-interventional study, no other withdrawal criteria were specified. Participants were free to withdraw consent at any time. Data were collected up to the time of withdrawal. All patients signed informed consent before enrolment. The study was approved by local Ethics Committees at each study site.

Assessments

Quality of life

Quality of life was measured with the Acromegaly Quality of Life (AcroQoL) questionnaire at baseline and then at visits 2, 3, and 6. The AcroQoL questionnaire is a validated disease-specific self-assessment questionnaire designed for use in clinical trials and everyday practice. The AcroQoL questionnaire includes 22 items relating to two dimensions: physical (8 items) and psychological (14 items), the latter being divided into two subdimensions: psychological appearance (7 items) and psychological personal relations (7 items) [6]. Each AcroQoL item is answered on a five-point Likert scale. Moreover, during all study visits, participants gave an overall assessment of treatment satisfaction on a five-point Likert scale (1–5; completely satisfied, rather satisfied, neither satisfied nor dissatisfied, rather dissatisfied, and completely dissatisfied).

Clinical and ancillary assessments

At baseline, we collected demographic data, date of acromegaly diagnosis, details on current and prior acromegaly treatment (medications, radiation therapy, or surgery), and tumour presence and size (microadenoma [< 10 mm], macroadenoma [≥ 10 mm, < 40 mm], giant tumour [≥ 40 mm], no tumour). At every visit, we looked for predefined acromegaly symptoms (headache, sweating, joint symptoms, and swelling) and predefined comorbidities (altered carbohydrate metabolism, hypertension, sleep apnoea, heart disease, hypopituitarism, hyperprolactinaemia, hyperthyroidism, hypogonadism, nodular goitre, simplex goitre, and malignant tumour). The dose of lanreotide and the injection interval were recorded at every visit. The tumour size was assessed by magnetic resonance imaging at baseline. The serum concentrations of glucose, GH, and IGF-1 were measured at every visit in local laboratories. Hormonal control was defined as GH concentrations < 2.5 μg/L and IGF-1 concentrations within age- and sex-specific normal ranges [14]. Adverse events were recorded at every visit; however, because this was a noninterventional study, only related adverse events were reported.

Statistical analysis

No inferential statistical analyses were planned or performed. All data are presented descriptively overall and by subgroups. The enrolled population was defined as all participants who signed an informed consent form. The study population included participants without major protocol deviations. As the primary endpoint, the AcroQoL total score, AcroQoL dimensions, and subdimensions scores were calculated per visit in the study population. The total AcroQoL score was obtained by adding scores from 22 items with the following formula:

$$[(X - 22)/(110 - 22)] \times 100$$

with higher scores indicating better QoL [6]. Secondary endpoints included the control of clinical symptoms, hormonal control, treatment satisfaction, and AcroQoL scores by subgroups. It was planned to enrol 150 patients because this sample size was deemed necessary to describe QoL in the following subgroups: controlled/uncontrolled disease, with/without prior radiotherapy, with/without prior surgery.

Results

Participants

Of the 152 patients enrolled in the study, 128 were finally included in the study population (24 patients were excluded due to major protocol deviations), and 115 completed the study (Fig. 1). The results presented herein are for the study population.

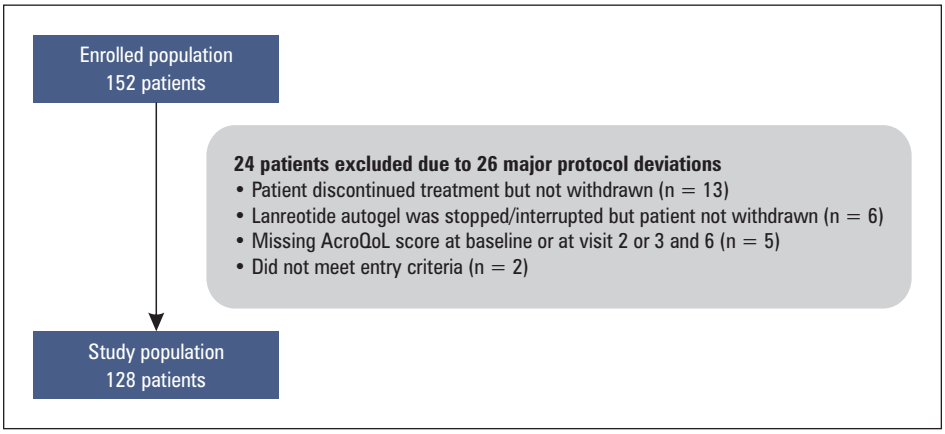

Figure 1. *Disposition of patients; AcroQoL — Acromegaly Quality of Life Questionnaire*

Patients had a long duration of acromegaly, with a median (95% confidence interval [CI]) time from diagnosis of 3.3 (2.8, 4.2) years. At baseline, 110 (86%) patients had symptoms of acromegaly. Most patients had headache (57%), sweating (58%), and joint symptoms (64%). Moreover, the comorbidity burden was high, with most patients having altered carbohydrate metabolism (56%), hypertension (60%), or nodular goitre (52%). At baseline, 74% of patients had visible pituitary tumours on magnetic resonance imaging. Hormonal control was achieved in 27% of patients at baseline. Other baseline characteristics are presented in Table 1.

Sixty-nine per cent of patients received another acromegaly therapy before lanreotide autogel (including surgery [87.5%], radiation therapy [13.6%], and medications [34.1%]; Tab. 1). At baseline, patients had received lanreotide autogel for a median (95% CI) of 13.4 (9.9, 17.3) months. The interval of lanreotide autogel 120 mg injections and concomitant medications for acromegaly at baseline are shown in Table 2.

Quality of life and satisfaction with treatment

The mean (95% CI) total AcroQoL score was 50.27 (47.25, 53.28) at baseline, and it did not change substantially during the study, with a mean increase from baseline to the end of the study of 1.21 (–1.39, 3.82) points. The mean (95% CI) AcroQoL physical dimension score was 48.76 (45.16, 52.37) at baseline, with a mean on-study increase of 1.08 (–2.09, 4.26). The mean (95% CI) AcroQoL psychological dimension score was 51.30 (48.20, 54.40) at baseline, with a mean on-study increase of 1.21 (–1.43, 3.84). The mean (95% CI) AcroQoL psychological appearance subdimension score was 40.65 (37.47, 43.83) at baseline, with a mean on-study increase of 3.81 (1.18, 6.45). The mean (95% CI) AcroQoL psychological personal relations subdimension score was 62.53 (58.82, 66.24) at baseline, with a mean on-study decrease of –1.38

Table 1. *Baseline characteristics in the study population*

	Study population (n = 128)
Age, mean ± SD [years]	51.6 ± 13.5
Women, n (%)	71 (55.5)
Height, mean ± SD [cm]	172.5 ± 10.5
Weight, mean ± SD [kg]	89.3 ± 19.6
BMI, mean ± SD [kg/m^2]	30.05 ± 6.40
Time since diagnosis [years], median (95% confidence interval)	3.3 (2.8, 4.2)
Clinical symptoms, n (%)	**110 (85.9)**
Headache	73 (57.0)
Sweating	74 (57.8)
Joint symptoms	82 (64.1)
Swelling	53 (41.4)
Comorbidities, n (%)	
Altered carbohydrate metabolism	71 (55.5)
Hypertension	77 (60.2)
Sleep apnoea	45 (35.2)
Heart disease	26 (20.3)
Hypopituitarism	35 (27.3)
Hyperprolactinaemia	20 (15.6)
Hyperthyroidism	7 (5.5)
Hypogonadism	29 (22.7)
Nodular goitre	66 (51.6)
Simplex goitre	8 (6.3)
Malignant tumours	6 (4.7)
Therapy before lanreotide autogel, n (%)	
None	40 (31.3)
Previous surgery	77 (87.5)[a]
Previous radiation therapy	12 (13.6)[a]

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Table 1. *Baseline characteristics in the study population*

	Study population (n = 128)
Previous medications (n = 30), n (%)	
Octreotide	20 (66.7)[b]
Lanreotide autogel 90 mg	1 (3.3)[b]
Dopamine agonists	11 (36.7)[b]
Tumour characteristics, n (%)	
No tumour visible	30 (25.9)
Microadenoma	27 (23.3)
Macroadenoma	57 (49.1)
Giant tumour	2 (1.7)
GH, n (%)	
< 2.5 μg/L	37 (51.4)
≥ 2.5 μg/L	35 (48.6)
IGF-1, n (%)	
Normal range	37 (40.7)
Outside normal range	54 (59.3)
Hormonal control[c], n (%)	23 (27.4)

a — of previously treated patients; b — of patients receiving medications; c — growth hormone (GH) concentrations < 2.5 μg/L and insulin growth factor 1 (IGF-1) concentrations within age- and sex-specific normal ranges (as specified by Scacchi and Cavagnini [14])

Table 2. *Lanreotide autogel dosing interval and treatment duration and concomitant acromegaly medications at baseline*

	Study population (n = 128)
Lanreotide autogel dosing interval, n (%)	
28 days	96 (75.0)
42 days	22 (17.2)
56 days	10 (7.8)
Mode of injection, n (%)	
Healthcare professional	124 (96.9)
Patient self-injection	4 (3.1)
Duration of lanreotide autogel treatment (months), median (95% confidence interval)	13.4 (9.9, 17.3)
Concomitant medication, n (%)	
Dopamine agonist	29 (22.7)
Octreotide (subcutaneous)	2 (6.5)

(–4.65, 1.89). The mean AcroQoL scores are shown in Figure 2.

The total AcroQoL scores remained similar in patients with or without hormonal control, prior acromegaly treatment, prior radiotherapy, and prior surgery (Fig. 3).

Treatment satisfaction

At baseline, 32% of patients were very satisfied with the treatment, 56% were satisfied, 10% were neither satisfied nor dissatisfied, and 2% were dissatisfied; none of them were very dissatisfied with the treatment. In 26% of patients, the satisfaction with treatment improved from baseline to the end of the study, in 62% of patients it did not change, and 12% showed a decrease in their satisfaction during the study.

Disease control and change in lanreotide dosing interval

The hormonal control status did not change in over 81% of patients, and 33% had hormonal control at the end of the study. Moreover, there was no change in clinical symptoms in over 82% of patients from baseline to the end of study.

We found no change in the presence of comorbidities or complications related to acromegaly, including altered carbohydrate metabolism, hypertension, sleep apnoea, heart disease, hypopituitarism, hyperprolactinaemia, hyperthyroidism, simplex goitre, and malignant tumour, in over 91% of patients. There was also no change in the presence of hypogonadism in over 85% of

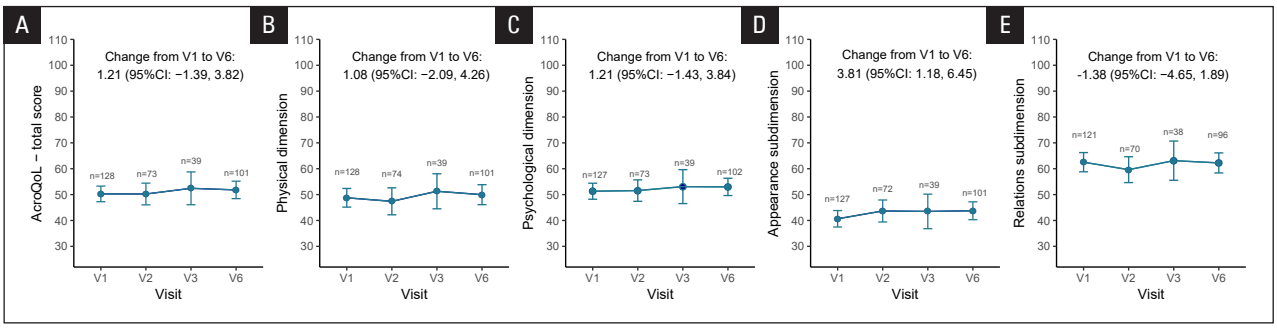

Figure 2. *Mean Acromegaly Quality of Life Questionnaire (AcroQoL) scores for the study population at visits (V) 1, 2, 3, and 6. Total AcroQoL scores (***A***), physical dimension (***B***), psychological dimension (***C***), psychological appearance subdimension (***D***), and psychological personal relations subdimension (***E***). Data are presented as means [95% confidence interval (CI)]*

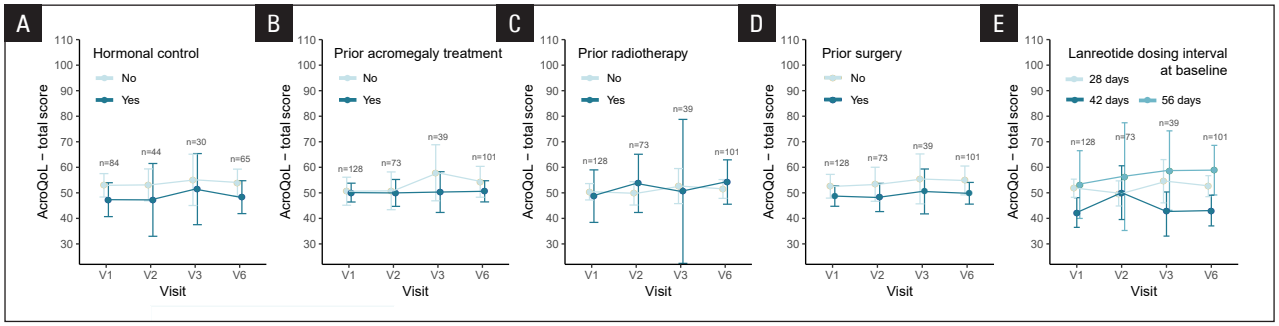

Figure 3. *Mean Acromegaly Quality of Life Questionnaire (AcroQoL) scores for the study population at visits (V) 1, 2, 3, and 6 according to hormonal control (***A***), prior acromegaly treatment (***B***), prior radiotherapy (***C***), prior surgery (***D***), and lanreotide autogel dosing interval (***E***). Data are presented as means (95% confidence interval [CI])*

patients or nodular goitre in over 83% of patients. Furthermore, there was no change in the presence of other comorbidities in more than 67% of patients.

Regarding lanreotide administration and dosing, 84% of patients in the study population did not change injection frequency from baseline to the end of the study, 63% of patients received lanreotide autogel once every 28 days, 12% once every 42 days, and 9% once every 56 days. No shift in the mode of injection (i.e. self-injection or injection by healthcare professionals) was observed in the study population. Lanreotide autogel was injected by healthcare professionals in ≥ 96% of patients throughout the study.

Adverse events

During the study, 15 adverse events associated or coinciding with study drug use (six serious, four non-serious, and five related to product administration) were reported in six participants from the enrolled population. Among the four non-serious adverse events, all were considered to be related to the study medication (diarrhoea [two events], nausea, headache). Among the six serious adverse events, three were considered possibly related to the study drug (diarrhoea, acute cholecystitis, headache). None of the 15 adverse events were associated with a fatal outcome. Three patients died during the study (events not reported as serious adverse events as per study protocol): one death without any details provided, one death for cardiovascular reasons, and one death due to haemorrhagic stroke. No new safety findings or safety issues requiring further investigation were identified in this study.

Discussion

This real-world, prospective, longitudinal study carried out among patients who had a long duration of acromegaly found that global QoL and its physical and psychological aspects remained stable, whereas the AcroQoL psychological appearance subdimension improved numerically. Most patients were satisfied or very satisfied with the treatment (and no patients were very dissatisfied). Hormonal control and symptoms and complications of acromegaly did not change in most patients over the study. The safety findings were in line with the known safety profile of lanreotide.

Our study provides information on QoL in patients with a long duration of acromegaly. At baseline, the median time since diagnosis was over three years, and the median time of lanreotide autogel treatment was approximately one year, with most patients having received other acromegaly treatments. Approximately 60% of the 128 patients had headache and joint symptoms, which can reduce QoL in those with acromegaly [15]. Indeed, previous research showed that patients with acromegaly and joint pain had a substantially lower QoL (AcroQoL score, ~59) than those without joint pain (AcroQoL, ~76) [16]. Similarly, patients with acromegaly and spinal joint complaints scored lower than those without these comorbidities on several QoL questionnaires, including AcroQoL (~61 vs. ~71 points) [17]. Headaches are also associated with decreased QoL or no improvement in QoL among patients with acromegaly [18, 19].

Overall, the QoL in our cohort was substantially reduced, with a mean total AcroQoL score of ~50, which is lower than healthy people and patients with acromegaly from previous studies. For example, in a study from Romania, the mean total AcroQoL was ~76 in healthy people and 61 in patients with acromegaly [20]. In another study, among patients with a "severe" reduction of QoL, the mean total AcroQoL was higher than in our study (AcroQoL, ~57) [3]. Yet, a similar QoL to our cohort was observed among patients with long-lasting acromegaly (> 10 years) and a significant disease burden (AcroQoL, ~54), and it did not change over five years [21]. Similarly, after treatment of GH excess, Biermasz et al. found that 118 patients with

acromegaly had persistently decreased QoL despite biochemical cure [22]. These findings suggest that long-lasting acromegaly causes a sustained reduction of QoL, despite disease-specific treatment.

Although the total AcroQoL score did not change substantially in our cohort, the improvement in the psychological dimension might be important to patients with acromegaly. Indeed, in a study that used AcroQoL to compare QoL between patients with acromegaly and people with obesity, the psychological appearance subdimension was the most reduced subscale in patients with acromegaly [23].

In a study among 90 treatment-naïve patients with acromegaly (mean disease duration of four months), who received lanreotide autogel 120 mg, Caron et al. found an improvement in all AcroQoL scores after one year of treatment (mean change of ~5% on the personal relations subdimension, ~10% in the total, physical, and psychological dimensions; and ~15% on the appearance subdimension) [24]. However, the difference in the characteristics of participants (i.e. the duration of acromegaly and type of treatment) could explain why the improvement in QoL was greater in the study by Caron et al. than in our study.

An improvement in QoL was also observed among 53 treatment-naïve patients with acromegaly, who received lanreotide autogel 120 mg (QoL assessed with the Nottingham questionnaire) [13]. In contrast, we found no change in QoL among patients in our cohort who had been on lanreotide treatment for up to three years (median of approximately one year). Meanwhile, a small study showed that AcroQoL scores improved during four years in patients who received octreotide [18]; however, this was a retrospective study that could have had selection bias (i.e. selective retainment of patients who perceived improvement). In line with this assumption, a 24-week prospective study found a modest improvement of QoL on octreotide only in the psychological subdimension, similarly to our study [25].

Similarly to most previous reports, we did not find that the hormonal status affected the QoL [26]. QoL remained stable in our cohort regardless of baseline hormonal control status, prior surgery, prior radiotherapy, or lanreotide dosing interval. Likewise, Matta et al. found that QoL in patients with a mean duration of acromegaly of 10 years was similar regardless of hormonal control (AcroQoL, ~60) [27]. However, another study showed that QoL was higher (AcroQoL, ~61–71) among patients with long-lasting acromegaly (>10 years) who achieved hormonal control than that observed in our cohort [17]. Thus, the importance of hormonal control of acromegaly for QoL requires further investigation.

Our study was limited by a heterogeneous sample (disease duration, previous treatments), and thus, the effect of lanreotide autogel treatment on QoL could be obscured by confounding factors. However, our study provides important real-world evidence that may be more relevant to clinical practice than the findings from clinical trials, in which only selected patients, typically shortly after diagnosis, are followed for a limited time. Our cohort of patients reflected, for example, the high prevalence of comorbidities that are typically observed among patients with acromegaly [28]. The available evidence indicates that, in the long-term, acromegaly causes considerable problems that may not be directly related to the biological aspects of the disease. These problems include everyday challenges like a negative body image and major life changes, such as employment issues [2, 29]. Our study presents a picture of the most common symptoms and complications of acromegaly among patients in Poland. As in previous studies, most patients had joint symptoms, headache, and sweating [30–32]. Arterial hypertension, altered glucose metabolism, and nodular goitre were also frequent [33, 34].

It is worth mentioning that despite the lack of improvement in symptoms and QoL, overall the patients in this study were kept on the same therapy. A potential reason is that at the time of the study, there were only two long-acting SSAs available for acromegaly treatment in Poland: octreotide LAR and lanreotide autogel. Other treatment options, such as pasireotide (a somatostatin analogue) and pegvisomant (a GH receptor antagonist), were not reimbursed at the time of the current study. Nonetheless, further symptomatic treatment, such as physiotherapy, offered in addition to disease-specific medications like lanreotide, could help improve QoL in patients with long-lasting acromegaly. Indeed, an interdisciplinary approach of treating the various comorbidities and symptoms present in patients with acromegaly seems to be more effective than disease-specific treatment alone [35,36]. Evidence-based guidelines for the treatment of acromegaly complications (including cardiovascular, endocrine, metabolic, and oncologic comorbidities, sleep apnoea, and bone and joint disorders) have recently been produced by the Acromegaly Consensus Group, and they could assist in improving QoL among patients with acromegaly [37].

Conclusions

We found that QoL remains stable in patients with long-lasting acromegaly and a substantial disease burden during two years of treatment with lanreotide autogel. Despite good control of symptoms throughout the study, the total AcroQoL scores, including those of

the AcroQoL physical and psychological dimensions, were unchanged. However, scores on the AcroQoL psychological appearance subdimension improved numerically, which is promising because this subscale is often significantly reduced in patients with acromegaly. Moreover, most patients remained satisfied with lanreotide autogel treatment during the study. Further studies into whether other interventions (like physiotherapy or the targeted treatment of acromegaly complications) combined with lanreotide autogel therapy improve QoL in patients with long-lasting acromegaly are warranted.

Disclosures

A.H., M.Ba. — employees of Ipsen; M.Bo., A.H.D., B.K.K., W.Z. — honoraria from Novartis, Pfizer, Ipsen, Recordati, Merck; M.R. — honoraria from Novartis, Pfizer, Ipsen, Berlin Chemie, Genzyme, Merck; P.W. — honoraria from Novartis, Pfizer, Ipsen, Berlin Chemie.

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