Acromegaly Disease Activity According to ACRODAT®, in Spain: ACROVAL Study

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Abstract

Objectives: To evaluate disease activity status using the Acromegaly Disease Activity Tool (ACRODAT®) in a cohort of Spanish acromegaly patients, to assess the relationship between the level of disease activity according to both ACRODAT® and the physicians’ clinical evaluation, and to study the potential discrepancies in the perception of symptoms between physicians and patients.

Design: Multicenter, observational, descriptive and cross-sectional study.

Methods: Disease activity was assessed in adult patients with acromegaly under pharmacological treatment during at least 6 months using ACRODAT®.

Results: According to ACRODAT®, 48.2%, 31.8% and 20.0% of a total of 111 patients were classified as having a stable disease (S), mild disease activity (M-DA) and significant disease activity (S-DA) respectively. ACRODAT® classification of disease activity significantly correlated with physicians’ opinion, with a moderate inter-rater agreement and a specificity of 92.45% (PPV=86.21%). No correlation was found between IGF-1 levels and severity of symptoms or quality of life (QoL). A decision to take clinical action was significantly more frequent in S-DA and M-DA patients than S patients but no action was taken on 5 (22.7%) and 27 (77.1%) S-DA and M-DA patients, respectively.

Conclusions: ACRODAT® detected disease activity in 51.8% of patients. Interestingly, although M-DA and S-DA patients were likely to be in the process of being controlled, action was not always taken on these patients. ACRODAT® is a validated and highly specific tool that may be useful to routinely monitor acromegaly and to identify patients with non-obvious disease activity by incorporating “patient-centered” parameters like symptoms and QoL to the clinical evaluation of acromegaly.

Introduction

Acromegaly, a rare and chronic disease usually caused by a pituitary adenoma, is characterized by hypersecretion of growth hormone (GH) with a consequent increase in insulin-like growth factor 1 (IGF-1). (1, 2) Acromegaly is associated with multiple co-morbidities, premature mortality, and physical disfigurement. (1) The most serious health consequences include type 2 diabetes, high blood pressure, increased risk of cardiovascular diseases, arthritis and sleep apnoea. (3, 4) In fact, the presence at the diagnosis of diabetes mellitus, cardiovascular disease and hypertension are significantly associated with reduced survival. (5) In addition, acromegaly patients experience decreased energy and psychological disturbances (loss of initiative, mood lability, impaired self-esteem, depression and anxiety) that significantly affect their quality of life (QoL). (6–9)

The goals of acromegaly treatment are to achieve overall long-term biochemical control, control tumour mass and decrease the risk of developing systemic comorbidities, thereby reducing mortality. (10, 11). Even when biochemical control is achieved, many patients still suffer from physical and psychological
residual morbidity that can lead to persistently impaired QoL. (6, 12–14) In fact, the correlation between “biochemical” severity (measured by IGF-1 levels) and impact of disease on patient’s lives is weak. (14, 15) Additionally, from the patient’s perspective, symptoms and QoL are critical parameters of disease control (6, 12), therefore they should be assessed in clinical practice for an adequate long-term management of acromegaly. (13)

Discrepancy between patient’s and physician’s ratings of general health status has been previously demonstrated. (6, 16, 17) The consequence of such a discordant viewpoint regarding disease activity is that decisions are often prone to not being shared between patients and physicians (16). Acromegaly patients place more importance on patient-centered parameters (i.e., signs/symptoms, comorbid conditions and QoL) than do expert endocrinologists. (6) Therefore, the patients’ own perspectives of their health status may be an important additional measure to assess the level of disease activity and support clinical decision-making and, together with IGF-1 level and tumour status could provide a more accurate assessment of the disease status (6, 18).

To aid in the global clinical management of acromegaly, a multidimensional clinical decision support tool, the Acromegaly Disease Activity Tool (ACRODAT®) was developed. (18) The ACRODAT® software medical device is a disease specific tool that allows the classification of acromegaly disease activity using a multidimensional approach in three categories: stable (S, adequately controlled), mild disease activity (M-DA: further evaluation of the patient’s condition is needed), or significant disease activity (S-DA: clinical action is required). (18) The development of this tool was based on the identification of five key health status parameters in acromegaly and the definition of three levels of severity for each of them: IGF-I level, tumour status, presence of co-morbidities (cardiac disease, diabetes, sleep apnoea), signs and symptoms and health-related QoL (Table 1). A scoring algorithm was built based on the classification of 243 hypothetical cases allowing the classification of the disease in the three above mentioned categories. (18)

Due to the recent development of the tool, its clinical application has not been studied yet. This study was aimed to evaluate disease activity status using ACRODAT® in a cohort of Spanish patients with acromegaly. Other secondary objectives included the assessment of the relationship between patient demographic characteristics and ACRODAT® disease categories; to assess the relation between classification of disease activity by ACRODAT® and by physician criteria and to study the potential discrepancies in the perception of symptoms between physicians and patients.

**Materials And Methods**

ACROVAL was an observational, cross-sectional, multicenter study conducted in 12 representative hospitals from all over Spain. The study included adult patients diagnosed with acromegaly, on pharmacological treatment for at least 6 months, and with complete clinical reports available. All patients provided their informed written consent. The study was approved by the Clinical Research Ethics
Committee of every participant site and it was conducted in accordance with the Declaration of Helsinki principles.

Data collection

Demographic data, acromegaly clinical history, co-morbidities, IGF-1 levels and tumour status were obtained from clinical records. Quality of life (QoL), severity of symptoms, job status, disease activity and decision taken regarding acromegaly treatment (surgery, radiotherapy, change in drug treatment or no action) were collected at the study visit. IGF-1 levels, tumour status and therapeutic decision at the visit before study visit was also collected from clinical records.

QoL was determined by the Acromegaly Quality of life Questionnaire (AcroQoL). (19) The AcroQoL questionnaire (19) is a 22-item, disease-specific QoL tool. Each question has five possible answers scored 1-5, with a total maximum score of 110. The score of 110 reflects the best possible QoL.

Severity of symptoms was quantified using the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) (20). The PASQ (12) comprises six questions that evaluate six acromegaly key symptoms. Each item is scored on a 9-point scale (0 no symptoms-8 severe incapacitating symptoms). The total PASQ score is the sum of the individual symptom scores (maximum = 48). An additional seventh question addresses the overall health status, which was scored ranging from 0 (best possible) to 10 (worst possible). The questionnaire was completed by physicians (phPASQ) and by patients (paPASQ) in order to compare both perspectives. phPASQ and paPASQ were mutually blinded. Symptoms status are measured in ACRODAT® by a Signs and Symptoms Score (SSS), an abbreviated version of the PASQ score that omits the numbness or tingling of the extremities and the overall health status questions. (18)

IGF-1 level was measured locally and recorded as IGF-1 level × the upper limit of normal (ULN) for the respective method used.

Tumour status was classified by the physician in the same three categories that use ACRODAT® (Table 1).

Disease activity level (stable, moderate disease activity and significant disease activity) according to physician's point of view was also recorded.

Comorbidities were assigned based on the presence or absence and severity of diabetes, sleep apnoea and cardiac disease (hypertension, hyperlipidaemia, or other cardiac abnormalities) (18) (Table 1).

The ACRODAT® tool was used to assess disease activity, entering the data collected in the study. According to the algorithm behind ACRODAT®, IGF-1 and tumour status are the predominant parameters in the classification of M-DA or S-DA. Only when the IGF-I level is ≤ 1.2 x ULN and tumour size did not significantly increase, the remaining three parameters contribute to the classification in a compensatory manner. Data were entered into the ACRODAT tool after the patient’s visits.
**Statistical methodology**

A descriptive statistical analysis of all the variables was performed, including central tendency and dispersion measures for continuous variables, and absolute and relative frequencies for categorical variables. *Student's t*-test, Mann-Whitney-U test or Kruskall Wallis H test were used to compare quantitative variables and Pearson's chi-square or Fisher's exact tests for qualitative variables. The p-values were two-sided and have not been adjusted for multiple testing. Statistical significance was considered when \( p < 0.05 \). The Kappa agreement coefficient was calculated to test concordance of disease activity status according to ACRODAT® vs. physicians’ clinical evaluation and to test the concordance between paPASQ and phPASQ. Predictive analysis of ACRODAT® was assessed by determining the values of sensitivity, specificity, the positive predictive value (PPV), and negative (NPV) predictive value. The gold standard used as a reference was the physicians’ clinical evaluation. Tests were two-tailed with a significance level of 5%. Data were analyzed using SPSS 19.0.

**Results**

**Patient characteristics**

113 patients from 12 centers were included, of whom 111 were considered evaluable in the analysis. Two patients were excluded because their duration of pharmacological treatment was lower than 6 months.

Table 2 summarizes demographic and clinical characteristics of patients. Macroadenoma was present in most patients (82.7%) at diagnosis (Table 2). However, in 97.1% of patients, tumour was not visible or had not changed in volume since prior MRI and only 3 patients (2.9%) had experienced a slight increase (\( \leq 20\% \)) since prior MRI (Table 2). IGF-1 levels were within normal limits in 64.0% of patients, above ULN but below 1.2 ULN in 16.2% of patients and above 1.2 ULN in 19.8% of patients.

The main comorbidity was cardiac disease (54.1%), followed by arthropathy (42.7%), diabetes (36.0%) and sleep apnoea (20.9%) (Table 2). Main comorbidities were controlled in most patients. However, 11.5% of patients presented an uncontrolled cardiac disease and 14.3% an uncontrolled sleep apnoea.

Disability was present in 23.6% of patients (Table 2) and 8.8% of patients were on work leave at the study visit. Most patients had undergone pituitary surgery (75.7%), a third of patients (35.1%) received radiotherapy (34.2% of patients had undergone surgery and radiotherapy), and 23.4% of patients had not undergone surgery nor radiotherapy.

**Disease activity**

According to ACRODAT®, 48.2% of patients were classified as controlled (S) and 51.8% as having active disease: 31.8% M-DA and 20.0% S-DA (Figure 1A).

S-DA patients were significantly younger, had a significantly higher headache severity, had a significantly higher number of medication changes in the last two years and their last change in medication was
significantly more recent compared to S patients (Table 2). Both M-DA and S-DA patients presented significantly higher values of IGF-1 compared with S patients (p<0.001) (Table 2, Figure 2A). Consistently with the algorithm behind ACRODAT®, 100% of S-DA patients had IGF-1 levels >1.2 ULN (Table 2, Figure 2A). There were no statistically significant differences in comorbidities or tumour status among S, M-DA or S-DA patients (Table 2, Figure 2B-C). Symptoms (phPASQ) were significantly more severe (p=0.004) and QoL significantly worse (p=0.005) in M-DA patients compared to S patients, and, in some items (joint pain and fatigue severity and physical component of AcroQoL) compared to S-DA patients (Table 2, Figure 2D-E).

According to physicians’ clinical evaluation, 73.9%, 17.1% and 9.0% were classified as S, M-DA or S-DA respectively (Figure 1B). ACRODAT® classification of disease activity significantly correlated with physicians’ opinion (Pearson's correlation coefficient 0.621, p<0.001), with a moderate inter-rater agreement [kappa agreement coefficient 0.569; 95% confidence interval (Cl95%): 0.402-0.678]. Predictive analysis between controlled (S) or active disease (M-DA + S-DA) groups according to ACRODAT vs. physicians’ opinion showed a fair inter-rater agreement (kappa agreement 0.356; Cl95% 0.207-0.506) a specificity value of 92.5% (Cl95%: 84.4-100), sensitivity 43.9% (Cl95%: 30.1- 57.6), PPV 86.2% (Cl95%: 71.9-100) and NPV 60.5% (Cl95%: 49.2-71.8).

Discrepancies between ACRODAT® classification of disease activity and physicians' criteria were observed in patients with IGF-1 levels above ULN (p<0.001), patients with higher symptomatology [joint pain (p<0.05), numbness or tingling (p<0.05) and global symptomatology (p<0.01) according to phPASQ, fatigue (p<0.05) according to paPASQ], worse health status [according to paPASQ (p<0.001) and phPASQ (p<0.01)] and patients showing higher QoL impairment (p<0.05). Moreover, discrepancies were also observed in patients with longer time since diagnosis (p<0.05) or since the beginning of treatment (p<0.05). A multivariant analysis showed that the existence of discrepancies between ACRODAT® classification and physicians’ criteria relied on IGF-1, phPASQ and time since diagnosis (p<0.05).

**Quality of life**

Overall, patients reported mild impairment in their QoL with a mean (SD) AcroQoL total score of 65.7 (19.2) (Table 2 and Table 3). Patients scored worse in the physical domain and in the psychological-appearance domain (Table 2 and Table 3).

According to ACRODAT® levels of severity for QoL (Table 1), 33.7% of patients presented a mild to moderate (21.2%) or significant (12.5%) impairment on QoL.

No correlation was found between IGF-1 levels and AcroQoL (Pearson's correlation coefficient 0.084, p=0.395).

Among the 65 patients (60.7%) with controlled IGF-1 and tumour status (IGF-1 < ULN and tumour not visible or without changes), 1 (1.5%) and 7 (10.8%) presented a significant and mild to moderate
impairment of QoL respectively. These patients presented a significant higher time since diagnosis than patients with no or minimal impairment of QoL (p=0.012).

Symptoms

Overall, patients suffered from mild-moderate acromegaly symptoms [mean (SD) phPASQ total score 12.9 (8.6)] (Table 4). According to ACRODAT® levels of severity for symptoms (Table 1), 73.6% of patients showed moderate (51.8%) or severe (21.8%) symptoms.

Physicians rated patient symptoms significantly lower in severity than patients (p<0.001). However, phPASQ significantly correlated with paPASQ with a substantial inter-rater agreement in both PASQ total score and individual symptoms sub-scores (Table 4). No characteristic traits in patients with discrepancies between phPASQ and paPASQ were found.

No correlation was found between IGF-1 levels and phPASQ (Pearson’s correlation coefficient: 0.049, p=0.615) or paPASQ (Pearson’s correlation coefficient: -0.011, p=0.911) neither in the total score nor in symptoms or health status sub-scores.

Among the 65 patients (60.7%) with controlled IGF-I and tumour status (IGF-I < ULN and tumour not visible or without changes), 13 (20.0%) and 34 (52.3%) presented severe and moderate symptoms respectively according to their phPASQ (32.3% and 53.8% respectively according to their paPASQ). No characteristic demographic traits were found for these populations of patients.

Therapeutic action

Overall, a therapeutic action regarding acromegaly management was taken in 28.0% of patients in the visit before study visit. A significantly higher rate of action was taken on patients with IGF-1 > 1.2 ULN than in patients with normal IGF-1 (71.4% vs 13.4; p<0.001) or IGF-1 > ULN but < 1.2 ULN at the visit before study visit (71.4% vs 33.3%; p<0.01).

Results of the therapeutic action taken in the previous visit was not successful in most of the patients: 88.9% (n=16) of patients with no IGF-I and/or tumour control, remained uncontrolled at the study visit. Similarly, 82.8% (n=53) of patients in which no action was taken in the last visit remained in the same control status. Most of them (83.9%, n=47) were controlled and remained controlled. 14.1% (n=9) of patients were controlled in terms of IGF-I and tumor status and, spontaneously, lost control at the study visit.

At the study visit, therapeutic action was taken in 27.9% of patients overall and a change of medication (dose or drug) was the most frequent action taken (20.7% of patients) (Table 5). In S-DA patients, therapeutic actions were taken on a significantly greater proportion (77.3%) compared to M-DA (22.9%, p<0.001) and S patients (11.3%, p<0.001) (Figure 3). However, no action was taken on 22.7% (n=5) of S-DA patients and in 77.1% (n=27) of M-DA patients.
In 3 of those 5 S-DA patients, a change in treatment (dose or drug) was taken in the last visit, that took place a mean (SD) of 5.2 (2.7) months. In the other 2 patients, no action was taken neither in the last visit nor in the study visit. Both presented IGF-I levels above ULN at both visits, but one of them was considered stable according to physician criteria.

Differences between M-DA patients in which no action was taken (n=27) vs patients in which action was taken (n=8) at the study visit were found regarding the disease activity classification by physician’s criteria (4 vs 24 classified as S-DA, p<0.05), time since the beginning of treatment (mean time 5.87 vs 10.41 years, p<0.05) and time since the last visit (mean time 3.96 vs 6.70 years, p<0.05).

Criteria that marked the decision to take a therapeutic action on S-DA and M-DA patients were IGF-1 levels and IGF-1 + tumour control at the last visit and at the study visit (p<0.01).

**Discussion**

Traditional clinical treatment goals for acromegaly are mainly based on the achievement of biochemical and tumour control. (6, 10) However, even when biochemical and tumour control is achieved, many patients continue to experience symptoms and impaired HRQoL (6, 12, 13, 21). Moreover, challenges in the IGF-1 measurement (22, 23) and subjectivity in tumour growth assessment (24) limits the use of these parameters as the sole assessment of disease activity.

ACRODAT® is a new software medical device designed to assess acromegaly activity from an integrated point of view as it includes not only clinical parameters of disease but also patients’ reported outcomes (PRO), such as symptoms and HRQoL. (18) AcroVoice, a study to determine which parameters matter to acromegaly patients for defining their disease, showed that, in contrast with the physician validation study, patients placed more value on the “patient-centered” parameters (6). Thus, validated patient reported outcomes (PRO) should be regularly documented in acromegaly patients as a patient-oriented indicator of treatment success. (13, 15) Indeed, objective tools such as ACRODAT® have been recently recommended to assess and monitor acromegaly disease activity (1, 25, 26).

Herein, we show the first real world data evaluating disease activity status using ACRODAT® and its correlation with physicians’ criteria, in a representative cohort of 111 Spanish patients attended in a normal clinical practice setting. Patient population was similar to other studies (27, 28), with a mean age of 59.7 years and 51.4% of women.

60.7% of patients were controlled in terms of IGF-1 and tumour volume. According to ACRODAT®, only 48.2% of patients were considered controlled or stable and 51.8% presented with active disease (Fig. 1A). According to the physicians’ clinical evaluation, 73.9% of patients were stable whereas 26.1% presented with active disease (Fig. 2B). ACRODAT® and physician’s opinion showed a fair inter-rater agreement. Thus, for patients who according to the physician were stable, 92.5% of them were classified by ACRODAT® as stable. However, ACRODAT® was able to identify more cases of active disease due to the integration of other than biochemical and tumour control parameters such as comorbidities, symptoms
and QoL in its definition of control. Discrepancies between ACRODAT® and physicians’ criteria were mainly observed in patients with IGF-1 above ULN, phPASQ (more severe signs and symptoms), patients showing higher QoL impairment (p < 0.05) and a longer time since diagnosis or since the beginning of treatment. Thus, ACRODAT® may be especially useful in determining disease activity in patients with these characteristics. A source of discrepancy may be the existing differences in the definition of biochemical control: while ACRODAT® considers an IGF-1 level > 1 ULN as active disease, the currently used cut-offs in clinical practice ranges from 1 to 1.5 ULN. (29) A possible reason is the distrust in the accuracy of IGF-1 levels due to the variability of the diagnostic assays. (22, 23, 30) However, all-cause mortality risk in acromegaly increases with higher serum IGF-1 levels and that IGF-I normalization (IGF-1 < ULN) is associated with all-cause mortality rates indistinguishable from the general population. (31)

IGF-1 levels do not correlate with symptoms or QoL as has been described in this and other studies (14, 15). In fact, we found that 12.3% of patients with IGF-1 and tumour control had a mild to moderate or significant impairment in QoL. Similarly, 72.3% of patients according to phPASQ, or 86.1% according to paPASQ, showed moderate or severe symptoms despite having reached IGF-1 and tumour control. phPASQ and paPASQ showed a substantial inter-rater agreement, however, physicians tended to rate the intensity of symptoms significantly lower than patients. These findings support the need to consider validated PROs in disease activity assessment although, currently, this is not common clinical practice: 53.8% and 30.8% of the physicians involved in this study affirmed not using PASQ and AcroQoL, respectively (data not shown). The study also showed that there were a proportion of patients with uncontrolled cardiac disease (11.5%) or sleep apnoea (14.3%). Comorbidities should be regularly monitored and appropriate therapeutic actions should be taken to minimize disease burden and mortality.

Most patients can achieve disease control if their treatment is adequately selected and adjusted according to patient characteristics and response (32). Indeed, Ragonese et al showed that, when adequately titrated, pegvisomant could achieve IGF-1 control in 89.6% patients (33), a higher proportion than reported when titration was suboptimal (24). In our study, therapeutic actions were taken in a significantly greater proportion of S-DA patients compared to M-DA and S patients, but no action was taken in a significant number of patients with disease activity according to ACRODAT® (22.7% of S-DA patients and 77.1% of M-DA patients) (Fig. 3). A possible explanation may be that these patients were in the process of treatment adjustment (S-DA patients had more changes of medication and more recently) and physicians were waiting to see a stabilization before making a decision. Time between visits in these cases should be optimized. Discrepancies in the IGF-1 cut-offs levels or the low reliability of IGF-1 determinations may explain the inaction on some M-DA patients. Indeed, Schöfl et al,(30) described that one of the main reasons not to change/escalate treatment in uncontrolled patients was the fluctuating IGF-1 levels. In any case, there were a significant number of patients with IGF-1 and tumour control but poor PROs that did not receive a possible change in treatment that they might have needed.

Therapeutic decision in S-DA and M-DA patients was guided by IGF-1 levels and IGF-1 + tumour control despite collecting patient PROs in the study visit, showing that collection may not be useful if it is not integrated and interpreted. ACRODAT® may support the decision-making process by providing an
integrated holistic view of the disease, even though in some cases it might be difficult to obtain all PROs in the time frame of a routine outpatient visit.

Some limitations derived from the cross-sectional nature of this study should be borne in mind. The data presented here are a static picture of a specific moment of the state of illness of patients with a long evolution of the disease. ACRODAT® is designed to long-term monitor changes at regular intervals that can facilitate better management of patients. Secondly, the PASQ used in ACRODAT® in this study was completed by physicians, although concordance was observed between the PASQ completed both by patients and physicians. Finally, therapeutic action collected in the study referred to acromegaly treatments, and specific treatment for comorbidities or symptoms were not collected.

In conclusion, ACRODAT® is a validated and highly specific tool that allows routinely monitoring of disease activity in a holistic manner by incorporating clinical, laboratory and radiological parameters (IGF-1, tumour status and comorbidities) as well as PRO parameters such as PASQ and AcroQoL. Monitoring changes at regular intervals may be useful to identify patients with non-obvious disease activity, facilitate better treatment decisions and support an integral approach to acromegaly disease management.

**Declarations**

**Declaration of interests**

LS-C and MD-M are employees of Pfizer (Spain). MLS works for Pfizer (Spain). MM, CB, IB, EM, RV, MP, MS-N have received compensation from Pfizer (Spain) for their participation as investigators of ACROVAL study. MM has received compensation from Pfizer (Spain) for their participation as research coordinator of ACROVAL study. MM, IB and MP have received speaker honoraria from Pfizer (Spain). MM, IB and MS-N have received speaker honoraria from Novartis. MM and CB have received speaker honoraria from Ipsen. MM has participated in advisory boards for Ipsen, Novartis and Pfizer (Spain). IB is a grant recipient and advisory board member for Pfizer. This study was sponsored by Pfizer. Medical writing support was provided by Esther Tapia PhD, and was funded by Pfizer.

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References

1. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JA, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552-61.

2. Vilar L, Vilar CF, Lyra R, Lyra R, Naves LA. Acromegaly: clinical features at diagnosis. Pituitary. 2017;20(1):22-32.

3. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev. 2004;25(1):102-52.

4. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol. 2008;159(2):89-95.

5. Rajasopya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf). 1994;41(1):95-102.

6. Jackson Y, Flood E, Rhoten S, Janssen EM, Lundie M. AcroVoice: eliciting the patients' perspective on acromegaly disease activity. Pituitary. 2019;22(1):62-9.

7. Kepicoglu H, Hatipoglu E, Bulut I, Darici E, Hizli N, Kadioglu P. Impact of treatment satisfaction on quality of life of patients with acromegaly. Pituitary. 2014;17(6):557-63.

8. Tiemensma J, Kaptein AA, Pereira AM, Smit JW, Romijn JA, Biermasz NR. Affected illness perceptions and the association with impaired quality of life in patients with long-term remission of acromegaly. J Clin Endocrinol Metab. 2011;96(11):3550-8.

9. Trepp R, Everts R, Stettler C, Fischli S, Allemann S, Webb SM, et al. Assessment of quality of life in patients with uncontrolled vs. controlled acromegaly using the Acromegaly Quality of Life Questionnaire (AcroQoL). Clin Endocrinol (Oxf). 2005;63(1):103-10.

10. Katznelson L, Laws ER, Jr., Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933-51.

11. Cordido F, Garcia Arnes JA, Marazuela Aspiroz M, Torres Vela E, grupo de Neuroendocrinologia de la Sociedad Espanola de Endocrinologia y N. [Practical guidelines for diagnosis and treatment of acromegaly. Grupo de Neuroendocrinologia de la Sociedad Espanola de Endocrinologia y Nutricion]. Endocrinol Nutr. 2013;60(8):457 e1- e15.

12. Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, et al. Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. J Clin Endocrinol Metab. 2008;93(10):3853-9.

13. Guitelman M, Abreu A, AL E-d-l-M, Mercado M. Patient-focussed outcomes in acromegaly. Pituitary. 2014;17 Suppl 1:S18-S23.
14. Webb SM, Badia X, Surinach NL, Spanish AcroQol Study G. Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: a 6-month prospective study. Eur J Endocrinol. 2006;155(2):269-77.

15. Sievers C, Brubach K, Saller B, Schneider HJ, Buchfelder M, Droste M, et al. Change of symptoms and perceived health in acromegalic patients on pegvisomant therapy: a retrospective cohort study within the German Pegvisomant Observational Study (GPOS). Clin Endocrinol (Oxf). 2010;73(1):89-94.

16. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum. 2012;64(9):2814-23.

17. Webber K, Davies AN, Cowie MR. Disparities Between Clinician and Patient Perception of Breakthrough Pain Control. J Pain Symptom Manage. 2016;51(5):933-7.

18. van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, et al. Development of ACRODAT(R), a new software medical device to assess disease activity in patients with acromegaly. Pituitary. 2017;20(6):692-701.

19. Badia X, Webb SM, Prieto L, Lara N. Acromegaly Quality of Life Questionnaire (AcroQoL). Health Qual Life Outcomes. 2004;2:13.

20. Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171-7.

21. Webb SM, Badia X. Quality of Life in Acromegaly. Neuroendocrinology. 2016;103(1):106-11.

22. Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ. Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. Clin Endocrinol (Oxf). 2007;67(1):65-70.

23. Algeciras-Schimnich A, Bruns DE, Boyd JC, Bryant SC, La Fortune KA, Grebe SK. Failure of current laboratory protocols to detect lot-to-lot reagent differences: findings and possible solutions. Clin Chem. 2013;59(8):1187-94.

24. Freda PU, Gordon MB, Kelepouris N, Jonsson P, Koltowska-Haggstrom M, van der Lely AJ. Long-term treatment with pegvisomant as monotherapy in patients with acromegaly: experience from ACROSTUDY. Endocr Pract. 2015;21(3):264-74.

25. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, et al. A Consensus on the Diagnosis and Treatment of Acromegaly Comorbidities: An Update. J Clin Endocrinol Metab. 2020;105(4).

26. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, et al. Multidisciplinary management of acromegaly: A consensus. Rev Endocr Metab Disord. 2020;21(4):667-78.

27. Bernabeu I, Pico A, Venegas E, Aller J, Alvarez-Escola C, Garcia-Arnes JA, et al. Safety of long-term treatment with Pegvisomant: analysis of Spanish patients included in global ACROSTUDY. Pituitary. 2016;19(2):127-37.

28. Camara R, Venegas E, Garcia-Arnes JA, Cordido F, Aller J, Samaniego ML, et al. Treatment adherence to pegvisomant in patients with acromegaly in Spain: PEGASO study. Pituitary. 2019;22(2):137-45.
29. van Esdonk MJ, van Zutphen EJM, Roelfsema F, Pereira AM, van der Graaf PH, Biermasz NR, et al. How are growth hormone and insulin-like growth factor-1 reported as markers for drug effectiveness in clinical acromegaly research? A comprehensive methodologic review. Pituitary. 2018;21(3):310-22.

30. Schofl C, Grussendorf M, Honegger J, Tonjes A, Thyroke-Gronostay D, Mayr B, et al. Failure to achieve disease control in acromegaly: cause analysis by a registry-based survey. Eur J Endocrinol. 2015;172(4):351-6.

31. Tritos NA, Mattsson AF, Vila G, Biller BMK, Klibanski A, Valluri S, et al. All-cause mortality in patients with acromegaly treated with pegvisomant: an ACROSTUDY analysis. Eur J Endocrinol. 2020;182(3):285-92.

32. Schofl C, Franz H, Grussendorf M, Honegger J, Jaursch-Hancke C, Mayr B, et al. Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register. Eur J Endocrinol. 2013;168(1):39-47.

33. Ragonese M, Grottoli S, Maffei P, Alibrandi A, Ambrosio MR, Arnaldi G, et al. How to improve effectiveness of pegvisomant treatment in acromegalic patients. J Endocrinol Invest. 2018;41(5):575-81.

Tables

**Table 1.** ACRODAT® disease activity categories
| Parameters         | Disease activity Level                                                                 |
|-------------------|----------------------------------------------------------------------------------------|
|                   | **S**                                                                                   |
| IGF-I levels      | Within normal limits                                                                    |
| Tumour status     | Tumour is not visible or has not changed since prior MRI                                 |
| Comorbidities*    | Well controlled: No diabetes, apnoea and cardiac disease or, if present, well controlled by therapy |
| Symptoms (PASQ)   | Mild: patient reports no or only mild symptoms (all rated ≤ 2)                           |
| QoL (AcroQoL)     | Score ≥ 60: No or minimal impairment in QoL                                               |
|                   | **M-DA**                                                                                 |
| IGF-I levels      | Exceeds the ULN but not >1.2 ULN, or is below LLN                                        |
| Tumour status     | A slight increase in tumour size (≤20%) since prior MRI                                  |
| Comorbidities*    | Partially controlled: Diabetes is well controlled by therapy, no apnoea, no cardiac disease (or, if present, well controlled by therapy) or no diabetes but presence of apnoea and/or cardiac disease not well controlled by therapy |
| Symptoms (PASQ)   | Moderate: patients report presence of some symptoms, but no single symptoms exceed a score of 6, and the mean score is ≤ 4 overall |
| QoL (AcroQoL)     | 40 ≤ score >60: mild to moderate impairment in QoL                                        |
|                   | **S-DA**                                                                                 |
| IGF-I levels      | > 1.2 ULN                                                                               |
| Tumour status     | A significant increase in tumour size (>20%) since prior MRI and/or tumour invasiveness and/or worsening in vision |
| Comorbidities*    | Non-controlled: Diabetes is not well controlled by therapy and presence of moderate/severe apnoea and/or uncontrolled cardiac disease |
| Symptoms (PASQ)   | Severe: patients report symptoms with a mean score >4 or one or more symptoms rated >6 |
| QoL (AcroQoL)     | Score <40: significant impairment in QoL                                                 |

S: stable; M-DA: mild disease activity; S-DA: significant disease activity; IGF-I: insulin-like growth factor-I; ULN: upper limit of normal; LLN: lower limit of normal; MRI: magnetic resonance imaging; Comorbidities*: cardiac disease (including hypertension, hyperlipidaemia, or other cardiac abnormalities), diabetes, sleep apnoea; PASQ: Patient acromegalic symptom questionnaire; AcroQoL: the Acromegaly Quality of life Questionnaire

Modified from Van der Lely AJ, et al. Pituitary 2017 Dec; 20 (6): 692-701.
|                          | Total | S     | M-DA  | S-DA  | p-value |
|--------------------------|-------|-------|-------|-------|---------|
|                          | 111   | 53    | 35    | 22    |         |
| Women, n (%)             |       |       |       |       |         |
|                          | 57 (51.4) | 26 (49.1) | 20 (57.1) | 10 (45.5) | NS      |
| Age, mean (SD), yr       |       |       |       |       | <0.001  |
|                          | 59.7 (14.8) | 59.6 (13.4) | 65.6 (12.0) | 50.0 (17.2)* |
| BMI, mean (SD), kg/m²    |       |       |       |       |         |
|                          | 29.5 (5.0) | 29.2 (4.89) | 30.1 (5.2) | 29.7 (5.2) | NS      |
| Macroadenoma, n (%)      |       |       |       |       |         |
|                          | 91 (82.7) | 43 (82.7) | 28 (80.0) | 20 (90.9) | NS      |
| Time since diagnosis, mean (SD), yr |       |       |       |       |         |
|                          | 10.8 (8.0) | 10.2 (7.6) | 12.4 (7.9) | 9.7 (9.3) | NS      |
| Time from diagnosis to the beginning of treatment, mean (SD), months |       |       |       |       |         |
|                          | 23.39 (51.99) | 19.56 (52.01) | 36.01 (60.75) | 14.90 (34.33) | NS      |
| IGF-1 levels at study visit |       |       |       |       |         |
| within normal limits, n (%) | 71 (64.0) | 52 (98.1) | 18 (51.4)** | 0 (0.0)**, ## | <0.001  |
| >ULN, ≤ 1.2 x ULN, n (%) | 18 (16.3) | 1 (1.9) | 17 (48.6)** | 0 (0.0)**, ## | <0.001  |
| >1.2 x ULN, n (%)        | 22 (19.8) | 0 (0.0) | 0 (0.0)** | 22 (100.0)**, ## | <0.001  |
| Tumor status             |       |       |       |       |         |
| Stable                   | 102 (97.1) | 49 (100.0) | 31 (93.9) | 21 (95.5) | NS      |
| Increase ≤ 20%           | 3 (2.9) | 0 (0.0) | 2 (6.1) | 1 (4.5) | NS      |
| Increase > 20%           | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NS      |
| Comorbidities            |       |       |       |       |         |
| Cardiac disease¹, n (%)  | 60 (54.1) | 26 (49.1) | 21 (60.0) | 12 (54.5) | NS      |
| Arthropathy, n (%)       | 47 (42.7) | 22 (41.5) | 18 (52.9) | 7 (31.8) | NS      |
| Diabetes, n (%)          | 40 (36.0) | 14 (26.4) | 17 (48.6) | 8 (36.4) | NS      |
| Apnea, n (%)             | 23 (20.9) | 10 (18.9) | 9 (25.7) | 3 (14.3) | NS      |
| Hypopituitarism, n (%)   | 22 (19.8) | 10 (18.9) | 7 (20) | 5 (22.7) | NS      |
| phPASQ score (0-48), mean (SD) | 12.9 (8.6) | 10.4 | 16.4 | 13.3 (9.6) | <0.05  |
| Condition                                      | Mean 1 (SD)     | Mean 2 (SD)     | Mean 3 (SD)     | Mean 4 (SD)     | p-value   |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------|
| Headache score (0-8), mean (SD)              | 1.6 (1.9)       | 1.1 (1.5)       | 1.9 (2.0)       | 2.2 (2.2)*      | <0.05    |
| Excessive sweating score (0-8), mean (SD)    | 1.9 (1.9)       | 1.8 (1.8)       | 2.1 (1.9)       | 2.0 (2.0)       | NS       |
| Joint pain score (0-8), mean (SD)            | 3.0 (2.4)       | 2.4 (2.0)       | 4.1 (2.7)**     | 2.6 (2.3)#      | <0.05    |
| Fatigue score (0-8), mean (SD)               | 2.7 (2.0)       | 2.2 (1.7)       | 3.6 (2.3)**     | 2.3 (1.7)#      | <0.05    |
| Swelling score (0-8), mean (SD)              | 1.7 (1.6)       | 1.4 (1.4)       | 2.0 (1.6)       | 2.2 (2.0)       | <0.05    |
| Numbness or tingling score (0-8), mean (SD)  | 2.0 (1.7)       | 1.6 (1.4)       | 2.6 (2.0)*      | 2.0 (1.7)       | <0.05    |
| Health Status PASQ, mean (SD)                | 3.7 (2.2)       | 3.0 (1.5)       | 4.9 (2.6)**     | 3.6 (2.3)       | <0.001   |
| AcroQoL score (0-100), mean (SD)             | 65.7 (19.2)     | 70.5 (14.4)     | 56.9 (21.8)**   | 66.1 (22.1)     | <0.01    |
| Physical (0-100) mean (SD)                   | 59.9 (24.5)     | 67.6 (17.5)     | 46.3 (27.5)**   | 63.2 (25.8)#    | <0.001   |
| Psychological (0-100), mean (SD)             | 68.0 (18.5)     | 71.8 (15.1)     | 61.4 (20.7)*    | 67.8 (21.1)     | <0.05    |
| Appearance (0-100), mean (SD)                | 58.2 (22.3)     | 61.9 (19.9)     | 49.8 (23.4)*    | 60.6 (23.1)     | <0.05    |
| Personal relations (0-100), mean (SD)        | 77.3 (18.5)     | 81.8 (13.6)     | 71.1 (21.1)*    | 75.0 (22.7)     | <0.05    |
| Degree of disability, n (%)                  | 26 (23.6)       | 11 (20.8)       | 11 (32.4)       | 4 (18.2)        | NS       |
| <33%, n (%)                                   | 7 (28.0)        | 4 (36.4)        | 1 (10.0)        | 2 (50.0)        | NS       |
| 33-66%, n (%)                                 | 12 (48.0)       | 5 (45.5)        | 6 (60.0)        | 1 (25.0)        | NS       |
| >66%, n (%)                                   | 6 (24.0)        | 2 (18.2)        | 3 (30.0)        | 1 (25.0)        | NS       |
| Prior Therapies                              |                 |                 |                 |                 |          |
| Surgery, n (%)                                | 84 (75.7)       | 44 (83.0)       | 25 (71.4)       | 15 (68.2)       | NS       |
| Time since surgery, mean (SD), yr            | 11.2 (8.0)      | 10.5 (7.3)      | 14.0 (8.3)      | 8.9 (8.9)       | NS       |
| Radiotherapy, n (%)                           | 39 (35.1)       | 16 (30.2)       | 14 (40.0)       | 9 (40.9)        | NS       |
| Time since radiotherapy, mean (SD), yr       | 10.3 (8.9)      | 10.8 (9.3)      | 11.5 (8.0)      | 7.1 (9.8)       | NS       |
| Time in pharmacological treatment, mean (SD), yr | 8.9 (6.9) | 8.6 (5.9) | 9.6 (7.1) | 8.6 (9.0) | NS |
Number of medication changes in the last two years\textsuperscript{2} <0.001

| None, n (%)                  | 40 (38.1) | 25 (50.0) | 10 (28.6) | 5 (25.0)\*,## | <0.001 |
|------------------------------|-----------|-----------|-----------|---------------|--------|
| 1                            | 28 (26.7) | 12 (24.0) | 16 (45.7) | 0 (0.0)\*,## | <0.001 |
| 2-3, n (%)                   | 31 (29.5) | 10 (20.0) | 7 (20.0)  | 14 (70.0)\*,## | <0.001 |
| ≥4, n (%)                    | 6 (5.7)   | 3 (6.0)   | 2 (5.7)   | 1 (5.0)\*,## | <0.001 |

Time since last medication change, mean (SD), mo

| Time since last medication change, mean (SD), mo | 28.1 (38.5) | 33.7 (38.8) | 32.5 (45.4) | 8.5 (11.4)* | <0.05 |

Time since last visit, mean (SD), mo

| Time since last visit, mean (SD), mo | 6.4 (3.8) | 6.9 (3.9) | 6.1 (3.6) | 5.6 (4.0) | NS |

\textsuperscript{1}includes hypertension, hyperlipidemia, or other cardiac abnormalities. \textsuperscript{2}Change of dose or treatment * p<0.05 vs S. ** p<0.01 vs S. # p<0.05 vs M-DA. ## p<0.01 vs M-DA. NS: not significant. S: stable; M-DA: mild disease activity; S-DA: significant disease activity

**Table 3.** Normalized (0-100) AcroQoL overall score and subscores included in the AcroQoL questionnaire.
| PHYSICAL SCORE                        | Normalized score (0-100) | Mean  | SD    |
|--------------------------------------|--------------------------|-------|-------|
| My legs feel weak                    | 63.7                     | 63.6  | 29.1  |
| I get depressed                      |                          | 63.6  | 28.9  |
| I have problems carrying out my usual activities (e.g. working, studying, doing household task, family or leisure activities) | 64.3                     | 64.3  | 31.9  |
| The illness affects my performance at work or in my usual tasks | 63.5                     | 63.5  | 34.2  |
| My joints ache                       |                          | 49.3  | 32.2  |
| I feel tired                         |                          | 50.0  | 27.8  |
| I feel like a sick person            |                          | 65.1  | 33.8  |
| I feel weak                          |                          | 59.7  | 30.2  |
| PSYCHOLOGICAL SCORE                  |                          | 68.0  | 18.5  |
| Appearance score                     |                          | 58.15 | 22.30 |
| I feel ugly                          |                          | 57.4  | 33.3  |
| I look awful in photographs          |                          | 46.6  | 34.6  |
| I look different in the mirror       |                          | 57.4  | 33.6  |
| Some parts of my body (nose, feet, hands, etc.) are too big | 49.1                     | 49.1  | 36.5  |
| I have problems doing things with my hands, for example, sewing or handling tools | 68.0                     | 68.0  | 32.1  |
| I snore at night                     |                          | 47.7  | 31.7  |
| It is hard for me to articulate words due to the size of my tongue |                         | 81.3  | 25.1  |
| Personal relations score             |                          | 77.3  | 18.52 |
| I avoid going out very much with friends because of my appearance | 89.4                     | 89.4  | 20.1  |
| I try to avoid socializing           |                          | 84.5  | 23.1  |
| I feel rejected by people because of my illness | 90.5                     | 90.5  | 20.0  |
| People stare at me because of my appearance | 82.0                     | 82.0  | 26.8  |
| I have problems with sexual relations |                          | 69.6  | 33.6  |
| The physical changes produced by my illness govern my life | 68.2                     | 68.2  | 33.2  |
| I have little sexual appetite        |                          | 53.0  | 34.3  |
Table 4. Agreement on symptoms severity between patients (paPASQ) and physicians (phPASQ). Each item was scored on a 9-point scale (0 no symptoms-8 severe incapacitating symptoms). The total PASQ score was the sum of the individual symptom scores (maximum = 48). Overall health status was scored ranging from 0 (best possible) to 10 (worst possible).

|                          | phPASQ | paPASQ | Pearson coefficient | p       | kappa |
|--------------------------|--------|--------|---------------------|---------|-------|
| Headache, mean (SD)      | 1.5 (1.9) | 1.9 (2.1) | 0.754               | <0.001 | 0.726 |
| Excessive sweating, mean (SD) | 1.9 (1.9) | 2.5 (2.5) | 0.773               | <0.001 | 0.625 |
| Joint pain, mean (SD)    | 3.0 (2.4) | 3.5 (2.7) | 0.752               | <0.001 | 0.641 |
| Fatigue, mean (SD)       | 2.7 (2.0) | 3.1 (2.6) | 0.641               | <0.001 | 0.570 |
| Swelling, mean (SD)      | 1.7 (1.6) | 2.2 (2.4) | 0.584               | <0.001 | 0.327 |
| Numbness or tingling, mean (SD) | 2.0 (1.7) | 2.7 (2.5) | 0.691               | <0.001 | 0.505 |
| Total PASQ (symptoms) score, mean (SD) | 12.9 (8.6) | 15.9 (11.0) | 0.759               | <0.001 | 0.624 |
| Health Status PASQ, mean (SD) | 3.7 (2.2) | 4.2 (2.8) | 0.749               | <0.001 | 0.662 |

PASQ: Patient-Assessed Acromegaly Symptom Questionnaire.

Table 5. Therapeutic action taken at the study visit.

| Action                          | Total (N) | S (N) | M-DA (N) | S-DA (N) | p-value |
|---------------------------------|-----------|-------|----------|----------|---------|
| Surgery evaluation              | 6 (5.4)   | 2 (3.8)| 2 (5.7)  | 2 (9.1)  | <0.001  |
| Change of medication (dose or drug) | 23 (20.7) | 4 (7.5)| 6 (17.1) | 13 (59.1)|         |
| Radiotherapy                    | 2 (1.8)   | 0 (0.0)| 0 (0.0)  | 2 (9.1)  |         |
| No action                       | 80 (72.1)| 47 (88.7)| 27 (77.1)| 5 (22.7)|         |

S: stable; M-DA: mild disease activity; S-DA: significant disease activity; ** p<0.001 vs S. # p<0.01 vs M-DA

Figures
Figure 1

Disease activity according to ACRODAT® (A) and Physicians' Criteria (B). S: stable; M-DA: mild disease activity; S-DA: significant disease activity.
Figure 2

Patients’ characteristics according to ACRODAT®. A. IGF-I: insulin-like growth factor-I. B. Tumour status. C. Comorbidities. D. phPASQ: Physician-assessed Acromegaly Symptom Questionnaire fulfilled by the physician. E. AcroQoL: Acromegaly Quality of Life Questionnaire. S: stable; M-DA: mild disease activity; S-DA: significant disease activity; *p<0.01 vs. S; **p<0.001 vs. S; ## p <0.001 vs. M-DA.
Figure 3

Therapeutic action taken depending on ACRODAT® classification at study visit. S: stable; M-DA: mild disease activity; S-DA: significant disease activity. **p<0.001 vs. S; ## p <0.001 vs. M-DA.