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Original Article

Characterizing the Burden of Uncontrolled Acromegaly – A Description of Real-world Patient Characteristics in Colombia

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Abstract

Objective: To describe the epidemiology and clinical characteristics relative to biochemical and disease control after treatment initiation in patients with acromegaly in Colombia.

Methods: A retrospective chart review of newly diagnosed acromegaly patients who initiated medical treatment at referral health institutions in Colombia. Patients with controlled vs. uncontrolled disease were analyzed, including comorbidities and treatment patterns. In addition, patients receiving somatostatin analogs (SSAs) as first-line treatment (SSA cohort) were compared with those receiving other medical therapy (non-SSA cohort).

Results: Data obtained from medical records of 53 patients showed a mean age of 49 years (SD 13.31) and a female preponderance (33 [62.26%]). After one year of treatment, ten (18.9%) patients from the SSA cohort achieved complete biochemical control, showing significantly lower levels of median growth hormone (GH) and insulin-like growth factor-1 (IGF-1) vs. 43 (81.1%) patients from the uncontrolled group (p = 0.0010 and p = 0.0001, respectively). During follow-up, acromegaly-related comorbidities were higher in patients with uncontrolled disease and the non-SSA group vs. the controlled group. Similarly, the percentage of physician visits was lower in the controlled (n =4/10, 40.0%) vs. uncontrolled (n = 31/43, 72.0%) group and in the SSA (n = 24/38, 63.2%) vs. non-SSA (n = 11/15, 73.3%) cohort.

Conclusion: In patients with acromegaly receiving medical therapy, GH and IGF-1 levels tended to decline over time with SSAs. Lower frequency of comorbidities and use of healthcare resources were associated with controlled acromegaly. Optimizing disease control with adequate patient follow-up and drug treatment may improve clinical outcomes and promote efficient use of healthcare resources.

Keywords: Acromegaly, somatostatin analogs, growth hormone, insulin growth factor-1, Colombia

Highlights

- Patients with controlled acromegaly have fewer complications and less use of healthcare resources
- The rate of acromegaly disease control with medical therapy is low
- Optimizing disease control may improve clinical outcomes

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Carga de la enfermedad en pacientes con acromegalia no controlada. Una descripción de las características del mundo real de pacientes colombianos

Resumen

Objetivo: describir la epidemiología y las características clínicas relacionadas con el control bioquímico de la enfermedad en pacientes con acromegalia en Colombia

Métodos: revisión retrospectiva de historias clínicas de pacientes con diagnóstico nuevo de acromegalia tratados medicamente en instituciones de salud de referencia en Colombia. Se analizaron pacientes controlados vs. no controlados, incluidas comorbilidades y patrones de tratamiento. Adicionalmente, se compararon pacientes que recibieron análogos de somatostatina como primera línea de tratamiento médicos vs. pacientes que recibieron otros tipos de tratamientos médicos.

Resultados: se obtuvieron informes médicos de 53 pacientes con una edad promedio de 49 años (DE 13.31), con predomino del sexo femenino (33 [62.26%]). Luego de un año de tratamiento, diez (18.9%) pacientes de la cohorte de análogos de somatostatina tenían control bioquímico completo de la enfermedad, con una mediana de GH e IGF1 más bajas comparado con el grupo no controlado (= 0.0010 y p = 0.0001, respectivamente). Durante el seguimiento, las comorbilidades relacionadas con la acromegalia fueron más frecuentes en pacientes con enfermedad no controlada y en el grupo sin análogos de somatostatina vs. el grupo controlado. Las visitas médicas fueron menos frecuentes en el grupo controlado (n = 4/10, 40.0%) vs. el no controlado (n = 31/43, 72.0%), lo mismo que en el grupo con análogos (n = 24/38, 63.2%) que el grupo sin análogos (n = 11/15, 73.3%).

Conclusión: en pacientes con acromegalia tratados medicamente, la GH y la IGF tienden a bajar con el tiempo con el uso de análogos de somatostatina. En los pacientes con control de la enfermedad hay menor frecuencia de comorbilidades y uso de recursos de salud. Optimizar el control bioquímico con un seguimiento y tratamiento farmacológico apropiados puede mejorar desenlaces crónicos y promover un uso eficiente de los recursos de salud.

Palabras clave: acromegalia, análogos de somatostatina, hormona de crecimiento, Colombia, factor de crecimiento similar a la insulina-1

Destacados

- Los pacientes con acromegalia controlada tienen menos complicaciones y usan menos los recursos de atención médica.
- La tasa de control de la enfermedad de acromegalia con terapia médica es baja.
- La optimización del control de la enfermedad puede mejorar los resultados clínicos.

Introduction

Acromegaly is caused by a pituitary adenoma in most cases. The disease is associated with symptoms and complications such as acral and soft tissue enlargement, joint pain, heart failure, respiratory distress, obstructive sleep apnea, diabetes mellitus, hypertension, hypopituitarism, and visual field defects (1, 2). The incidence of the disease is estimated to be 3–4 cases per million per year, with an occurrence rate of 40–100 people per million (3, 4). The prevalence of acromegaly in Colombia has not been documented, but according to the Registry of Health Services Provision, reported in the Colombian Social Protection Information System SISPRO, the frequency has been established as 170–300 new cases per year (5). The prevalence rate of acromegaly shows a female dominance (0.56 and 0.42 per 100 people each in females and males, respectively) (6). The most common comorbidities associated with acromegaly are those related to the cardiovascular system (2), followed by musculoskeletal, respiratory, and endocrine/metabolic systems (7, 8).

Acromegaly is frequently reported in the elderly and includes a long undiagnosed period. Its insidious onset leads to a significant delay in diagnosis, contributing to a difference of more than five years from the mean age of occurrence (32 years) to the mean age of diagnosis (40–45

years) (9). Once confirmed, obtaining biochemical remission requires surgical management, medical therapy, and radiotherapy. Although surgery remains the first-line therapy for acromegaly, pharmacological therapy could also aid in treating the disease, especially in patients with macroadenomas, as they have been associated with lower rates of surgical cure. Establishing appropriate medical control is a significant treatment factor in managing acromegaly, which may consequently lower morbidity and mortality (10–14).

According to the Endocrine Society Clinical Practice Guidelines published in 2014, the use of either somatostatin analogs (SSAs); dopamine agonists (DAs), such as cabergoline; or somatostatin receptor ligands is indicated as medical therapy for patients with acromegaly across several stages of the disease (15).

Optimal management of acromegaly includes biochemical control (growth hormone [GH] level < 2.5 µg/L and normal standardized insulin-like growth factor-1 [IGF-1]) and control of tumor growth (which may be independent of biochemical control) along with comprehensive treatment of associated symptoms and comorbidities. Therefore, control and remission of acromegaly are defined mainly in terms of specific biochemical targets (GH and IGF-1 levels), as they predict or correlate with symptoms, comorbidities, and mortality (16).

This study aimed to provide real-world information regarding the epidemiology and characteristics of patients with acromegaly undergoing medical treatment in Colombia.

Methods

This observational, retrospective chart review study evaluated newly diagnosed patients with acromegaly from January 2005 to December 2015 at referral health institutions in Colombia (Bogota, Cali, and Medellin). The study was approved by the local ethics committee and conducted following Good Clinical Practice guidelines. Patient records were collected from the clinical sites as per feasibility assessments conducted by the clinical experts.

Inclusion and exclusion criteria

Records from patients aged ≥ 18 years newly diagnosed with acromegaly from January 2005 to December 2015 who initiated medical treatment for acromegaly were included. Patients could have received other non-medical therapies, such as pituitary surgery or radiotherapy, if diagnosed during the observation period (January 2005 to December 2015) and were later prescribed pharmacological treatment. All the patients had received medical treatment for acromegaly with at least 12 ± 2 months of follow-up and availability of reports for GH and IGF-1 levels.

The exclusion criteria included patients diagnosed and treated for acromegaly before the observation period and patients who did not receive any medical therapy or were without GH or IGF-1 information in their clinical records.

Data analysis

All the study variables were analyzed descriptively in controlled and uncontrolled disease subgroups, as per biochemical parameters for GH and IGF-1. In addition, the SSA (patients receiving SSAs as first-line treatment) and non-SSA (patients not receiving SSAs as first-line treatment) cohorts were defined as per medical treatment choice. Study measures included the proportion of patients falling under the controlled group (i.e., GH < 2.5 µg/L and normal IGF-1 for age and sex) at month 12 ± 2 after treatment initiation. Comorbidities associated with acromegaly were analyzed at baseline and during the follow-up period; treatment patterns and health resource utilization were also evaluated.

Statistical analysis

The proportion of patients falling under the controlled group (GH < 2.5 µg/L and normal standardized IGF-1 for age and sex) at month 12 ± 2 after treatment initiation was calculated. In this retrospective study in patients diagnosed with acromegaly from January 2005 to December 2015, biochemical control was defined as GH level < 2.5 µg/L and standardized IGF-1, rather than the stringent criteria of GH level < 1 µg/L and standardized IGF-1, as per the 2014 Endocrine Society Clinical Practice Guidelines (15). The

proportion of patients with controlled vs. uncontrolled disease was summarized as number (n) and percentage along with the 95% confidence interval (CI). Additionally, subgroup analyses for all parameters were performed according to previous treatment(s), tumor type, age groups, and GH level, among others (gender, previous surgical treatments, and proportion of subjects falling under the controlled category after treatment initiation). Given the exploratory nature of this study and the expected small sample size, all study measures were analyzed descriptively, performing statistical tests as applicable according to the final data collection results. The 95% CI was calculated for the proportion of controlled disease using the Clopper-Pearson method for exact CI for a binomial proportion. The p-value was calculated using Chi-square/Fisher's exact test to assess the association between age groups and disease status (controlled and uncontrolled).

Results

Baseline characteristics

Overall, 64 patients' records were analyzed, 53 of which fulfilled all the study inclusion criteria. Eleven patients were lost to follow-up during the observation period. At diagnosis, the mean age of the enrolled population was 49.0 (SD 13.3) years. A predominance of female patients (female: 62.26%, male: 37.74%) and Hispanic/Latin American ethnicity (47 [88.68%]) was observed. More than half of the patients (30 [56.60%]) were diagnosed with acromegaly within the past five years (from 2010 to 2015), and nearly two-thirds (39 [73.58%]) were enrolled in a contributive social security health system (formal workers health plan). The mean body mass index (BMI) of the total enrolled patients was 29.0 (SD 4.50) kg/m2. At baseline, most patients had high BMI values and were overweight (19 [35.85%]) or obese (14 [26.42%]). Regarding disease evolution, the median time from symptoms initiation to confirmation of acromegaly diagnosis was 5.8 (SD 6.59) years, and the median time from diagnosis to medical treatment initiation was 2.9 (SD 2.47). Thirty-eight cases (71.7%) were macroadenoma, 12 (22.6%) were microadenoma, and in three cases (5.7%), the initial size was not available. Transsphenoidal surgery was performed on 24 (45.3%) subjects overall.

Biochemical control and treatment patterns

During the observation period (mean 3.0 years [0.05–7.82]), the reported treatment patterns included surgery, radiation therapy, SSAs, DAs, and GH receptor antagonists (GHRAs). A total of 38 (72%) patients received SSAs as first-line medical treatment (SSA cohort) (Tables 1 and 2).

Of 53 patients enrolled in the study, 28 (52.8%) had undergone surgery, of whom 24 had undergone pituitary-transsphenoidal surgery. Thirty-eight (71.7%) patients were diagnosed with macroadenomas; seven (13.21%) received radiotherapy. During the first 12 months of follow-up, most of the patients received SSAs: lanreotide (28 [52.8%]) and octreotide (26 [49.1%]), followed by cabergoline (9 [17.0%]). After 24 months, three patients received pasireotide, a second-generation SSA (Figure 1). Overall, the total patient population received an SSA at some point in their treatment, either as a first-line or second-line medical therapy.

Patients received treatment for acromegaly for an average of 2.8 years. During the follow-up period, patients received SSAs (n = 53, 100%), DAs (n = 11, 20.7%), and GHRAs (n = 1, 1.8%). Eight patients received treatment combinations of SSAs + DAs during the first year, lowering to four and three patients during years 2 and 3, respectively.

Biochemical control (GH level < 2.5 µg/L and standardized normal IGF-1 level) was achieved by 10/53 (18.9%), 4/34 (11.7%), 8/21 (38%), and 4/19 (21%) patients under medical treatment at 12 ± 2, 24 ± 2, 36 ± 2, and 48 ± 2 months, respectively (Table 3 and Figure 1). Patients with GH < 2.5 ug/L but abnormal IGF-1 levels were considered uncontrolled.

During the observation period, a higher proportion of patients remained with uncontrolled disease than the controlled disease (ratio 2–7:1), with GH ranging from 0.3 to 1.1 µg/L in the controlled group vs. 0.9 to 12.3 µg/L in the uncontrolled group. The median concentration

Table 1. Demographics and Baseline Characteristics – All Enrolled (N = 53)

Statistic/Category, n (%)a	All Enrolled (N = 53)	SSA Cohort b (N = 38)
Age (years), median (range)	51.0 (21.0:69.0)	54.0 (21.0:69.0)
Sex, female	33 (62.26%)	22 (57.89%)
Race/ethnicity		
African American/Black	0 (0.00%)	0 (0.00%)
White/Caucasian	1 (1.89%)	1 (2.63%)
Hispanic/Latin American	47 (88.68%)	35 (92.11%)
Indigenous	0 (0.00%)	0 (0.00%)
Other	1 (1.89%)	1 (2.63%)
Unknown	3 (5.66%)	1 (2.63%)
Health system enrollment (regime)		
Contributory	39 (73.58%)	28 (73.68%)
Subsidized	6 (11.32%)	3 (7.89%)
Private health insurance	1 (1.89%)	0 (0.00%)
Patient	0 (0.00%)	0 (0.00%)
Not known	7 (13.21%)	7 (18.42%)
BMI (kg/m^2)		
N	39	27
Median (range)	27.5 (21.8:42.1)	27.3 (21.8:42.1)
BMI categories		
Underweight	14 (26.42%)	11 (28.95%)
Normal	6 (11.32%)	5 (13.16%)
Overweight	19 (35.85%)	16 (42.11%)
Obese	14 (26.42%)	6 (15.79%)

Abbreviations: BMI = body mass index, SSA = somatostatin analogue

Note: aPercentages were calculated by taking the column header as the denominator
bSSA cohort: This set represents patients receiving SSAs as first-line medical treatment

Source: Own data.

Table 2. Disease Evolution of Acromegaly Patients at Baseline

Statistic/Category, n (%) a	All Enrolled (N = 53)	SSA Cohort (N = 38)
Year of diagnosis of acromegaly:		
2005–2009	23 (43.40%)	15 (39.47%)
2010–2015	30 (56.60%)	23 (60.53%)
Length of the observation period (years)a,		
Mean ± SD [median]	3.00 ± 2.04 [2.5]	2.90 ± 2.08 [2.2]
Range (Min:Max)	(0.05:7.82)	(0.30:7.82)
Length of the observation perioda,		
< 1 year	10 (18.87%)	7 (18.42%)
1 to < 5 years	33 (62.26%)	24 (63.16%)
5 to < 10 years	10 (18.87%)	7 (18.42%)
≥ 10 years	0 (0.00%)	0 (0.00%)
Time of disease evolution (years)b, n	n = 50	n = 36
Mean ± SD [median]	5.8 ± 6.59 [4.5]	5.4 ± 6.59 [3.5]
Range (Min:Max)	(0.08:36.67)	(0.08:36.67)
Time from year of diagnosis to medical treatment initiation (years)c, n	n = 34	n = 24
Mean ± SD [median]	2.9 ± 2.47 [2.0]	3.4 ± 2.47 [2.5]
Range (Min:Max)	(1.00:8.00)	(1.00:8.00)

Notes: aLength of observation period = (last follow-up visit date−First visit date)/365.25
bTime of disease evolution (years) = time from symptoms initiation to diagnosis confirmation in years or fraction of a year cTime for medical treatment initiation (years) = year of initial medical treatment initiation–year of diagnosis of acromegaly

Source: Own data.

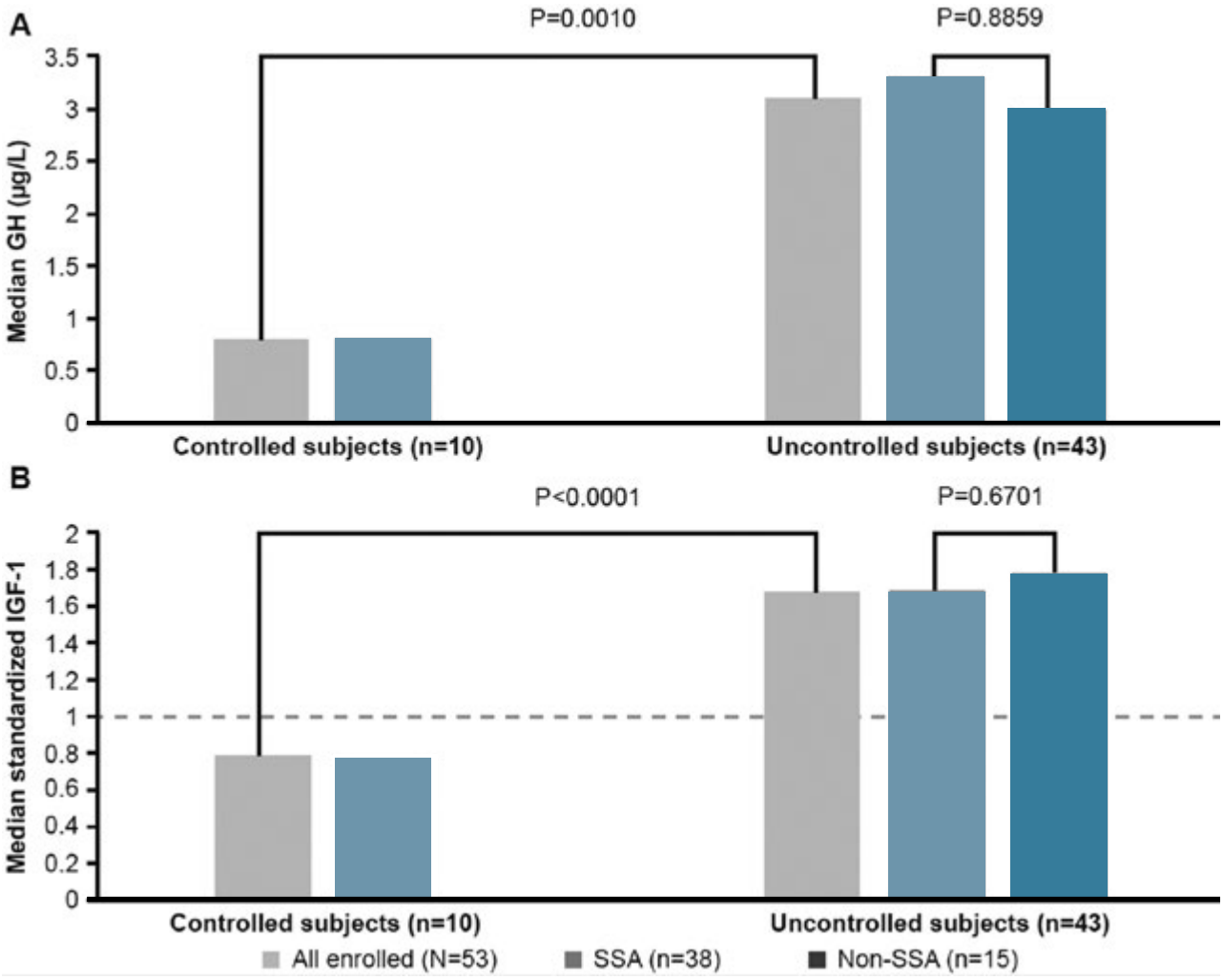


Figure 1. Biochemical Parameters in the Observed Population as per Controlled and Uncontrolled Disease A) Median GH and B) Median Standardized IGF-1

Source: Own data.

Abbreviations: GH = growth hormone; **IGF-1 =** insulin growth factor-1; **SSA =** somatostatin analogue

General Note: ·Controlled disease: GH < 2.5 µg/L and standardized IGF-1 ·Uncontrolled disease: GH > 2.5 µg/L or IGF-1 > ULN (upper limit of normal) age and sex-matched. Standardized IGF-1 defined as IGF-1/ULN

of GH and IGF-1 levels was significantly lower ($p < 0.05$) in the controlled group compared with the uncontrolled group (GH: 0.8 vs. 3.1 µg/L and IGF-1: 0.8 times the upper limit of normal [ULN] vs. 1.7 times ULN); nevertheless, patients under medical treatment showed a trend toward lower GH levels, especially those receiving SSA therapy (Figure 2 and Table 3).

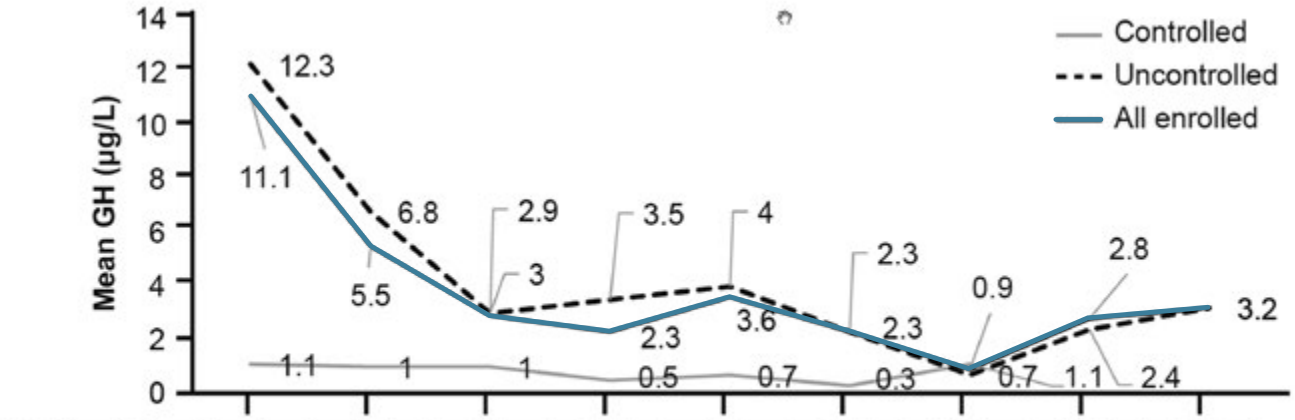
Table 3. Patients with Controlled Disease (GH < 2.5 µg/L and Standardized IGF-1*) and Uncontrolled Disease During the Observation Period – All Enrolled (N = 53)

Patients with GH and IGF-1 information (mean ± SD [median]), [1]	Controlled (N = 10)	Uncontrolled (N = 43)	All Enrolled (N = 53)
Month 12 ± 2 (*N = 52*), *n*	(n = 10)	(n = 42)	(n = 52)
GH (µg/L)	1.0 ± 0.73 (0.8)	6.6 ± 8.43 (3.3)	5.5 ± 7.85 (2.7)
IGF-1	0.8 ± 0.13 (0.8)	1.9 ± 0.76 (1.8)	1.6 ± 0.82 (1.6)
Month 24 ± 2 (*N = 34*), *n*	(*n* = 4)	(*n* = 30)	(*n* = 34)
GH (µg/L)	1.0 ± 0.77 (0.8)	3.2 ± 2.79 (2.6)	2.9 ± 2.71 (2.2)
IGF-1	0.7 ± 0.23 (0.6)	1.4 ± 0.61 (1.3)	1.3 ± 0.63 (1.1)
Month 36 ± 2 (*N = 20*), *n*	(*n* = 8)	(*n* = 12)	(*n* = 20)
GH (µg/L)	0.5 ± 0.48 (0.4)	3.8 ± 5.01 (3.2)	2.3 ± 3.94 (0.8)
IGF-1	0.8 ± 0.05 (0.8)	1.2 ± 0.51 (1.1)	1.0 ± 0.34 (0.8)
Month 48 ± 2 (*N = 18*), *n*	(*n* = 4)	(*n* = 14)	(*n* = 18)
GH (µg/L)	0.7 ± 0.61 (0.6)	4.7 ± 9.79 (0.6)	3.6 ± 8.48 (0.6)
IGF-1	0.7 ± 0.21 (0.7)	1.4 ± 0.62 (1.4)	1.2 ± 0.61 (1.0)
Month 60 ± 2 (*N = 12*), *n*	(*n* = 2)	(*n* = 10)	(*n* = 12)
GH (µg/L)	0.3 ± 0.14 (0.3)	2.8 ± 2.84 (2.3)	2.3 ± 2.74 (0.8)
IGF-1	0.6 ± 0.32 (0.6)	1.4 ± 0.71 (1.1)	1.1 ± 0.71 (1.0)

Abbreviations: GH = growth hormone, **IGF-1 =** insulin like growth factor-1, **SD =** standard deviation; **ULN =** upper limit of normal

Note [1]: ·Controlled disease: GH < 2.5 µg/L and standardized IGF-1. ·Uncontrolled disease: GH > 2.5 µg/L or IGF-1 > ULN (upper limit of normal) age and sex matched. *Standardized IGF-1 defined as IGF-1/ULN

Source: Own data.



Visit (months)	Baseline	12±2	24±2	36±2	48±2	60±2	72±2	84±2	96±2
Controlled (n)	4	10	4	8	4	2	1	0	0
Uncontrolled (n)	32	42	30	12	14	10	3	4	1
All enrolled (n)	36	52	34	20	18	12	4	4	1

Figure 2. Mean Growth Hormone (GH) level (µg/L) in Controlled and Uncontrolled Patients during the Observation Period

Source: Own data.

Abbreviations: GH = growth hormone; **IGF-1 =** insulin growth factor-1

General Note: ·Controlled disease: GH < 2.5 µg/L and standardized IGF-1. ·Uncontrolled disease: GH > 2.5 µg/L or IGF-1 > ULN (upper limit of normal) age and sex-matched

Table 4. Prevalence of Comorbidities during the Follow-up Period - All Enrolled (N = 53)

Comorbidity	Proportion of subjects (%)			
	Controlled disease (N = 10)	Uncontrolled disease (N = 43)	SSA set (N = 38)	Non-SSA set (N = 15)
Skeletal	20.0	39.5	28.9	53.3
Gastrointestinal	10.0	16.3	13.2	20.0
Cardiovascular	50.0	67.4	65.8	60.0
Endocrine and metabolic system	40.0	76.7	68.4	73.3
Pulmonary system	20.0	30.2	31.6	20.0
Neoplasia	10.0	4.7	7.9	0.0
Others	60.0	65.1	52.6	93.3

Abbreviations: Non-SSA = non-somatostatin analogue; **SSA =** somatostatin analogue

Source: Own data.

Acromegaly-related comorbidities

A total of 45 (84.9%) patients presented with at least one comorbidity at baseline, and 15 (27%) patients had more than three comorbidities during the follow-up period. The number of patients experiencing comorbidities was higher in the uncontrolled group compared with the controlled group. Endocrine-, cardiovascular-, skeletal-, and gastrointestinal-related comorbidities were the most frequent (Figure 3, Table 4, Supplementary Table 1).

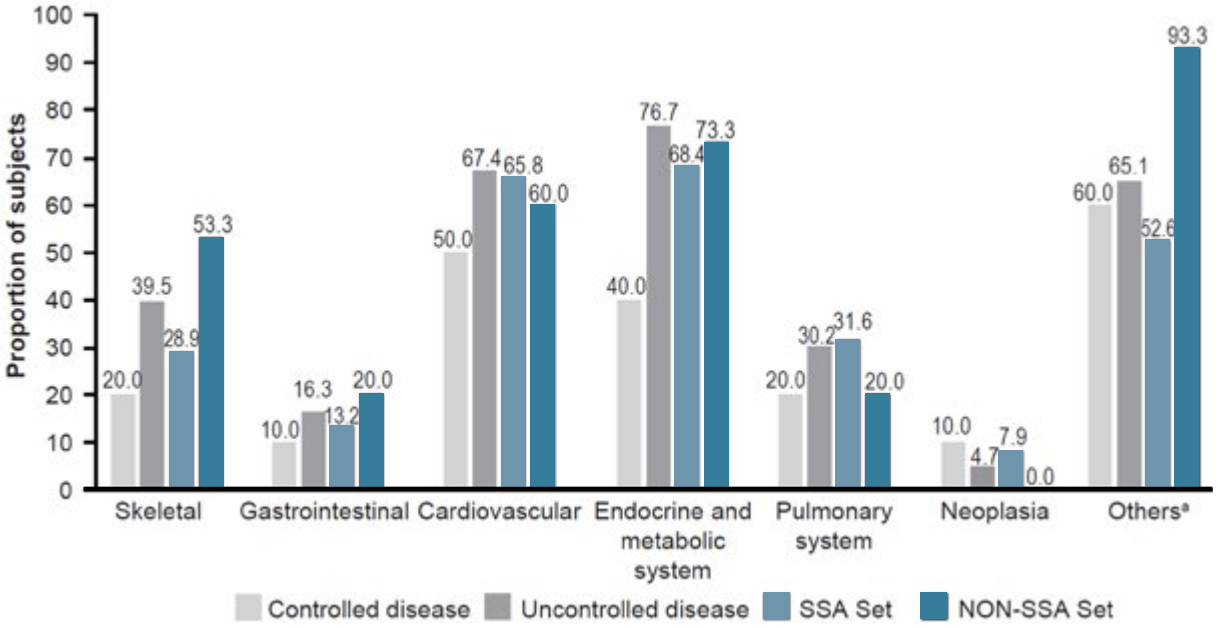


Figure 3. Prevalence of Comorbidities During the Follow-up Period – All Enrolled (*N = 53*)

aOther comorbidities reported in > 10% of patients included endocrine disorders (24.5%), musculoskeletal and connective tissue disorders, nervous system disorders (15.1% each), eye disorders, and skin and subcutaneous tissue disorders (11.3% each)

Abbreviations: Non-SSA = non-somatostatin analogue; SSA = somatostatin analogue

Source: Own data.

Supplementary Table 1. Summary of Comorbidities and symptoms at Baseline – All Enrolled (*N = 53*)

	All Enrolled (N = 53)		SSA Set* (N = 36)		NON-SSA Set (N = 17)	
Category, n (%) [1]	**No. of subjects with disease condition**	**Associated with acromegaly**	**No. of subjects with disease condition**	**Associated with acromegaly**	**No. of subjects with disease condition**	**Associated with acromegaly**
Skeletal	17(32.1)	16 (30.2)	10(27.8)	9 (25.0)	7 (41.2)	7 (41.2)
Arthropathy / Arthralgia	23(43.4)	22 (41.5)	10(27.8)	9 (25.0)	13(76.5)	13 (76.5)

	All Enrolled (N = 53)		SSA Set* (N = 36)		NON-SSA Set (N = 17)	
Category, n (%) [1]	**No. of subjects with disease condition**	**Associated with acromegaly**	**No. of subjects with disease condition**	**Associated with acromegaly**	**No. of subjects with disease condition**	**Associated with acromegaly**
Gastrointestinal	6 (11.3)	3 (5.7)	3 (8.3)	2 (5.6)	3 (17.6)	1 (5.9)
Colon polyps	7 (13.2)	3 (5.7)	3 (8.3)	2 (5.6)	4 (23.5)	1 (5.9)
Cardiovascular	28(52.8)	22 (41.5)	20(55.6)	17 (47.2)	8 (47.1)	5 (29.4)
Hypertension	26(49.1)	17 (32.1)	16(44.4)	12 (33.3)	10(58.8)	5 (29.4)
Myocardial hypertrophy	9 (17.0)	8 (15.1)	7 (19.4)	6 (16.7)	2 (11.8)	2 (11.8)
Other cardiovascular diseases	4 (7.5)	3 (5.7)	3 (8.3)	2 (5.6)	1 (5.9)	1 (5.9)
Endocrine and metabolic system	33(62.3)	27 (50.9)	22(61.1)	20 (55.6)	11(64.7)	7 (41.2)
Abnormalities of the menstrual cycle	6 (11.3)	5 (9.4)	4 (11.1)	3 (8.3)	2 (11.8)	2 (11.8)
Dyslipidemia	11(20.8)	8 (15.1)	6 (16.7)	5 (13.9)	5 (29.4)	3 (17.6)
Glucose metabolism abnormality	17(32.1)	13 (24.5)	8 (22.2)	7 (19.4)	9 (52.9)	6 (35.3)
Nodular thyroid disease	15(28.3)	8 (15.1)	6 (16.7)	4 (11.1)	9 (52.9)	4 (23.5)
Obesity	23(43.4)	20 (37.7)	11(30.6)	10 (27.8)	12(70.6)	10 (58.8)
Pulmonary system	8 (15.1)	7 (13.2)	5 (13.9)	4 (11.1)	3 (17.6)	3 (17.6)
Sleep apnea	10(18.9)	9 (17.0)	5 (13.9)	4 (11.1)	5 (29.4)	5 (29.4)
Neoplasia	1 (1.9)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy	1 (1.9)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)

Note: [1] Percentages were calculated using the column header as the denominator.
[1] Missing frequencies are represented as "0(0.0%)"

Source: Own data.

Use of medical resources

The overall percentage of visits to the physician was lower in the SSA cohort (24/38 – 63.2%) and controlled (4/10 – 40.0%) group than the non-SSA (11/15 – 73.3%) and non-controlled group (31/43 – 72.1%). Similarly, patients in the uncontrolled group reported a higher number of laboratory tests performed (40/49 patients), as well as a higher frequency of emergency room visits (4/5 patients) and hospitalizations (5/5 patients).

Discussion

This study presents the characteristics, associated comorbidities, and treatment patterns of patients with acromegaly in Colombia receiving medical therapy from 2005 to 2015. No previous real-world data have been reported in the country on the prevalence of acromegaly complications, treatment patterns, or disease control.

In the current study, the mean age at diagnosis and female predominance were in line with reports from other studies (1, 6, 17–19). Similarly, patients with higher BMI, overweight or obese with uncontrolled disease presented more frequently with acromegaly-associated comorbidities, especially cardiovascular, endocrine, and metabolic disorders. This observation supports the results from earlier studies highlighting the association of higher BMI with acromegaly-associated comorbidities (20, 21).

Overall, 52.8% of the enrolled patients had a history of pituitary surgery, which tended to be lower (66%) compared to a study conducted in Sweden (18). An earlier study reported that the cure of macroadenomas using surgical treatment is low (10–20% remission rate for invasive macroadenomas), resulting in an increase in GH levels (22). In this study, most tumor cases were reported as macroadenomas compared to microadenomas (38 vs. 12), like other study reports. In patients with macroadenomas vs. microadenoma tumors from the SSA and non-SSA cohorts, there was no significant difference in GH and IGF-1 levels at any point in time during the chart review.

In this study, patients with acromegaly had a high frequency of comorbidities (84.9%), and 27% of patients had more than three acromegaly-related comorbidities. Patients with controlled disease had lower comorbidities than those uncontrolled; this observation is also like other reports (18). The most common comorbidities associated with acromegaly in this study population were related to the endocrine and metabolic system, followed by those related to the cardiovascular system, which differs from previous studies where cardiovascular comorbidity was reported to be the most common (21, 23). Control of the disease has been associated with improvement in acromegaly comorbidities; therefore, strict control of GH and IGF-1 is mandatory and in line with the recommendations of the current clinical guideline (15).

Biochemical control (GH level < 2.5 µg/L and standardized IGF-1) was achieved in ten (18.9%) patients after 12 months of medical treatment. All patients were from the SSA cohort. During the subsequent three-year follow-up, the number of patients did not increase (4–8 patients), which could be explained by a lack of continuity in the follow-up and thereby a lower number of patients during the follow-up periods (52 patients in year 1 vs. 19 patients in year 4). A previous clinical trial (C2305 study) in patients with newly diagnosed acromegaly demonstrated that biochemical control was achieved in 31.3% patients receiving pasireotide long-acting release (LAR) and 19.2% of patients receiving octreotide LAR at 12 months (24). In the PAOLA study that compared a second-generation SSA (pasireotide) vs. octreotide LAR in patients with persistent uncontrolled acromegaly, ten (15%) patients in the pasireotide 40 mg group and 13 (20%) in the pasireotide 60 mg group achieved biochemical control, compared with no patients who continued octreotide/lanreotide at 24 weeks (25). In the current study, biochemical control was lower than in the C2305 and PAOLA global studies (24, 25). However, the interpretation must be made with caution due to the observational nature of this study; biochemical control was reported overall, for SSA or non-SSA cohorts rather than individual drugs.

In a study conducted on 554 patients with acromegaly in Germany, an increase in the percentage of patients with GH < 2.5 µg/L and normal IGF-1 levels was reported in the SSA cohort. However, there was no significant difference between short-acting octreotide (GH > 2.5 µg/L in 39.4% and IGF-1 normal in 30.4%) and octreotide LAR (GH > 2.5 µg/L in 32.0% and IGF-1 normal in 31.9%) (25). Similarly, in the present study, the proportion of patients with controlled GH and standardized IGF-1 levels, in combination and individually, was higher in the SSA cohort than in the non-SSA cohort.

SSAs were widely used as all patients were treated with first- or second-generation SSAs at any point during the observation period. DAs were used by eleven (16.9%) patients and GHRAs by one (1.8%), which tended to be lower than in the study in Sweden (20% and 10% patients, respectively). The most common first-line treatment was surgery (60%), followed by SSAs (21%) and DAs (14%) (18). Acromegaly treatment was used for an average of 2.8 years. Eight patients received treatment combinations of SSAs + DAs during the first year, lowering to four and three patients during years 2 and 3, respectively. These treatment patterns are in line with current clinical guidelines.

The mortality rate in patients with active acromegaly is 2–4 times higher than in the general population; as disease control improves, the mortality due to acromegaly and associated comorbidities decreases (27, 28). No death was reported in the present study compared with previous data presenting lower death rates in controlled acromegaly patients (1, 22), which could be associated with shorter follow-up timelines.

This study showed a higher frequency of medical services (physician visits, laboratory tests, and hospitalization) in patients with uncontrolled disease compared to those with controlled disease, which is in line with other economic studies where acromegaly management was approximately 1.6 times more expensive (29). Although healthcare costs were not calculated in the present study, we found that patients with controlled acromegaly had fewer physician visits and laboratory tests. Further, the incidence of hospitalization was reported in more than 10% of the population from the uncontrolled group.

Thus, optimizing disease control with proper drug treatment, for both the disease and associated comorbidities, in patients with acromegaly may improve clinical outcomes and decrease health check-up visits. This may reduce the direct and indirect costs of acromegaly treatment and potentially improve the effectiveness of acromegaly management.

The most common complications in our cohort were hypertension (49.1%), obesity (43.4%), and arthralgia (43.4%). In a large registry study from Mexico, hypertension was also a common comorbidity but in a lower percentage (27%). The difference in the percentage of complications may be due to a delayed diagnosis in our country (30). The percentage of complications is similar to a more extensive Colombian report (31), which is consistent with findings reported in the literature, where hypertension is the predominant comorbidity, with a prevalence of 11% to 54.4% (31). Obesity is also a common complication in patients with acromegaly; 43.4% of our patients were obese. The average BMI in the RAPACO study was 28.11, and 78.6% had overweight. The mechanisms of obesity in acromegaly may be related to decreases in ghrelin and leptin (31).

The study limitations include the retrospective nature of the data collection, which may restrict the accuracy and completeness of the data. A lack of continuity in patient follow-up was observed, significantly beyond three years. These factors made it difficult to assess long-term comorbidities and the use of resources. In Colombia, universal health coverage is provided; however, the healthcare system does not provide medical care in a single expert center, which may explain some of the loss to follow-up and the low mortality. In addition, patients with acromegaly in Colombia face many challenges, including a lack of pituitary expert centers and frequent changes in medical providers. As per the design and inclusion criteria, this study does not include acromegaly patients cured with surgery; however, it is the first to report acromegaly complications, treatment patterns, and disease control related to biochemical response in Colombia.

In conclusion, the study examined the real-world characteristics, comorbidities, and outcomes associated with treating patients with acromegaly in Colombia through clinical records from main referral endocrinology service centers. Results showed that IGF-1 and GH levels tended to decline over time, with more normalization observed in patients receiving SSAs as first-line medical therapy. However, proper patient follow-up and disease control levels could be improved, especially considering the broader availability of therapeutic alternatives recommended by clinical guidelines.

In this study, patients with controlled acromegaly were found to have a lower level of severe comorbidities and less utilization of health resource services; nevertheless, fragmentation of healthcare services can pose challenges to optimal treatment care with longer and continued follow-up and more efficient use of resources.

Abbreviations: BMI = body mass index; **CI =** confidence interval; **DA =** dopamine agonist; **GH =** growth hormone; **GHRA =** growth hormone receptor antagonist; **IGF-1 =** insulin-like growth factor-1; **LAR =** long-acting release; **SSA =** somatostatin analogue; **ULN =** upper limit of normal

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Conflicts of interest

Abreu A, Román-González A, Tovar H, Builes-Barrera C, Nessim E, and Rojas W have received clinical research site fees for data collection from Novartis Pharmaceuticals during the conduct of the study. Román-González A has also received speaker fees from Amgen, Novartis, Sanofi, and PTC Therapeutics outside the conduct of this study. Maestre K and Herrera D have received personal fees from Novartis during the study.

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