BMC Endocrine Disorders

RESEARCH

Open Access

Predictors of biochemical and structural response to medical therapy in patients with active acromegaly following surgery: a real-world perspective

Maryam Rafieemanesh[1†], Manizhe Ataee Kachuee[2†], Ali Zare Mehrjardi[3], Alireza Khajavi[4], Mohammad Ghorbani[5], Mohammad Reza Mohajeri-Tehrani[6], Nahid Hashemi-Madani[7*] and Mohammad E. Khamseh[7]

Abstract

Background Somatostatin receptor analogs (SRAs) and dopamine agonists (DAs) are the main medical treatments for patients with acromegaly who fail to achieve remission after surgery. We aimed to explore the potential role of select clinical, biochemical, and radiological factors in predicting biochemical and structural responses to medical therapy in a real-world setting.

Methods This retrospective cohort study included 58 patients with active acromegaly following surgery treated with Octreotide long-acting release (LAR) (± Cabergoline). Biochemical outcomes were defined as the tight biochemical response (TBR; normal insulin-like growth factor-1(IGF-1)) and biochemical control (BC; IGF-1 ≤ 1.2 upper limit of normal (ULN)). The structural response was defined as > 25% reduction in one dimension of the tumor at the last visit. Univariate and multivariate analyses assessed the predictors of biochemical and structural response.

Results The mean age of the participants was 41.5 ± 11.7 years. They were followed for a median of 27.6 (19.2–43.2) months. At the last visit, TBR and BC were achieved in 48.3% and 51.7% of the patients. Moreover, 51.4% of the patients showed a structural response. Applying the age-sex adjusted model, post-operative IGF-1 was inversely associated with TBR [OR 0.34, $P=0.006$] and BC [OR 0.30, $P=0.004$]. Moreover, Knosp grading < 3 compared to ≥ 3, and T2-hypointensity compared to the non-T2-hypointensity were associated with higher odds of TBR [OR 3.98, $P=0.04$], [OR 27.63, $P=0.01$], and BC [OR 5.80, $P=0.01$], [OR 35.15, $P=0.01$], respectively.

Conclusions Post-operative IGF-1, Knosp grading, and T2-hypointensity could be considered for an individualized treatment plan in acromegaly. Accordingly, we propose an individual multidisciplinary treatment approach for patients not achieving remission after surgery.

†Maryam Rafieemanesh and Manizhe Ataee Kachuee contributed equally to this work as co-first authors.

*Correspondence:
Nahid Hashemi-Madani
nahid.hashemimadani@gmail.com

Full list of author information is available at the end of the article

Keywords Acromegaly, Somatostatin receptor analogs, Dopamine agonists, Biochemical response, Structural response

Introduction

Acromegaly is a chronic disease mainly caused by growth hormone (GH) secreting pituitary adenoma [1]. In the absence of biochemical response, long-term exposure to inappropriately high levels of GH and insulin-like growth factor 1 (IGF-1) leads to a broad range of systemic complications, including metabolic impairment, as well as cardiovascular, respiratory, and osteoarticular disease [2, 3]. These complications ultimately lead to a reduced quality of life and increased mortality risk [2, 3].

Surgical resection of the pituitary adenoma is recommended as the first choice of treatment [4]. However, the long-term remission rate following surgery ranges between 60.0 and 82.2% depending on the tumor size and surgical technique [5]. Persistent disease after surgery is the main indication for using medical therapy in acromegaly [6]. First-generation long-acting release (LAR) somatostatin receptor analogs (SRAs) (i.e., Octreotide or Lanreotide) are recommended as the first-line medical therapy in these patients [4]. Cabergoline can also be used as the first line of medical therapy if IGF-1 is less than 2.5 times the upper limit of normal (ULN), or as the add-on therapy to SRA providing that IGF-1 is moderately elevated [4]. Moreover, somatostatin receptor ligands (i.e., Pasireotide) and GH-receptor antagonists (i.e., Pegvisomant) are recommended as the second line of medical therapy [4].

Considering the different options currently available for the treatment of acromegaly and the efforts toward precision medicine, it is important to identify patient characteristics that make a particular drug more appropriate to a particular individual. Several factors, related to both patient and tumor characteristics, have been proposed as predictors of response to SRAs and Cabergoline. These characteristics include age, gender, GH and IGF-I levels, adenoma signal intensity in MRI T2-weighted sequence, cytokeratin granulation pattern, and some biomarkers such as somatostatin receptor subtype 2 (SSTR-2) expressions [7, 8, 9, 10]. However, there is some diversity in the designs of these studies. Federica Nista et al. investigated predictors of response to the first- generation SRAs in a population of treatment naïve patients with acromegaly [11]; while another study prospectively evaluated the factors associated with response to medical therapy in patients who received first-or-second- generation of SRAs following an unsuccessful surgery [7]. Thus, we conducted this study to investigate predictors of biochemical and structural response in a population of Iranian people with acromegaly who have received medical therapy because of persistent disease after surgery.

Methods

Patients and study design

This retrospective cohort study was conducted among a population of Iranian people with acromegaly referred to a tertiary care center between 2017 and 2023. The study included all patients inadequately controlled after surgery and had received first-generation SRAs for at least six months. Persistent disease after surgery was defined as IGF-1 level more than the age-sex matched range and nadir GH more than 1 ng/ml. Patients who received radiotherapy and those with incomplete data were excluded from the study. The study was conducted in line with the recommendations of the Declaration of Helsinki (ethical code IR.IUMS.REC.1401.963). Written informed consent was obtained from all the patients to use the available data for research purposes.

Data collection

All required data were extracted from the electronic medical record system. These data included demographic data (age, sex, BMI), data regarding pituitary function (central hypogonadism, central hypothyroidism, and central hypocortisolism), and plasma levels of GH, IGF-1, and prolactin (PRL), the characteristics of magnetic resonance imaging (MRI), and histopathology data. Information regarding MRI and histopathology is detailed below. The serum level of IGF-1 was measured using the enzyme-linked immunosorbent assay (ELISA) (LDN, Nordhorn, Germany), Serum GH level was determined using an ELISA kit (Diazist, Tehran, Iran) based on the manufacturer's protocol, and serum level of PRL was determined by ELISA, using PRL ELISA kit (Pishtaz tab diagnostics-Iran). Duration of follow-up was considered from the initiation of medical therapy until the last visit or death.

Magnetic resonance imaging

In this tertiary care center, MRI is routinely performed within 3 to 6 months after surgery; and it is annually repeated after initiation of medial therapy. The images are done using a limited number of scanners and reviewed by one experienced radiologist (MAK). Maximum tumor size, tumor invasiveness based on the revised Knosp classification [12], and T1/T2-weighted signal intensity (T1/T2WSI) [13] are evaluated for all patients. Briefly, Knosp scores are as follows: grade 0; the adenoma does not encroach on the cavernous sinus (CS) space, grade 1; the tumor passes the medial tangent of the intra-cavernous and supra-cavernous internal carotid arteries (ICAs) but does not extend beyond the

inter-carotid line, grade 2; the tumor extends beyond the inter-carotid line but not passes the lateral tangent of the intra-cavernous and supra-cavernous ICAs. In grade 3 the tumor extends laterally to the lateral tangent of the intra-cavernous and supra-cavernous ICAs into the superior (3a) or inferior (3b) CS compartments, grade 4; there is the total encasement of the intra-cavernous carotid artery [12]. T1/T1WSI was evaluated qualitatively and classified as hypointense, isointense, hyperintense, and heterogeneous [13].

Histopathology and immunohistochemistry

In this tertiary care system, all histopathology results on pituitary tissues are reviewed by a single pathologist (AZM). Immunohistochemistry (IHC) staining for tumor type (GH or GH-PRL) and adenoma granularity pattern are reported for all patients who underwent surgery in our hospital. According to the cytokeratin IHC distribution pattern, adenomas are categorized into densely granulated (perinuclear pattern) and sparsely granulated adenomas (para-nuclear pattern) [14]. However, IHC studies were unavailable for patients who underwent surgery at another hospital.

Table 1 Baseline clinical, biochemical, and radiological characteristics of the participants

Variable	Value
Sex (*n*, %; female)	40/58 (69.0%)
Age (mean, SD; year)	41.5 (± 11.7)
BMI (mean, SD; Kg/m^2)	27.3 (± 4.8)
IGF-1 (median, IQR; ng/ml)	798 (595–945)
IGF-1× ULN (median, IQR; times ULN)	2.9 (2.1–3.5)
GH (median, IQR; ng/ml)	16.1 (5.8–40)
Prolactin (median, IQR; ng/ml) *	15.4 (7.2–39.9)
Maximum tumor diameter (median, IQR; mm)	20 (16–28)
Macroadenoma (*n*, %)	50/53 (94.3%)
Knosp grading (*n*, %)	
0	1/52 (1.9%)
1	7 /52 (13.5%)
2	13/52 (25.0%)
3	19/52 (36.5%)
4	12/52 (23.1%)
T1-weighted MRI signal (*n*, %)	
Isointense	37/50 (74.0%)
Hypointense	12/50 (24.0%)
Hyperintense	1/50 (2.0%)
T2-weighted MRI signal (*n*, %)	
Isointense	21/50 (42.0%)
Hypointense	9/50 (18.0%)
Hyperintense	15/50 (30.0%)
Heterogeneous	2/50 (4.0%)
Mixed	3/50 (6.0%)
Central Hypogonadism (*n*, %)	32/50 (62.8%)
ACTH deficiency (*n*, %)	28/50 (58.3%)
Central hypothyroidism (*n*, %)	5/50 (10.2%)
Panhypopituitarism (*n*, %)	22/50 (44.9%)

Categorical variables are expressed as number (*n*) and percentage (%) and continuous variables are expressed as median and IQR. BMI, Body Mass Index; IGF-1, Insulin-like Growth Factor 1; ULN, upper limit of normality range, Growth Hormone; ACTH, Adrenocorticotropic hormone; TSH, Thyroid Stimulating Hormone. *Prolactin less than 20 ng/ml in men and less than 25 ng/ml in women are considered as normal values

Outcomes

Tight biochemical response (TBR) was defined as "normal age-sex matched IGF-1 level", and biochemical control (BC) as "age-sex matched IGF-1 value ≤ 1.2 ULN" [4]. Structural response was defined as "more than 25% reduction in a single tumor dimension" at the last visit compared to the imaging at the time of initiation of medical therapy. Moreover, complete response considered if more than 25% reduction in a single tumor dimension occurred and the last IGF-1 was within the normal age-sex-matched range.

Statistical analysis

The continuous variables were described as mean ± standard deviation (SD) or median (interquartile range (IQR)), depending on being normally distributed or not. The inferential tools of t-test and Mann-Whitney were utilized in these two scenarios. The normality was assessed using the Kolmogorov-Smirnov test. The discrete variables were expressed as numbers (percentages), and the Chi-squared test was applied. Considering the binary nature of the response variables, logistic regression models were fitted to them, which led to reporting odds ratios (ORs) as measures of association. The analyses were performed using Stata ver. 13. The significance level was set at 0.05.

Results

Patients and tumor characteristics

Table 1 demonstrates the characteristics of patients and tumors before surgery. A total of 58 patients (40 females (69.0%)) were included in this study. The mean age of the participants was 41.5 ± 11.7 years. The mean body mass index (BMI) was 27.3 ± 4.8 kg/m^2. The median IGF-1 level was 798 (595–945) ng/ml. The median GH level was 16.1 (5.8–40) ng/ml. Median maximum tumor diameter was 20 [16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28] mm. Macro-adenoma was found in 50 (94.3%) patients. Regarding the Knosp classification, 36.5% ($n = 19$) of tumors were classified as grade 3, followed by 25.0% ($n = 13$), 23.1% ($n = 12$), 13.5% ($n = 7$), and 1.9% ($n = 1$) classified as grade 2, 4, 1, and 0, respectively. T1-WSI showed isointensity in 74.0% ($n = 37$), hypointensity in 24.0% (n-12), and hyperintensity in 2.0% ($n = 1$). T2-WSI was isointense in 42.0% ($n = 21$), hyperintense in 30.0%($n = 15$), hypointense in 18.0% ($n = 9$), mixed in 6.0%, and heterogeneous in 4.0% ($n = 2$).

Table 2 indicates the characteristics of patients and tumors three months after surgery, before initiation

of medical therapy. The median IGF-1 level was 514 (345–703) ng/ml. Median GH level was 3.5 (1.8–6.2) ng/ml. The median maximum tumor diameter was 8.5 (3.3–12.0) mm. Macro-adenoma was found in 49.1% ($n=26$) patients. Results of tumor histopathology indicated positive GH staining in 78.1% ($n=32$) and positive mixed GH-PRL staining in 21.9% ($n=9$) of the tumors. The granulation pattern showed a sparse pattern in 51.6% ($n=16$) and a dense pattern in 48.4% ($n=15$) of the tumors.

Biochemical and structural response

TBR (normal IGF-1) was found in 31.8% of patients within 12 months of treatment and in 48.3% of them at the last follow-up visit. BC (IGF-1 ≤ 1.2 ULN) was identified in 38.6% of patients within 12 months of treatment and in 51.7% of them at the last follow-up visit (Fig. 1). The percentage of patients who achieved BC at the last visit was equal in the group that received Octreotide LAR alone and that received Cabergoline as an add-on therapy to the Octreotide LAR. Moreover, 51.4% of patients achieved more than a 25% reduction in tumor size at the last visit, while 29.7% fulfilled the criteria of complete response to medical therapy.

Potential predictors of biochemical and structural response

All patients included in this study received the first-generation SRA (Octreotide LAR) due to persistent disease after surgery. 50% of them received Cabergoline as add-on-therapy. The initial dose of Octreotide LAR was 20 mg every 28 days; it was up-titrated every 3 months to the maximum dose of 40 mg every 28 days. The majority of patients (86.2%) received 30 mg monthly. The initial dose

Table 2 Characteristics of the participants at 3 months' post-operation

Variable	Values
IGF-1 (median, IQR; ng/ml)	514 (345–703)
IGF-1× ULN (median, IQR; ng/ml)	1.9 (1.40–2.50)
GH (median, IQR; ng/ml)	3.5 (1.8–6.2)
PRL (median, IQR; ng/ml) *	8.5 (3.9–24.0)
Maximum tumor diameter (median, IQR; mm)	8.5 (3.3–12.0)
Macroadenoma (*n*, %)	26/53 (49.1%)
Granulation pattern (*n*, %)	
Densely granulated	15/31 (48.4%)
Sparsely granulated	16/31 (51.6%)
IHC results (*n*, %)	
GH	32/41 (78.1%)
GH + PRL	9/41 (21.9%)
Central Hypogonadism (*n*, %)	26/57 (45.6%)
ACTH deficiency (*n*, %)	24/58 (41.4%)
Central hypothyroidism (*n*, %)	28/58 (48.3%)
Panhypopituitarism (*n*, %)	23/57 (40.4%)

Categorical variables are expressed as number (*n*) and percentage (%) and continuous variables are expressed as median and IQR. BMI, Body Mass Index; IGF-1, Insulin-like Growth Factor 1; ULN, upper limit of normality range; GH, Growth Hormone; IHC, Immunohistochemistry staining pattern; GH + PRL, mixed growth hormone-prolactin; ACTH, Adrenocorticotropic hormone; TSH, Thyroid Stimulating Hormone. *Prolactin less than 20 ng/ml in men and less than 25 ng/ml in women are considered as normal values

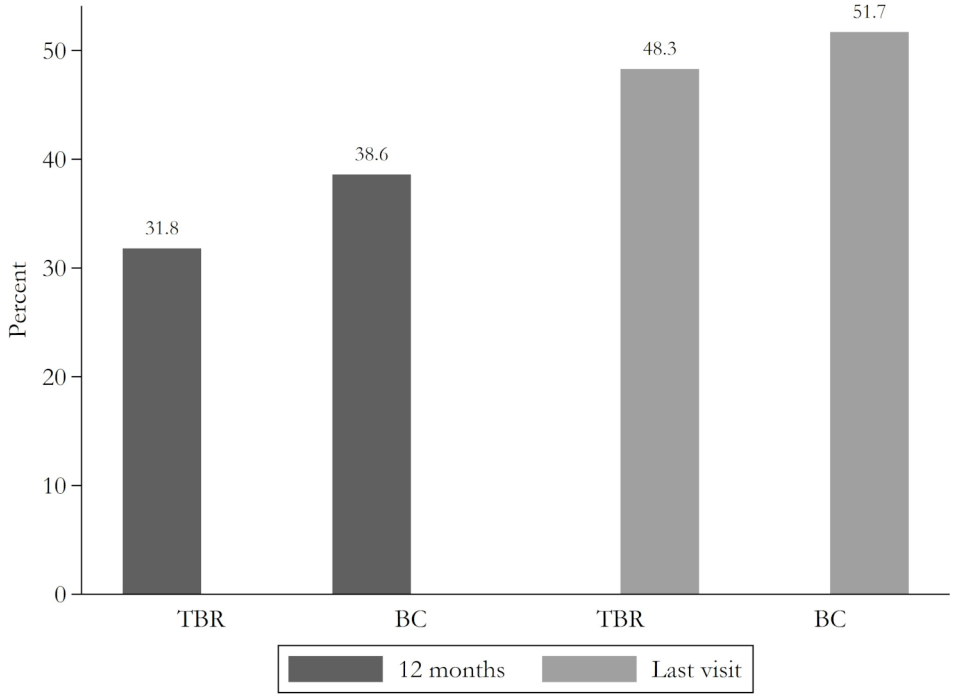

Fig. 1 Biochemical response at 12 months after initiation of medical therapy and the last visit, compared to the IGF-1 values before initiation of SRA. TBR, Tight biochemical response; BC, Biochemical control; SRA, somatostatin receptor agonists

of Cabergoline was 2 mg weekly and it was increased by 1 mg weekly every month to the maximum dose of 5 mg weekly. 42.8% of patients received 3 mg weekly. The patients were followed for a median of 27.6 (19.2–43.2) months.

Characteristics of the patients based on biochemical control defined as normal age-sex matched IGF-1 are presented in Supplementary Table 1. The results indicated that compared to the patients who did not reach biochemical control, those who achieved biochemical control had lower pre-medication IGF-1 (1.6 ULN vs. 2.4 ULN, $p=0.001$) and were more likely to present with T2-hypointensity in MRI imaging (29.6% vs. 4.4%, $p=0.03$) and their tumors were less likely to be classified as grade 3 or more (44.8% vs. 78.3%, $p=0.02$). Logistic regression analyzed the factors associated with biochemical and structural response to medical therapy at the last follow-up visit. Applying the age-sex adjusted model, pre-medication IGF-1 was inversely associated with TBR [OR 0.34 (95% CI 0.16, 0.74), $P=0.006$] and BC [OR 0.30 (95% CI 0.13, 0.69), $P=0.004$]. Moreover, the age-sex adjusted model indicated Knosp grading < 3 comparing with ≥ 3 was associated with higher odds of TBR [OR 3.98 (95% CI 1.10, 14.43), $P=0.04$] and BC [OR 5.80 (95% CI 1.44, 23.41), $P=0.01$]. T2-hypointensity compared to the non-T2-hypointensity was associated with higher odds of TBR [OR 27.63 (95% CI 2.07, 369.09), $P=0.01$] and BC [OR 35.15 (95% CI 2.32, 532.47), $P=0.01$]. However, pre-operative tumor size and granulation pattern did not show any association with the biochemical response. Moreover, none of the biochemical, radiological, or histopathological factors were associated with structural and completed response except for post-operative IGF-1 value that was inversely associated with complete response [OR 0.18(95% CI 0.04, 0.77), $P=0.02$] (Table 3).

Considering the fact that Pegvisomant and the Pasireotide LAR are not available in all countries, we suggest an individualized multidisciplinary treatment approach for the management of acromegaly in such special areas. If post-operative IGF-1 is ≤ 1.2 ULN and the patient is clinically asymptomatic, monitoring of IGF-1 is recommended. If post-operative IGF-1 is < 2 ULN Cabergoline could be a good choice. In the cases with post-operative IGF-1 ≥ 2 ULN first generation of SRAs is recommended. Moreover, in patients on medical treatment, if IGF-1 is

Table 3 Logistic regression analysis to predict factors associated with biochemical and structural response to medical therapy at last visit

Variable	**Univariate -Tight Biochemical Response, OR (95%CI)**	***P*-value**	**Multivariate -Tight Biochemical Response, OR (95%CI)**	***P*-value**
Post-operative IGF-1 (fold ULN), median (IQR)	0.34 (0.16, 0.73)	0.005	0.34 (0.16, 0.74)	0.006
Knosp (< 3 vs. ≥ 3)	3.46 (1.06, 11.33)	0.04	3.98 (1.10, 14.43)	0.04
T1-Hypointensity	2.22 (0.57, 8.65)	0.25	2.08 (0.52, 8.31)	0.30
T2-Hypointensity	10.22 (1.17, 89.39)	0.04	27.63 (2.07, 369.09)	0.01
Granulation (SG vs. DG)	6.00 (1.26, 28.55)	0.02	4.21 (0.79, 22.53)	0.09
Variable	**Univariate-Biochemical control, OR (95%CI)**	***P*-value**	**Multivariate-Biochemical control, OR (95%CI)**	***P*-value**
Post-operative IGF-1 (fold ULN), median (IQR)	0.31 (0.14, 0.67)	0.003	0.30 (0.13, 0.69)	0.004
Knosp (< 3 vs. ≥ 3)	4.43 (1.29, 15.19)	0.02	5.80 (1.44, 23.41)	0.01
T1-Hypointensity	2.00 (0.51, 7.78)	0.32	1.84 (0.46, 7.42)	0.39
T2-Hypointensity	9.26 (1.06, 80.93)	0.04	35.15 (2.32, 532.47)	0.01
Granulation (SG vs. DG)	4.50 (0.97, 20.83)	0.05	2.66 (0.48, 14.74)	0.26
	Univariate-structural response, OR (95%CI)	***P*-value**	**Multivariate-Structural response, OR (95%CI)**	***P*-value**
Post-operative IGF-1 (fold ULN), median (IQR)	0.75 (0.31, 1.83)	0.53	0.74 (0.29, 1.90)	0.53
Knosp (< 3 vs. ≥ 3)	0.92 (0.23, 3.66)	0.91	1.10 (0.26, 4.62)	0.90
T1-Hypointensity	0.87 (0.18, 4.18)	0.86	0.96 (0.19, 4.83)	0.96
T2-Hypointensity	0.42 (0.03, 5.06)	0.49	0.33 (0.02, 5.75)	0.50
Granulation (SG vs. DG)	1.39 (0.22, 8.92)	0.73	1.75 (0.23, 13.38)	0.59
	Univariate-Complete response, OR (95%CI)	***P*-value**	**Multivariate-Complete response, OR (95%CI)**	***P*-value**
Post-operative IGF-1 (fold ULN), median (IQR)	0.21 (0.05, 0.79)	0.02	0.18 (0.04, 0.77)	0.02
Knosp grade (< 3 vs. ≥ 3)	1.29 (0.29, 5.67)	0.74	1.37 (0.30, 6.31)	0.69
T1-Hypointensity	1.50 (0.29, 7.81)	0.60	1.52 (0.28, 8.25)	0.63
T2-Hypointensity	1.15 (0.09, 14.19)	0.91	2.46 (0.14, 43.98)	0.54
Granulation (SG vs. DG)	4.00 (0.35, 45.38)	0.26	3.79 (0.30, 47.97)	0.30

IGF-1, Insulin-like Growth Factor 1; ULN, upper limit of normality range; GH, Growth Hormone; IHC, Immunohistochemistry staining pattern; OR, odds ratio; 95%CI, 95% confidence interval. *p*-value ≤ 0.05 values are statistically significant. Data are adjusted for age and sex

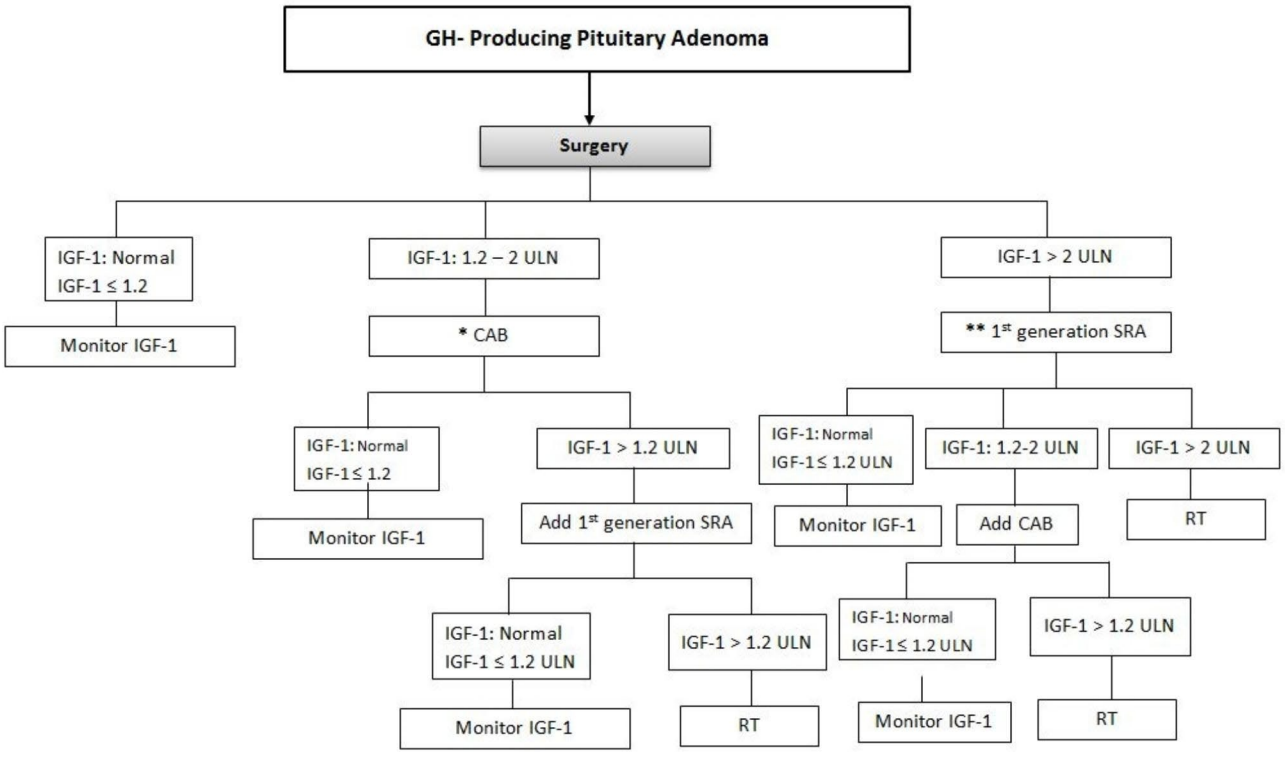

Fig. 2 Algorithm for the Multidisciplinary Management of Acromegaly. IGF-1; insulin-like growth factor-1, ULN; upper limit of normal, CAB; cabergoline, SRA; somatostatin receptor agonists. *Cabergoline dose: 3–5 mg/week, **1st generation SRA dose: 20–40 mg every 28 days

≤ 1.2 ULN and the patient is clinically asymptomatic, no further intervention is required (Fig. 2).

Discussion

In this study, we investigated select clinical, biochemical, histopathological, and radiological factors associated with biochemical and structural response to Octreotide LAR (± Cabergoline) in a population of Iranian people with acromegaly who suffered from persistent disease after surgery. The results demonstrated in a real-life setting where the first-generation SRAs and Cabergoline are the sole available medications for acromegaly, postoperative IGF-1 level, T2-WSI in MRI imaging, and Knosp grading are determinants of biochemical response to medical therapy. However, none of the investigated factors could predict the structural response to these medications.

During the follow-up period of 27.6 (19.2–43.2) months, 48.35% of patients who received medical therapy with Octreotide LAR (± Cabergoline) achieved TBR (normal age-sex matched IGF-1), and 51.7% of them achieved BC (IGF-1 ≤ 1.2 ULN). Previous studies indicated 30–55% of patients with acromegaly achieve normal IGF-1 using SRAs [15]. A recent meta-analysis of 90 cohorts of patients with acromegaly received SRAs indicated a response rate of 55% for IGF-1 normalization [16]. However, there was a wide range of variations among the included studies [16]. A very recent study that provided details of medical treatment from nine international centers indicated that 75.8% of patients receiving either Octreotide or Lanreotide as monotherapy were controlled. The difference in the patients' characteristics might be a reason for the discrepancy in the response rate. Moreover, they included patients who used either Octreotide or Lanreotide while all our participants received Octreotide LAR as the first generation of SRAs [17].

Another meta-analysis of 5 studies showed Cabergoline as an add-on-therapy to SRA-normalized IGF-1 in 52% of patients [18]. Differently from the previous studies, we investigated biochemical response after a period of medical therapy with Octreotide LAR alone or combined with Cabergoline. We focused on IGF-1 because the most recent consensuses recommend the normalization of IGF-1 as it is known as the best reflection of disease control [4, 19]. Other than the normalization of IGF-1 (TBR), we investigated biochemical control defined as IGF-1 ≤ 1.2 ULN. Previous studies showed in patients not controlled by standard doses of Octreotide LAR, higher doses (60 mg every 28 days) can improve the biochemical control rate [20]. However, the study of this cohort indicated the standard dose of Octreotide LAR (30–40 mg every 28 days) combined with Cabergoline (3–5 mg weekly) can result in a comparable response rate. This

approach could be applied as a cost-benefit alternative, especially in regions with limited access to SRAs.

We found that T2-hypointensity and lower Knosp grading in MRI imaging is associated with a higher rate of TBR and BC. Several studies have recently investigated the association of pituitary MRI characteristics with the response to SRAs. Higher knosp classification and tumor invasiveness are well-known predictors of resistant tumors [21]. Moreover, some studies, including ours, indicated that T2-hypointense lesions are associated with a better biochemical response to SRAs [11, 22, 23]. However, these studies simply compared the difference in the percentage of IGF-1 reduction between patients with T2-hypointense and T2-non-hypointense lesions [11, 22, 23, 24]. Moreover, most of them investigated the association of T2-WSI and response to SRAs in patients followed for a maximum duration of 12 months [11, 22, 23]. We conducted the study in a "real world" setting with a relatively long duration of follow-up. As we did in our study, Domingo et al. included patients who had active disease after surgery [24]. Similarly, they found patients with T2-hypointense lesions were more likely to achieve normal IGF-1 levels at 6 and 12 months after treatment with SRAs [24].

Furthermore, some studies indicated that T2-hypointens lesions in MRI imaging are more likely to be densely granulated [10]. On the other hand, densely granulated adenomas have been reported as a good predictor of response to SRAs [7, 25]. However, we could not find any association between granulation patterns in IHC staining and response to medical therapy. This might be due to the lack of IHC results in about 50% of patients included in this analysis. Previous studies reported a higher expression of the SSTR-2 in densely granulated adenomas [25, 26]. These findings suggested that a better response to SRAs might be, to some extent, based on differences in SSTR expression. Many studies investigated histological markers of response to medical treatment in acromegaly, concluded SSTR-2, but not SSTR-5, dopamine receptor subtype 5 (DR-5), but not DR-1, KI67%<3%, low beta-arrestin expression, and E-cadherin level are associated with a better response to medical treatment [27, 28, 29, 30, 31].

Some clinical and biochemical factors have also been reported as predictors of response to medical treatment. Some studies indicated younger age at the diagnosis and higher baseline GH/IGF-1 levels have been associated with a lower rate of response to medical therapy [32, 33]. While some others demonstrated higher IGF-1 levels at baseline are associated with a better response to medical therapy [11, 34]. We found post-operative IGF-1 level is inversely associated with biochemical response to the medical therapy. However, we found no association between age or other clinical characteristics and biochemical response to the medications. These controversies might be explained by various definitions applied to biochemical response. Moreover, post-operative IGF-1 level, reflecting the size of residual tumor, might be a better determinant of response to medical therapy after surgery, rather than baseline IGF-1 level. Additionally, several molecular predictors and signaling pathway disruption are identified to play an important role in the response to SRAs [35]. For example, higher KI-67 index, lower immunoreactivity of Zac1 (a tumor suppressor gene), and higher B-arrestin expression are found to be associated with resistance to SRAs [36, 37, 38]. Furthermore, a more recent study, applying machine learning models, indicated the usefulness of several predictive factors specifically low GH nadir in the acute Octreotide test, T2 MRI hypointensity, SSTR2, and E-cadherin expression, as well as a densely granulated pattern [39].

In addition to biochemical response, tumor size reduction is considered an important criterion of response to medical therapy. In standard clinical practice, a reduction of 20–25% in a single tumor dimension is considered a significant change in response to SRAs [4]. In this study, clinically significant tumor size reduction occurred in 51.4% of patients. A recent meta-analysis of studies assessed the effect of Octreotide on tumor shrinkage reported structural response in 53.0% of patients while the response increased to 66.0% when restricted to the patients who received Octreotide LAR [40]. However, the included studies reported any size reduction, as the response to medical therapy, while we strictly and quantitatively defined the structural response to medical therapy. Moreover, some studies evaluated predictors of structural response to medical therapy indicated T2-hypointensity in MRI imaging is associated with a greater reduction in tumor size [22, 23]. We found no association between clinical, biochemical, or radiological factors and structural response to medical therapy. However, the comparison of studies that investigated tumor shrinkage and the associated factors is challenging, since there is heterogeneity in techniques applied for tumor measurements, duration of follow-up, and type of treatment (primary or adjuvant therapy) [41].

This study was conducted in a real-world setting with a long duration of follow-up. Another strength of this study is the evaluation of different potential predictors of response to medical therapy including clinical, biochemical, and radiological factors. Moreover, biochemical, structural, and complete remission were precisely defined and evaluated. Another strength of our study is that all the images were reported by a single experienced radiologist. However, the retrospective design of this study and the lack of availability of some data such as the pattern of granulation in pathology results are the main limitations of this study.

Conclusion

In conclusion, we found lower Knosp grading and T2-hypointensity at MRI imaging as well as post-operative IGF-1 levels are robust predictors of biochemical response (namely normal IGF-1 and IGF-1 ≤ 1.2 ULN) to medical therapy after an unsuccessful surgery. Moreover, post-operative IGF-1 level could be considered as a predictor of complete response to medical therapy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01856-w.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
MR, MAK, MEK, and NHM: Conceptualization, methodology, writing-original draft. AK: formal analysis. AZM, MG, and MRMT: Investigation (diagnosis, inclusion, follow-up), data collection and curation, project administration. All authors contributed to the article and approved the submitted version.

Funding
No fund was received.

Data availability
Data will be available upon request.

Declarations

Ethics approval and consent to participate
The study was conducted in line with the recommendations of the Declaration of Helsinki and written informed consent was obtained from all the patients for using the available data for research purposes. The ethics committee of the Iran University of Medical Sciences approved the study (ethical code IR.IUMS.REC.1401.963).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Author details
[1]Endocrine Research Center, Institute of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Radiology, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran
[3]Department of Pathology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[4]School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Division of Vascular and Endovascular Neurosurgery, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[6]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[7]Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Vali-e-Asr Square, Behafarin Street, P.O. box: 1593747811, Tehran, Iran

Received: 15 September 2024 / Accepted: 23 January 2025
Published online: 03 February 2025

References

1. Colao A, Grasso LF, Giustina A, Melmed S, Chanson P, Pereira AM, et al. Acromegaly Nat Reviews Disease Primers. 2019;5(1):20.
2. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BM, Boguszewski C, et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. J Clin Endocrinol Metabolism. 2020;105(4):e937–46.
3. Gadelha MR, Kasuki L, Lim DS, Fleseriu M. Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr Rev. 2019;40(1):268–332.
4. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JA, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Reviews Endocrinol. 2018;14(9):552–61.
5. Chen C-J, Ironside N, Pomeraniec IJ, Chivukula S, Buell TJ, Ding D, et al. Microsurgical versus endoscopic transsphenoidal resection for acromegaly: a systematic review of outcomes and complications. Acta Neurochir. 2017;159:2193–207.
6. Fleseriu M, Biller BM, Freda PU, Gadelha MR, Giustina A, Katznelson L, et al. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2021;24:1–13.
7. Ilie MD, Tabarin A, Vasiljevic A, Bonneville JF, Moreau-Grangé L, Schillo F, et al. Predictive Factors of Somatostatin Receptor Ligand response in Acromegaly-A prospective study. J Clin Endocrinol Metab. 2022;107(11):2982–91.
8. Colao A, Auriemma RS, Lombardi G, Pivonello R. Resistance to somatostatin analogs in acromegaly. Endocr Rev. 2011;32(2):247–71.
9. Kasuki L, Dalmolin MD, Wildemberg LE, Gadelha MR. Treatment escape reduces the effectiveness of cabergoline during long-term treatment of acromegaly in monotherapy or in association with first-generation somatostatin receptor ligands. Clin Endocrinol. 2018;88(6):889–95.
10. Liu C-X, Wang S-Z, Heng L-J, Han Y, Ma Y-H, Yan L-F, et al. Predicting subtype of growth hormone pituitary adenoma based on magnetic resonance imaging characteristics. J Comput Assist Tomogr. 2022;46(1):124–30.
11. Nista F, Corica G, Castelletti L, Campana C, Zoppoli G, Ferone D, et al. Clinical and radiological predictors of biochemical response to first-line treatment with somatostatin receptor ligands in acromegaly: a real-life perspective. Front Endocrinol. 2021;12:677919.
12. Micko AS, Wöhrer A, Wolfsberger S, Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. J Neurosurg. 2015;122(4):803–11.
13. Potorac I, Petrossians P, Daly AF, Schillo F, Ben Slama C, Nagi S, et al. Pituitary MRI characteristics in 297 acromegaly patients based on T2-weighted sequences. Endocr Relat Cancer. 2015;22(2):169–77.
14. Obari A, Sano T, Ohyama K, Kudo E, Qian ZR, Yoneda A, et al. Clinicopathological features of growth hormone-producing pituitary adenomas: difference among various types defined by cytokeratin distribution pattern including a transitional form. Endocr Pathol. 2008;19:82–91.
15. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, et al. Multidisciplinary management of acromegaly: a consensus. Reviews Endocr Metabolic Disorders. 2020;21(4):667–78.
16. Carmichael JD, Bonert VS, Nuño M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. J Clin Endocrinol Metab. 2014;99(5):1825–33.
17. Giustina A, Uygur MM, Frara S, Barkan A, Biermasz NR, Chanson P, et al. Standards of care for medical management of acromegaly in pituitary tumor centers of excellence (PTCOE). Pituitary. 2024;27(4):381–8.
18. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327–35.
19. Giustina A, Biermasz N, Casanueva FF, Fleseriu M, Mortini P, Strasburger C, et al. Consensus on criteria for acromegaly diagnosis and remission. Pituitary. 2024;27(1):7–22.
20. Giustina A, Bonadonna S, Bugari G, Colao A, Cozzi R, Cannavo S, et al. High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial. Eur J Endocrinol. 2009;161(2):331–8.
21. Bioletto F, Berton AM, Prencipe N, Varaldo E, Bona C, Grottoli S. Markers of aggressiveness in Pituitary tumors: Update and perspectives. J Clin Med. 2022;11:21.

22. Tortora F, Negro A, Grasso LFS, Colao A, Pivonello R, Splendiani A, et al. Pituitary magnetic resonance imaging predictive role in the therapeutic response of growth hormone-secreting pituitary adenomas. Gland Surg. 2019;8(Suppl 3):S150–8.
23. Potorac I, Petrossians P, Daly AF, Alexopoulou O, Borot S, Sahnoun-Fathallah M, et al. T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. Endocrine-related Cancer. 2016;23(11):871–81.
24. Puig-Domingo M, Resmini E, Gomez-Anson B, Nicolau J, Mora M, Palomera E, et al. Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. J Clin Endocrinol Metabolism. 2010;95(11):4973–8.
25. Brzana J, Yedinak CG, Gultekin SH, Delashaw JB, Fleseriu M. Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: a large single center experience. Pituitary. 2013;16:490–8.
26. Kato M, Inoshita N, Sugiyama T, Tani Y, Shichiri M, Sano T, et al. Differential expression of genes related to drug responsiveness between sparsely and densely granulated somatotroph adenomas. Endocr J. 2012;59(3):221–8.
27. Liu W, Xie L, He M, Shen M, Zhu J, Yang Y et al. Expression of somatostatin receptor 2 in somatotropinoma correlated with the short-term efficacy of somatostatin analogues. International journal of endocrinology. 2017;2017.
28. Neto LV, Machado EO, Luque RM, Taboada GF, Marcondes JB, Chimelli LM, et al. Expression analysis of dopamine receptor subtypes in normal human pituitaries, nonfunctioning pituitary adenomas and somatotropinomas, and the association between dopamine and somatostatin receptors with clinical response to octreotide-LAR in acromegaly. J Clin Endocrinol Metabolism. 2009;94(6):1931–7.
29. Fernandez-Rodriguez E, Casanueva F, Bernabeu I. Update on prognostic factors in acromegaly: is a risk score possible? Pituitary. 2015;18:431–40.
30. Gatto F, Biermasz NR, Feelders RA, Kros JM, Dogan F, van der Lely A-J, et al. Low beta-arrestin expression correlates with the responsiveness to long-term somatostatin analog treatment in acromegaly. Eur J Endocrinol. 2016;174(5):651–62.
31. Fougner SL, Lekva T, Borota OC, Hald JK, Bollerslev J, Berg JP. The expression of E-cadherin in somatotroph pituitary adenomas is related to tumor size, invasiveness, and somatostatin analog response. J Clin Endocrinol Metabolism. 2010;95(5):2334–42.
32. Van der Lely A, Harrls A, Lamberts S. The sensitivity of growth hormone secretion to medical treatment in acromegalic patients: influence of age and sex. Clin Endocrinol. 1992;37(2):181–5.
33. Bhayana S, Booth GL, Asa SL, Kovacs K, Ezzat S. The implication of somatotroph adenoma phenotype to somatostatin analog responsiveness in acromegaly. J Clin Endocrinol Metabolism. 2005;90(11):6290–5.
34. Coopmans EC, Korevaar TI, van Meyel SW, Daly AF, Chanson P, Brue T, et al. Multivariable prediction model for biochemical response to first-generation somatostatin receptor ligands in acromegaly. J Clin Endocrinol Metabolism. 2020;105(9):2964–74.
35. Cuevas-Ramos D, Fleseriu M. Somatostatin receptor ligands and resistance to treatment in pituitary adenomas. J Mol Endocrinol. 2014;52(3):R223–40.
36. Theodoropoulou M, Stalla GK, Spengler D. ZAC1 target genes and pituitary tumorigenesis. Mol Cell Endocrinol. 2010;326(1–2):60–5.
37. Gatto F, Feelders R, van der Pas R, Kros JM, Dogan F, van Koetsveld PM, et al. β-Arrestin 1 and 2 and G protein-coupled receptor kinase 2 expression in pituitary adenomas: role in the regulation of response to somatostatin analogue treatment in patients with acromegaly. Endocrinology. 2013;154(12):4715–25.
38. Florio T. Molecular mechanisms of the antiproliferative activity of somatostatin receptors (SSTRs) in neuroendocrine tumors. Front Biosci. 2008;13(1):822–40.
39. Marques-Pamies M, Gil J, Jordà M, Puig-Domingo M. Predictors of response to treatment with first-generation somatostatin receptor ligands in patients with acromegaly. Arch Med Res. 2023;54(8):102924.
40. Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. PLoS ONE. 2012;7(5):e36411.
41. Buchfelder M, Schlaffer S, Droste M, Mann K, Saller B, Brübach K, et al. The German ACROSTUDY: past and present. Eur J Endocrinol. 2009;161(Suppl 1):S3–10.

Publisher's note