Efficacy and adverse events of octreotide long-acting release in acromegaly: a real-world retrospective study

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Background: Octreotide long-acting release (LAR) is a common drug used for acromegaly that aims to normalize serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1). However, only a few studies have evaluated its efficacy and safety in Chinese patients. This retrospective study aimed to assess its efficacy and safety in a cohort of Chinese patients with acromegaly.

Methods: A total of 163 patients with acromegaly, who received continuous and regular octreotide LAR treatment at least three times at Peking Union Medical College Hospital between 2010 and 2020, were enrolled. Clinical characteristics, acromegaly activity, and other laboratory tests before and after treatment were collected for analysis.

Results: The study enrolled 163 patients, including 71 men (43.6%) with a mean age of 40.94±13.00 years. After octreotide LAR treatment, 34.4% of the patients achieved GH control (<2.5 ng/mL), while IGF-1 levels were normalized in 23.3% of the patients. Also, fasting GH levels were downregulated from 4.95 ng/mL [interquartile range (IQR) 2.225, 10.325 ng/mL] at baseline to 3.2 ng/mL (IQR 1.5, 6.6 ng/mL) (P<0.001), and IGF-1/upper limit of the normal (ULN) declined from 1.89 (IQR 1.22, 2.40) to 1.41 (IQR 0.97, 1.89) (P<0.001). In addition, 65 patients experienced moderate adverse events. During the follow-up, none of the patients discontinued octreotide LAR. Further logistic regression showed that comorbidity [odds ratio (OR), 3.19; 95% confidence interval (CI): 1.20–9.27; P=0.025] and previous surgery only (OR, 0.21; 95% CI: 0.08–0.58; P=0.003) were two risk factors for the development of adverse events.

Conclusions: Our findings revealed that octreotide LAR treatment is effective in normalizing GH and IGF-1 levels in Chinese patients with acromegaly. In addition, adverse events related to octreotide LAR use were moderate and well tolerated by the patients.

Keywords: Acromegaly; octreotide LAR treatment; retrospective study; adverse events

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Introduction

Acromegaly is a chronic progressive disease characterized by excessive secretion of growth hormone (GH). The GH hypersecretion leads to subsequent high circulating level of insulin-like growth factor-1 (IGF-1), which results in somatic overgrowth, physical disfigurement and multisystem complications, particularly cardiovascular disease and metabolic disorders (1). Treatments of acromegaly involve surgery, pharmacological therapy, and radiotherapy, which aim to normalize serum GH and IGF-1 levels, reduce, or control tumor size and relieve multiple comorbidities, thereby improving patient outcomes and quality of life (2,3).

Medical therapy plays a significant role in the management of acromegaly, which is recommended in patients who are not suitable for surgery or with persistent symptoms after surgery (4). First-generation somatostatin receptor ligands (SRLs) are considered as the first-line medical therapy in acromegaly patients, in which octreotide long-acting release (LAR) and lanreotide autogel (LAN) are commonly used (5). According to other studies, 44–68% of patients with acromegaly reached GH <2.5 μg/L and 34–70% of patients normalized IGF-1 levels after octreotide LAR therapy (6,7). In addition, a Japanese study enrolling 30 patients reported that 50.6% achieved GH level ≤2.5 μg/L and 53.3% returned to normal IGF-1 levels following octreotide LAR treatments (8).

As is known, octreotide LAR has a well-established safety profile. The most common adverse effects related to this drug are the pain at the injection site and moderate gastrointestinal reactions including abdominal pain, diarrhea, and nausea (9). However, the cases of treatment discontinuation due to adverse drug reactions are rare. Recently, a study reported that 23.3% and 20.4% of acromegaly patients who received SRLs treatment developed gallbladder stones and biliary sludge, respectively (10). Also, another study pointed out that octreotide LAR treatment posed a risk of gallstones with longer duration of treatment (11). A Japanese study using the changes in HbA1c as an indicator investigated the effect of octreotide LAR treatment on glucose tolerance and found that somatostatin analogue may have little influence on glucose tolerance (8). Nevertheless, some researchers indicated that acromegaly patients with diabetes mellitus should be monitored owing to the potential alteration of octreotide on glucose metabolism (12). The limited number of studies on Asian patients showed different efficacy and safety profiles from European or American research (8,13), suggesting that patients of different ancestries may exert various response towards octreotide LAR due to their genomic differences. Current results regarding this regimen are mainly generated from European or American patients with acromegaly whereas there is still too little real-world evidence of octreotide LAR treatment in Chinese patients. Also, since octreotide LAR was covered by Chinese national medical insurance system, this drug has been increasingly applied to patients with acromegaly in China, especially those with no remission or recurrence after surgeries. Thus, this retrospective cohort study is of great clinical importance to determine the efficacy and safety of octreotide LAR therapy in a population of Chinese patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-414/rc).

Methods

Patients

We conducted a retrospective study of patients with acromegaly who received treatment at Peking Union Medical College Hospital between 2010 and 2020. The patients were recruited from different regions of China. As shown in the inclusion diagram (*Figure 1*), acromegaly patients who received continuous and regular treatment with octreotide LAR at least three times with complete basal information were enrolled, and these were the inclusion criteria for this study. Exclusion criteria were as follows: (I) patients who received less than three consecutive octreotide LAR treatments or irregular treatments; (II) patients who previously received other SRLs, such as lanreotide or pasireotide; (III) absence of basal information; and (IV) patients simultaneously undergoing surgery or radiotherapy during octreotide LAR treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of

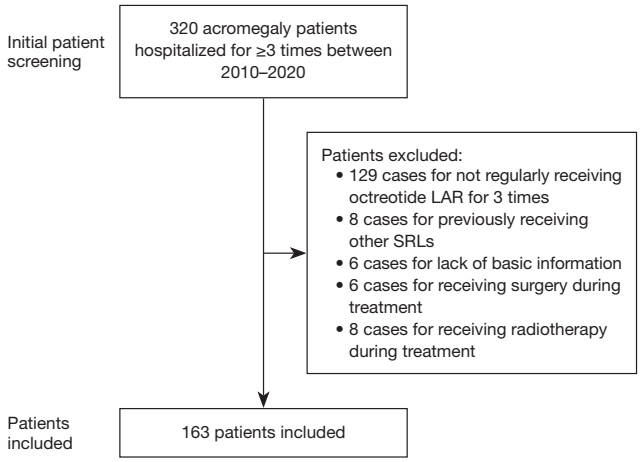

Figure 1 Diagram of patient inclusion and exclusion process. LAR, long-acting release; SRL, somatostatin receptor ligand.

Peking Union Medical College Hospital (approval number: S-K1617) and individual consent for this retrospective analysis was waived.

Diagnosis of acromegaly

When acromegaly was clinically suspected based on the typical facial and acral deformity of patients, a diagnosis was made based on biochemical detection, including serum IGF-1 concentrations higher than the upper limit of the normal (ULN) reference range and the lack of GH suppression to 1 ng/mL during an oral glucose load. As described previously, the serum IGF-I and GH levels were measured by performing a fully automated 2-site, solid-phase, chemiluminescent enzyme immunometric assay (Immulite 2000®; Siemens Healthcare Diagnostics, Los Angeles, CA, USA) following the manufacturer's instructions (14). Magnetic resonance imaging (MRI), which provides information on the size and invasiveness of the tumor, was also used to support the diagnosis of acromegaly.

Data collection

Patients received an intramuscular injection of 20 mg octreotide LAR (Sandostatin LAR; Novartis, Basel, Switzerland) once every 4 weeks. Before octreotide LAR treatment, the demographic characteristics of each patient were recorded, including sex, age before treatment, age at onset, disease duration, body mass index (BMI), blood pressure, comorbidity, pituitary tumor size classification (microadenoma for tumors with a maximum diameter <10 mm; macroadenoma for tumors with maximum diameter ≥10 mm), and previous treatments (surgery or radiotherapy). In addition, the number of courses of the octreotide LAR treatments was recorded. Thereafter, acromegaly activity (fasting serum GH concentrations, IGF-1, and normalized IGF-1 levels), electrocardiography results, abdominal ultrasound test, and other laboratory tests [blood routine tests, γ-glutamyl transferase (GGT), aspartate transaminase, alanine transaminase (ALT), blood bilirubin values, fasting glucose, serum cholesterol, and triglyceride levels] both at baseline and during follow-up were collected from clinical records. Concomitant symptoms other than acromegaly were also recorded at every visit. IGF-1 levels were corrected according to the ULN for age and sex of the Chinese population reported in our previous study (14). Missing data were recorded as unknowns. By comparing the examination results or descriptions of symptoms at baseline and after treatments, the adverse events and the corresponding grades were determined according to Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE V5.0).

Statistical analyses

Descriptive analysis was carried out, and data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. To compare GH and IGF-1 levels before and after treatment, a matched Wilcoxon signed-rank test was performed. To control for confounding factors, subgroup analyses were performed and a multivariate regression model was constructed. For subgroup analysis among multiple groups, the Kruskal-Wallis test followed by the Mann-Whitney U test was used. For comparisons between two groups, continuous data were analyzed using the Mann-Whitney U test or Student's *t*-test, as appropriate, and categorical data were analyzed using the chi-square test or Fisher's exact test. Multivariable logistic regression was performed to determine the risk factors for the occurrence of adverse events. For multivariable regression analysis, clinical-related factors or variables that showed a univariate association with adverse events were included in the model construction. The inclusion of variables was carefully determined based on the sample size. Statistical significance was set at $P<0.05$. All statistical analyses were performed using SPSS ver. 20.0 software.

Table 1 Baseline characteristics of enrolled patients (n=163)

Characteristics	N (%) or value
Sex	
Male	71 (43.6)
Female	92 (56.4)
Age at first treatment of octreotide LAR, mean ± SD	40.94±13.00
Age at onset, mean ± SD	32.56±11.47
≤20	20 (12.3)
21–30	63 (38.7)
31–40	41 (25.2)
41–50	26 (16.0)
>50	13 (8.0)
Disease duration (year), mean ± SD	8.38±7.75
0–5	70 (42.9)
6–10	53 (32.5)
11–15	21 (12.9)
≥16	19 (11.7)
BMI (kg/m^2), mean ± SD	25.74±3.66
SBP (mmHg), mean ± SD	121.26±15.45
DBP (mmHg), mean ± SD	75.52±12.34
Comorbidities	
Yes	110 (67.5)
Diabetes	35 (21.5)
Hypertension	33 (20.2)
No	53 (32.5)
Pituitary tumor size classification	
Microadenoma	6 (3.7)
Macroadenoma	98 (60.1)
Unknown[†]	59 (36.2)
Previous treatments	
Surgery and radiotherapy both	48 (29.4)
Surgery only	68 (41.7)
Radiotherapy only	6 (3.7)
No previous treatment	41 (25.2)
Courses of octreotide LAR treatment	
3–5	44 (27.0)
6–11	53 (32.5)
≥12	66 (40.5)
GH level (ng/mL)	
Mean ± SD	16.03±41.12
Median (P25, P75)	4.95 (2.225, 10.325)
IGF-1 level (ng/mL)	
Mean ± SD	599.36±282.47
Median (P25, P75)	559 (366, 799.5)
IGF-1/ULN	
Mean ± SD	1.95±0.95
Median (P25, P75)	1.89 (1.22, 2.40)

[†], some patients lacked the tumor size data because they could not provide detailed surgery records or MRI results from other hospitals. LAR, long-acting release; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of the normal; MRI, magnetic resonance imaging.

Results

Baseline clinical characteristics

We retrospectively enrolled 320 patients with a definitive diagnosis of acromegaly. According to the inclusion and exclusion criteria of this study, 163 patients (71 males and 92 females) were eventually enrolled for analysis (*Figure 1*), with a mean age of 40.94±13.00 years at the beginning of the first treatment and 32.56±11.47 years at the onset of disease. The baseline characteristics of the included patients are shown in *Table 1*. Most patients had developed acromegaly for less than 5 years (70, 42.9%) at the first dose of octreotide LAR. The average BMI of all 163 patients was 25.74±3.66 kg/m^2. The mean systolic and diastolic blood pressures of all enrolled patients were 121.26±15.45 and 75.52±12.34 mmHg, respectively. Moreover, approximately two-thirds of patients (67.5%) had comorbidities, including diabetes (35/163, 21.5%) and hypertension (33/163, 20.2%). Other comorbidities, such as hyperlipidemia, coronary disease, and osteoporosis, were also observed. More than half of the patients had macroadenomas (60.1%), whereas only six cases were reported as microadenomas (3.7%). In addition, the tumor sizes in 59 cases were unknown

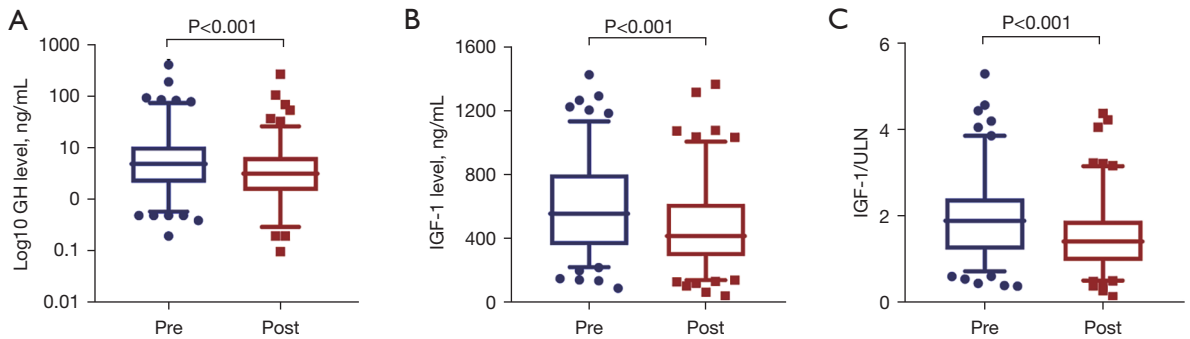

Figure 2 Improvements of GH, IGF-1, and IGF-1/ULN levels by octreotide LAR treatment. (A) Fasting GH levels before and after octreotide LAR treatment. (B) IGF-1 levels before and after octreotide LAR treatment. (C) IGF-1/ULN before and after treatment. GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of the normal; LAR, long-acting release.

Table 2 Improvements of GH, IGF-1, and IGF-1/ULN levels by octreotide LAR treatment

Variables	Baseline	After treatment
GH (ng/mL)		
Mean ± SD	16.03±41.12	8.47±25.49
Median (P25, P75)	4.95 (2.225, 10.325)	3.2 (1.5, 6.6)
IGF-1 level (ng/mL)		
Mean ± SD	599.36±282.47	479.78±256.62
Median (P25, P75)	559 (366, 799.5)	419 (297.5, 611)
IGF-1/ULN		
Mean ± SD	1.95±0.95	1.53±0.79
Median (P25, P75)	1.89 (1.22, 2.40)	1.41 (0.97, 1.89)

GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of the normal; LAR, long-acting release; SD, standard deviation.

because some could not provide detailed surgical records or MRI results from other hospitals. According to previous treatments before octreotide LAR, the patients were divided into four groups: surgery and radiotherapy both (48, 29.4%), surgery only (68, 41.7%), radiotherapy only (6, 3.7%), and no previous treatments (41, 25.2%).

Treatment with octreotide LAR in our study was administered at a dose of 20 mg intramuscularly at least three times. Briefly, 44 patients (27.0%) underwent 3–5 courses of octreotide LAR treatment, 53 (32.5%) received 6–11 courses, and 66 (40.5%) were administered the drug at least 12 times. At baseline, the median fasting GH level was 4.95 ng/mL (IQR 2.225, 10.325 ng/mL), the median IGF-1 level was 559 ng/mL (IQR 366, 799.5 ng/mL), and the median IGF-1/ULN was 1.89 (IQR 1.22, 2.40).

Treatment outcome

After octreotide LAR treatment, 34.4% of the patients met the criteria for controlled GH levels (<2.5 ng/mL) in our study. Meanwhile, octreotide LAR normalized IGF-1 levels to sex/age-matched ULN in 23.3% of the patients. Furthermore, a complete response (GH <2.5 ng/mL and IGF-1 normalization) was obtained in 29 patients (17.8%), while a partial response (a decrease in GH and/or IGF-1 ≥50%) was achieved in 41 patients (25.2%). In contrast, 57.1% of patients showed no response to octreotide LAR treatment. In addition, fasting GH levels were dramatically downregulated from 4.95 ng/mL (IQR 2.225, 10.325 ng/mL) at baseline to 3.2 ng/mL (IQR 1.5, 6.6 ng/mL) after treatment (P<0.001; *Figure 2A* and *Table 2*). Similarly, IGF-1 levels significantly decreased from 559 ng/mL (IQR 366, 799.5 ng/mL) to 419 ng/mL (IQR 297.5, 611 ng/mL) (P<0.001; *Figure 2B* and *Table 2*), and corresponding IGF-1/ULN also declined from 1.89 (IQR 1.22, 2.40) to 1.41 (IQR 0.97, 1.89) (P<0.001; *Figure 2C* and *Table 2*).

To further explore the factors that may influence the efficacy of octreotide LAR in acromegaly, we compared GH levels, IGF-1 levels, IGF-1/ULN, and their controlling rates among patients receiving different prior treatments. The results showed that previous surgery or radiotherapy had no effect on drug efficacy (Table S1). Baseline comorbidities were also not associated with drug efficacy (data not shown).

In addition, we compared the biochemical results among patients receiving different courses of octreotide LAR treatment and found that patients with long treatment

Table 3 Number of patients with or without adverse events during octreotide LAR treatment

Number of adverse events	Number and proportions of patients, n (%)
0	98 (60.1)
1	29 (17.8)
2	29 (17.8)
3	4 (2.5)
4	3 (1.8)
Total	163 (100.0)

LAR, long-acting release.

periods (≥12 times) had significantly lower baseline GH levels, IGF-1 levels, and IGF-1/ULN than those treated with fewer courses of octreotide LAR (Table S2). Moreover, patients receiving treatment ≥12 times showed significantly lower changes in GH levels than those of the other two groups, though the changes in IGF-1 and IGF-1/ULN showed no remarkable differences (Table S2). In addition, the number of courses of octreotide LAR treatment exerted no influence on the rates of GH control and IGF-1 normalization (Table S2).

Adverse events of octreotide LAR

According to the CTCAE 5.0 criteria, we determined the adverse events of all the 163 patients in our study. During treatment with octreotide LAR, 65 patients developed adverse events, ranging from one to four (*Table 3*). Among them, 29 patients had one adverse event, 29 developed two kinds of adverse reactions, 4 had three types, and 3 experienced four kinds. Collectively, 111 events were detected in the 163 enrolled patients with acromegaly.

As shown in *Table 4*, among all the adverse events, 37 gastrointestinal disorders occurred after treatment, including gastrointestinal reactions (26 cases, 16.0%), cholelithiasis or sludge (4 cases, 2.5%), increased GGT (4 cases, 2.5%), increased blood bilirubin (2 cases, 1.2%), and increased ALT (1 case, 0.6%). Gastrointestinal reactions included abdominal distension, pain, diarrhea, nausea, and vomiting. The median number of therapies received prior to the onset of each event is also demonstrated in *Table 4*, showing that most of the gastrointestinal reactions occurred following the first dose of octreotide LAR (*Figure 3A*), while cholelithiasis or sludge occurred after longer periods of treatment (P=0.001, *Figure 3B*). All gastrointestinal adverse events were of grade 1 or 2. In addition, adverse events of the hematological system were observed during octreotide LAR treatment. These events included 15 cases of anemia (9.2%), 15 cases of decreased white blood cell count (9.2%), 13 cases of decreased neutrophil count (8.0%), and 4 cases of decreased lymphocyte count (2.5%). The median onset course number of events of the hematological system was similar, ranging between 4 and 5 courses. Except for three cases of decreased neutrophil count of grade 4 and two of decreased lymphocyte count of grade 3, most hematological system events were of grade 1 or 2. Other adverse events such as hyperglycemia (12 cases, 7.4%), high cholesterol (3 cases, 1.8%), hypertriglyceridemia (6 cases, 3.7%), headache (2 cases, 1.2%), and fever (1 case, 0.6%) were detected. Among these events, only one case of hypertriglyceridemia was of grade 3 and all the others were of grade 1. In addition, three cases of prolonged QT interval (one of grade 3 and two of grade 1) developed after a median of three rounds of octreotide LAR treatment. During treatment, none of the patients discontinued octreotide LAR due to adverse events.

Risk factors of adverse events

To further investigate the association between adverse events and the efficacy of octreotide LAR treatment, we compared biochemical features and response rates between patients with or without adverse events. The results showed that the occurrence of adverse events was not associated with serum GH and IGF-1 levels before or after octreotide LAR treatment (Table S3). Besides, we found that patients with adverse events tended to have relatively higher rates for meeting GH control criteria (45.9% *vs.* 36.4%; P=0.056) and higher rates of IGF-1 normalization (32.2% *vs.* 23.8%; P=0.146) without statistical significance, compared to patients without adverse events after octreotide LAR treatment (Table S3).

We then compared the baseline information between patients with and without adverse events and found that sex, age, age at onset, disease duration, BMI, blood pressure, only previous radiotherapy, and both previous surgery and radiotherapy were not related to the occurrence of adverse events. However, patients with adverse events had a remarkably higher proportion of comorbidities than those without adverse events (84.6% *vs.* 56.1%, P<0.001; *Table 5*). Meanwhile, the occurrence of adverse events was found to be associated with a lower rate of only previous surgery (24.6% *vs.* 53.1%, P<0.001; *Table 5*). These data collectively suggest

Table 4 Adverse events developed during octreotide LAR treatment

Adverse events	No. (%)	Onset time, courses, median [P25, P75]	Grade
Gastrointestinal disorders			
Gastrointestinal reactions	26 (16.0)	1 [1, 2]	Grade 1: 25; Grade 2: 1
Cholelithiasis or sludge	4 (2.5)	11 [9, 11.5]	Grade 1: 4
Increased GGT	4 (2.5)	6.5 [5.5, 9]	Grade 1: 3; Grade 2: 1
Increased blood bilirubin	2 (1.2)	5 [4, 6]	Grade 1: 2
Increased ALT	1 (0.6)	3 [–]	Grade 2: 1
Blood system disorders			
Anemia	15 (9.2)	4 [3, 5]	Grade 1: 12; Grade 2: 3
Decreased white blood cell	15 (9.2)	4 [3, 6]	Grade 1: 14; Grade 2: 1
Decreased neutrophil	13 (8.0)	5 [4, 7]	Grade 1: 8; Grade 2: 2; Grade 4: 3
Decreased lymphocyte	4 (2.5)	4.5 [3.75, 5.25]	Grade 2: 2; Grade 3: 2
Metabolism and nutrition disorders			
Hyperglycemia	12 (7.4)	4 [3, 6.25]	Grade 1: 12
High cholesterol	3 (1.8)	4 [3.5, 7.5]	Grade 1: 3
Hypertriglyceridemia	6 (3.7)	9 [6.5, 11.5]	Grade 1: 5; Grade 3: 1
Nervous system disorders			
Headache	2 (1.2)	2 [1.5, 2.5]	Grade 1: 2
General disorders			
Fever	1 (0.6)	3 [–]	Grade 1: 1
Cardiac disorders			
Prolonged QT interval	3 (1.8)	3 [3, 4.5]	Grade 1: 2; Grade 3: 1

LAR, long-acting release; GGT, γ-glutamyl transferase; ALT, alanine aminotransferase.

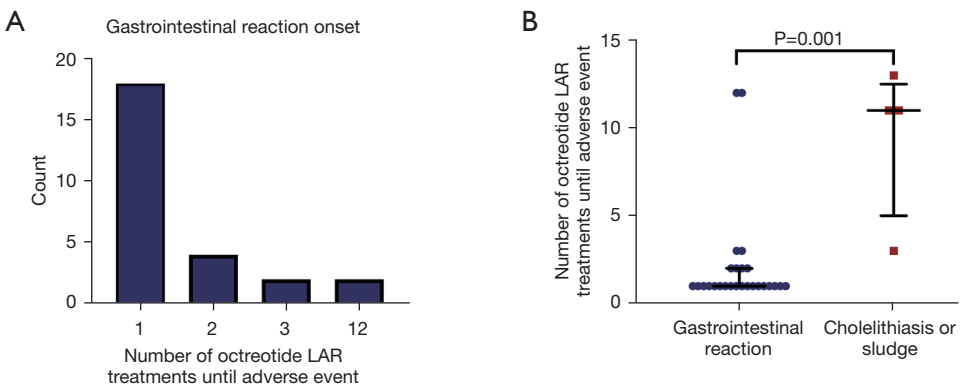

Figure 3 Onset time of gastrointestinal adverse events. (A) Distribution of treatment numbers to onset of gastrointestinal reactions. (B) Treatment numbers to onset of gastrointestinal reactions and cholelithiasis or sludge. LAR, long-acting release.

Table 5 Clinical features of patients with adverse events or without adverse events at baseline

Variables	No AE	AE	P value
n	98	65	
Sex, n (%)			
Male	46 (46.9)	25 (38.5)	0.285
Female	52 (53.1)	40 (61.5)	
Age at first treatment of octreotide LAR	40±13	43±15	0.234
Age at onset, n (%)	33±12	34±13	0.493
≤20	13 (13.3)	7 (10.8)	0.300
21–30	42 (42.9)	21 (32.3)	
31–40	20 (20.4)	21 (32.3)	
41–50	17 (17.3)	9 (13.8)	
>50	6 (6.1)	7 (10.8)	
Disease duration (year), median [P25, P75]	5.5 [3, 10]	8 [4.5, 11]	0.109
BMI (kg/m^2), mean ± SD	25.35±3.73	26.36±3.53	0.132
SBP (mmHg), mean ± SD	119.98±14.81	123.47±16.74	0.246
DBP (mmHg), mean ± SD	75.48±10.81	76.33±12.62	0.885
Comorbidities, n (%)			
Yes	55 (56.1)	55 (84.6)	<0.001
No	43 (43.9)	10 (15.4)	
Previous treatments†, n (%)			0.002
Surgery and radiotherapy both	25 (25.5)	23 (35.4)	0.317
Surgery only	52 (53.1)	16 (24.6)	<0.001
Radiotherapy only	4 (4.1)	2 (3.1)	0.386
No previous treatment	17 (17.3)	24 (36.9)	

†, for *post-hoc* pairwise comparisons among previous treatments, patients in no previous treatment group were considered as reference. AE, adverse event; LAR, long-acting release; BMI, body mass index; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

that comorbidities might be a risk factor for adverse event occurrence after octreotide LAR treatment, while only previous surgery might be a protective factor.

Furthermore, sex, age, disease duration, BMI, comorbidity, and previous treatments were included in the logistic regression analyses. The results showed that the presence of comorbidities [odds ratio (OR), 3.19; 95% confidence interval (CI): 1.20–9.27; P=0.025] and previous surgery only (OR, 0.21; 95% CI: 0.08–0.58; P=0.003) remained significant predictors of adverse events (*Figure 4*).

Discussion

Acromegaly is a rare disorder that affects approximately 7 people per 100,000 individuals (1). Apart from neurosurgical removal of pituitary tumors, pharmacological therapies have become increasingly important for patients with acromegaly (2,4). The optional regimens include SRLs (i.e., octreotide, lanreotide, and pasireotide), GH receptor antagonists, and dopamine receptor agonists (1). In the past decades, the first-generation SRL octreotide LAR

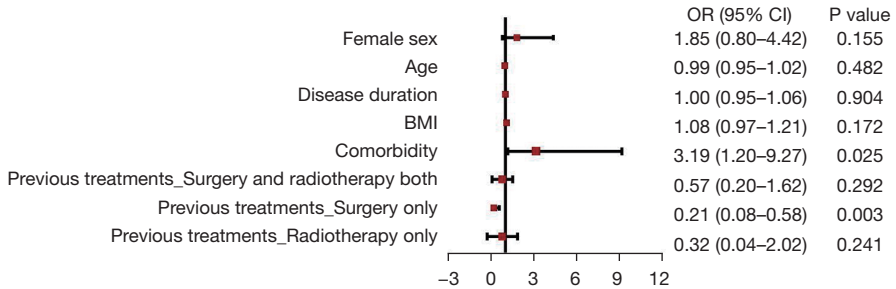

Figure 4 Logistic regression model to predict the adverse events during octreotide LAR treatment. BMI, body mass index; OR, odds ratio; CI, confidence interval; LAR, long-acting release.

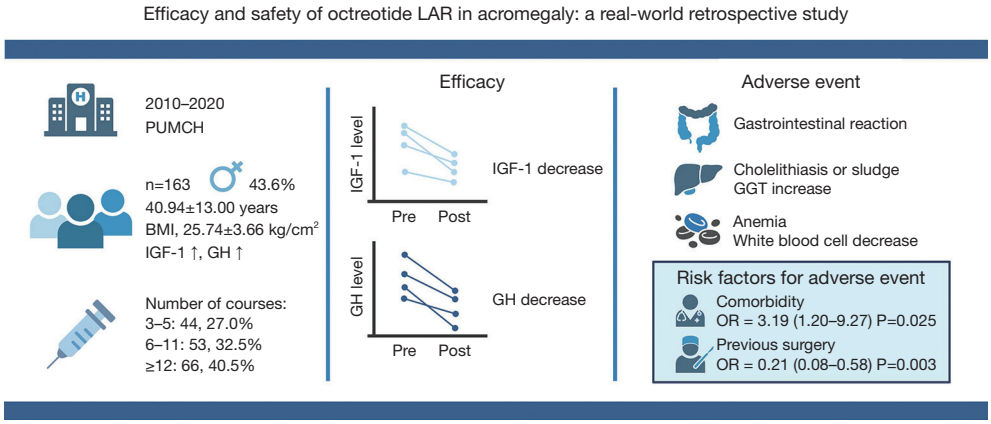

Figure 5 Summary of the study. LAR, long-acting release; PUMCH, Peking Union Medical College Hospital; BMI, body mass index; IGF-1, insulin-like growth factor-1; GH, growth hormone; GGT, γ-glutamyl transferase; OR, odds ratio.

has been widely applied as the first-line drug in selected patients with acromegaly, showing a biochemical control rate varying from 25% to 70% and well-tolerated safety profiles in multiple clinical trials (15). However, few studies have evaluated the therapeutic effects and adverse effects of octreotide LAR in Chinese patients with acromegaly. Therefore, our current retrospective study, which first investigated 163 Chinese patients with acromegaly who received continuous treatment with octreotide LAR to assess its efficacy and safety, is of great importance for the use of this medication in Chinese patients. A summary of the results of our study is presented in *Figure 5*.

Our recent analysis found that only part of patients with acromegaly who were treated in our hospital were Beijing residents, while most of them came from all over the country. Therefore, our data are a partial representation of acromegaly and its medication in Chinese patients. First, the baseline clinical features reflected some characteristics of acromegaly in China. Several studies reported no difference in prevalence between sexes (1,16,17), and male patients accounted for nearly half of the cases in our study. In addition, 51% of the patients were younger than 30 years at the onset of disease; this may raise the question whether acromegaly with a genetic background affected our results since they are known to be difficult to treat (18). Although not all the young-onset patients underwent genetic testing in our study, genetic disorders involving acromegaly are very rare, which may have limited influence on our results. Intriguingly, for the duration of symptoms before diagnosis, almost half of the patients (42.9%) experienced a delay of 0–5 years and nearly one-third of the patients (32.5%) had a relatively increased delay of 6–10 years, which is similar to the duration reported by other investigations (1,19). However, in some patients, it took over 15 years until diagnosis. Since the duration of disease activity can determine the severity of its complications, our results suggest that enhancing education and awareness of this rare disease is of great importance for doctors and patients.

In addition, approximately 75% of the patients received surgery or radiotherapy before octreotide LAR treatment. Notably, a relatively high proportion (33.3%) of these patients underwent previous radiotherapy. This is either because the large number of patients with macroadenoma in our study required additional radiation for better control or radiotherapy is an effective and economical option for patients who cannot afford long-term octreotide LAR treatment. Among the 54 patients who received previous radiotherapy, 23 (42.6%) underwent radiotherapy <2 years before octreotide LAR treatment, 16 (29.6%) for 2–5 years, and 15 (27.8%) for ≥5 years. These results suggest that the efficacy of radiotherapy might still be existent in some of these patients when they began octreotide LAR treatment. Given that previous surgery or radiotherapy and the duration of octreotide LAR treatments may theoretically influence the efficacy of octreotide LAR, we performed subgroup analyses to eliminate the confounding effects of these factors. The results showed that previous surgery, previous radiotherapy, and number of octreotide LAR treatments did not affect disease control of octreotide LAR in our study, suggesting that patients receiving previous therapies or with relatively short octreotide LAR treatments can be included in our overall analysis of efficacy with limited bias.

According to the current Endocrine Society Clinical Practice Guidelines for acromegaly, the critical goal of treatment is to normalize the serum levels of GH and IGF-1 (20). In our study, 163 patients with acromegaly showed significantly lowered GH and IGF-1 levels after octreotide LAR treatment, suggesting the effective biochemical control of this drug. Biochemical control rates were used to evaluate the efficacy of octreotide LAR. Fasting GH <2.5 ng/mL was chosen as the control criterion according to the 2013 Chinese guidelines on acromegaly (21), since the patients enrolled in our study received octreotide LAR treatments from 2010 to 2020. We demonstrated that the rates of GH <2.5 ng/mL (34.4%) and IGF-1 normalization (23.3%) were relatively lower than those of some other reported clinical trials (GH <2.5 ng/mL, 57%; normal IGF-1, 67%) (22), which may be caused by the differences between real-world studies and clinical trials. In addition, a prospective investigation of 67 patients with acromegaly showed that after a median follow-up of 48 months, safe GH levels, and normalized IGF-1 levels were achieved in 68.7% and 70% of the patients, respectively (23). In another long-term real-world retrospective study conducted in 157 acromegaly patients receiving octreotide LAR treatments for a median of 27 months, more than 60% of patients attained GH <2.5 ng/mL while 36.3–37% achieved normal IGF-1 levels (<1.2× ULN) (24). In addition, a retrospective analysis based on the German acromegaly registry included 145 patients who received primary SRL treatments (including short-acting octreotide, octreotide LAR, and lanreotide), and found that GH and IGF-1 levels normalized after 3 months of treatment in 36.3% and 30.5% of patients, respectively. Furthermore, the control rates of GH and IGF-1 increased to 40.8% and 43.1%, respectively, after a longer treatment duration (>365 days) (25). The results of biochemical control rates vary significantly among different studies owing to several reasons, such as patient selection, previous therapies, and duration of treatment. Compared to these studies, the patients in our study achieved relatively lower rates of GH and IGF-1 control. One possible reason may be that all patients were treated with 20 mg octreotide LAR every 4 weeks without dose up-titration. In addition, the high proportion of patients with previous radiotherapy (33.3%) indicated that some of these patients might have more aggressive tumors and were more likely to be refractory to therapy, which may partially explain the low rate of responders in our study.

When exploring the effect of treatment duration on efficacy, we found that patients undergoing ≥12 treatments tended to have lower baseline IGF-1, IGF-1/ULN, and GH levels. One possible explanation may be that patients with lower basal IGF-1 and GH levels may benefit more from octreotide LAR than those with high levels, so they received durable treatments over a long period. Consistently, baseline IGF-1 and GH levels have also been reported to be critical predictors of responsiveness to octreotide in other studies (24,26).

Consistent with the safety profiles of octreotide LAR in other trials (9), the most common adverse effects observed in our study were gastrointestinal reactions, such as abdominal pain, diarrhea, and nausea. Asymptomatic cholelithiasis and sludge caused by the inhibitory effects of octreotide on bile salt secretion were also observed after treatment. Other studies reported that these biliary alterations developed in 5–60% of patients (27,28), while our study had a relatively lower frequency (2.5%). As expected, gastrointestinal reactions occurred at early stages, whereas cholelithiasis and sludge occurred after more than 10 courses of treatment, suggesting that physicians should concentrate on different side effects at different stages of octreotide LAR treatment.

Although octreotide LAR treatment can theoretically interfere with glucose metabolism in patients with acromegaly owing to its inhibition of insulin secretion, it can also compromise insulin resistance by decreasing GH levels. Therefore, the effects of octreotide on glucose homeostasis may be controversial in different studies (12,28). One related meta-analysis revealed an overall minor influence of octreotide treatment on glucose metabolism in patients with acromegaly (12). Notably, most cases with abnormal glucose levels associated with octreotide LAR use are moderate and controllable, despite some severe glucometabolic side effects reported in some special cases (29). Consistently, our study showed that 7.4% of patients had grade 1 hyperglycemia, and there were no hypoglycemia events. Among the 111 adverse events, only 7 were relatively severe at grade 3 or 4, and these included decreased neutrophil count, decreased lymphocyte count, hypertriglyceridemia, and prolonged QT interval. More importantly, no patient discontinued octreotide LAR due to adverse events during treatment. Taken together, the adverse events after octreotide LAR treatment were moderate with low frequencies, suggesting that this drug is well tolerated by patients with acromegaly.

For some regimens, adverse events were associated with efficacy. We also compared the biochemical features and response rates between patients with and without adverse events and found that patients with adverse events had higher rates of GH control and IGF-1 normalization. These results suggest the potential role of adverse events as a predictor of efficacy in patients with acromegaly receiving octreotide LAR, which requires further validation in our future investigation. Furthermore, the risk factors for adverse events were explored using subgroup analyses and logistic regression. We found that patients with adverse events after octreotide LAR treatment had a higher proportion of comorbidities and a lower proportion of previous surgeries, indicating that these factors are possible predictors of adverse events. Furthermore, we carefully selected the variables for multivariable logistic analysis. In the regression model, comorbidities and previous surgery were identified as two important risk factors. We assume that, for patients with comorbidities, some other systems are impaired by disease; therefore, they may be more susceptible to the development of adverse events. Consistently, history of diabetes, hypertension, and dyslipidemia has been reported to be risk factors for hyperglycemia related to pasireotide treatment in acromegaly (30). Additionally, another multivariate analysis in a multicenter study that investigated patients with neuroendocrine tumors receiving SRL treatments reported that prior surgery before medical treatment was an independent risk factor for adverse biliary stone events (31). However, the detailed potential reasons why these two risk factors influence the occurrence of adverse events require further investigation.

There were some limitations due to the retrospective design of our study. These include a lack of GH suppression tests for many patients and complete GH levels during the entire octreotide LAR treatment. In addition, the tumor sizes of 59 patients were unknown because of the lack of surgical records or MRI results from other hospitals. Furthermore, in our study, all patients received 20 mg of octreotide LAR every 4 weeks without dose increase or interval reduction owing to the high cost of the medication, which might limit the efficacy of this drug. Besides, the relatively small sample size owing to the rarity of acromegaly is another limitation. However, our current study is the first and largest to assess the efficacy and safety of octreotide LAR in Chinese patients with acromegaly.

In conclusion, our results revealed that octreotide LAR treatment is effective in normalizing GH and IGF-1 levels in patients with acromegaly. In addition, all the adverse events related to octreotide LAR use were moderate and well tolerated by the patients. Moreover, comorbidities and previous surgery may be two risk factors for the occurrence of adverse events.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-414/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-414/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.

amegroups.com/article/view/10.21037/atm-22-414/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Peking Union Medical College Hospital (approval number: S-K1617) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 The association between previous treatments and biochemical results

	Surgery and radiotherapy both	Surgery only	Radiotherapy only	No previous treatment	P value
Pre-treatment GH level (ng/mL)	4.60 (2.45, 14.10)	4.10 (1.60, 7.50)	9.50 (0.875, 18.925)	7.85 (2.575, 24.20)	0.125
Post-treatment GH level (ng/mL)	3.80 (1.45, 6.85)	3.00 (1.80, 4.80)	3.90 (1.65, 8.625)	3.815 (1.275, 8.25)	0.810
Change of GH level (ng/mL)	−1.40 (−5.35, −0.15)	−0.60 (−3.40, 0.20)	−3.15 (−13.975, 0.325)	−2.65 (−8.625, −0.40)	0.134
Pre-treatment IGF-1 level (ng/mL)	482 (353.5, 823)	516.5 (336.75, 772)	458 (333, 669.5)	710 (426.5, 833.5)	0.352
Post-treatment IGF-1 level (ng/mL)	438 (339.5, 631.5)	398.5 (290.5, 557.25)	201 (160.5, 666)	409 (258.5, 762.5)	0.511
Change of IGF-1 level (ng/mL)	−48 (−230.5, 56.5)	−60.5 (−262.75, 31)	−217 (−290.5, 94.5)	−100 (−313.5, 41.5)	0.698
Pre-treatment IGF-1/ULN	1.89 (1.22, 2.42)	1.80 (1.22, 2.42)	1.89 (1.22, 2.42)	1.80 (1.22, 2.42)	0.854
Post-treatment IGF-1/ULN	1.33 (0.94, 1.89)	1.44 (1.11, 1.89)	1.33 (0.94, 1.89)	1.44 (1.11, 1.89)	0.433
Change of IGF-1/ULN	−0.24 (−0.87, 0.10)	−0.19 (−0.79, 0.17)	−0.24 (−0.87, 0.10)	−0.19 (−0.79, 0.17)	0.467
Achieving GH < 2.5 ng/mL	31.3%	32.4%	33.3%	41.5%	0.729
Achieving normal IGF-1	14.6%	29.4%	33.3%	22.0%	0.232

GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of the normal.

Table S2 The association between courses of treatment and biochemical results

	3-5 times	6-11 times	≥12 times †	P value
Pre-treatment GH level (ng/mL)	6.85 (3.825, 16.575) **	5.8 (2.6, 22.05) **	3.95 (1.3, 7.15)	0.007
Post-treatment GH level (ng/mL)	3.6 (1.175, 7.825)	3.3 (1.725, 6.55)	3.15 (1.425, 5.05)	0.616
Change of GH level (ng/mL)	−1.6 (−7.35, 0) *	−2.15 (−10.65, −0.425) **	−0.45 (−1.825, 0.6)	0.004
Pre-treatment IGF-1 level (ng/mL)	631 (433, 830) **	728.5 (427.5, 840) **	448 (308.5, 614.25)	0.001
Post-treatment IGF-1 level (ng/mL)	486 (374, 641)	451 (297.25, 765.75)	403.5 (270.75, 520.5)	0.112
Change of IGF-1 level (ng/mL)	−100 (−289, 50)	−79 (−297.75, 18.75)	−29 (−216.25, 34.5)	0.344
Pre-treatment IGF-1/ULN	2.13 (1.27, 2.58) *	2.14 (1.37, 2.61) **	1.54 (1.07, 2.02)	0.008
Post-treatment IGF-1/ULN	1.30 (0.94, 2.26)	1.51 (1.06, 2.11)	1.38 (0.91, 1.80)	0.330
Change of IGF-1/ULN	−0.31 (−0.97, 0.13)	−0.29 (−0.88, 0.05)	−0.11 (−0.70, 0.13)	0.350
Achieving GH < 2.5 ng/mL	31.8%	35.9%	34.9%	0.912
Achieving normal IGF-1	20.5%	20.8%	27.3%	0.614

†, for post-hoc pairwise comparisons, patients with octreotide LAR treatments ≥12 times were considered as reference. *, P<0.05, **, P<0.01. GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of the normal.

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Table S3 Association of octreotide LAR treatment efficacy and adverse event occurrence

	AE group	No AE group	P value
Pre-treatment GH level	4.6 (2.2, 10.7)	5.5 (2.15, 10.7)	0.990
Post-treatment GH level	3.1 (1.45, 6.55)	3.3 (1.55, 6.7)	0.855
Change of GH level	–1.2 (–4.8, 0.45)	–1.2 (–5.75, –0.05)	0.986
Pre-treatment IGF-1 level	458 (339, 729)	586.5 (426.75, 822)	0.123
Post-treatment IGF-1 level	396 (248, 552)	451 (327.25, 641.25)	0.111
Change of IGF-1 level	–82 (–231, 46)	–63 (–262.75, 31.75)	0.888
Pre-treatment IGF-1/ULN	1.80 (1.21, 2.29)	1.94 (1.25, 2.58)	0.275
Post-treatment IGF-1/ULN	1.29 (0.95, 1.80)	1.47 (0.99, 2.05)	0.177
Change of IGF-1/ULN	–0.26 (–0.72, 0.13)	–0.20 (–0.86, 0.08)	0.939
Achieving GH < 2.5 ng/mL	45.9%	36.4%	0.056
Achieving normal IGF-1	32.2%	23.8%	0.146

AE, adverse event; GH, growth hormone; IGF-1, insulin-like growth factor 1; ULN, upper limit of the normal.

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