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Original Article

Long-Term Results of Long-Acting Somatostatin Analog Therapy in Children with Congenital Hyperinsulinism

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Abstract
Background and objectives: Congenital hyperinsulinism (CHI) is a rare condition caused by dysregulation of pancreatic insulin secretion, leading to severe hypoglycemia in children. In diazoxide-unresponsive patients, somatostatin analogs are recommended as a treatment option. The aim of the present study was to evaluate the clinical characteristics, growth patterns, side effect profiles, and long-term follow-up of CHI patients who received octreotide long-acting release (octreotide-LAR) therapy.
Methods: In the study, data from 23 CHI patients (F/M: 9/14) who received octreotide-LAR therapy between 2010 and 2025 were collected retrospectively. Data regarding glycemic control, growth parameters, and treatment-related adverse events were collected. The initial dose of octreotide-LAR was calculated as the total monthly dose of short-acting octreotide and was thereafter adjusted based on blood glucose monitoring results.
Results: The median age at diagnosis was 15 days (2–120), and the most common presenting symptom was hypoglycemic seizures (78.2%). Genetic mutations were identified in 14 patients (60.8%). Octreotide-LAR therapy was initiated at a median age of 14 (25^{th}-75^{th} quartiles: 9–24) months, and the mean treatment duration was 71.6±38.2 months (min-max: 7–162). Initial dose was calculated as total monthly dose of short acting octreotide which was adjusted per blood glucose monitoring results. Mean growth velocity during treatment was 6.4±1.1 cm/year with no concern of negative growth outcome. Neurodevelopmental delay was observed in 10 patients (43.4%). Apart from gallstones in three patients and mild, transiently elevated liver enzyme levels in six patients, no serious treatment-related side effects were observed.
Conclusion: In our cohort, long-term octreotide-LAR therapy achieved normoglycemia in the majority of patients without negativegrowth outcome. Transient elevations in liver enzymes and cholelithiasis were the most frequently observed side effects, indicating a safety profile comparable to that of short-acting octreotide. These results suggested that octreotide-LAR therapy is an effective and safe treatment option for diazoxide-unresponsive patients with CHI.
Keywords: Congenital Hyperinsulinism, Hypoglycemia, Octreotide LAR, KATP Channels

What is already known on this topic?
-Congenital hyperinsulinism is a common cause of persistent hypoglycemia in infants and children.
-Diazoxide is the first-line treatment; however, a substantial proportion of patients are unresponsive.
-Somatostatin analogs such as octreotide are used as second-line therapy, but data on the long-term use of long-acting octreotide (octreotide-LAR) in children are limited.

What this study adds?
-This study presents long-term follow-up data of children with congenital hyperinsulinism treated with octreotide-LAR.
-Octreotide-LAR provided sustained glycemic control in most patients without adverse effects on linear growth.
-Treatment-related adverse events were mild and manageable, supporting the long-term safety of octreotide-LAR therapy.

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Introduction

Congenital hyperinsulinism (CHI) is a rare disorder characterized by dysregulated insulin secretion from the pancreatic beta cell and severe persistent hypoglycemia in neoantes and children (1,2). In most cases, CHI presents in the neonatal period; however, in approximately 10% of cases, onset occurs during childhood (3,4). The underlying etiology of CHI is dysregulated insulin secretion resulting from defects in key genes (*ABCC8, KCNJ11, HADH, GLUD1, HNF1A, HNF4A, GCK, SLC16A1, UCP2, FOXA2, CACNA1D*) that regulate insulin secretion from pancreatic beta cells (5). Mutations in the *ABCC8* and *KCNJ11* genes, which encode the SUR1 and Kir6.2 subunits of the K_{ATP} channel, represent the most common cause of persistent CHI which was also shown as the most common etiology in our country (4,6).
There are two main histological subtypes of CHI; focal and diffuse disease (2). In focal forms, the preferred treatment option is limited lesionectomy or partial pancreatectomy, which can provide a cure with no post-surgical long-term complications. In the diffuse form, medical therapy is the first-line treatment option. However, in patients with diffuse CHI who are unresponsive to medical treatment, subtotal or near-total pancreatectomy, in which approximately 95–98% of the pancreas is removed, may be considered. This approach remains controversial, as it carries a high risk of serious long-term complications, such as the recurrence of hypoglycemia, development of diabetes, and exocrine pancreatic insufficiency (7,8).
Diazoxide, the first and only FDA-approved medication, is the first-line treatment for children with CHI (5,9). Nevertheless, there is a high rate of diazoxide unresponsiveness, particularly in cases with mutations in genes encoding the K_{ATP} channel proteins, Kir6.2 and SUR1. Of those, about half of the cases have a focal form that can be cured with a limited lesionectomy or partial pancreatectomy (5). The genetic basis

of focal disease is a paternally inherited heterozygous variant in ABCC8 or KCNJ11, along with somatic loss of the maternal allele ("second hit or loss of heterozygosity") (4).
Somatostatin analogs (short-acting octreotide and long-acting somatostatin analogs, octreotide-LAR and lanreotide) are second-line treatment options for diazoxide-unresponsive CHI (9). Short-acting octreotide has been used as a long-term treatment option for diazoxide-unresponsive CHI cases to achieve normoglycemia, either to avoid pancreatectomy or to manage persistent hypoglycemia after subtotal pancreatectomy (9). Since short-acting octreotide therapy has challenges due to multiple daily injections or continuous subcutaneous administration via microinfusion pumps, the use of long-acting somatostatin analogs has emerged as an alternative. Long-acting somatostatin analogs are administered every 4 weeks as deep intramuscular injections which also improve the quality of life for patients and caregivers. However, data about the long-term use of long-acting octreotide are scarce. Given the potential negative effects of somatostatin on the pituitary hormones, particularly growth hormone(GH) secretion, a careful evaluation by assessment of growth and other side effects is required
The aim of the present study is to evaluate the long-term efficacy, and side effect profiles of octreotide long-acting release (Octreotide-LAR), a long-acting somatostatin analog, in a pediatric cohort with CHI.

Patients and Methods
Medical records of 23 patients with CHI who received octreotide-LAR therapy at Diyarbakır Children's Diseases Hospital between January 2010 and January 2025 were retrospectively reviewed. The age of presentation, gender, birth weight, gestational age, consanguinity status, all treatments received, Δ height SDS (height SDS at latest follow-up visit - height SDS prior to initiation of LAR treatment), annual growth velocity, genetic results, octreotide-LAR dose, and the number of hypoglycemic episodes were collected. In addition, liver function tests, thyroid function tests (TFT), hepatobiliary ultrasonography (USG), and insulin-like growth factor I (IGF-I) levels were evaluated to assess treatment-related side effects. Patients with CHI who did not receive octreotide-LAR therapy, those with transient hyperinsulinism, chronic or metabolic diseases, and syndromic conditions were excluded from the study. Congenital hyperinsulinism was diagnosed based on previously described criteria released in the latest international consensus guideline (9). Genetic analysis was performed on patients diagnosed with persistent CHI. 6-fluoro-(18F)-L-3,4-dihydroxyphenylalanine PET (18F-DOPA PET/CT) imaging was performed for two patients with paternally inherited heterozygous mutations in *ABCC8* gene.
Patients with CHI were initially treated with frequent oral or intragastric feeding or intravenous glucose infusion for stabilization of blood glucose. Diazoxide (5-15 mg/kg/day) was introduced as the first-line medication for long-term management of hypoglycemia. Three patients in whom hypoglycemia persisted received glucagon infusion, and one patient was treated with nifedipine. In patients whose normoglycemia could not be achieved or who did not meet the criteria for diazoxide responsiveness, diazoxide unresponsiveness was considered, and subcutaneous short-acting octreotide (5-20 μg/kg/day) was initiated (1,9). Once patients reached at least 6 months of age or 10 kg of body weight, octreotide-LAR was administered every 4 weeks, with an initial dose calculated as the total monthly short-acting octreotide dose (9). Subsequent octreotide-LAR doses were adjusted based on the glycemic response. Patients' concomittant medications was stopped in a stepwise approach. After the first dose of octreotide the doses was reduced immediately once hyperglycemia occured. Otherwise, 25% dose reduction was applied weekly and entirely stopped after 3rd dose of octreotide-LAR as long as normoglycemia sustained.
The patients' blood glucose levels were monitored at home by family members using capillary blood glucose meters (Self-Monitoring of Blood Glucose, SMBG). Fasting/premeal blood glucose levels were measured at least 3–4 times daily. Octreotide-LAR responsiveness was defined as achieving normoglycemia on at least 90% of blood glucose measurements or reducing hypoglycemia with a decreased need for additional medications (1). Neurodevelopmental status of the patients was evaluated based on the patients' medical records, parental discretion and available neurodevelopmental assessment data by physicians with no formal neurodevelopmental testing performed.
Ethical approval for this study was obtained from the Ethics Committee of Gazi Yaşargil Training and Research Hospital, University of Health Sciences (Approval number: 2025/582).
Statistical Evaluation
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 for Windows (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess the normality of data distribution. Normally distributed data were presented as mean ± standard deviation, whereas non-normally distributed data were expressed as median (interquartile range, 25th–75th percentiles). A paired t-test was used to compare the mean pre- and post-treatment values. A p-value of <0.05 was considered statistically significant.
Results
In total, 23 patients (F/M: 9/14) were diagnosed with persistent CHI and received octreotide -LAR therapy. The median age at diagnosis was 15 days (ranges 2-120 days). The presenting characteristics of the patients are shown in Table 1. A pathogenic variant was detected in 14 (60.8%) patients (13 in the *ABCC8* gene and 1 in the *HADH* gene). The most common presenting symptom was hypoglycemic convulsion, observed in 78.2% of patients.
The patient with the *HADH* mutation initially showed a favourable response to diazoxide. However, due to limited availability, poor compliance with diazoxide doses, and family preference due to extreme hypertrichosis, octreotide-LAR was added at a dose of 20 mg/month. Subsequently, diazoxide was discontinued, and glycemic control was maintained with octreotide-LAR monotherapy. Pancreatectomy was performed in two patients. One patient with a monoallelic *ABCC8* mutation had a focal lesion detected by 18F-DOPA PET/CT and underwent partial pancreatectomy. The other patient, who had no detectable mutation, underwent near-total pancreatectomy. As hypoglycemia persisted postoperatively in both patients, diazoxide therapy was reintroduced but did not achieve normoglycemia. Therefore, octreotide-LAR therapy was added, and diazoxide therapy was stopped during follow-up since octreotide-LAR achieved normoglycemia.
The average monthly octreotide-LAR dose was 0.65±0.25 mg/kg, with a higher dose in patients with a mutation (0.77±0.25 mg/kg) compared to those without a mutation (0.57±0.22 mg/kg), though the difference was borderline statistically significant ($p=0.057$). In 12 of 23 patients, octreotide-LAR therapy was initiated before age 12 months. None of these patients experienced thyroid dysfunction, elevated liver enzymes, or gallstones. Besides, all had a favourable growth outcome with a mean increase in height SDS of 0.37 ± 0.56.
All patients whose blood glucose levels remained stable on short-acting octreotide therapy were switched to octreotide-LAR at a median age of 14 months (min 7, max 125) using a previously published protocol (9). Prior to octreotide-LAR therapy, patients experienced an average of 4-5 hypoglycemic episodes per week. After treatment initiation, hypoglycemia occurred in three patients only during periods of poor oral intake on sick days, in three patients once weekly, and did not occur at all in 17 patients. While octreotide-LAR therapy achieved normoglycemia with no hypoglycemia episodes in 20 (86.9%) patients, and in 3 (13%) patients normoglycemia was achieved in most SMBG readings with occasional hypoglycemic episodes occured. The Octreotide-LAR dose was reduced in 3 (13%) patients who experienced hyperglycemia. Treatment intervals were extended to every 45 days in two patients and to every two months in one patient. The longest

follow-up period during octreotide-LAR therapy was 13.5 years. Transient elevations in liver transaminases were observed in 6 (26%) patients, and cholelithiasis in 3 (13%) patients. Two patients with cholelithiasis were treated with ursodeoxycholic acid (UDCA), which reduced gallstone size.

Evaluation of the growth patterns revealed that none of the patients had a height SDS value below -2. No statistically significant difference was found between the height SDS measured prior to initiation of octreotide-LAR and height SDS at the latest follow-up visit (p =0.543) (Fig. 2). Three (13%) patients had a BMI SDS > 2. None of the patients developed abnormal thyroid function test results during octreotide-LAR treatment. Patients' follow-up characteristics, including experienced side effects, are shown in Table 2 and Table 3.

Discussion

In the present study, evaluating the long-term results of octreotide-LAR therapy in 23 patients with diazoxide-unresponsive CHI, octreotide-LAR was shown to reduce hypoglycemic episodes in the vast majority of the patients, while hyperglycemia occurred in 13%, necessitating dose reduction or extension of the dose interval during the follow-up. These results demonstrate that octreotide-LAR can sustainably improve glycemic control.

Although diazoxide is the first-line treatment option, the rate of responsiveness in patients with CHI has been reported to range from 41% to 64%, suggesting a substantial unmet treatment need, particularly in cases with K_{ATP} gene mutations (9,10). In diazoxide-unresponsive cases, long-acting somatostatin analogues are the second option, offered as an alternative therapy to surgery, which may be complicated by the development of diabetes mellitus and exocrine pancreatic insufficiency in the short- and long-term course (11). In one patient with a biallelic *ABCC8* mutation, subtotal pancreatectomy was performed due to lack of response to medical treatments. In another patient with a paternally inherited heterozygous *ABCC8* mutation who had a focal lesion in the tail of the pancreas, distal pancreatectomy was performed. Nevertheless, both patients experienced hypoglycemia post-surgery, which was successfully managed by using octreotide-LAR therapy. These findings suggest that octreotide LAR is an effective treatment option not only for patients unresponsive to diazoxide but also for patients who underwent pancreatectomy but for whom hypoglycemia persists post-surgery. Although postsurgical persisting hypoglycemia has been reported at a high rate for diffuse CHI, achieving cure for a focal case has been reported at a very high rate (9). Failure in achieving normoglycemia in our case with focal CHI was suggested to be due to lack of correct localisation of the lesion, thereby incomplete resection of the lesion. Because, normoglycemia was achieved with a lower dose of octreotide-LAR compared to pre-surgery. *HADH* mutations are rare, accounting for approximately 1% of CHI cases, and patients with these mutations are diazoxide-responsive (12). In one of our patients with a *HADH* mutation and diazoxide-responsive CHI, diazoxide therapy was switched to octreotide-LAR due to limited availability of diazoxide on the market, poor family compliance with diazoxide doses and family preference due to extreme hypertrichosis.

Regular screening for side effects is recommended during octreotide therapy. Growth monitoring, hepatobiliary ultrasonography (USG), liver function tests, and thyroid function tests (TFTs) are recommended every 6 months (9). Somatostatin slows gastric emptying by reducing gastrointestinal motility and gallbladder contractility, which may increase the risk of gallstone formation, with reported rates ranging from 10% to 34% (13-15). Prevalence of biliary abnormalities was found to be similar between octreotide and octreotide-LAR therapies (16). In adult studies, developing gallstones as a side effect has been reported with a rate of 10% and 23.5% in patients receiving octreotide-LAR therapy (14,15). In the study of Demirbilek et al., conducted in 28 pediatric patients, gallbladder pathology was detected in 32% of patients, with no association with treatment duration or octreotide dose (17). In our study, gallbladder pathology was observed at a lower rate (13%) than in the latest study, and was not significantly associated with duration or dose of octreotide-LAR (17). Ursodeoxycholic acid (UDCA) was initiated in two patients with cholelithiasis, reducing gallstone size. Our other patients with gallstones did not require any intervention and remained asymptomatic. Elevation of liver transaminases during somatostatin therapy has been reported in 37% to 46.4% of cases (1,17). Among our patients, the rate of transiently elevated liver enzymes (26%) was lower, and these levels recovered during follow-up without treatment discontinuation.

Since somatostatin suppresses GH secretion, a reduction in growth rate may occur during treatment with somatostatin analogs. However, the risk of permanent growth retardation has been reported to be low (<5%) (18). In the study conducted by Le Quan Sang et al., 10 children receiving octreotide-LAR showed normal growth rates over 17 months of follow-up, with no side effects and a favourable glycemic response (19). In another study, a slight decrease in linear growth was observed, along with low levels of insulin-like growth factor I (IGF-I) and insulin-like growth factor–binding protein 3 (IGFBP-3) in two patients (20). In a multicenter study of 27 patients, height was evaluated in 17, and 7 (41.1%) were reported to have only a slight growth deceleration at the end of a mean follow-up of 18 months (1). In the present study, we assessed growth parameters for the longest follow-up duration of 71 months. There was no decline in growth velocity assessed before and during octreotide-LAR treatment. Besides, none of the patients had a height SDS below -2. Overall, somatostatin analog therapy does not appear to have a clinically meaningful negative effect on growth.

Neurodevelopmental delay and epilepsy are among the long-term complications of congenital hyperinsulinism (CHI) due to recurrent hypoglycemia (11). The rate of developmental delay has been reported to be higher in diazoxide-unresponsive patients compared to diazoxide-responsive CHI cases (34% vs.52.9%) (21). This higher rate is likely related to difficulties in achieving adequate glycemic control in the diazoxide-unresponsive group. In another study including both diazoxide-responsive and -unresponsive patients, neurodevelopmental delay and epilepsy were reported in 30% and 52% of patients (22). In our study, the rate of neurodevelopmental delay (43.4%) and epilepsy (30.4%) was comparable with previously reported rates from our country (21,23).

Our study had limitations: first, it was retrospective, which may have led to missing data; second, continuous glucose monitoring (CGM) data were not available to better document glycemic outcome. However, the present study has some strengths. First, congenital hyperinsulinism is a rare disorder, and the inclusion of 23 patients receiving long-term octreotide-LAR therapy represents a substantial clinical experience. Second, with a median follow-up of up to 71 months, this study provides one of the longest follow-up periods for octreotide-LAR treatment in CHI. This allowed evaluation of long-term efficacy, safety, growth, and neurodevelopmental outcomes.

Conclusion

In the present study, which evaluated the long-term follow-up of a large number of CHI cases, normoglycemia was achieved in the vast majority of patients, with no clinically meaningful negative impact on long-term growth outcomes. Transient elevation in liver enzyme and cholelithiasis were the most frequently observed side effects, indicating a safety profile comparable with short-acting octreotide. These results suggested that octreotide-LAR therapy is an effective and safe treatment option for CHI patients.

Declarations

Ethics approval: This study was performed in line with the principles ofthe Declaration of Helsinki. Approval was granted by Health Sciences, Diyarbakir Gazi Yasargil Training and Research Hospital Noninvasive Clinical Research Ethical Committee (Approval number: 2025/582).

Competing interests: The authors declare no competing interests.

Financial disclosure. The authors have no financial relationships relevant to this article to disclose.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Authors' Contributions:

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Table 1. Presenting characteristics of the patients

Female/male (n)	9/14
Gestational age (week), (mean±SD)	38 (37-39)
Birth weight (gr), (mean±SD)	3.463 ±549

Age at presentation (day), median (min-max)	15 (2-120)
Parental consanguinity, n (%)	17 (73.9 %)
Family history of CHI, n (%)	6 (26%)
Plasma glucose (mg/dL), (mean±SD)	33.7 ±9.4
Insulin (mU/L), median (min-max)	14.7 (9.5-21)

Table 2. Characteristics of octreotide long-acting release (LAR) therapy and observed side effects

Parameter	**Value**
Age at initiation of octreotide LAR therapy (months), median (min-max)	14 (min 7, max 125)
Duration of octreotide LAR therapy (months)	71.6±38.2
Dose of octreotide LAR therapy (mg), median (min-max)	20 (10-25)
Annual growth velocity during octreotide LAR therapy (cm/year) (mean±SD)	6.4±1.1
Elevation of liver transaminases, n (%)	6 (26%)
Cholelithiasis, n (%)	3 (13%)
Neurodevelopmental delay, n (%)	10 (43.4%)
Epilepsy, n (%)	7 (30.4%)
IGF-1 SDS (mean±SD)	-0.1±1
Δ height SDS (height SDS at last visit - height SDS prior to octreotide-LAR treatment) (mean±SD)	0.09 ±0.7

Data are expressed as mean ±SD or median (25th-75th percentiles)

Table. 3. Clinical, Genetic and Treatment Characteristics of Patients Receiving Octreotide-LAR

Family/ Patient Number	Age at Diagnosis (d/m)	GA/BW (Week/g)	Sex, Consanguinity	Gen	Location, DNA/Protein description	Variant classi-ficationaccord-ing to ACMD guidelines, zygosity	Treatment received before octreotide LAR	Octreotide-LAR initiation age	Octreotide LAR dosage (mg/m)	Duration for Octreotide LAR (m)
1	10d	36/3100	F, Yes	*ABCC8*	Exon 28 c.3554C>A p.Ala1185Glu (p.A1185E)	Missense, HM	Diazoxide, Octreotide	13months	30	111
2.1	10 d	40/4400	M, Yes	*ABCC8*	c.3554C.A; p.Ala1185Glu	HM	Diazoxide, Octreotide	8m	20	52
2.2	3d	33/2500	M, Yes	*ABCC8*	c.3554C.A; p.Ala1185Glu	HM	Diazoxide, Octreotide	16m	30	132
3.1	2d	37/4340	M, Yes	*ABCC8*	c.3512del, p.(Leu1171fs)	HM	Diazoxide, Octreotide	9m	20	51
3.2	2d	38/4380	F, Yes	*ABCC8*	c.3512del, p.(Leu1171fs)	HM -	Diazoxide, Octreotide, Nifedipine, Glucagon	9m	20	48
4	25d	38/3100	M, No	HADH	c.706C>T, p.(Arg236Ter)	Pathogenic, HM	Diazoxide	12m	20	94
5	30m	38/2800	M,Yes	No mutation			Diazoxide, Octreotide	48m	20	36
6	70d	39/3400	F, Yes	*ABCC8*	c.3509del p.Leu1170Argfs*38	Pathogenic, HM	Diazoxide, Octreotide	8m	15	63
7	1d	39/3300	F,Yes	*ABCC8*	c.176A>C p.His59Pro (p.H59P)	Missense, HM	Diazoxide, Octreotide, Glucagon	16m	15	115
8	15d	39/3160	M, Yes	*ABCC8*	c.4212_4214del p.(Ile1405del)	Pathogenic, HM	Diazoxide, Octreotide	9m	10	63
9	2d	38/3700	M, Yes	No mutation			Diazoxide, Octreotide, Glucagon Near-total pancreatectomy	14m	10	69

10	4m	37/3400	M, No	No mutation			Diazokxide, Octreotide	48	30	91
11	4d	38/3650	F,Yes	*ABCC8*	c.3512del p.(Leu1171fs)	Pathogenic, HM	Diazoxide, Octreotide	14	10mg/45d	68
12	15d	38/4310	M, Yes	No mutation			Diazoxide, Octreotide	8m	10	25
13	2d	38/3700	E, Yes	ABCC8	Exon28 c.3554 C>A p.Ala1185Glu (p.A1185E)	Missense, HM	Diazoxide, Octreotide	40m	30	103
14	7m	38/3300	M, No	No mutation			Diazoxide, Octreotide	125 m	30	32
15	7m	38/3050	F,Yes	No mutation			Diazoxide, Octreotide	19m	10	26
16	4m	39/3580	M, Yes	*ABCC8*	c.3617C>A p.Ala1206Glu	Missense, HT	Diazoxide, OctreotidePartial pancreatectomy	18m	7	7
17	7d	38/3200	M, Yes	No mutation			Diazoxide, Octreotide	7m	10	59
18	15d	39/3900	F, Yes	No mutation			Diazoxide, Octreotide	50m	30	100
19	38d	37/2600	M,No	No mutation			Diazoxide, Octreotide	18m	20	162
20	2d	34/3000	F,Yes	ABCC8	c.176A>Cp. (His59Pro)	uncertain significance, HM	Diazoxide, Octreotide	12 m	10	45
21	6m	39/3800	F, No	ABCC8	c.4045_4061delinsT(p.N1349fs)	HT	Diazoxide, Octreotide	24m	10mg/bi-monthly	96
GA: Gestational age, BW: Birth weight, M: Male, F: Female, d:day, m:month, y:year, HT: Heterozygous, HM: Homozygous										

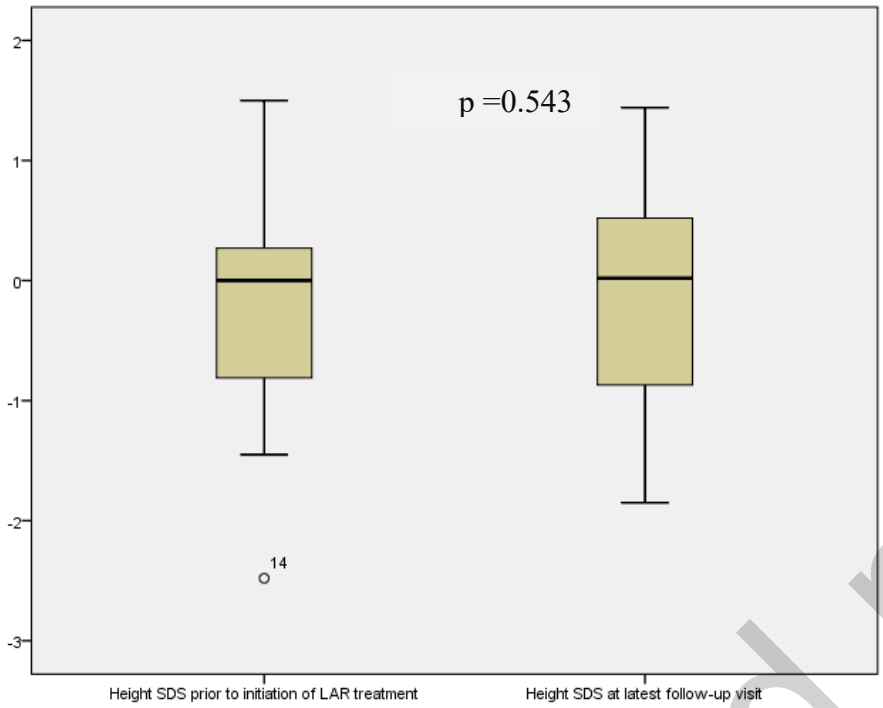

Figure 1. Comparison of height SDS of CHI patients before initiation of octreotide-LAR treatment and height SDS at the latest follow-up visit did not show a negative impact of octreotide-LAR therapy on longterm growth outcome.