A Multicenter Experience with Long-Acting Somatostatin Analogues in Patients with Congenital Hyperinsulinism

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Abstract

Background/Aims: Congenital hyperinsulinism (CHI) is a rare disease characterized by recurrent severe hypoglycemia. In the diffuse form of CHI, pharmacotherapy is the preferred choice of treatment. Long-acting somatostatin analogues have been used in children as off-label medication. However, the efficacy, outcomes, and adverse effect profiles of long-acting somatostatin analogues have not been described in multicentered studies. The aim of this retrospective study is to summarize the experience with long-acting somatostatin analogues in a large group of children with CHI. Methods: Data were obtained retrospectively from 27 patients with CHI who received long-acting somatostatin analogues in 6 different centers in Europe. These included information on glycemic stability, auxology, and adverse effect profile in clinical follow-up assessments. Results: Blood glucose control improved in most patients (89%). No life-threatening side effects occurred. Thirteen patients (48%) experienced side effects; in 3 patients (11%), the side effects were the main reason for discontinuation of the treatment. The most frequent side effect was elevated liver enzymes ($n = 10$, 37%). Conclusion: Long-acting somatostatin analogues are effective in glycemic control of patients with CHI. However, in 37% of all patients increased liver enzymes were observed. It is important to monitor liver function in all patients receiving long-acting somatostatin analogue therapy.

Introduction

Congenital hyperinsulinism (CHI) is characterized by persisting hypoglycemia due to dysregulated and excess secretion of insulin [1]. It comprises a heterogeneous group of disorders, with the underlying genetic etiology...
identified in approximately 40% of the patients. Until now, 9 different causative mutations have been described [2–4]. Early recognition and accurate management of CHI is of major importance in order to prevent brain damage and consequent neurodevelopmental problems [5–8].

In the focal form of CHI, hyperfunctioning pancreatic β-cells are localized in a solitary region of the pancreas, as a focal entity which can be detected by [F18]FDOPA-PET/CT [9–11]. The treatment of choice for the focal form is surgical excision of the lesion [1, 5, 12, 13]. Instead, in patients with the diffuse form of CHI, the treatment of choice consists of supplemental glucose and pharmacotherapy. Subtotal pancreatectomy is reserved for children in whom medical therapy is unable to achieve satisfactory glucose stability and/or is complicated by unacceptable side effects. However, this procedure inevitably results in the development of diabetes mellitus at a later age and in many cases exocrine pancreatic dysfunction [5, 12, 14]. Therefore, medical treatment is preferred over subtotal pancreatectomy to preserve pancreatic function while ensuring glycemic stability to protect the developing brain in early childhood. However, the pharmacological treatment of CHI is limited in choice and is often complicated by inefficacy and adverse events. Current medications in use are not licensed in children with CHI. There are no randomized clinical trials of novel therapies in CHI, which may be due to several factors, including the limited number of patients worldwide and the complexity of multicentered trial organization. Guidelines for medical therapy vary between centers with most treatment decisions being based primarily on expert opinion [15]. In the absence of robust evidence-based treatment regimens for CHI, it is important to collate international experience in new therapies for optimum clinical management.

Recommended first-line pharmacological treatment consists of diazoxide in combination with the diuretic chlorothiazide [5, 11]. Diazoxide acts on the ATP sensitive K+ (K-ATP) channel to reduce cell depolarization, thereby reducing insulin secretion [12]. However, not all patients respond to this treatment, particularly those with mutations in K-ATP channel genes (ABCC8, KCNJ11) [3, 16]. Diazoxide therapy is often complicated by side effects, such as fluid retention, thrombocytopenia, hypotrichosis, and gastrointestinal dysmotility, which may lead to discontinuation of the treatment [12]. Nifedipine, a calcium antagonist, has been prescribed in the past as second-line treatment if children do not respond to diazoxide. However, nifedipine is rarely used in clinical practice as the clinical response to this drug is generally unsatisfactory [12]. Continuous subcutaneous glucagon is another therapy choice and has been utilized not only in initial therapy of hypoglycemia but also in long-term treatment of CHI [11, 12]. However, the commercially available preparation of glucagon precipitates in slow-moving solutions within indwelling catheters causing obstruction and unreliable drug delivery [17]. Therefore, continuous glucagon is not currently envisaged for long-term treatment of CHI.

Somatostatin is a hormone that preserves electrical stability of the pancreatic β-cell membrane and therefore inhibits the release of insulin. Octreotide, a short-acting somatostatin analogue, is commonly used as second-line treatment of CHI, in preference over nifedipine or continuous glucagon. [12, 18]. The half-life of octreotide is relatively short at around 100 min; therefore, octreotide has to be administered by continuous intravenous infusion, frequent subcutaneous injections, or by continuous subcutaneous pump therapy [12]. Long-term subcutaneous octreotide treatment is demanding on the patient and family; multiple daily injections of home management or pump therapy are not always feasible. Side effects of octreotide treatment include gastrointestinal dysmotility and tachyphylaxis, requiring escalating drug dosage to maintain efficacy. Gallbladder sludge and/or stones are commonly reported, while a reduction in growth velocity has been occasionally reported [5]. Octreotide has the potential to reduce splanchnic circulation, with some groups reporting early- and late-onset necrotizing enterocolitis [19, 20]. Octreotide treatment can also cause drug-induced elevated liver transaminases [21, 22], necessitating drug reduction or withdrawal.

Longer-acting somatostatin analogues have been suggested as alternative treatment options for CHI, with the advantage of less frequent administration and possibly improving quality of life for patients and families [23–26]. However, the experience of long-acting somatostatin analogues is limited to isolated case reports and small groups of patients. Two long-acting somatostatin analogues are currently available, octreotide long-acting release (sandostatin-LAR) and somatuline autogel (lanreotide) [23, 25], although both drugs are not licensed for use in children with CHI. Both analogues are injected either subcutaneously or intramuscularly every 4–6 weeks, replicating therapy in adults with pituitary and gastrointestinal neuroendocrine tumors. The experience with sandostatin-LAR and lanreotide is limited to a few observational case reports in single centers reporting favorable outcomes [23–25]. The collective experience of long-act-
ing somatostatin analogue therapy needs to be reviewed to understand long-term efficacy, side effects, and application to CHI clinical management. In this study, we have collected information on the experience of long-acting somatostatin analogues in a large group of patients in several European centers.

**Patients and Methods**

In this multicenter study, we report the use of long-acting somatostatin analogues in patients with CHI. We gathered a total of 27 patients from 6 different pediatric departments in Europe – 8 patients at the Otto-von-Guericke University in Germany, 7 patients at the Odense University Hospital in Denmark, 2 patients at the Royal Manchester Children’s Hospital in the United Kingdom, 2 patients at the University Medical Center Utrecht, 2 patients at the Radboud University Medical Center in Nijmegen, and 6 patients at the University Medical Center Groningen, with the last 3 centers being located in the Netherlands.

Ethical approval for the study in the Netherlands was obtained from the Medical Ethical Committee from the University of Groningen, The Netherlands. In Germany, ethical approval was obtained according to national standards (IRB No. 27/08). In Denmark, the study was conducted according to the declaration of Helsinki and approved by The Research Ethics Committee (ref. No. 54947) and The Danish Data Protection agency (J. No. 16/28242). For the United Kingdom, this study was supported by The North West Research Ethics Committee (project reference No.: 07/H1010/88).

Informed consent was not necessary for this study as was stated by the Ethical Committees; however, it was obtained from the parents.

A uniform protocol was designed to collect specific standardized information in all patients. Additional information was recorded in each treatment center depending on local protocols of treatment. Patient data were collected by the treating physician, assimilated by the corresponding author in anonymous fashion, and stored in a secure database. The following data were collected: age at manifestation, sex, height standard deviation scores before and during treatment, genetic confirmation of CHI, type, dose of somatostatin analogue, whether local anesthetics were used before administration of the drug, the number of hypoglycemic episodes per week before and during treatment and/or interpretation of the treatment physician on hypoglycemia correction, and additional treatment options including pancreatic surgery. Drug side effect profile was based on biochemical testing of liver enzymes, thyroid function, insulin-like growth factor I, combined with ultrasound of the liver and gallbladder, and by noting abnormal clinical features not explained by the CHI disease process.

Follow-up arrangements to monitor adverse drug reaction were performed by the treating physician. In most cases, they performed an ultrasound of the liver and gallbladder in combination with biochemical testing every 3 months after initiating the treatment.

None of the patients responded sufficiently to diazoxide, or diazoxide had to be terminated due to side effects. The medical treatment was complemented with enriched feeds and enteral nutrition. All patients received octreotide for a period of 1–4 weeks. When octreotide treatment achieved a stable glycemic status, patients were switched to a long-acting somatostatin analogue. The decision on the type of long-acting somatostatin analogue depended on the choice of the treating clinician and local preferences. Sandostatin-LAR was easier to access in Denmark. All other centers used lanreotide due to convenience of drug access and local pharmacy support.

All patients started treatment in their respective hospitals. If glucose levels stabilized in the follow-up period after the first injection, subsequent injections were provided in the community by home care nurses. Almost all patients received some form of local anesthesia before administration of sandostatin-LAR and lanreotide. In some cases, depending on local policy, local anesthesia was combined with paracetamol or midazolam.

Sandostatin-LAR and lanreotide are produced in standard syringes of 10 and 60 mg, respectively. All patients started with the use of one standard syringe, which was administered once a month. Dose was not adjusted to the specific weight of the patients. There were a few exceptions to this rule; 4 patients had relatively low weights and a clinical decision was made in each case to administer half a syringe, i.e., a dose approximating 30 mg every 4 weeks. Other patients received lanreotide once every 6 weeks, which equals to 40 mg every 4 weeks.

Treatment response was defined as a reduction in hypoglycemia (defined by a glucose level below 3.5 mmol/L) with 90% of blood glucose measurements being in the normal range or if there was less need for other medication or reliance on enteral nutritional therapy.

Continuous subcutaneous glucose monitoring was performed occasionally during treatment. In most patients, this was not done on a regular basis and was reserved only for a period of 5–7 days. However, all patients had regular daily blood glucose monitoring using home glucose monitoring devices. These devices were not standardized; choice was dependent on local availability.

**Results**

In this study, we included 27 patients with CHI. Data derived from these patients are shown in Table 1. A total of 13 patients (48%) had ABCG8 mutations, of whom 2 children had focal CHI and 11 children had diffuse CHI. Three patients (11%) had KCNJ11 mutations. Four patients (15%) had Beckwith-Wiedemann syndrome, 1 patient was diagnosed with congenital disorder of glycosylation type 1A, and in the remaining 6 patients (22%), no mutation was identified.

Patients were treated with a mean duration of 18 months, with a range of 1–72 months. A total of 18 patients are presently being treated. Patients started long-acting somatostatin analogues at a median age of 12 months (range 2 months to 17 years).

In total, 15 patients received monotherapy with a long-acting somatostatin analogue combined with glucose-en-
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of manifestation</th>
<th>Diagnosis/mutation</th>
<th>Diffuse/ focal</th>
<th>Pancreatectomy</th>
<th>Long-acting somatostatin Duration of treatment</th>
<th>Reported side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>After birth</td>
<td>Beckwith-Wiedemann</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 3 months</td>
<td>Elevated γ-glutamyltransferase and gallstones</td>
</tr>
<tr>
<td>2</td>
<td>20 months</td>
<td>Congenital disorder of glycosylation type 1a</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 1 month</td>
<td>Elevated liver enzymes (ASAT, ALAT, and AF)</td>
</tr>
<tr>
<td>3</td>
<td>After birth</td>
<td>Heterozygous KCNJ11 mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (30 mg/month) 11 months (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>After birth</td>
<td>Beckwith-Wiedemann</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 1 year</td>
<td>Elevated liver enzymes and sludging of gallbladder, no gallstones</td>
</tr>
<tr>
<td>5</td>
<td>After birth</td>
<td>Compound heterozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>Yes, partial</td>
<td>Lanreotide (60 mg/month) 10 months (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>After birth</td>
<td>Heterozygous ABCC8 gene mutation</td>
<td>Focal</td>
<td>No, excision focal lesion</td>
<td>Lanreotide (60 mg/month) 2 months</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>After birth</td>
<td>No mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 4 years (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>After birth</td>
<td>Heterozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 3½ years</td>
<td>None</td>
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<tr>
<td>9</td>
<td>After birth</td>
<td>No mutation</td>
<td>Diffuse</td>
<td>Yes, partial</td>
<td>Lanreotide (60 mg/month) 2 years (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>After birth</td>
<td>Homozygous KCNJ11 gene mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 4 years (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>2 months</td>
<td>Heterozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>Yes, partial</td>
<td>Lanreotide (60 mg/6 weeks) 2 years (ongoing)</td>
<td>Mildly elevated liver enzymes (ASAT + ALAT)</td>
</tr>
<tr>
<td>12</td>
<td>4 months</td>
<td>Paternal heterozygous ABCC8 gene mutation</td>
<td>Focal</td>
<td>Yes, excision focal lesion</td>
<td>Lanreotide (60 mg/month) 6 months</td>
<td>Mildly elevated liver enzymes (ASAT + ALAT), low IGF-1</td>
</tr>
<tr>
<td>13</td>
<td>After birth</td>
<td>Heterozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 6 months (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>After birth</td>
<td>Homozygous KCNJ11 gene mutation</td>
<td>Diffuse</td>
<td>Yes, partial</td>
<td>Lanreotide (60 mg/month) 2 years (ongoing)</td>
<td>Sludging of gallbladder + hepatomegaly</td>
</tr>
<tr>
<td>15</td>
<td>After birth</td>
<td>Homozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month) 2 years</td>
<td>Increased liver enzymes (AF). Reluctant to have injections, therefore difficulty in administering</td>
</tr>
<tr>
<td>16</td>
<td>6 months</td>
<td>No mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Sandostatin-LAR (10 mg/month) 6 years</td>
<td>Low IGF-1</td>
</tr>
<tr>
<td>17</td>
<td>After birth</td>
<td>Heterozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>Yes, subtotal</td>
<td>Sandostatin-LAR (10 mg/month) 2 years (ongoing)</td>
<td>Thyroid hormone abnormalities (TSH depression), mildly elevated liver enzymes (ALAT)</td>
</tr>
<tr>
<td>18</td>
<td>After birth</td>
<td>Heterozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>Yes, subtotal</td>
<td>Sandostatin-LAR (5 mg/month) 1 year (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>19</td>
<td>After birth</td>
<td>No mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Sandostatin-LAR (7 mg/month) 1 year (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>20</td>
<td>After birth</td>
<td>Beckwith-Wiedemann</td>
<td>Diffuse</td>
<td>Yes, subtotal</td>
<td>Sandostatin-LAR (10 mg/month) 6 months (ongoing)</td>
<td>Mildly elevated AF</td>
</tr>
<tr>
<td>21</td>
<td>4 days</td>
<td>No mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Sandostatin-LAR (10 mg/month) 6 months (ongoing)</td>
<td>None</td>
</tr>
<tr>
<td>22</td>
<td>4 months</td>
<td>No mutation</td>
<td>Diffuse</td>
<td>Yes, subtotal</td>
<td>Sandostatin-LAR (5 mg/month) 4 months (ongoing)</td>
<td>None</td>
</tr>
</tbody>
</table>
Enriched feeds. Eight patients received combined treatment with diazoxide, and 2 patients continued treatment with nifedipine. Two patients discontinued treatment with long-acting somatostatin analogues because of normalization of glucose levels; in both patients, normal glucose levels persisted after treatment withdrawal.

Two patients with focal CHI associated with paternal heterozygous mutations in ABCC8 were treated with lanreotide until surgical excision of the focal lesion was performed. Among the remaining 25 patients with diffuse CHI, partial (approximately 30%) or subtotal pancreatectomy (approximately 90%) was performed in 10 patients due to insufficient glucose control with medical treatment. Three patients among this group had been treated with long-acting somatostatin analogue prior to surgery, while in 7 patients, treatment with long-acting somatostatin analogue was initiated after pancreatectomy.

Long-acting somatostatin was noted to stabilize blood glucose levels to clinically acceptable levels in 24 patients (89%). In the remaining 3 patients, treatment benefit was less clear and was suboptimal. In those patients, glucose levels were not maintained in 90% of measurements despite treatment with long-acting somatostatin analogues.

Side effects were noted in 13 of 27 patients (48%). There were no life threatening acute events which needed hospitalization. In 3 patients (11%), the side effects were the main reason for discontinuation of the medication. One patient suffered from recurrent abscess formation at the site of injection, which needed surgical intervention. In 2 patients, elevated liver enzymes were the reason for discontinuation.

The most frequently reported side effect was elevated liver enzymes (37% of all patients). One patient developed asymptomatic cholelithiasis, observed during ultrasound examination. After cessation of treatment, liver enzymes normalized, and after commencing ursodeoxycholic acid, gallstones disappeared. Two patients developed biliary sludging in the gallbladder; in one, hepatosplenomegaly was also present. In 5 patients mildly elevated transaminases levels (defined by transaminase levels 50–80 U/L) were present. These patients continued treatment without further increase in liver enzymes. There was a substantial rise in transaminases in 2 patients. In 1 patient, liver enzymes had already been mildly elevated prior to lanreotide therapy. Following lanreotide treatment, liver enzymes increased significantly; aspartate aminotransferase increased to 418 U/L and alanine aminotransferase increased to 950 U/L. After stopping lanreotide, all enzymes normalized within 3 months. In another patient, an elevated transaminase >80 U/L was noted following initiation of lanreotide therapy. However, as transaminase levels did not rise further with subsequent injections, treatment was continued for 1 year. Following withdrawal of lanreotide treatment, transaminase levels normalized within 6 months. In 2 patients, alkaline phosphatase levels were raised, while transaminase and γ-glutamyltransferase levels remained

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of manifestation</th>
<th>Diagnosis/mutation</th>
<th>Diffuse/focal</th>
<th>Pancreatectomy</th>
<th>Long-acting somatostatin</th>
<th>Duration of treatment</th>
<th>Reported side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>After birth</td>
<td>ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month)</td>
<td>1 year and 9 months (ongoing)</td>
<td>Local skin fibrosis</td>
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<td>24</td>
<td>After birth</td>
<td>Beckwith-Wiedemann</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60–90 mg/month)</td>
<td>1 year (ongoing)</td>
<td>Mildly elevated liver enzymes (ASAT + AF)</td>
</tr>
<tr>
<td>25</td>
<td>After birth</td>
<td>Homozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>Yes, partial</td>
<td>Lanreotide (30–60 mg/month)</td>
<td>4 months</td>
<td>Skin abscess formation</td>
</tr>
<tr>
<td>26</td>
<td>After birth</td>
<td>Homozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>Yes, partial</td>
<td>Lanreotide (60–90 mg/month)</td>
<td>2 years and 8 months (ongoing)</td>
<td>Mildly elevated liver enzymes (ALAT)</td>
</tr>
<tr>
<td>27</td>
<td>After birth</td>
<td>Homozygous ABCC8 gene mutation</td>
<td>Diffuse</td>
<td>No</td>
<td>Lanreotide (60 mg/month)</td>
<td>8 weeks</td>
<td>None</td>
</tr>
</tbody>
</table>

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; AF, alkaline phosphatase; IGF-1, insulin-like growth factor 1; TSH, thyroid-stimulating hormone.
Long-Acting Somatostatin Treatment in Congenital Hyperinsulinism

normal. Alkaline phosphatase levels spontaneously normalized while on treatment.

In 1 patient, low serum thyroxine levels were reported, and he was treated with levothyroxine. A total of 2 patients reported adverse local skin reactions. Longitudinal growth was evaluated in 17 patients (63%). Although 7 patients showed a mild decrease in growth, there were no patients in whom the height for age decreased below –2 standard deviations. The weight for height was evaluated in 18 patients (67%). In most patients, the weight for height decreased to near normal. Only 3 patients continued to have a weight for height above 2 standard deviations. During treatment, there were no patients who reported tachyphylaxis. No patients developed signs of necrotizing enterocolitis during treatment.

Discussion

The aim of this retrospective study is to share our international experience with long-acting somatostatin analogues in young patients with CHI. In our experience, long-acting somatostatin analogues are an effective treatment option in most patients with diazoxide-unresponsive CHI. Serious side effects did not occur; however, in 37 percent of the patients, increased liver enzymes were observed. Minor side effects were observed in the majority of the patients. We therefore recommend close monitoring of side effects during treatment with long-acting somatostatin analogues.

CHI is a relatively rare disease where hypoglycemia can be resistant to conventional treatment. Patients who are unresponsive to diazoxide can be treated with octreotide either by frequent subcutaneous injections or by pump therapy. Both require intensive daily care, so alternative therapies are sought. Recently, there have been a few reports about the use of long-acting somatostatin analogues in diazoxide-unresponsive patients [23–26]. At present, experience with this treatment is limited and data about side effects are lacking. Our study has provided an overview of efficacy and safety data in a retrospective and observational cohort.

The present study has several limitations, mostly due to its retrospective nature. The efficacy on glycemic profile is based upon the interpretation of the treating physician, since continuous glucose monitoring data before and during treatment were not available in all the patients. In a previous study, a decreased incidence of hypoglycemic episodes had been observed in 6 patients who switched from octreotide 3–4 times a day to lanreotide [24]. Another study described 2 patients with adequate glucose regulation on continuous octreotide therapy, with comparable regulation after switching to lanreotide [23]. Our findings in a larger cohort are similar to those previously described.

Patients included in this study were treated with a long-acting somatostatin analogue, either lanreotide or sandostatin-LAR. Both are octapeptides and proved effective in glucose regulation, but differ by their pharmacokinetic profiles [27]. Lanreotide starts with a rapid-release phase, followed by a long-lasting phase of slow release. Sandostatin-LAR is formulated as microspheres of biodegradable polymer containing the active peptides. After a single intramuscular injection, the plasma concentration remains very low during the first 2 weeks and then increases quickly to reach a plateau, which remains stable between 3 and 4 weeks [26, 27]. There is no specific data available about the difference in efficacy or side effects between the different long-acting somatostatin analogues. Further research is needed to evaluate which one is more preferable in children with CHI; our study was not designed to address the efficacy and safety performance of one over the other. In the present study, increased liver enzymes were observed in the lanreotide group as well as in the sandostatin-LAR group. Recently, a new somatostatin analogue, called pasireotide, has been available with a more specific binding to somatostatin receptor subtypes [28]. In the future, this could also be of use in the treatment of CHI, with potentially fewer side effects. However, pasireotide has not been used in children for any medical indication.

The most favorable dose of lanreotide in terms of efficacy and side effects is not known. One study used 30 mg [23] and another study used 60 mg [24], with no comparable data to choose a higher or lower dose. In our study, most patients received lanreotide 60 mg administered as the entire contents of a prefilled syringe. Our study highlights the need to undertake a rigorous trial with efficacy and safety outcomes to standardize drug dosage of lanreotide.

Somatostatin has inhibitory effects on gastrointestinal motility, gallbladder contractility, and splanchnic blood flow, which can result in gastrointestinal symptoms, cholelithiasis, hepatitis, and necrotizing enterocolitis. Therefore, there are theoretical grounds to be cautious about the prescription of somatostatin analogues to very young patients or patients with compromised intestinal perfusion. However, none of our patients developed necrotizing enterocolitis. Nevertheless, it would be prudent to limit long-acting somatostatin analogue treatment to in-
fants beyond the neonatal period and avoid treatment in those predisposed to necrotizing enterocolitis.

The most common side effect in the present study was the increase of hepatic enzymes, a sign of hepatitis. Short-acting somatostatin analogues are well recognized to cause hepatitis, manifested by elevated liver enzymes (transaminases and γ-glutamyltransferase) in patients with CHI [21, 22]. As sandostatin-LAR and lanreotide are long acting and depot preparations of somatostatin analogues, liver enzyme elevation is not an unexpected adverse reaction, resulting from the long transit time of the active drug in the body. Earlier research reported that this side effect is reversible after cessation of treatment [15]. In patients who stopped treatment, liver enzymes normalized, suggesting that drug-induced hepatitis is reversible.

Since a major part of the treatment of CHI consists of high concentration of carbohydrate feeds, almost all patients developed obesity prior to treatment with long-acting somatostatin analogue therapy. Subsequent treatment with long-acting somatostatin analogues did not increase the risk of obesity.

In conclusion, the summary of our patient data showed that monthly injections of long-acting somatostatin analogues were effective in maintaining euglycemia without serious side effects in the majority of patients. Increased liver enzymes were observed in 37% of the patients, which should be carefully monitored.

Based on our common experience, we recommend the following:
− Consider long-acting somatostatin analogues in diazoxide-unresponsive patients after a trial of treatment with octreotide. If octreotide is effective and no severe side effects occur after a trial period, lanreotide (start dosage 30–60 mg subcutaneously every 4 weeks) or sandostatin-LAR (start dosage 10 mg intramuscularly every 4 weeks) could be considered.
− Avoid treatment with somatostatin analogues in patients with an increased risk of necrotizing enterocolitis.
− Patients receiving long-acting somatostatin analogue treatment should be monitored by blood glucose monitoring and/or continuous subcutaneous glucose monitoring to ensure satisfactory treatment response.
− Monitor liver enzymes every 4–6 weeks and repeat abdominal ultrasound every 3–6 months. If asymptomatic cholelithiasis is present, ursodeoxycholic acid may be added to the treatment regimen.
− Monitor growth and thyroid function at least 6-monthly. If tests indicate hypothyroxinemia, levothyroxine treatment may be required.

Disclosure Statement
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References


