Full title: Use of Long-Acting Somatostatin Analogue (Lanreotide) in three children with Focal Forms of Congenital Hyperinsulinaemic Hypoglycaemia.

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Established Facts

- Long-Acting Somatostatin Analogue (Lanreotide) is effective in the management of patients with Congenital Hyperinsulinaemic Hypoglycaemia (CHI) unresponsive to Diazoxide.

- To date there are no publications regarding the effect of Lanreotide in CHI patients with focal pancreatic lesions.

Novel Insights

- Focal lesions in the pancreatic head associated with CHI can be surgically challenging; hence conservative treatment would be preferable.

- Lanreotide may be a novel and effective therapeutic option for CHI patients with inoperable focal lesions.

ABSTRACT

Background: Long-Acting Somatostatin Analogue (Lanreotide) is used in the management of Diazoxide-unresponsive diffuse form of Congenital Hyperinsulinism (CHI). However, no reports of its use in the focal form of CHI exist.

Case 1: A one-month-old boy diagnosed with Diazoxide-unresponsive CHI due to a paternal heterozygous *ABCC8* gene mutation showed partial response to Octreotide. 18F-DOPA-PET/CT scan revealed a focal lesion in the pancreatic head. Surgical removal of the lesion was unsuccessful. He was switched to monthly Lanreotide treatment at the age of 11 months, which stabilised his blood glucose over a 12 month period.

Case 2: A one-month-old boy with diazoxide-unresponsive CHI due to a paternal heterozygous *KCNJ11* gene mutation was partially Octreotide-responsive. 18F-DOPA-PET/CT scan confirmed a focal pancreatic head lesion. Over 6 months, he underwent three lesionectomies and afterwards responded to Octreotide. At the age of 9 months, treatment was switched to monthly Lanreotide. Currently, he is aged 3, with stable glycaemia and improved fasting tolerance.

Case 3: A three–week-old girl with a paternal heterozygous *ABCC8* gene mutation was diazoxide-unresponsive. 18F-DOPA-PET/CT scan confirmed a focal pancreatic head lesion. She responded to octreotide and parents preferred to avoid pancreatic surgery. At the age of 20 months, treatment was switched to monthly Lanreotide, resulting in euglycaemia over the last 7 months.

Conclusion: CHI patients with focal pancreatic head lesions are challenging, especially if not surgically amenable. Conservative treatment is preferable and Lanreotide might be an option. The therapeutic impact of Lanreotide treatment in focal forms of CHI should be confirmed in prospective studies, with close monitoring of the side effects.

Background:

Congenital hyperinsulinism (CHI) is characterised by the inappropriate, excessive secretion of insulin from the pancreatic beta-cell, and is the most common cause of persistent hypoglycaemia in infancy (1). CHI is a heterogeneous disorder with respect to clinical presentation, imaging, histology and genetics. Mutations in at

least eleven different genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A*, *HNF1A, PMM2, HK*) have been reported so far as the genetic causes of CHI (1, 2, 3, 4, 5). There are two main histological types of CHI: diffuse and focal; these are clinically identical but differ in the underlying genetic mechanism, histopathology and management. The focal lesions are characterised by nodular hyperplasia of islet-like cell clusters with ductulo-insular complexes and scattered giant beta-cell nuclei with normal surrounding tissue (6), whereas in the diffuse form, the entire pancreas has enlarged islets with hypertrophied beta-cells.

Focal CHI results from a paternally inherited heterozygous *ABCC8* or *KCNJ11* mutation, together with a somatic loss of the maternal chromosome in the 11p15 region (most likely caused by paternal isodisomy) (6, 7, 8). Fluorine-18 L-3, 4 dihydroxyphenylalanine positron emission tomography computed tomography (18F-DOPA–PET/CT) scan can help to differentiate focal from diffuse forms of CHI and subsequently aid in the management of these patients (9). Focal CHI is usually medically unresponsive, although diazoxide-responsive focal CHI has recently been described (10). Targeted surgical removal of the lesion will cure the patient (11). Sometimes, the management of focal CHI presents paediatric endocrinologists with a choice of unsatisfactory treatments either due to an inoperable position of the lesion or due to post pancreatectomy complications such as failure to cure hypoglycaemia and eventual diabetes mellitus at puberty (11, 12).

The three cases presented in this report (Table 1) pioneered a more conservative approach in successfully treating CHI patients with a focal lesion in the pancreatic head with Lanreotide together with frequent feeds. Using this approach, we were able to achieve euglycaemia and normal growth. The most important aspect was the quality of life improvement, since the daily care of our patients was simpler with one injection every 4 weeks leading to improved blood glucose regulation.

Case 1:

A 1-month-old boy born at 38 weeks gestation, with a birth weight of +0.05 SDS, with normal antenatal history, was diagnosed with CHI on the first day of life. He was unresponsive to maximum doses of Diazoxide (20 mg/kg/day) and Chlorothiazide (7 mg/kg/day) and subsequently commenced on Octreotide (10 mcg/kg/day given as 4 subcutaneous injections). He was fed by nasogastric tube (NGT) on a three-hourly regimen of high calorie milk feeds (CHO 10%), with complete aversion to oral feeds and a weight on the 99.6[th] centile. He continued to

have episodes of hypoglycaemia and was transferred to our unit for further management. Upon arrival, blood glucose was stabilised on intravenous fluids (iv) (20% dextrose = 4.3mg/kg/min), octreotide injections and three hourly feeds.

Genetic testing revealed a heterozygous nonsense *ABCC8* gene mutation [c.2464C>T; p.Gln822Ter]. ^{18}F-DOPA-PET/CT scan confirmed a focal lesion in the head of the pancreas (Figure 1). Lesionectomy via laparotomy was unsuccessfully attempted as the focal lesion was found to be extensive, occupying the pancreatic head with infiltration of duodenum and common bile duct, requiring Whipples procedure. Multiple pancreatic biopsies from the head and surrounding structures confirmed focal CHI. Parents were not keen to undertake radical pancreatic surgery and wished to attempt medical treatment, failing which a more extensive procedure could be planned at a later date.

Consequently, therapy with Sirolimus (mTOR inhibitor) was started (maximum: 6 mg/m^2/day) along with six hourly sc Octreotide injections (maximum: 40 mcg/kg/day) and 2 hourly oral feeds (12% CHO) during the day and 12 hours of overnight continuous 12% Vitajule® via percutaneous gastrostomy (PEG). Following several infections including line sepsis, and inadequate response to sirolimus, it was decided to suspend this medication.

A trial of Lanreotide (Somatuline autogel) was then commenced after parental consent. Four weekly sc Lanreotide at a dose of 30mg achieved euglycaemia, and Octreotide injections were weaned over 3 months and then stopped. Over the last twelve months, he has been on sc Lanreotide injection combined with 3 hourly oral feeds and continuous overnight 12% Vitajule® feeds via PEG. His blood glucose is stable and he is able to fast for up to three hours during the daytime. Consequently, his quality of life has markedly improved and he was discharged home on one injection every 4 weeks, with appropriate neurodevelopmental milestones.

<u>Case 2:</u>

A one-month-old boy was admitted for further management of CHI as he was unresponsive to Diazoxide. He was born by spontaneous vaginal delivery at 38 weeks gestation with a birth weight of +4.1 SDS, with no history of maternal diabetes mellitus. A few hours after birth he was found to be hypoglycaemic and further biochemical investigations confirmed CHI, hence he was commenced on Diazoxide and Chlorothiazide, but was unresponsive to maximum doses. He was subsequently commenced on six hourly sc Octreotide injections and had a partial response to a

maximal dose (40mcg/kg/day). He continued to be on 3 hourly feeds and iv dextrose (up to 12 mg/kg/min).

Sanger sequencing identified a paternally inherited heterozygous missense *KCNJ11* mutation [p.G40D, c.119G>A]. ^{18}F-DOPA PET/CT scan confirmed increased uptake of ^{18}F-DOPA in the head of the pancreas (SUVmax 4.0), compatible with a focal lesion (Figure 1).

He underwent removal of the focal lesion from the head of the pancreas at the age of three months. The histopathology report confirmed focal endocrine cell hyperplasia. Unfortunately, post-surgery he continued to have multiple episodes of hypoglycaemia that required iv administration of high glucose concentrations, and he had to be recommenced on infusions of sc Octreotide (40mcg/kg/day) and iv Glucagon (5mcg/kg/hour) in order to maintain normoglycaemia.

In view of persistent severe CHI, a second ^{18}F-DOPA-PET/CT scan was performed which showed an increase in tracer uptake in the pancreatic head/uncinate process (SUVmax 7.9) with lower grade activity in the pancreatic body (SUVmax 3.6). A second pancreatic resection was attempted at the age of 4 months, with removal of the whole head of the pancreas and histopathology sections confirmed focal endocrine hyperplasia.

However hypoglycaemia persisted and he required continuous infusions of sc Octreotide (40mcg/kg/day) and iv Glucagon (5mcg/kg/hour). Since the patient was not fully responsive, a trial of Sirolimus (maximum 16mg/m^2/day) was given, but was later stopped in view of a poor response and episodes of central line sepsis, a probable side effect of sirolimus-related immunosuppression.

At 7 months of age, he continued to have hypoglycaemia and a third pancreatic resection was attempted for removal of the residual pancreatic head and margins of distal pancreas, with formation of a Roux-en Y anastomosis to the body of the pancreas and common bile duct. The histopathology report showed that the lesional cells expressed proinsulin and insulin, glucagon and somatostatin with only minimal expression of pancreatic polypeptide. Ki67 immunostaining confirmed increased proliferation in the lesional cells and normal pancreas at the resected margin. Paraffin section adjacent to this margin showed some lesional tissue in close proximity, but not at the margin.

Interestingly, after the third pancreatic resection, the patient responded to sc Octreotide injections (30mcg/kg/day divided in 4 injections a day) and 3 hourly oral feeds during the day with 12 hours overnight continuous gastrostomy feeds. At nine

months of age his treatment was switched from Octreotide to Lanreotide 30mg every four weeks. Octreotide dose was weaned gradually over 2 months and then stopped. Over the last 2.5 years, he has been on sc Lanreotide injections now stretched to 30mg every 5 weekly with 4 hourly oral feeds during the day and continuous overnight continuous gastrostomy feeds. His blood glucose concentrations are currently stable and he is able to fast for eight hours at the age of 3 years. The child has developed pancreatic exocrine insufficiency needing pancreatic enzyme supplements, and so far he has not experienced any adverse reactions to Lanreotide. His quality of life and fast tolerance improved after switching to monthly injections of somatostatin analogue.

Case 3:

A 21-day old girl diagnosed with CHI on the first day of life was admitted to our hospital for further management of her condition. She was born at 39^{+1} weeks gestation, with a birth weight of +0.03 SDS and there was no history of gestational diabetes. She was unresponsive to maximum doses of Diazoxide (20 mg/kg/day) and Chlorothiazide (7.5 mg/kg/day). She was subsequently stabilised on iv infusion of Glucagon (maximum: 5mcg/kg/hr) and sc infusion of Octreotide (maximum: 30 mcg/kg/day) and this seemed to improve her blood glucose concentrations. At that point, genetic testing revealed a heterozygous nonsense *ABCC8* gene mutation [p.G1401R] and subsequently the ^{18}F-DOPA-PET/CT scan confirmed a focal lesion in the head of the pancreas (Figure 1). The option of lesionectomy was discussed with the family, but due to the high risk of surgical complications, the parents preferred to attempt medical treatment.

Consequently, normoglycaemia was successfully established on sc Octreotide injections (maximum: 35mcg/kg/day) four times per day and on 3-4 hourly oral feeds with a maximum fasting duration of 4 hours. However, she still continued to have occasional hypoglycaemia and at the age of 20 months, a trial with Lanreotide (Somatuline autogel) was commenced after parental consent. Four weekly Lanreotide at a dose of 30mg achieved euglycaemia, and Octreotide injections were weaned over 3 months and then stopped. Over the last seven months, she has been on sc Lanreotide injections 30mg every 4 weeks, and on 4-5 hourly oral feeds. Her blood glucose is currently stable, she is able to fast for twelve hours and achieved appropriate neurodevelopmental milestones.

Discussion

Lanreotide is a synthetic octapeptide analogue of somatostatin, a naturally occurring inhibitory hormone that blocks the release of several other hormones, including growth hormone, thyroid-stimulating hormone (TSH), insulin and glucagon. Lanreotide binds to the same receptors as somatostatin, although with higher affinity to peripheral receptors, and has similar activity. It has a high binding affinity for human somatostatin receptors (SSTR) 2 and 5, and a reduced binding affinity for human SSTR 1, 3 and 4. Given that Lanreotide has a much longer half-life than somatostatin, it generates more prolonged effects (13). The use of Lanreotide in the treatment of acromegaly due to both pituitary and non-pituitary growth hormone-secreting tumours is well documented, as is its use in the management of symptoms caused by neuroendocrine tumours, particularly carcinoid tumours and VIPomas. Lanreotide also shows activity against non-endocrine tumours, and, along with other somatostatin analogues, is being studied as a possible general anti-tumour agent (14, 15).

Recently, Lanreotide has been used for the treatment of CHI. Three long-acting formulations, namely octreotide LAR, Lanreotide acetate and an aqueous slow-release depot preparation (Autogel) have been developed, in an effort to increase the dosing interval and provide a more sustained clinical effect (16, 17, 18). Previous studies (19, 20, 21, 22, 23) concluded that Lanreotide acetate may be a safe and effective alternative therapy in patients with diffuse forms of CHI, offering an improved quality of life, since it is well tolerated and contributes to a clear simplification of the medical care. It is recommended that longer follow-up of a larger patient cohort is needed to establish this therapeutic option for CHI patients and to define the optimal age for initiating treatment (19). Shah et al. reported a significantly improved outcome in quality of life post-Lanreotide injection in an adolescent with severe side-effects due to diazoxide (22). Van Der Steen I. *et al* have recently reported two patients with focal CHI associated with paternal heterozygous mutations in *ABCC8* successfully treated for a limited period of 2 and 6 months with Lanreotide until surgical excision of the focal lesion was performed. One patient did not experience any side effects, while the other one developed mildly elevated liver enzymes (ASAT, ALAT) and low IGF-1 (23). In our case series, none of the patients demonstrated side effects within a period of 7–27 months, hence Lanreotide remains their on-going therapy along with glucose-enriched feeds. Moreover, case 1 and 3 have been on Lanreotide therapy for 12 and 7 months respectively contributing to the avoidance of complex pancreatic surgery and its complications. We have also reported that, compared to other studies, a lower dose of Lanreotide is sufficient to manage children with hyperinsulinism.

Lanreotide causes the same adverse effects as other somatostatin analogues (24). A retrospective study of 27 patients with CHI who received long-acting somatostatin analogues

reported side effects in 13 of 27 patients (48%), without any life threatening acute events, whilst in 3 patients (11%) medication was discontinued due to side effects (*23*). Side effects include mild to moderate pain at the injection site and gastrointestinal disturbances, such as diarrhoea, nausea, vomiting and less frequently, necrotizing enterocolitis. However, long-term treatment with Lanreotide has been associated with gallstone formation, cholestatic jaundice and elevated liver enzymes that are reversible after cessation of treatment (20, 23). Furthermore, Lanreotide can inhibit growth hormone and TSH secretion causing growth issues or thyroid dysfunction. In conclusion, it is important to monitor for side effects in children on long-acting somatostatin analogue therapy.

These cases illustrate that focal CHI may be managed with Lanreotide injections, even during the first years of life, especially those CHI patients with inoperable focal lesions in the pancreatic head. This conservative therapeutic option seems to achieve adequate glycaemic control in CHI patients in a more acceptable manner (monthly injections instead of frequent daily Octreotide injections) and is associated with fewer complications such as gastrointestinal symptoms, hypertrichosis, reduced orality, obesity and episodes of sepsis than the previously used medical options (Diazoxide, Octreotide, Sirolimus). Furthermore, this therapeutic option was less stressful for the patients and their families, by either avoiding pancreatic surgery completely (Case 1 and 3), or by avoiding more extensive pancreatectomy (Case 2). This is particularly important as emerging evidence suggests that CHI might become milder with the passage of time (24). Therefore, therapies such as Lanreotide offer the patient the opportunity to avoid pancreatic surgery, and consequently its associated immediate and long-term post-operative complications. Somatostatin receptor expression studies in focal and diffuse forms of CHI performed by our group showing that somatostatin receptor 2 (SSTR2) is expressed in some focal pancreatic tissues (to be published). This suggests that Lanreotide is likely to work in focal CHI due to its effect via SSTR2 to inhibit insulin secretion. However, more studies need to be undertaken to look for a correlation between genetics and somatostatin receptor expression in the islets. The beneficial therapeutic impact of Lanreotide treatment observed in these patients should be confirmed in prospective studies and the patients should be closely monitored for potential side effects.

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Figure 1: ^{18}F-DOPA-PET/CT scan confirm a focal lesion in the head of the pancreas: Case 1, Case 2, Case 3

Table 1. Clinical, genetic and imaging characteristics and therapeutic responses in three patients with focal CHI.