Efficacy and safety of octreotide for the treatment of congenital hyperinsulinism: a prospective, open-label clinical trial and an observational study in Japan using a nationwide registry

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Abstract. Octreotide, a long-acting somatostatin analog, has been used for treating hypoglycemia caused by congenital hyperinsulinism (CHI). However, octreotide has not been evaluated in clinical trials and has not been approved in any developed country. We aimed to test the efficacy and safety of octreotide for diazoxide-unresponsive CHI through a combination of a single-arm, open-label clinical trial (SCORCH study) and an observational study to collect data on the clinical course of patients treated off-label in Japan (SCORCH registry). In the SCORCH study, 5 patients were stabilized (blood glucose > 45 mg/dL) by hypertonic glucose infusion, and treated by continuous subcutaneous octreotide infusion at a dose of 5-25 μg/kg/day. Continuous blood glucose monitoring was performed between -24 and +48 hours. In 3 patients, a clinically meaningful rise in blood glucose was achieved and therapy was continued. The glucose infusion was gradually decreased and stopped after 5, 11, and 174 days, respectively. In one case, remission of CHI was reached after 606 days and octreotide was discontinued. The SCORCH registry included 19 diazoxide-unresponsive patients treated by subcutaneous octreotide, by continuous infusion or multiple daily injections. Of the 17 patients treated with hypertonic glucose infusion, the infusion rate was reduced after 4 weeks to less than 50% in 11 patients (64.7%) and stopped in 9 (52.9%). During the combined observation period of 695.4 patient-months in both studies, no severe adverse events related to octreotide were observed. In conclusion, subcutaneous octreotide injection was effective and well tolerated in the majority of patients with diazoxide-unresponsive CHI.

Key words: Congenital hyperinsulinism, Hypoglycemia, Octreotide

CONGENITAL HYPERINSULINISM (CHI) is the most common cause of persistent hypoglycemia in neonates and infants caused by dysregulated excessive secretion of insulin from the pancreatic β cells. The incidence of persistent CHI is low and estimated at 1 in 35,400 live births in Japan (2011 National Survey) [1]. Nonetheless, appropriate treatment is critically important as profound and repeated episodes of hypoglycemia often cause severe psychomotor retardation [2, 3]. Histologically, the majority of CHI cases can be categorized into one of two forms: the focal form, in
which abnormal β cells are confined to a restricted area of the pancreas; and the diffuse form, in which all β cells in the pancreas are abnormal [4-6]. The focal form of CHI is associated with a monoallelic, recessive paternally-inherited mutation in one of the genes, KCNJ11 or ABCC8, which code for the two subunits of the ATP-sensitive potassium channel (K<sub>ATP</sub> channel). When a second event of a somatic loss of the maternal allele occurs during the development of the pancreas, the cell develops dysregulated insulin secretion and a growth advantage, eventually growing into a focal lesion [4-6]. Recent advances in the molecular diagnosis and 18F-fluoro-L-dihydroxyphenylalanine (18F-DOPA) PET scan have made it possible to diagnose and localize the focal form of CHI [7, 8]. If a focal lesion is successfully resected, the patient will be cured without postsurgical sequelae [9]. Focal lesions in the body or tail of the pancreas are usually easily resected. When a focal lesion is identified in the head of the pancreas, resection is not always easy because of the risk of damaging the main pancreatic duct or the common bile duct. But still, they are amenable to resection by removal of the head of the pancreas and distal pancreaticojejunostomy using a Roux-en-Y loop [10]. On the contrary, treatment of the diffuse form remains far from ideal. Near-total/subtotal pancreatectomy has generally been performed in patients with hypoglycemia that is unresponsive to medical treatment. However, the postsurgical course is generally unsatisfactory with residual hypoglycemia or iatrogenic diabetes mellitus. Reports indicate that 96% of patients undergoing subtotal pancreatectomy > 95% developed diabetes after 11 years [11]. Furthermore, there are no differences in the neurological prognosis between patients treated by pancreatectomy and patients treated medically [12].

Therefore, it is important to develop optimal medical treatment in order to minimize the need for near-total/subtotal pancreatectomy. The only medication approved for CHI, in addition to hypertonic glucose infusion, is diazoxide, a K<sub>ATP</sub>-channel opener. However, diazoxide is ineffective in the majority of early-onset K<sub>ATP</sub> channel CHI cases [13]. Therefore, off-label use of subcutaneous injection of octreotide has been widely used in these cases [14].

Octreotide is a long-acting somatostatin analog acting mainly on the somatostatin receptor 2. In the pancreatic β cells, it activates the K<sub>ATP</sub> channel leading to hyperpolarization of the cell membrane and inhibition of the voltage-gated calcium channel to suppress secretion of insulin. It also acts on the signal transduction pathway mainly through inhibition of the cAMP production [15]. The efficacy of octreotide in the treatment of CHI has long been recognized [16, 17]. However, as this is a rare disorder, no formal clinical trial has been performed and the use of octreotide for CHI has not been approved in any developed country. In this study, in order to systematically assess the efficacy and safety of subcutaneous injection of octreotide for diazoxide-unresponsive CHI, we conducted a prospective, open-label clinical trial, in addition to an observational, registry study to collect the clinical course of patients treated off-label in Japan.

**Subjects and Methods**

The overall study (SCORCH, subcutaneous octreotide for congenital hyperinsulinism) consists of two sub-studies; (a) a prospective, single-arm, open-label clinical trial to treat patients with continuous subcutaneous infusion of octreotide (SCORCH study); and (b) an observational study, to collect clinical course data of patients treated off-label with octreotide in Japan, by subcutaneous administration, in any form (SCORCH registry).

The SCORCH study was intended to treat a small number of eligible patients with a predefined protocol to eliminate any biases in ascertainment and interpretation. The SCORCH registry was an observational study aiming to accumulate real-world data on the efficacy and safety of octreotide from as many patients as possible. In both studies, the study subjects were Japanese patients with diazoxide-unresponsive CHI, aged between 2 weeks and 1 year. The studies were conducted as a project of the Japanese Society for Pediatric Endocrinology, approved by the Institutional Review Board at each participating institution, and registered with the University Hospital Medical Information Network as UMIN 000012620 (SCORCH study) and UMIN 000011356 (SCORCH registry), respectively.

**SCORCH study**

**Subjects**

Diazoxide-unresponsive persistent CHI was defined as persistent hypoglycemia fulfilling the criteria below at diagnosis: (a) serum insulin > 3 μU/mL when blood glucose < 45 mg/dL; (b) requirement of a continuous glucose infusion > 6 mg/kg/min to maintain blood glucose > 60 mg/dL; (c) inability to maintain blood
glucose > 60 mg/dL with a diazoxide dose of 15 mg/kg/day. The following exclusion criteria were set out: (1) patients with hypoglycemia secondary to other causes (not hyperinsulinemia); (2) patients with respiratory distress; (3) patients with intestinal disorders; (4) patients with severe hepatic dysfunction, transaminases and bilirubin above 3x the upper limit of normal, or with hepatic failure above score C, according to the Child-Pugh criteria [18]; (5) patients with severe renal dysfunction with urea nitrogen or creatinine above 3x the upper limit of normal; (6) patients with other severe comorbidities. In response to the e-mail announcement of the Japanese Society for Pediatric Endocrinology, a total of 31 university hospitals and pediatric tertiary care centers across Japan were registered as the trial treating hospitals. Approval for the trial was obtained from the Institutional Review Board of each institution. Eligible patients presenting to these hospitals between January 2014 and March 2016 were recruited and registered by the responsible physicians after obtaining written informed consent from the guardians.

Methods

Intervention

After confirming patient eligibility and registration for the trial, fasting blood glucose levels were measured at least 4 times per day and stabilized at > 45 mg/dL, using treatment other than octreotide, including hyperglycemic glucose infusion, continuous enteral feedings, glucagon, or calcium antagonists for 24 hours before the commencement of octreotide treatment. Patients were then placed on continuous glucose monitoring (CGM; CGMS-Gold, Medtronic, Minneapolis, USA) and electrocardiography (ECG) monitoring. After 24 hours of monitoring, continuous subcutaneous infusion of octreotide was initiated at a dose of 5 μg/kg/day using an insulin pump (TOP8200, TOP Corporation, Tokyo, Japan). Fasting blood glucose was measured by a glucometer at least once a day. When fasting glucose was < 110 mg/dL, the rate of octreotide administration was raised by 5 μg/kg/day up to 25 μg/kg/day. When fasting glucose was > 200 mg/dL on two consecutive occasions, the glucose infusion rate (GIR) was decreased by 10-20%. During the first 48 hours, CGM and ECG monitoring were continued. Other supportive treatment for hypoglycemia remained unchanged during the first 48 hours, and control of blood glucose was achieved by changing the GIR and the rate of octreotide administration. After the initial 48 hours, octreotide therapy was continued and hypertonic glucose infusion was reduced when a clinically meaningful rise of blood glucose was obtained.

Data collection

The responsible physicians submitted the relevant data at defined intervals (Supplemental Table 1) to the data center, located in a Contract Research Organization, FIVERINGS Co., LTD. (Osaka, Japan), which conducted the central monitoring of the data and issued data clarification forms when necessary. The following data were collected: (1) physical growth (height, weight, head circumference); (2) octreotide dosage, (3) amount of glucose infusion for treatment; (4) details of supportive therapies for hypoglycemia; (5) adverse events; (6) laboratory test results, including blood glucose, complete blood counts (CBC), insulin, free T4, TSH, insulin-like growth factor 1 (IGF1), blood chemistry (aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin (TBil), direct bilirubin (DBil), gamma glutamyltransferase (GGT), urea nitrogen (BUN), creatinine (CRE), total protein (TP), albumin (ALB), total cholesterol (Tcho)), electrolytes (calcium, sodium, potassium, chloride), serum concentration of octreotide; (7) abdominal ultrasound; (8) cardiac ultrasound; and (9) assessment of psychomotor development. Conventional laboratory tests were performed at laboratories routinely used in each participating hospital. Serum concentrations of octreotide were measured at the central laboratory of Osaka City General Hospital, using the Octreotide – EIA kit (S1341, Peninsula Laboratories International, CA). Following hospital discharge, patients were requested to measure fasting blood glucose at least once a day at home, using a portable glucometer. Data were collected from the commencement of octreotide until the end of the treatment or, with ongoing treatment, until the end of July 2016.

Mutational analysis and 18F-DOPA PET scan

Patients were requested to undergo mutational analysis of the K_ATP channel genes, KCNJ11 and ABCC8, as described previously [19]. Then, mostly for patients with a paternally-inherited monomelic mutation in one of these genes, 18F-DOPA PET scans were performed at Kizawa Memorial Hospital, as described previously [20], to explore the possibility of surgical resection of a focal lesion.

Endpoints for efficacy

The primary endpoint was glucose level, measured as short term increments in blood glucose within 48 hours.
of the commencement of octreotide therapy, compared to glucose levels measured during the 24 hours preceding treatment. Secondary endpoints were (1) the reduction in GIR at defined intervals; (2) the frequency of hypoglycemia (< 45 mg/dL) during treatment, detected by a portable glucometer or by laboratory determination of blood glucose; and (3) psychomotor development, assessed by the Kyoto Scale of Psychological Development one year after treatment [21].

Assessment of safety
The following data were collected as indices of safety: adverse events recorded during octreotide treatment, abnormalities of laboratory data, abnormalities in abdominal and cardiac ultrasound, ECG abnormalities during the first 48 hours of treatment, and abnormal physical growth. Serious adverse events during the study were discussed within both the research group and the Independent Data and Safety Assessment Board, consisting of Drs. Kou Kawada (Department of Pediatrics, National Hospital Organization Kyoto Medical Center), Shinya Hirano (Department of Neonatology, Osaka Medical Center and Research Institute for Maternal and Child Health), and Kaoru Obinata (Department of Pediatrics, Juntendo University Urayasu Hospital). At the end of the data collection, source data verification was performed by FIVERINGS Co., LTD. at each participating hospital. After the verification of all data, an evaluation on the efficacy and safety of the entire trial was presented to the Independent Data and Safety Assessment Board.

SCORCH registry
Subjects
Subject inclusion criteria were the same as those for SCORCH study. Patients aged between 2 weeks and 1 year, satisfying the study criteria and undergoing treatment with subcutaneous octreotide injection (according to any dosage schedule) were recruited through announcements for members of the Japanese Society for Pediatric Endocrinology. The responsible physicians registered the patients after obtaining the approval of the Institutional Review Board at each institution and written informed consent from the guardians.

Methods
Clinical data collection
After confirming eligibility, the responsible physicians submitted the relevant clinical and laboratory data at defined intervals (Supplemental Table 2) to the data center placed at FIVERINGS Co., LTD., which conducted cleaning of the data when necessary. Collected data included: (1) physical growth (height, weight, head circumference); (2) dosage and route of administration of octreotide; (3) amount of glucose infusion for treatment; (4) other supportive therapy for hypoglycemia; (5) adverse events; (6) laboratory tests, including blood glucose, CBC, blood chemistry (AST, ALT, ALP, TBil, DBil, BUN, CRE, TP, ALB), electrolytes (calcium, sodium, potassium, chloride); (7) abdominal ultrasound; and (8) assessment of psychomotor development. Data were collected from the commencement of octreotide treatment until the end of treatment or, with ongoing treatment, until the end of July 2016.

Mutational analysis and 18F-DOPA PET scan
As in the SCORCH study, sequencing analysis of the $K_{ATP}$ channel genes was offered to the patients who had not undergone mutational analysis. Furthermore, 18F-DOPA PET scans were offered at Kizawa Memorial Hospital to patients with paternally-inherited monoallelic mutations, for the identification and localization of the focal form.

Endpoints for efficacy
The primary endpoint was the reduction in GIR to maintain euglycemia at 4 weeks after the commencement of octreotide treatment. Secondary endpoints were the GIR after 4 weeks and psychomotor development after one year of treatment.

Assessment of safety
The following data were collected as indices of safety: adverse events occurring during octreotide treatment, abnormal laboratory test results, abnormalities detected by abdominal ultrasound, and abnormal physical growth.

Results

SCORCH study
A total of 5 patients (2 males and 3 females) were enrolled in the SCORCH study. The baseline data and treatment details of these patients are summarized in Table 1. Of these, three patients (patients S-03, S-04, S-05) had a paternally-inherited monoallelic mutation in the $K_{ATP}$ channel genes, one (patient S-02) had a maternally-inherited monoallelic mutation, and one patient (patient S-01) did not have a mutation in the $K_{ATP}$ Channel genes. 18F-DOPA PET scans were performed on all patients showing either diffuse lesions or a focal lesion in the head of the pancreas. However, the
Octreotide for hyperinsulinism

Efficacy

Fig. 1 shows the glycemic response of each patient starting from 24 hours before to 48 hours after the start of octreotide, as measured by CGM. All patients were on continuous glucose infusion to maintain euglycemia at the commencement of continuous subcutaneous octreotide infusion. In patients S-01 and S-02, only a transient rise of blood glucose was observed following the commencement of octreotide treatment at 5 μg/kg/day. Glucose levels then returned to baseline, and no further response was observed with gradual increments in the octreotide dosage, up to 25 μg/kg/day. Treatment was therefore discontinued after 48 hours and the pre-trial treatment regimen was resumed.

In patients S-03 and S-04, sustained elevation of blood glucose was observed with the commencement of octreotide treatment at 5 μg/kg/day. Glucose levels then returned to baseline, and no further response was observed with gradual increments in the octreotide dosage, up to 25 μg/kg/day. Treatment was therefore discontinued after 48 hours and the pre-trial treatment regimen was resumed.

In patient S-05, the most prominent glycemic response was observed with an average increment reaching 195.8 mg/dL during the first 6 hours. However, this patient had the most severe form of hyperinsulinism, and required a glucose infusion for the longest period, despite continued dosage titration of octreotide. After reaching the maximal octreotide dose of 22.3 μg/kg/day, the glucose infusion was gradually decreased with continued octreotide treatment and withdrawn after 174 days, at the octreotide dosage of 17.8 μg/kg/day.

After withdrawal of glucose infusion, octreotide treatment was continued in all 3 patients (patients S-03, S-04, S-05). Among these, patient S-03 reached a remission of CHI and octreotide was discontinued after 606 days of treatment. Patients S-04 and S-05 remained on octreotide after 616 and 416 days of treatment, with final recorded dosages of 17.1 and 16 μg/kg/day, respectively.

Home and laboratory blood glucose monitoring of a total of 77.6 patient-months at 282 points revealed a total of 11 episodes of hypoglycemia below 45 mg/dL (ranges 38–43 mg/dL), once in patient S-01, twice in patient S-04 and 8 times in patient S-05). Three of these were symptomatic and, in one of these episodes, glucose infusion was performed to correct for the hypoglycemia.
In all patients, neurological development after 1 year of treatment was within the normal range (78–90) as assessed by the same Kyoto Scale of Psychological Development.

Octreotide serum concentrations were measured for each patient during the course of treatment (Supplemental Table 3). Except for patient S-02, octreotide concentration ranged between 2.37 and 5.88 ng/mL. It is postulated that these levels occupy 50–100% of somatostatin receptor 2 and are comparable concentrations to those achieved in patients requiring octreotide treatment for other reasons, such as neuroendocrine tumors [22]. Interestingly, in patient S-02, for whom octreotide was only transiently effective, the serum concentration was much higher at 16.04 ng/mL, suggesting that in some patients the serum concentration could be highly elevated in the absence of renal or hepatic dysfunction.

**Safety**

A total of 30 adverse events were recorded during the observation period, of which 6 were considered to be caused by octreotide (Supplemental Table 4); vomiting in 1 (patient S-01), whitish stool in 1 (patient S-04), elevation of ALP in 1 (patient S-05), lymphocytosis in 1 (patient S-05), eosinophilia in 1 (patient S-05), and hair thinning in 1 (patient S-05). None of these were sufficiently severe to stop octreotide treatment. The ECG monitoring during the initial treatment and cardiac/abdominal ultrasounds at defined intervals did not reveal any abnormalities. Two episodes of severe adverse events (bronchial asthma) were observed in a single patient (patient S-03). Since both episodes could be easily managed while continuing octreotide, these episodes were considered not related to octreotide by the research group, the Institutional Review Board, and the Independent Data

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**Fig. 1** Results of 72-hour continuous glucose monitoring for each patient in the SCORCH study

Glucose values between -24 and +48 hours of octreotide treatment are shown. Arrows indicate the commencement of the octreotide infusion. In patient S-05, the shaded area was excluded from the calculation of average increment of blood glucose as the GIR was reduced owing to excessive hyperglycemia.
and Safety Assessment Board. In the 3 patients undergoing continued treatment, the height standard deviation score changed from -1.09 to -0.63 (patient S-03), 1.10 to -1.13 (patient S-04), and 3.76 to 0.43 after 1 year, respectively. During the same period, IGF1 levels changed from 91 ng/mL to 66 ng/mL (patient S-03), 149 ng/mL to 72 ng/mL (patient S-04), and 67 ng/mL to 32 ng/mL (patient S-05), respectively. Therefore, the height changes were not related to the changes in IGF1 levels, as these remained within the age matched normal range in all patients.

**SCORCH registry**

A total of 19 patients (8 males and 11 females) were registered for the SCORCH registry. The baseline data and treatment details are summarized in Table 2. Mutations in one of the $K_{ATP}$ channel genes (KCNJ11 or ABCC8) were identified in 15 patients: biallelic mutation in 1, paternally-inherited monoallelic mutation in 10, maternally-inherited monoallelic mutation in 1, and de novo monoallelic mutation in 3. 18F-DOPA PET scans were performed in 11 patients; 7 with a paternally-inherited monoallelic $K_{ATP}$ channel gene mutation, 1 each with a de novo, maternal, or biparental mutation, and 1 without a mutation. Of these, 4 patients had a focal form on 18F-DOPA PET scan and the remaining 7 had a diffuse form, respectively. The median age at the onset of hypoglycemia was 0 day (range 0–228.0) and octreotide was initiated at the median age of 18.0 days (range 4.0–521.0 days). The route of administration was multiple daily injection in 2, continuous subcutaneous infusion in 3, and initial daily injection with subsequent transfer to continuous subcutaneous infusion in 14. These patients were followed up for the median duration of 29.7 months (range 1.6–137.0) and data from a total of 617.8 patient-months (275 observation points) were collected.

### Table 2: Baseline characteristics and treatment details of patients in the SCORCH registry

| Patient No. | R-01 | R-02 | R-03 | R-04 | R-05 | R-06 | R-07 | R-08 | R-09 | R-10 | R-11 | R-12 | R-13 | R-14 | R-15 | R-16 | R-17 | R-18 | R-19 |
|-------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Sex         | M    | M    | M    | M    | M    | M    | M    | F    | F    | F    | F    | F    | F    | F    | F    | F    | F    | F    | F    |
| Gestational age, weeks | 41   | 37   | 38   | 22   | 39   | 37   | 39   | 39   | 36   | 39   | 37   | 39   | 38   | 37   | 39   | 38   | 40   | 40   | 34   |
| Birth weight, g | 3,894 | 3,232 | 2,950 | 530  | 3,108 | 3,422 | 4,228 | 3,790 | 3,330 | 3,792 | 3,052 | 3,414 | 3,788 | 3,884 | 3,612 | 4,743 | 4,640 | 4,078 | 3,141 |
| Age at onset, days | 0    | 1    | 228  | 0    | 67   | 1    | 3    | 1    | 0    | 2    | 0    | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Blood glucose at diagnosis, mg/dL <20 | 26   | 38   | 42   | 40   | 29   | 8    | 37   | 31   | 2    | 37   | 17   | 35   | 36   | 24   | 16   | 15   | 15   | 15   | 15   |
| Mutation | KCNJ11 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 | ABCC8 |
| cDNA (protein) | 376G>C | T129C>A | 3621C>T | 3622 | C3657T>A | 3870G>A | 3886G>A | 4190G>A | 4202G>A | 4222G>A | 4233G>A | 4243G>A | 4248G>A | 4253G>A | 4259G>A | 4260G>A | 4261G>A | 4262G>A | 4263G>A | 4264G>A |
| Parental origin | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT | PAT, PAT |
| 18F-DOPA PET | diffuse | diffuse | diffuse | nd    | nd    | nd    | focal | focal | focal | focal | nd    | nd    | nd    | diffuse | diffuse | focal | focal | nd    | nd    | nd    | nd    |
| Age at start of OCT, days | 16   | 19   | 250  | 319  | 521  | 19   | 18   | 17   | 11   | 15   | 47   | 403   | 12    | 9    | 18   | 29   | 32   | 18   | 32   |
| Observation period, months | 34.5 | 42.7 | 52.4 | 2.1  | 45.5 | 39.7 | 29.7 | 16.9 | 17.3 | 18.2 | 137.0 | 49.7   | 49.3  | 4.8   | 2.3   | 17.9 | 6.1   |
| Route of administration | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI | CSI, CSI |
| Dosage, μg/kg/day | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | 0.2   |
| GHR, mg/kg/min | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    |
| Pretreatment | 13.9 | 5.4  | –    | 3.4  | 2.5  | 17   | 13.8 | 16   | 20.2 | 6.3  | –    | 2.1   | 14.5  | 14.5  | 16   | 13.9 | 9.8  | 14    |
| At 2 weeks | 0    | 0    | –    | 2.8  | 0    | 0.9  | 11.4 | 0    | 16.2 | 2    | –    | 4.2   | 10.8  | 3    | 14.9 | 0.74  | 5    |
| At 4 weeks | 0    | 0    | –    | 0.25 | 0    | 0.8  | 6.8  | 0    | 13.1 | 2.5  | –    | 0.7   | 6.6   | 15   | 0    | 5.9  | 0    |
| Withdrawal of glucose infusion, days | 11   | 12   | –    | 49   | 6    | 21   | 57   | 12   | 158  | 42   | –    | 18    | 97    | 195   | NO   | 11   | NO   | 21   |
| Clinical course | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    | –    |

R-03 and R-11 were not on glucose infusion at the commencement of octreotide treatment. PAT, paternally; MAT, maternal; BI, biparental; CSI, continuous subcutaneous infusion; MDI, multiple daily injection; MDI/CSI, initial MDI with subsequent transfer to CSI; nd, not done; GHR, glucose infusion rate; LAR, long acting.
Efficacy

Treatment details and the response of each patient are shown in Table 2 and Fig. 2. Two of the registered patients (R-03, R-11) were not on a continuous glucose infusion to maintain euglycemia; therefore, treatment efficacy was assessed in the remaining 17 patients. The median GIR of these patients at the start of therapy was 13.9 mg/kg/min (range 2.1–20.2). After 4 weeks of treatment, the median dosage of octreotide was 19.0 μg/kg/day (range 4.8–72.0). In 11 of these patients (64.7%), the GIRs could be reduced to less than 50% of those before the treatment, and in 9 of them (52.9%), glucose infusion was withdrawn completely at 4 weeks. After a continued median treatment period of 21.0 days (range 6–195 days), glucose infusion was withdrawn in 15 (88.2%). In addition, over the course of the treatment, the dosage of octreotide could also be reduced in all patients from the median maximal dose of 23.8 μg/kg/day (range 6.6–72.0) to the median latest dosage of 5.7 μg/kg/day (range 0.1–13.1).

Octreotide was discontinued during the observation period in 11 patients, after pancreatectomy in 6 patients (R-08, R-09, R-10, R-15, R-17, R-18), and after continued medical treatment in 5 patients (R-01, R-02, R-04, R-16, R-19) (Fig. 2). Of the 6 patients who underwent pancreatectomy, octreotide was stopped immediately in 3 patients (R-08, R10, R-18), following successful identification and resection of the focal lesions. In patients R-15 and R-17, octreotide was discontinued soon after subtotal pancreatectomy (90–98%). An 85% pancreatectomy was performed on patient R-09 and treatment with a decreased level of octreotide was continued and then switched to monthly intramuscular long-acting octreotide (octreotide LAR) after 518 days. Of those who discontinued octreotide after continued medical treatment, in 3 (R-01, R-02, R-19), octreotide could be gradually decreased and discontinued without surgery at ages 2.0, 2.7, and 0.2 years, respectively. Patient R-16 was switched to intramuscular octreotide LAR after 2.3 months of treatment. Patient R-04 was successfully treated by octreotide although he died of respiratory failure during treatment (details in the safety section).

The remaining 8 (R-03, R-05, R-06, R-07, R-11, R-12, R-13, R-14) are still being treated with octreotide, aged 5.0, 5.2, 3.7, 2.5, 11.4, 5.2, 3.8, and 4.1 years, respectively, with a median dosage at the end of observation of 5.7 μg/kg/day (range 0.1–13.1).

![Fig. 2](Image) Duration of glucose infusion, octreotide treatment, and total observation period (SCORCH registry)

Total length of each bar represents the duration of the observation. The shaded area shows the duration of octreotide treatment and the solid-black area shows the duration of octreotide treatment with glucose infusion, respectively. Patient R-11 was treated with octreotide for 137 months (until 11.4 years).
Assessment of neurological development could be performed in 9 patients at least one year after the commencement of octreotide treatment. In all patients, the developmental quotient was normal with the average developmental quotient of 100.0 (range 81–128).

**Safety**

Supplemental Table 5 shows a list of the adverse events potentially related to the use of octreotide and observed in 617.8 patient-months. To summarize, a total of 47 adverse events were observed, of which 23 were considered to be related to octreotide. Gallstone/biliary sludge was the most common, observed in 5 patients (26.3 %), followed by mild to moderate gastrointestinal symptoms (vomiting in 4 patients, diarrhea/whitish stool in 1, and poor gastric emptying in 1 patient).

One fatal adverse event (patient R-04) was recorded during the observation period for which causality of octreotide was considered negative by the responsible physician, the research group, and the Independent Data and Safety Assessment Board. The patient was born at 22 weeks of gestation, with a birth weight of 530 g. Severe asphyxia was noted and the Apgar score was 2 at 5 minutes. Therefore, the patient was transferred to a neonatal intensive care unit. The clinical course was complicated by intraventricular hemorrhage, patent ductus arteriosus associated with functional pulmonary stenosis, left pulmonary effusion, and chronic lung disease. The patient developed hyperinsulinemic hypoglycemia at 7 months with blood glucose levels of 42 mg/dL and insulin levels of 10.6 μU/mL. Treatment with diazoxide and dexamethasone was commenced; however, the patient still required continuous intravenous glucose infusion to maintain euglycemia. The patient gradually developed generalized edema associated with worsening hypertrophic cardiomyopathy. Octreotide was introduced at 10 months with a low dose (5.1 μg/kg/day) and increased to 22.5 μg/kg/day. This was effective in controlling hypoglycemia and intravenous glucose, diazoxide, and dexamethasone were reduced and discontinued. Two months after commencement of octreotide treatment, the patient developed worsening respiratory failure, associated with signs of infection and adrenal failure with circulatory collapse, leading to multiple organ failure and death on the 382nd day of life.

Finally, of the 11 patients treated with octreotide for >1 year, the median change in height standard deviation score was -0.47 (range, -1.67–0.64).

**Discussion**

Since the original reports showing effectiveness in patients with CHI [16, 17], octreotide has been used off-label as the second-line therapy for diazoxide unresponsive patients [14]. There have been two retrospective studies, with a relatively large study population, showing the efficacy and safety of octreotide. Yorifuji et al. [23] reported the clinical outcome of 15 Japanese patients (3 with biallelic and 12 with monoallelic K<sub>ATP</sub> channel mutations) treated by continuous subcutaneous infusion of at 5-25 μg/kg/day for 0.3-5.9 years. The therapy was effective in raising blood glucose levels in all patients. One patient underwent a 90% pancreatectomy because the intravenous glucose infusion could not be withdrawn completely. Except for reversible growth deceleration in patients treated at higher dosage, mild gastrointestinal symptoms were the only reported adverse effects. Similarly, Demirbilek et al. [24] reported the clinical outcome of 28 patients (25 with mutations in the K<sub>ATP</sub>-channel genes) treated at Great Ormond Street Hospital for Children in the United Kingdom between 2001 and 2013 by multiple daily octreotide injection of 5-30 μg/kg/day for a mean period of 52.4 months. Therapy was effective in avoiding surgery in 42.8% of patients and elevated transaminases (46.4%) and gall bladder pathology (32%) were the most frequently observed adverse events. There was no evidence of growth deceleration.

The current study combines a prospective intervention study on 5 patients (SCORCH study) with an observational study on 19 patients for a longer period of treatment (SCORCH registry). The patients in the SCORCH registry do not overlap with those previously reported by Yorifuji et al. in Japan [23] and includes patients with a broader range of genetic backgrounds, some without K<sub>ATP</sub>-channel mutations. When sustained rise in blood glucose levels was used as an outcome measure, the therapy was effective in 60% of patients in the SCORCH study. When a GIR reduction at 4 weeks to < 50% of the initial rate was used as a common outcome measure, the therapy was effective in 60% of patients in the SCORCH study and 64.7% of patients in the SCORCH registry, respectively. Octreotide effectiveness appeared to be less than that reported by Yorifuji et al. in which most of the patients responded to the treatment [23] and comparable to the findings reported by Demirbilek et al. [24]. The reason for these different findings is unknown. This could be
due to the differences in patient genetic background. The two patients who did not respond in the SCORCH study had either no mutation or a maternally-inherited monoallelic mutation in the $K_{ATP}$-channel genes while the patients in the study reported by Yorifuji et al. had either biallelic mutation with diffuse lesion or paternally-inherited monoallelic mutation, suggesting the presence of a focal lesion [23]. In the SCORCH registry, there were 4 patients who did not have mutations in the $K_{ATP}$-channel genes (patients R-13, R-14, R-17 and R-19, Table 2). In 3 (75%) of them, octreotide was only partially effective, and they required either subtotal pancreatectomy or intravenous glucose infusion for over 3 months. In contrast, in the remaining 13 patients with $K_{ATP}$-channel mutations, there were only 2 such patients (15.3%).

Maternally-inherited monoallelic mutation in patient S-02 suggests the presence of rare, dominantly inherited $K_{ATP}$-channel CHI. This form of CHI could be resistant to medical treatment, including octreotide, thus requiring surgery [25, 26]. Further studies are required as the number of patients in the current study was too small to address the possibility of genotype-phenotype correlation in octreotide responsiveness.

Overall, octreotide was effective in the majority of patients who were unresponsive to diazoxide. The efficacy defined by the clinical trial was approximately 60% for both the SCORCH study and the SCORCH registry. However, we feel that any levels of sustained glycemic response which allows for a reduction of GIR is meaningful, because octreotide is relatively safe and, with reduced GIR, it becomes much easier to manage the patients for an extended period of time. Although GIR was reduced to < 50% in only 60% of the patients at 4 weeks, a reduction in GIR > 10% was observed in 19 out of the 22 patients who were on glucose infusion at the start of octreotide (3/5 in the SCORCH study, 16/17 in the SCORCH registry), and in 14 of these 19 patients, glucose infusion could be stopped without surgery within a month.

Both multiple daily injections and continuous subcutaneous infusion of octreotide were effective, as shown by the results of the SCORCH registry (Table 2, Fig. 2). However, parents tended to prefer continuous infusion with an insulin pump as this reduced the requirements for needle puncture of the skin. Furthermore, previous reports have shown that the total dosage of octreotide administered by continuous infusion was lower than for that administered by multiple subcutaneous injections [23]. The required dosage of octreotide gradually decreased over time and treatment was stopped in a proportion of the patients. It is likely that treatment could be withdrawn in most patients over time, as it is known that the disorder remits spontaneously after several years [27].

Octreotide was the likely cause of 29 recorded adverse events over a total of 695.4 patient-months for the SCORCH study and the SCORCH registry. As previously reported [14, 23, 24], mild to moderate gastrointestinal events at the start of treatment and gall bladder pathology were the most common adverse events, and no severe adverse event related to the use of octreotide was observed. Of note, rare adverse events, such as necrotizing enterocolitis [14, 28, 29], long QT syndrome [30], convulsion after cessation of treatment [31], or prolonged hepatic dysfunction [32-35], have been associated with the use of octreotide for CHI. Necrotizing enterocolitis is of particular concern, due to the high fatality rate [28]. The number of patients in the current study is not large enough to detect these rare events, therefore, it is important to be aware of early signs of severe abdominal symptoms, even after a prolonged use of octreotide [29].

Finally, our data on serum concentration of octreotide suggest that in some patients the serum concentration could be much higher than in other patients treated with a comparable octreotide dose. A high concentration of octreotide could lead to paradoxically diminished effectiveness [36] and could also cause adverse events; therefore, titration of dosage according to the serum concentration may be desirable to achieve the optimal response.

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**Disclosures**

The authors have nothing to disclose.

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**Supplemental Table 1** Treatment and observation schedule of the SCORCH study

| Medical history | At registration Day-7 to 1 | At start of OCT 0-48Hrs | 1 week | 2 weeks | 3 weeks | 4 weeks | Every 3 months while continued | At end of OCT or at 12 months | After 1 year |
|-----------------|--------------------------|--------------------------|--------|--------|--------|--------|-------------------------------|-----------------------------|----------------|
| DOSAGE OF OCT   | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Glucose infusion rate | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Other supportive therapy | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Adverse events  | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Physical growth | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Blood glucose (laboratory) | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Blood glucose (glucometer) | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| CBC, blood chemistry, electrolytes | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Insulin         | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| Thyroid test, IGF1 | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |
| OCT blood concentration | X                        | X                        | X      | X      | X      | X      | X                             | X                          | X              |

OCT, octreotide; US, ultrasound; CGM, continuous blood glucose monitoring; CBC, complete blood count; IGF1, insulin-like growth factor 1. Xa; From -24 hours to +48 hours. Xb; Once within a period. Xc; The 2nd CGM is performed when the patient is able to withdraw from octreotide.
References

1. Yorifuji T, Masue M, Nishibori H (2014) Congenital hyperinsulinism: Global and Japanese perspectives. Pediatr Int 56: 467-476.
2. Menni F, de Lonlay P, Sevin C, Touati G, Peigné C, et al. (2001) Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics 107: 476-479.
3. Ludwig A, Ziegenhorn K, Empting S, Meissner T, Marquard J, et al. (2011) Glucose metabolism and neurological outcome in congenital hyperinsulinism. Semin...
4. Verkarre V, Fournet JC, de Lonlay P, Gross-Morand MS, Devillers M, et al. (1998) Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. J Clin Invest 102: 1286-1291.

5. de Lonlay P, Fournet JC, Rahier J, Gross-Morand MS, Poggi-Travert F, et al. (1997) Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycaemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. J Clin Invest 100: 802-807.

6. Damaj L, le Lorcy M, Verkarre V, Verl C, Hubert L, et al. (2008) Chromosome 11p15 paternal isodisomy in focal forms of neonatal hyperinsulinism. J Clin Endocrinol Metab 93: 4941-4947.

7. Otonkoski T, Näätö-Salanen K, Seppänen M, Veijola R, Huopio H, et al. (2006) Noninvasive diagnosis of focal hyperinsulinism of infancy with [18F]-DOPA positron emission tomography. Diabetes 55: 13-18.

8. Blomberg BA, Moghbel MC, Saboury B, Stanley CA, Alavi A (2013) The value of radiologic interventions and 18F-DOPA PET in diagnosing and localizing focal congenital hyperinsulinism: systematic review and meta-analysis. Mol Imaging Biol 15: 97-105.

9. de Lonlay-Debeney P, Poggi-Travert F, Fournet JC, Sempoux C, Dionisi Vici C, et al. (1999) Clinical features of 52 neonates with hyperinsulinism. N Engl J Med 340: 1169-1175.

10. Laje P, Stanley CA, Palladino AA, Becker SA, Adzick NS (2012) Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. J Pediatr Surg 47: 130-135.

11. Arya VB, Senniapan S, Demirbilek H, Alam S, Flanagan SE, et al. (2014) Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. PLoS One 9: e98054.

12. Mazor-Aronovitch K, Gillis D, Lobel D, Hirsch HJ, Pinhas-Hamiel O, et al. (2007) Long-term neurodevelopmental outcome in conservatively treated congenital hyperinsulinism. Eur J Endocrinol 157: 491-497.

13. Touati G, Poggi-Travert F, Ogier de Baulny H, Rahier J, Brunelle F, et al. (1998) Long-term treatment of persistent hyperinsulinemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. Eur J Pediatr 157: 628-633.

14. Welters A, Lerch C, Kummer S, Marquard J, Salgin B, et al. (2015) Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers. Orphanet J Rare Dis 10: 150.

15. Theodoropoulou M, Stall GK (2013) Somatostatin receptors: from signaling to clinical practice. Front Neuroendocrinol 34: 228-252.

16. Glaser B, Hirsch HJ, Landau H (1993) Persistent hyperinsulinemic hypoglycaemia of infancy: long-term octreotide treatment without pancreatectomy. J Pediatr 123: 644-650.

17. Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA (1993) Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. J Pediatr 123: 637-643.

18. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973) Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60: 646-649.

19. Yorifuji T, Wakakita R, Nagai S, Sugimine A, Doi H, et al. (2011) Molecular and clinical analysis of Japanese patients with persistent congenital hyperinsulinism: predominance of paternally-inherited monoallelic mutations in the KATP channel genes. J Clin Endocrinol Metab 96: E141-145.

20. Masue M, Nishihori H, Fukuyama S, Yoshizawa A, Okamoto S, et al. (2011) Diagnostic accuracy of [18F]-fluoro-L-dihydroxyphenylalanine positron emission tomography scan for persistent congenital hyperinsulinism in Japan. Clin Endocrinol (Oxf) 75: 342-346.

21. Koyama T, Osada H, Tsuji H, Kurita H (2009) Utility of the Kyoto Scale of Psychological Development in cognitive assessment of children with pervasive developmental disorders. Psychiatry Clin Neurosci 63: 241-243.

22. Woltering EA, Salvo VA, O’Dorisio TM, Lyons J 3rd, Li G, et al. (2008) Clinical value of monitoring plasma octreotide levels during chronic octreotide long-acting repeatable therapy in carcinoid patients. Pancreas 37: 94-100.

23. Yorifuji T, Wakakita R, Hosokawa Y, Fujimaru R, Matsubara K, et al. (2013) Efficacy and safety of long-term, continuous subcutaneous octreotide infusion for patients with different subtypes of KATP-channel hyperinsulinism. Clin Endocrinol (Oxf) 78: 891-897.

24. Demirbilek H, Shah P, Arya VB, Hincheley L, Flanagan SE, et al. (2014) Long-term follow-up of children with congenital hyperinsulinism on octreotide therapy. J Clin Endocrinol Metab 99: 3660-3667.

25. Saint-Martin C, Zhou Q, Martin GM, Vaury C, Leroy G, et al. (2015) Monoallelic ABC8C8 mutations are a common cause of diazoxide-unresponsive diffuse form of congenital hyperinsulinism. Clin Genet 87: 448-454.

26. Flanagan SE, Kapoor RR, Banerjee I, Hall C, SmithVV, et al. (2011) Dominantly acting ABC8C8 mutations in patients with medically unresponsive hyperinsulinemic hypoglycaemia. Clin Genet 79: 582-587.

27. Salomon-Estebanez M, Flanagan SE, Ellard S, Rigby L, Bowden L, et al. (2016) Conservatively treated Congenital Hyperinsulinism (CHI) due to K-ATP channel gene mutations: reducing severity over time.
28. Laje P, Halaby L, Adzick NS, Stanley CA (2010) Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr Diabetes* 11: 142-147.

29. Hawkes CP, Adzick NS, Palladino AA, De León DD (2016) Late Presentation of Fulminant Necrotizing Enterocolitis in a Child with Hyperinsulinism on Octreotide Therapy. *Horm Res Paediatr* 86: 131-136.

30. Celik N, Cinaz P, Emeksiz HC, Hussain K, Çamurdan O, et al. (2013) Octreotide-induced long QT syndrome in a child with congenital hyperinsulinemia and a novel missense mutation (p.Met115Val) in the ABCC8 gene. *Horm Res Paediatr* 80: 299-303.

31. Baş VN, Ozkan M, Zenciroğlu A, Cavuşoğlu YH, Cetinkaya S, et al. (2012) Seizure due to somatostatin analog discontinuation in a case diagnosed as congenital hyperinsulinism novel mutation. *J Pediatr Endocrinol Metab* 25: 553-555.

32. Avatapalle B, Padidela R, Randell T, Banerjee I (2012) Drug-induced hepatitis following use of octreotide for long-term treatment of congenital hyperinsulinism. *BMJ Case Rep* 2012. pii: bcr2012006271.

33. Levy-Khademi F, Irina S, Avnon-Ziv C, Levmore-Tamir M, Leder O (2015) Octreotide-associated cholestasis and hepatitis in an infant with congenital hyperinsulinism. *J Pediatr Endocrinol Metab* 28: 449-451.

34. Koren I, Riskin A, Barthlen W, Gillis D (2013) Hepatitis in an infant treated with octreotide for congenital hyperinsulinism. *J Pediatr Endocrinol Metab* 26: 183-185.

35. Ben-Ari J, Greenberg M, Nemet D, Edelstein E, Eliakim A (2013) Octreotide-induced hepatitis in a child with persistent hyperinsulinemia hypoglycemia of infancy. *J Pediatr Endocrinol Metab* 26: 179-182.

36. Abell SK, Teng J, Dowling A, Hofman MS, MacIsaac RJ, et al. (2015) Prolonged life-threatening hypoglycaemia following dose escalation of octreotide LAR in a patient with malignant polysectrating pancreatic neuroendocrine tumour. *Endocrinol Diabetes Metab Case Rep* 2015: 140097.