Experience With Teduglutide in Pediatric Short Bowel Syndrome: First Real-life Data

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See ''Use of GLP-2 May Herald a New Era of Improved Outcome of Short Bowel Syndrome-associated Intestinal Failure'' by Hill on page 697.

ABSTRACT

Objectives: The aim of the study was to describe the experience with teduglutide of several Spanish hospitals in pediatric patients with SBS (SBS).
Methods: Seventeen pediatric patients with intestinal failure associated with SBS were treated with teduglutide. Patients received 0.05 mg · kg^{-1} · day^{-1} of subcutaneous teduglutide. Patients' demographics and changes in parenteral nutrition (PN) needs, fecal losses, and citrulline level initially and at 3, 6, and 12 months were collected, as well as any adverse events.
Results: Patients were receiving 55 ml · kg^{-1} · day^{-1} and 33 kcal · kg^{-1} · day^{-1} of parenteral supplementation on average at baseline (2 patients received only hydroelectrolytic solution). A total of 12/17 patients achieved parenteral independence: 3 patients after 3 months of treatment, 4 patients at 6 months, and 5 after 12 months. One patient discontinued treatment 1 year after the beginning as no changes in parenteral support or fecal losses were obtained. All others decreased their intravenous requirements by 50%. One patient suffered an episode of cholecystitis, and another one with a pre-existing cardiac disease, developed a cardiac decompensation.
Conclusions: Teduglutide seems to be a safe and effective treatment in the pediatric SBS population with better results than in the pivotal study as well as in the adult population.

Key Words: intestinal adaptation, intestinal failure, intestinal growth factors, parenteral nutrition, SBS

An infographic is available for this article at: *http://links.lww.com/MPG/B921*.

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What Is Known

- Teduglutide is a glucagon-like-peptide-2 analog that has proved its efficacy in promoting intestinal adaptation in patients with short bowel syndrome.
- Several studies of the treatment of adult and pediatric patients have proven this efficacy and demonstrated a good overall safety profile.

What Is New

- The present work is the first real-life study conducted in a pediatric population, with teduglutide showing even better results than in adult patients.
- The study adds data on response after 12 months of treatment in children.

Intestinal failure (IF) has been defined as the reduction in gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, requiring intravenous supplementation in order to maintain health and/or growth (1). The leading cause of IF in childhood is short bowel syndrome (SBS). SBS-associated IF is a highly disabling condition. After the event that leads to SBS, the remnant intestine tries to increase absorption in order to recover homeostasis and the adaptation process begins. The remnant bowel undergoes morphological and functional changes. This adaptation process is more effective when the residual intestine is ileum. Numerous growth factors have been implicated in this process. Glucagon-like-peptide-2 (GLP-2) is an endogenous growth factor strongly associated with intestinal growth and postresection intestinal adaptation. It is released by the enteroendocrine L cells of the distal jejunum, ileum, and colon, triggered by food intake. It has potent intestinotrophic properties inducing mucosal growth in the small and large intestine through an increase of crypt cell proliferation and a reduction of villous cell apoptosis. Patients with end jejunostomy and no colon have the

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poorest prognosis. This group of patients has a markedly impaired postprandial GLP-2 response, probably caused by a lack of functioning L-cell mass (2–4).

These facts have raised hopes that GLP-2 therapy might enhance intestinal mass and function in patients with SBS and it has already been shown to improve intestinal function in children with SBS (5,6).

Endogenous GLP-2 is degraded by dipeptidyl peptidase IV (DPPIV), so the half-life of intravenous GLP-2 is 7 minutes. Teduglutide (Revestive, Gattex) is a GLP-2 analog with a substitution of glycine in position 2 that blocks DPPIV degradation. This extends the GLP-2 half-life to approximately 3 hours and confers greater biological potency.

The hypothesis is that teduglutide can be an efficient and safe therapeutic option in patients with IF because of SBS. Small bowel transplantation is the alternative in those patients that develop complications associated with this condition. It, however, involves a high-risk surgery and is dependent on life-long immunosuppression. Teduglutide can be an alternative for these PN-dependent patients. Several studies have been published describing encouraging results in adult and pediatric patients affected with SBS and treated with teduglutide (7–13). There is only 1 pivotal study published that acknowledges its potential use and effects on pediatric patients. The aim of this work is to describe the results of a pediatric cohort, the first reported series after the clinical studies (5,6).

PATIENTS AND METHODS

It is a prospective study that involves 17 pediatric patients affected with SBS from 8 Spanish centers treated with $0.05\,mg \cdot kg^{-1} \cdot day^{-1}$ of subcutaneous teduglutide (Revestive) between February 2017 and June 2019. Criteria for inclusion were patients SBS (remnant bowel less of 100 cm) between 1 and 18 years of age, dependent on PN, and with no surgical interventions or changes in PN in the last 3 months. Two children had an unknown length of intestine (only duodenum) so they had <100 cm at the time of surgery. Two patients had more than 100 cm of remnant bowel but they were dependent on PN. No patients with more of 150 cm were included. One patient was affected with pediatric intestinal pseudo-obstruction (PIPO), but he underwent 1 stoma in the proximal jejunum, so he was considered a SBS.

Follow-up was planned following a national Guide of Use (14) (every 2 weeks in the first month, once a month the next 2 months and every 3 months thereafter if the patient was stable). Parenteral volume and nutritional support and stool losses were collected at baseline, 3, 6, and 12 months after initiating treatment. Plasma citrulline, an amino acid produced by enterocytes of the intestinal mucosa, is regarded as a biomarker of the functional enterocyte mass (15–19), so citrulline levels were also collected. Adverse events were also gathered. Enteral nutrition approach was heterogeneous but all centers followed the National Guide of Use criteria for advancing enteral feeds (14). PN was decreased by 10% to 20% and enteral feeding was increased if weight gain was obtained, diuresis was at least 25 to $30\,ml \cdot kg^{-1} \cdot day^{-1}$ and the frequency of stools was stable or less than the initial or the consistency had improved or, in the case of a stoma, the daily volume of stoma output had decreased. A patient in whom the PN support could be reduced by 20% or more was considered a ''responder.''

No ethical approval from local IRB was needed because teduglutide is approved in our country since October 2017 for its use in children older than 1 year.

RESULTS

Patients' characteristics are described in Table 1. All patients developed IF in the neonatal period, so all patients had parenteral supply from birth. The most frequent cause of SBS was necrotizing enterocolitis (NEC) (35%) followed by intestinal atresia and volvulus (17%). Patients had 52 cm of remnant bowel on average (range 14–144), 5 of them with less than 20 cm. Six children had the entire colon, 3 remnant hemicolon, 5 only sigmoid, and 3 no colon at all. They were receiving $55\,ml \cdot kg^{-1} \cdot day^{-1}$ of volume infusion (8–210) and $33\,kcal \cdot kg^{-1} \cdot day^{-1}$ (0–65) at baseline. Two patients were only on intravenous hydroelectrolytic support. Patients also received standard of care drugs (antisecretory drugs, antidiarrheal, ursodeoxycholic acid, etc). The initial mean plasma citrulline level was 20 μmol/l (7.8–51). The age at the beginning of treatment ranged between 12 and 121 months (68 months on average). All patients have been treated for at least 12 months except for patient number 16 (treated for only 6 months) and patient 17. The latter patient had a pre-existing hypertrophic cardiomyopathy and discontinued treatment after 4 months of initiation because of cardiac decompensation. He resumed treatment 11 months later.

At month 3, 3 patients (18%) achieved enteral autonomy. The rest of the patients decreased their parenteral fluid and calorie requirements by an average of 18% and 20%, respectively.

At month 6, 4 additional patients were weaned off PN, 6 decreased their parenteral requirements (28% and 30%) and 3 exhibited no changes.

At 12 months (15 patients), 3 more patients achieved independence from PN and 5 decreased their support needs (Fig. 1).

All patients completed 1 year of treatment but 1 (14 out of 15 subjects) experienced improvement (decrease of $\geq$20%) in terms of PN support requirement, with a response rate of 47% at month 3, 87% at 6 months, and 93% at 1 year. The percentage of patients that were able to be weaned off PS was 17%, 44%, and 60% at 3, 6, and 12 months, respectively. Therefore, 11 out of 16 children (69%) who received teduglutide for 12 months achieved enteral autonomy, 4 decreased their parenteral requirements, and only 1 patient did not experience any change, without any intercurrent event that could interfere in the success of treatment. All patients who weaned off PN maintained an ascendant growth curve (following the paediatric growth centile chart).

Stool output was measured in all patients. Most stoma carriers (4/6) improved their output in 43% on average (33–50), 1 did not show improvement, and 1 showed increased losses. Regarding nonstoma carriers (11 patients), 8 decreased bowel movements and 3 had no changes.

At baseline, citrulline ranged between 7.8 and 51 μmol/l (20 μmol/l on average) (SD 11.7). After initiating treatment, level increased to 37.5 (SD 15), 46.75 (SD 17.5), and 37.9 μmol/l (SD 18.4) on average at 3, 6, and 12 months, respectively (Table 2).

No relevant adverse events were reported apart from 1 episode of cholecystitis in which a cholecystectomy was needed, and a self-limited intestinal subobstruction. Mild abdominal pain and mucosal hypertrophy of the stoma were also reported.

Patient number 17 was affected by long segment Hirschsprung disease. He also suffered from other comorbidities including a mild hypertrophic cardiomyopathy. Due this last complication, hydroelectrolytic disturbances caused cardiac decompensations and difficulties in management. Moreover, he did not show any improvement, so teduglutide administration was discontinued after 4 months of treatment. One year later, he restarted it and 3 months after reinitiating, he was weaned off PN.

Treatment was very well tolerated with mild abdominal pain in some patients and 1 transient intestinal obstruction spontaneously resolved in a few hours. Only 2 subjects reported relevant adverse events: 1 cholecystitis and 1 fluid overload in a patient with previous cardiac impairment.

TABLE 1. Patient demographics and baseline data

	Short bowel ethiology	Remnant functional bowel	Ileocecal valve	Colon	Ostomy	Ostomy output ($ml \cdot kg^{-1} \cdot day^{-1}$)	Stool losses	Age at initiation of teduglutide	Initial weight kg (*z*-score)	Initial height cm (*z*-score)	PN ($mL \cdot kg^{-1} \cdot day^{-1}$)	PN ($kcal \cdot kg^{-1} \cdot day^{-1}$)	Teduglutide treatment duration	Responder at 12 months (>20% PN reduction)	Weaned off (months)
1	Necrotizing enterocolitis	30 cm	No	Sigmoid	No		75 ml/kg	88 m	27 (0.81)	134 (1.83)	85	25	29 m	Yes	Yes (12 m)
2	Necrotizing enterocolitis	Duodenum + partial jejunum	No	Sigmoid	No	38		86 m	13.7 (−4.35)	108 (−2.74)	69	55	24 m	Yes	Yes (12 m)
3	Volvulus	<20 cm	No	Hemicolon	No		4–5 stools/day	35 m	10.7 (−2.34)	84.6 (−3)	42	55	21 m	Yes	No
4	PIPO	15 cm	No	Defunctionalized	Yes	35		121 m	23.3 (−2.08)	126 (−2.05)	65	54	21 m	Yes	No
5	Gastroschisis	44 cm	No	Entire	No		y3–4 stools/day	45 m	10.4 (−3.39)	90.5 (−2.72)	38	25	13 m	No	No
6	Hirschsprung disease	120 cm	No	No	Yes	100		38 m	12.8 (−1.12)	9.8 (0.18)	33	14	20 m	Yes	Yes (3 m)
7	Necrotizing enterocolitis	85 cm	No	Rectum	Yes	80		102 m	27.2 (0.12)	137 (1.21)	37	0	20 m	Yes	Yes (3 m)
8	Intestinal atresia	20 cm	No	Hemicolon	No		3 stools/da	90 m	20.9 (−1.19)	117.9 (−1.37)	65	65	17 m	Yes	No
9	Volvulus	44 cm	Yes	Entire	No		3–4 stools/day	111 m	26.8 (−0.48)	138.5 (0.76)	8	10	15.5 m	Yes	Yes (6 m)
10	Necrotizing enterocolitis	35 cm	No	Entire	No		2 stools/day	39 m	12.2 (−1.58)	9.33 (−1.17)	35	33	15.5 m	Yes	No
11	Necrotizing enterocolitis	75 cm	No	Sigmoid	Yes	75		77 m	20 (−0.54)	116 (−0.47)	25	0	14.5 m	Yes	Yes (6 m)
12	Intestinal atresia	144 cm	No	Hemicolon	No		4 stools/day	66 m	11.4 (−4.04)	92 (−4.09)	65	51	13 m	Yes	No
13	Gastroschisis	97 cm	No	Entire	No		7–9 stools/day	98 m	16.8 (−3.37)	107.5 (−3.62)	30	30	13 m	Yes	Yes (12 m)
14	Necrotizing enterocolitis	42 cm	No	Sigmoid	No		9 stools/day	57 m	10 (−4.54))	90.5 (−3.95)	60	50	12.5 m	Yes	Yes (3 m)
15	Intestinal atresia	19 cm	Yes	Entire	No		69 ml/kg	48 m	17.6 (0.71)	102 (−0.05)	50	34	12 m	Yes	Yes (6 m)
16	Volvulus	Duodenum	Yes	Entire	No		4–5 stools/day	56 m	17.7 (−0.92)	103 (−2.37)	30	15	7 m	Yes	Yes (6 m)
17	Hirschsprung disease	80 cm	No	No	Yes	95		12 m	6.7 (−3.35)	72 (−1.68)	210	56	4.5 m + 3 m*	n.a.	n.a

PIPO = pediatric intestinal pseudo-obstruction.
*Patient discontinued treatment after 4 months of initiation because of cardiac decompensation. He resumed treatment 11 months later.

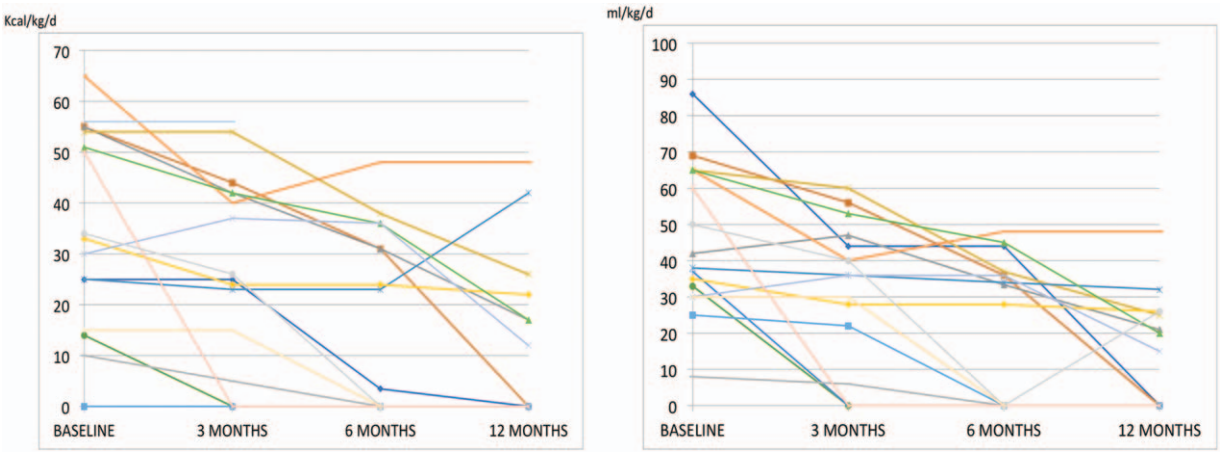

FIGURE 1. Evolution of parenteral support from baseline till 12 months of treatment with teduglitide.

DISCUSSION

Home PN is the treatment of choice for patients with IF. Patients with parenteral support (PS), however, face challenges to their quality of life and are at risk of developing further complications.

Clinical effectiveness of administration of exogenous analog of GLP-2 (Teduglutide) was analyzed in a phase III placebo-controlled trial (STEP) (9) and in STEPS-2 (13) and STEPS-3 (12), a 2 and 3 years, respectively open-label extension of that study. Characteristics of these studies are shown in Table 3. The responder rate in these studies was 63% at week 24 and 93% at 2 years. It can be concluded that there is a good early response but there is a group of ''late responders.''

The results in phase III clinical pediatric studies had been promising (5,6) with a high rate of patients with a 20% reduction in PS in the 24 weeks pediatric study. Teduglutide treatment was associated with a decrease in PN requirements and an increase in enteral intake in a cohort of SBS patients who had not experienced any clinical improvement for ≥3 months. These results are confirmed in our series and they are even more encouraging. These findings support the effectiveness of treatment in the pediatric population, and although response is good in the early phase of treatment, it can be further increased later. That means that most patients were late responders, and currently it is not possible to know, which is the best moment to evaluate treatment efficacy.

TABLE 2. Evolution in serum citrulline levels (μmol/L) from baseline until 12 months after start of treatment with Teduglutide

Patients	Baseline	3 months	6 months	12 months
1	14.7	60	52.1	56
2	26	n.r	n.r.	50
3	n.r.	26	n.r.	n.r.
4	7.8	32	52	32.6
5	10	24	31	27
6	16	37	28	n.r.
7	23	55	51	67
8	n.r	n.r.	n.r.	n.r.
9	21	29	n.r.	25
10	19	39	n.r.	24
11	39	50	72	n.r.
12	32	38	51	47
13	51	n.r.	65	n.r.
14	24	n.r	24	36
15	7.5	20.6	5.4	9
16	11	8	n.r	n.a.
17	11	52	n.a.	n.a.
Average	23.6	37.5	46.7	37.9
Median	22	37.5	51	36

n.a. = nonapplicable; n.r. = nonreported.

Regarding factors associated with response, it seems that patients with high baseline requirements, a long-standing dependency on PS, patients with jejunostomy or ileostomy and no colon remaining had a significantly higher PS reduction (22). No clear association was detected between change in plasma citrulline levels and specific weekly PS volume in adult phase III clinical studies. In the pediatric model, no conclusions were drawn because of the wide variability of baseline values. Our cohort presents several difficulties regarding this issue. Not all the patients were completely assessed, the group is heterogeneous and the tests were done in different laboratories. A trend towards an increase in mean value was, however, observed mainly in the early period of treatment. Further clinical evidence is required to determine whether citrulline may be a biomarker for changes induced by teduglutide.

The most commonly reported adverse reactions across all clinical studies were abdominal pain (30%), injection-site reactions (22.4%), nausea (18.2%), headache (15.9%), abdominal distension (13.8), and upper respiratory tract infection (11.8%) (23). Most of these reactions were mild or moderate. The safety of teduglutide has been assessed in several series including any potential carcinogenic effects. In a multicenter, prospective, randomized, placebo-controlled study, no differences neither in dysplasia nor atypia, dysplasia or malignancy were found between both, treatment and control groups, among this cohort of patients (24). A recent systematic review indicates that treatment with GLP-2 without any known pre-existing cancer did not confer an increased risk of intestinal neoplasia in patients but treatment in animals with pre-induced cancer showed that it may promote the growth of existing neoplasia (25). A colonoscopy of the entire colon with the removal of polyps should be, however, conducted before initiating therapy and is also recommended after 1 year of treatment (26). Gastrointestinal obstruction and stenosis have also been described. Teduglutide should be discontinued until the obstruction resolves. Pharmacological effects of teduglutide are localized not only in the intestine but also in the biliary tract and pancreas, so gallbladder, biliary, and pancreatic disease can appear. Three patients were diagnosed with cholecystitis during the placebo-controlled adult

TABLE 3. Efficacy results in clinical trials

	Jeppesen 2011 (5)	STEPS (6)	STEPS-2 (16)	STEPS-3 (9)	CARTER 2017 (10) (ped)	KOCOSHIS 2019 (11) (ped)
Subjects	83	86	88	13	42	59
Duration	24 weeks	24 weeks	2 years	3 years	12 weeks	24 weeks
Outcomes	≥20% reduction of PS-volume requirement in 46% patients ↑lean body mass, total body mineral content, intestinal villous height and plasma citrulline	≥20% reduction of PS-volume requirement in 63% patients. Mean of PS-volume reduction of 4.4 ± 3.8 L/week (32% ± 19%) versus 2.3 ± 2.7 L/week (21% ± 25%) reduction in placebo group	≥20% reduction of PS-volume requirement in 93% patients. Reduction of ≥1 day/week of PN dependence in 68% patients 20% patients achieved full enteral autonomy	Mean of PS-volume reduction of 50% 2 patients more achieved full enteral autonomy	Mean of PS-volume and calories reduction of 25% and 52%, respectively 3/15 patients of cohort achieved independence from PN	≥20% reduction of PS-volume requirement in 69.2% patients 3/26 patients achieved independence from PN

Model from Vipperla and O'Keefe (26) and Burgos Pelaez et al (29). PN = parenteral nutrition; PS = parenteral support.

trials, all of whom had a prior history of gallbladder disease and all in the treatment group (27). Fluid overload and congestive heart failure have been reported in adult clinical trials related to enhanced fluid absorption. This effect is crucial when an underlying cardiac disease exists and we must pay attention in order to decrease parenteral fluid if necessary to avoid this event.

As for the economic impact, the estimated cost of teduglutide is approximately $300,000/year/patient in the United States. Even though it is a very expensive drug, it is expected to offset some of the economic burdens of SBS-IF, which have been estimated at $150 to 500,000/year/patient and to improve the Quality of Life (QoL) (20,28).

In conclusion, the results of our series, the first pediatric series outside a clinical trial, show promising data about the improvement in SBS prognosis, confirm the findings of the pediatric clinical trials and add additional data of longer term improvement. Our study, however, has limitations. It is a small series, with heterogeneous anatomical conditions and belonging to 8 different centers.

Management of patients with SBS requires a comprehensive multidisciplinary approach. Teduglutide is a new resource available to expert multidisciplinary teams that can be more useful than other drugs available to this type of patient. Some authors suggested that the reduction in parenteral needs (not only PN wean-off) can lead to an improvement in QoL (29). We do not, however, have enough data to evaluate efficiency and safety in the long-term, so more studies are needed.

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