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EXPERIENCE WITH TEDUGLUTIDE IN PEDIATRIC SHORT BOWEL SYNDROME: FIRST REAL-LIFE DATA

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ABBREVIATIONS: IF: Intestinal Failure; SBS: Short Bowel Syndrome; GLP-2: Glucagon-like-peptide-2; DPPIV: dipeptidyl peptidase IV; PN: Parenteral Nutrition; NEC: necrotizing enterocolitis; PIPO: Pediatric Intestinal Pseudo-Obstruction; PS: Parenteral Support

ABSTRACT

Objectives: To describe the experience with teduglutide of several Spanish hospitals in pediatric patients with short bowel syndrome (SBS).

Methods: Seventeen pediatric patients with intestinal failure associated with short bowel syndrome were treated with teduglutide. Patients received 0.05 mg/kg/d 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/d and 33 Kcal/kg/d 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 one year after the beginning because 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.

KEYWORDS

Intestinal failure, short bowel syndrome, intestinal growth factors, intestinal adaptation, parenteral nutrition.

ABBREVIATIONS

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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 this study adds:

- 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.

Introduction

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 intestinal failure 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 post-resection 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 poorest prognosis. This group of patients has a markedly impaired post-prandial GLP-2 response, probably caused by a lack of functioning L-cell mass[2,3,4].

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 intestinal failure due to SBS. Small bowel transplantation is the alternative in those patients that develop complications associated with this condition. However, it 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 one 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 seventeen pediatric patients affected with SBS from eight Spanish centers treated with 0.05 mg/kg/d 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 < 100cm 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 one stoma in the proximal jejunum, so he was considered a SBS.

Follow up was planned following a national Guide of Use[14] (every two weeks in the first month, once a month the next two months and every three 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 10-20% and enteral feeding was increased if weight gain was obtained, diuresis was at least 25-30 ml/kg/day 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 intestinal failure 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), five 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/kg/d of volume infusion (8-210) and 33 Kcal/kg/d (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 six months) and patient 17. The latter patient had a pre-

existing hypertrophic cardiomyopathy and discontinued treatment after four months of initiation because of cardiac decompensation. He resumed treatment 11 months later.

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

At 12 months (15 patients), three more patients achieved independence from PN and five decreased their support needs **(Figure 1).**

All patients that completed one year of treatment but one (14 out of 15 subjects) experienced improvement (decrease of ≥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%) that received teduglutide for 12 months achieved enteral autonomy, four decreased their parenteral requirements and only one patient did not experience any change, without any intercurrent event that could interfere in the success of treatment. All patients that 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), one did not show improvement and one increased losses. Regarding non-stoma 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 one episode of cholecystitis in which a cholecystectomy was needed, and a self-limited intestinal sub-obstruction. 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, hydroelectrolitic 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 three months after reinitiating, he was weaned off PN.

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

Discussion

Home PN is the treatment of choice for patients with IF. However, patients with parenteral support 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 parenteral support 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 that 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.

Regarding factors associated with response, it seems that patients with high baseline requirements, a long-standing dependency on parenteral support (PS), patients with jejunostomy or ileostomy and no colon remaining had a significantly higher PS reduction[20]. 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. However, a trend towards an increase in mean value was 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%)[21]. 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[22]. 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[23]. However, a colonoscopy of the entire colon with the removal of polyps should be conducted prior to initiating therapy and is also recommended after one year of treatment[24]. 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 trials, all of whom had a prior history of gallbladder disease and all in the treatment group [25]. 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 $150-500,000/year/patient and to improve the Quality of Life (QoL)[26,27].

In conclusion, **t**he results of our series, the first paediatric series outside a clinical trial, show promising data about the improvement in short bowel syndrome prognosis, confirm the findings of the pediatric clinical trials and add additional data of longer-term

improvement. However, our study has limitations. It is a small series, with heterogeneous anatomical conditions and belonging to eight 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 Quality of Life[28]. However, we do not have enough data to evaluate efficiency and safety in the long term, so more studies are needed.

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Figure 1. Evolution of parenteral support from baseline till 12 months of treatment with Teduglitide.

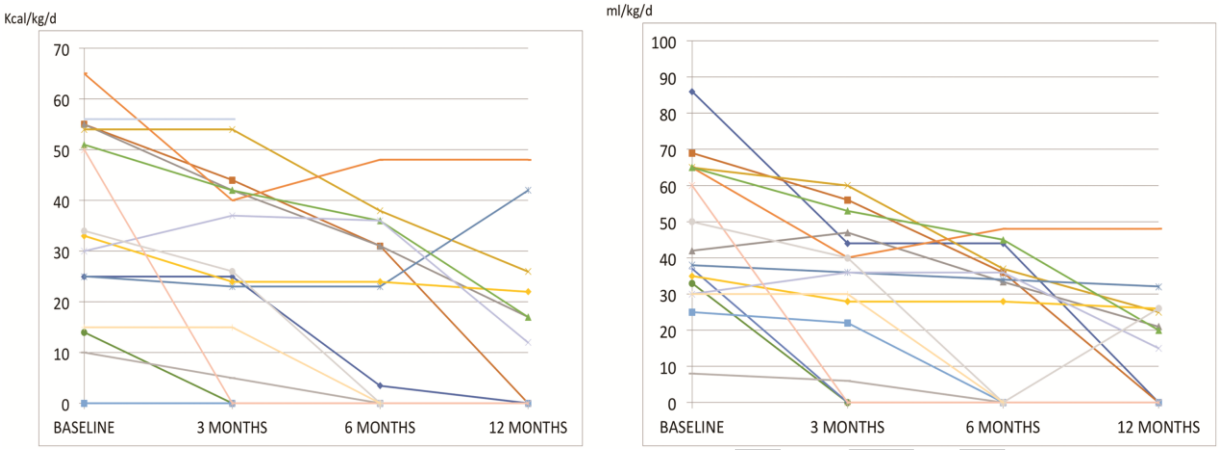

Table 1. Patient demographics and baseline data

	SHORT BOWEL ETHIOLOGY	REMNANT FUNCTIONAL BOWEL	ILEOCECAL VALVE	COLON	OSTOMY	OSTOMY OUTPUT (ml/kg/d)	STOOL LOSSES	AGE AT INITIATION OF TEDUGLUTIDE	INITIAL WEIGHT Kg (z-score)	INITIAL HEIGHT cm (z-score)	PN (ml/kg/d)	PN (kcal/kg/d)	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/d	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		3-4 stools/d	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/d	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/d	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/d	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/d	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/d	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/d	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/d	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

* Patient discontinued treatment after four months of initiation because of cardiac decompensation. He resumed treatment 11 months later.

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.r.: non reported. n.a.: non applicable

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	≥20% reduction of PS-volume requirement in 63% patients.	≥20% reduction of PS-volume requirement in 93% patients.	Mean of PS-volume reduction of 50%	Mean of PS-volume and calories reduction of 25% and 52 % respectively	≥20% reduction of PS-volume requirement in 69.2% patients
	↑lean body mass, total body mineral content, intestinal villous height and plasma citrulline.	Mean of PS-volume reduction of 4.4 ±3.8 L/week (32%±19%)vs 2.3±2.7 L/week (21%±25%) reduction in placebo group.	Reduction of ≥1 day/week of PN dependence in 68% patients 20% patients achieved full enteral autonomy	2 patients more achieved full enteral autonomy	3/15 patients of cohort achieved independence from PN	3/26 patients achieved independence from PN

Mod from Vipperla[25] and Burgos[28]

PS: Parenteral support, PN: Parenteral Nutrition