The Variable Response to Teduglutide in Pediatric Short Bowel Syndrome: A Single Country Real-Life Experience

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ABSTRACT

Objectives: The glucagon-like peptide-2 analog Teduglutide has been shown to enhance intestinal absorption and decrease parenteral nutrition (PN) requirements in short bowel syndrome (SBS). As data in children is limited, we evaluated nationwide real-life experience and treatment outcome in children with SBS.

Methods: Longitudinal data of children treated with Teduglutide for ≥3 months was collected. Data included demographic and medical background, anthropometrics, laboratory assessments and PN requirements. Treatment response was defined as >20% reduction in PN requirement.

Results: The study included 13 patients [54% males, median (interquartile range {IQR}) age of 6 (4.7–7) years]. The most common SBS etiology was necrotizing enterocolitis (38%), and median (IQR) small bowel length was 20 (15–40) cm. Teduglutide treatment ranged between 3 and 51 months [median (IQR) of 18 (12–30) months], with 10 patients (77%) treated >1 year. Response to treatment was observed in 8 patients (62%), with a mean [±standard deviation (SD)] treatment duration of 5.9 (±3.2) months. Among responders, 2 patients were weaned off PN and additional 4 decreased PN needs by >40%. There was a median (IQR) reduction in PN volume/kg of 36% (15%–55%) and in PN energy/kg of 27% (6%–58%). Response was not associated with patients' background, and no correlation was found with bowel length or PN dependency at baseline.

Conclusions: Real-life response to Teduglutide is highly variable among children with SBS. While most patients did reach 20% reduction in PN, less achieved further significant reduction or enteral autonomy. No predictive factors of response to treatment were identified, and large multicenter studies are needed to elucidate predictive factors and long-term outcome.

Key Words: enteral autonomy, glucagon-like peptide-2, intestinal failure, parenteral nutrition, short bowel syndrome, short gut, weaning

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What Is Known

- Glucagon-like peptide-2 (GLP-2) is a key regulator of intestinal adaptation in short bowel syndrome (SBS).
- The GLP-2 analog Teduglutide has been shown to decrease parenteral nutrition (PN) requirements in patients with SBS.
- Publications reporting the use of Teduglutide in children are still scarce.

What Is New

- Real-life response to Teduglutide is highly variable among children with SBS.
- No predictive factors of response to treatment were identified in this population.
- Most patients reached a primary response of 20% reduction in PN within 6 months of treatment.
- Further significant improvement was observed in some patients over longer duration of treatment, with enteral autonomy achieved in 15%.

Short bowel syndrome (SBS) occurs after resection or loss of a major portion of the bowel leading to intestinal malabsorption, being the most common cause of pediatric intestinal failure (IF) (1). SBS results in IF when there is a critical reduction in gut function below the minimum necessary for absorption, to the extent that intravenous supplementation is required to maintain health and growth (2). The management of SBS-associated IF (SBS-IF) is aimed to support adequate nutrition and growth while minimizing the risk of complications, alongside the desired goal of achieving independence from parenteral nutrition (PN), or "enteral autonomy" (3). Following an extensive bowel resection, a compensatory process of intestinal adaptation occurs naturally, involving

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structural and functional changes that improve nutrient and fluid absorption in the remnant bowel (4). The enteric hormone glucagon-like peptide-2 (GLP-2) appears to be a key regulator in the process of adaptation (5). Naturally, GLP-2 is synthesized and secreted by the enteroendocrine L-cells in the small and large bowel, mainly in response to undigested nutrients in the gut (6). GLP-2 circulates both locally and via the blood stream and activates its specific receptors on enteroendocrine cells, enteric neurons and myofibroblasts of the intestine. Numerous effects of GLP-2 stimulation support both intestinal absorption and intestinal adaptation, including an increase in mesenteric blood flow, slow intestinal motility, reduction in enteric secretions, and an indirect trophic effect manifested by reduced enterocytes apoptosis as well as villi and crypt elongation and proliferation (5).

Teduglutide is a GLP-2 analog, aimed to enhance intestinal absorption and decrease PN dependency in patients with SBS (7,8). The use of Teduglutide in pediatric population is still scarce, and data from clinical studies as well as real-life reports from this age group are limited (9). Two clinical trials (10,11) have demonstrated the efficacy of Teduglutide treatment in children with SBS. Based on limited data, a pooled analysis of the long-term trials in pediatric patients (12) reported a good overall tolerance and safety profile.

In this longitudinal multi-center study, we have aimed to describe the real-life experience and treatment outcome in children with SBS treated with Teduglutide in Israel.

METHODS

Study Population

The study included pediatric patients treated with Teduglutide, in 8 medical centers across Israel, between April 2017 and November 2021. The cohort represents all pediatric SBS patients treated with Teduglutide in Israel during this period, except for 1 patient for whom data were unavailable. Inclusion criteria included age range between 1 and 18 years, the diagnosis of SBS and IF, and Teduglutide treatment period of at least 3 months.

Teduglutide (Gattex, NPS Pharmaceuticals, Bedminster, NJ, USA) was provided by the local distributer of Teduglutide, free of charge following a request for compassionate use. However, the distributer was not involved in any part of the study prior to the initiation and during follow-up and was not involved in any part of the data analysis or manuscript preparation.

The institutional ethical review board approved the study protocol.

Variables

Data included patients' demographics, medical background, surgical background, and residual anatomy of the bowel. Anthropometric and laboratory measurements were longitudinally assessed every 3 months. Anthropometrics included weight, height, and body mass index (BMI), described as age and sex adjusted *z* scores.

Enteral intake was assessed by dietitians, and presented as overall daily energy consumed both by mouth (table food and/or liquid supplementary formula) and via gastrostomy tube when relevant.

PN needs and regimen changes over the treatment period were also assessed longitudinally, presented as weekly PN calories and as volume per the patients' body weight. Treatment response was defined as >20% reduction in PN volume from baseline.

Analysis and Statistics

Categorical variables were described as frequencies and percentages, while continuous variables were described as median and interquartile range (IQR). General estimated equation model was used for repeated measures analysis. Mann-Whitney test was used to compare continuous variables, and Fisher's exact test was used for categorical variables. Kaplan-Meier estimator was used to describe events during follow-up period. Association between events and categorical variables was studied using log-rank test, while Cox regression was applied for the continuous variables.

All statistical tests were 2-tailed and $P < 0.05$ was considered statistically significant. The software SPSS version 25 (IBM corp., Armonk, NY, USA, 2017) was used for all statistical analyses.

RESULTS

The study population included 13 patients (54% males), with a median (IQR) age of 6 (4.7–7) years. Patients' background characteristics are detailed in Table 1. The most common SBS etiology was necrotizing enterocolitis (38%), ileocecal valve (ICV) was present in 23%, and median (IQR) residual small bowel length was 20 (15–40) cm. None of the patients had an end stoma, and all had intact colon except for one patient with ileo-anal anastomosis. None of the patients was diagnosed with IF-associated liver disease (13). The duration of Teduglutide treatment ranged between 3 and 51 months [median (IQR) of 18 (12–30) months], with 10 patients (77%) treated for longer than 1 year.

Patients' PN support during follow-up is detailed in Table 2. The average reduction in PN requirements, evaluated using the general estimated equation model, was −7.85 mL/kg/wk [95% confidence interval (CI): −11.6 to −4.1] and −4.95 kcal/kg/wk (95% CI: −7.65 to −2.25), for each month of Teduglutide treatment ($P < 0.001$ for both). Compared to each patient's baseline requirements, there was a median (IQR) reduction in PN volume per kg of 36% (15%−55%) and in PN energy per kg of 27% (6%−58%), respectively. The longitudinal changes in PN volume requirements per body weight are provided in Figure 1.

Response to treatment, defined as >20% reduction of PN volume, was observed in 8 patients (62%), within a mean [±standard deviation (SD)] treatment duration of 5.9 (±3.2) months. Cumulative incidence of response in the study group is provided in Figure 2. Three patients have discontinued Teduglutide treatment during follow-up: patients no. 6 and 7 due to lack of response (after 30 and 6 months, respectively), and patient no. 9 due to no further improvement after 18 months of treatment. No major treatment-related adverse events were reported.

Among responders, 4 patients decreased their PN needs by more than 40%, and 2 additional patients were weaned off PN during the study period (after 12 and 27 months of Teduglutide treatment; Table 2).

There were no significant changes in weight-for-age and height-for-age *z* scores, despite the changes in PN regimen along follow-up ($P = 0.2$ and 0.5, respectively). Longitudinal data regarding enteral intake were available in 10 of 13 (77%) of patients, half of them combined oral and gastrostomy-tube feeding, and half consumed all feeds by mouth. Although there was an average increase in the daily enteral intake per weight from baseline [mean (±SD) of 57% (±129%)], the results were highly variable (both among responders and non-responders) and did not reach statistical significance ($P = 0.1$).

The study did not demonstrate any associations between response to Teduglutide and patients' baseline characteristics, including gender ($P = 0.4$); history of prematurity ($P = 0.7$); residual small bowel length ($P = 0.6$); the presence ICV ($P = 0.9$); age at treatment initiation ($P = 0.8$); PN volume and energy at baseline ($P = 0.7$ and $P = 0.3$, respectively); and enteral intake at baseline ($P = 0.3$).

TABLE 1. General characteristic of study population

Patient no.	Gender	Week of gestation	SBS etiology	Age at bowel resection	Residual bowel length, cm	ICV present	Other comorbidities	Age at Teduglutide initiation, y
1	Male	28	Volvulus	12 d	18	No	-	4.7
2	Female	Full term	NEC	3 d	75	No	-	7.8
3	Male	29	NEC	10 d	38	No	-	6.5
4	Male	30	NEC	80 d	10	No	-	1.4
5	Female	34	Atresia	2 d	16	Yes	-	5.0
6	Male	33	Volvulus	9 d	20	Yes	-	6.3
7	Male	35	Gastroschisis	1 d	55	No	-	7.0
8	Female	34	Diaphragmatic hernia	15 d	20	No	Global developmental delay	5.4
9	Female	32	NEC	27 d	8	Yes	Global developmental delay	6.0
10	Female	Full term	Vascular accident	11 y	15	No	Connective tissue disease	11.1
11	Male	Full term	Hirschsprung disease	20 d	85	No	-	9.0
12	Female	33	NEC	52 d	40	No	-	2.8
13	Male	33	Gastroschisis	23 d	2	No	-	4.7

ICV = ileocecal valve; NEC = necrotizing enterocolitis; SBS = short bowel syndrome.

DISCUSSION

The main findings from our real-life pediatric SBS-IF cohort is that the majority (63%) of patients have reached the primary outcome of response to Teduglutide treatment, expressed by the reduction of PN requirements compared to baseline. These results support the previous findings from the pediatric 24-week clinical trial (11) that demonstrated a response rate of 69%. Moreover, 2 of 13 (15%) of our patients were able to achieve enteral autonomy, also in concordance with the 11.5% rate of PN weaning, reported in the clinical trial.

Discordant with the positive findings, it is important to note that there was a wide spectrum of time to response in our pediatric population. While most patients reached 20% PN reduction within 3 months of treatment, it may have taken as long as 1 year to reach this outcome. These results suggest that lack of primary response after 1 year indicates treatment failure. However, for those achieving primary response after 1 year, long-term treatment may result in significant improvement over time. The wide variability of response to Teduglutide is also demonstrated by the magnitude of reduction in PN requirements—from no response to complete weaning from PN. Only a third of the patients have reached more than 50% reduction of their PN volume during treatment, implying an overall modest improvement in our cohort.

Prior to our current study, only a single report of real-life experience in pediatric population was published (9). In that study, recently published by Ramos Boluda et al (9), there was a higher rate of response to Teduglutide reaching 93% by 1 year of treatment, with up to 70% of the patients who continued 1 year of treatment that were able to wean-off PN. Both the response rate and the rate of achieving PN weaning in our cohort were much lower than in the Ramos Boluda et al's (9) study. These differences in outcomes may be explained by the different characteristics of participants in the studied populations. Overall, patients in our cohort were more dependent on PN support prior to Teduglutide treatment (reflected by the average weekly PN volume and energy per body weight), and had shorter small bowel remnant on average with 8 of 13 (62%) of them with ≤20 cm. These factors that reflect the severity of SBS in our study population could suggest an inferior potential to achieve enteral autonomy in these complicated patients, although we cannot rule out that longer period of treatment could be beneficial for some of them.

As pediatric SBS-IF is not a common disease, and the patients are often heterogenous in their clinical presentation (including length and anatomy of the residual bowel, PN dependency prior to treatment, oral and enteral intake, other comorbidities and associated conditions), most current studies may lack the power to provide significant evidence for predictive factors for treatment response. A recent publication by Chen et al (14), in adult patients with SBS, has identified the presence of stoma as well as the absence of ICV as positive predictors for early response to Teduglutide. However, the proportion of patients in that study with end stomas was high (49%), with 93% lacking ICV, as opposed to much lower proportions in our cohort. This is in concordance with a prior post-hoc analysis of a phase III trial in adults (15), which demonstrated a greater effect of PN volume reduction in patients with jejunostomy/ileostomy. On the contrary, a real-life study in adult population from France (16), in which the proportion of patients with colon in continuity was higher than in the aforementioned studies, did not show a significant association between response to Teduglutide and bowel anatomy. The study from France, however, as opposed to our study, did demonstrate an association between baseline PN volume and the reduction in PN requirements during a 6-month period of treatment. Facing the contradictory results from different studies in adults so far, together with our current study which could not identify any significant prognostic factor for response to treatment, larger multi-center studies are needed in pediatric population of SBS-IF, in order to identify subgroups of patients which could benefit the most from Teduglutide treatment.

Some limitations to our study should be acknowledged. As this is an observational study rather than a controlled clinical trial, no causality between treatment and outcomes could be claimed and hence only associations and clinical observations are reported. The criteria for Teduglutide initiation as well as the overall treatment practices and multidisciplinary availability have varied between the different centers, and hence these findings represent the real-life clinical experience in practice. Also, the reduction in

TABLE 2. Parenteral nutrition support and changes during treatment

	Baseline (prior to Teduglutide initiation)					End of follow-up/treatment cessation					Change		
Patient no.	Weight, kg	WAZ	Weekly PN volume per weight, mL/kg	Weekly PN energy per weight, kcal/kg	Days on PN per week	Treatment duration, mo	WAZ	Weekly PN volume per weight, mL/kg	Weekly PN energy per weight, kcal/kg	Days on PN per week	Change in PN volume	Change in PN energy	Days reduction
1	16.7	−0.5	461	344	7	51	−0.1	129	122	6	−72%	−64%	−1
2	21	−1.1	333	300	7	45	−2.6	0	0	0	−100%	−100%	−7 (weaning)
3	17.2	−1.4	610	563	7	21	−2.2	276	238	7	−55%	−58%	0
4	8.7	−2.6	828	510	7	18	−1.8	641	478	7	−23%	−6%	0
5	15	−1.3	476	411	7	30	−1.5	0	0	0	−100%	−100%	−7 (weaning)
6	18	−1.5	300	233	6	30	−2.2	317	244	6	6%	4%	0
7	17.6	−2.1	676	393	7	6	−2.4	574	344	7	−15%	−12%	0
8	15.8	−1.4	377	319	7	45	−1.7	320	233	5	−15%	−27%	−2
9	13.4	−3.5	815	534	7	18	−3.8	434	434	7	−47%	−19%	0
10	33.5	−0.6	522	229	7	12	−1.5	530	333	7	2%	46%	0
11	23.9	−1.1	151	118	4	18	−2.8	81	69	2	−46%	−42%	−2
12	13	−0.2	135	102	5	6	−0.5	130	103	5	−4%	2%	0
13	18.6	0.4	536	320	7	3	0.7	345	228	7	−36%	−29%	0
Median (IQR)	17.2 (15–18.6)	−1.3 (−1.5 to −0.6)	476 (333–610)	320 (233–411)	7 (7–7)	18 (12–30)	−1.8 (−2.4 to −1.5)	317 (129–434)	233 (103–333)	6 (5–7)	−36% (−55% to −15%)	−27% (−58% to −6%)	0 (−2 to 0)

IQR = interquartile range; PN = parenteral nutrition; WAZ = weight-for-age *z* score; Wt = weight.

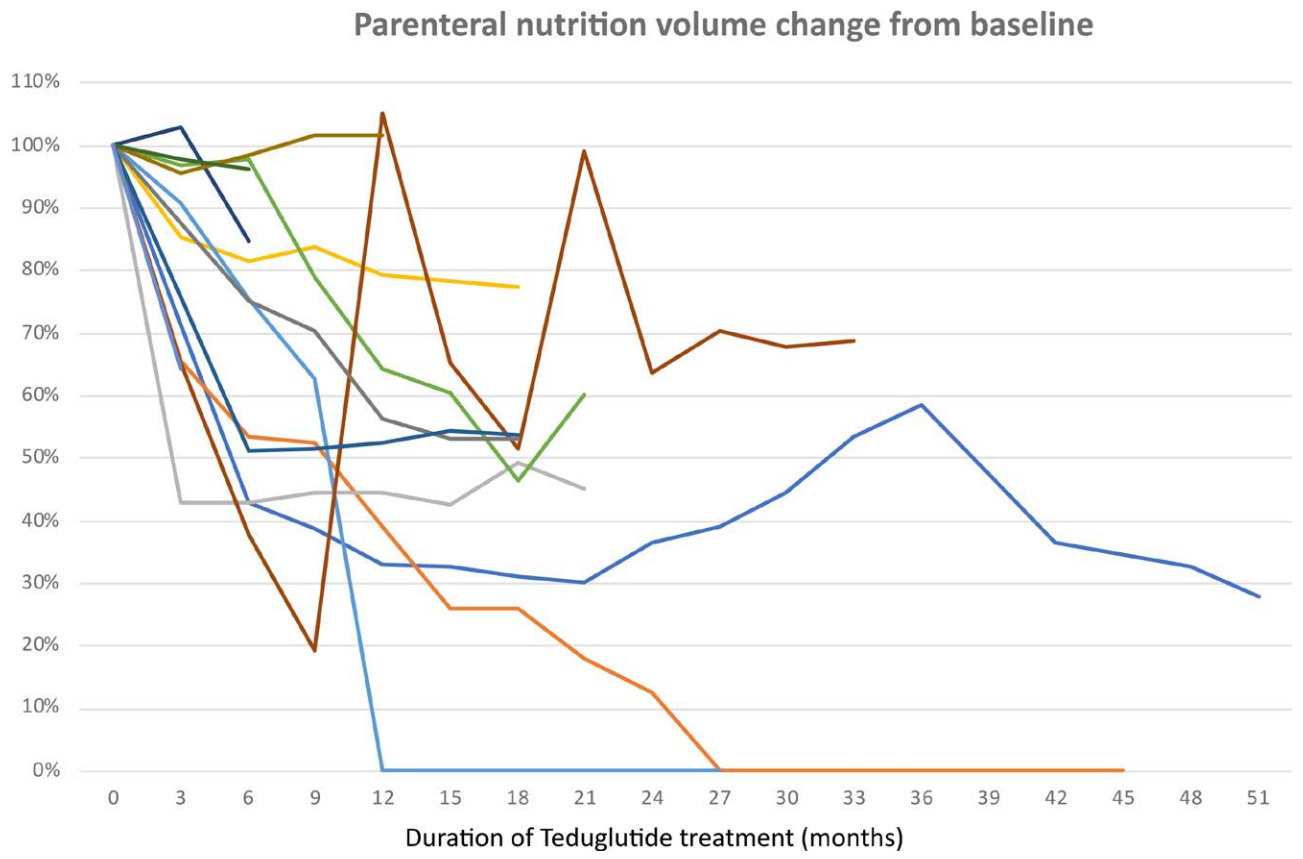

FIGURE 1. Parenteral nutrition volume change from baseline.

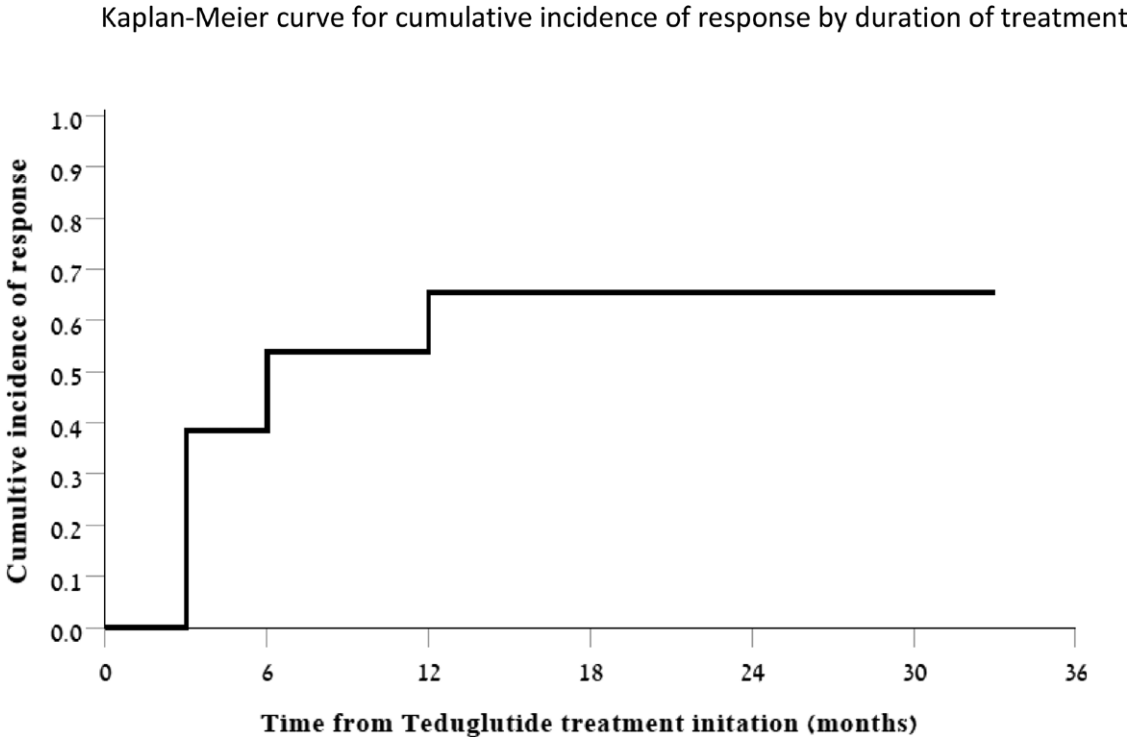

FIGURE 2. Kaplan-Meier curve for cumulative incidence of response by duration of treatment.

PN requirements could in part be attributed to the natural adaptation of the gut, although most of the patients in our cohort had long-lasting SBS beyond the expected time of spontaneous adaptation. Changes in PN regimen could also be influenced by the physician's and families' efforts to reduce PN dependency (rather than as result of pure reduction in metabolic requirements), however the stable anthropometric indices despite reduction in PN support suggest an improvement in gut function. In addition, some missing data are important to acknowledge, including enteral intake in several patients, stool output before and during treatment, as well as plasma citrulline levels which were not available in most contributing centers. Finally, despite being able to provide a nationwide report of SBS-IF patients on Teduglutide, this cohort of patients is rather small. Still, it represents a wide variety of patients treated in different medical centers across Israel, and reflects a real-life experience with an orphan drug.

CONCLUSIONS

In conclusion, the real-life response to Teduglutide is highly variable in pediatric patients with SBS-IF. This study demonstrates a response to treatment in most patients within 6 months of treatment that can benefit by achieving a reduction in their PN requirement. However, only a minority of children achieved further significant reduction or reached enteral autonomy. No predictive factors of response to treatment were identified in this heterogeneous cohort, and hence large multicenter studies are much needed to elucidate predictive factors and long-term outcome of Teduglutide in children with SBS.

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