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CASE REPORT

Nutrition

Optimizing peripubertal growth in a child with short bowel syndrome on full oral feeding with glucagon-like peptide 2 analog

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Abstract

Teduglutide is a glucagon-like peptide 2 (GLP-2) analog which acts by increasing intestinal absorption of the remnant bowel for children with short bowel syndrome (SBS) dependent on parenteral nutrition. We present a 13-year-old male patient with type 2 SBS (55 cm of jejunum) from necrotizing enterocolitis on full oral feeding from the age of 12 months. Because of faltering growth from the age of 11 despite oral hyperphagia, he started Teduglutide at the standard dose. Eighteen months after Teduglutide start the young boy gained 10 kg in weight and 13 cm in height with a significant reduction in bowel distension. No adverse events were reported during the treatment. Pubertal spurt might be impaired in children with SBS on full oral feeding if the caloric need is not met by the residual intestinal absorption rate. GLP-2 analog might represent an option to sustain pubertal spurt in SBS children on full oral feeding with hyperphagia.

KEYWORDS

hyperphagia, intestinal failure, pubertal spurt, teduglutide

1 | INTRODUCTION

Intestinal failure (IF), is defined as decline in intestinal function below the level required for macronutrient and/or water and electrolyte absorption, such that intravenous supplementation (IVS) is required to maintain health and/or growth.[1] Short bowel syndrome (SBS) is the leading cause of IF in the pediatric age and is caused by intestinal resection in childhood due to congenital or acquired intestinal defects. Important factors for survival and adaptation are the residual length of the small intestine, the presence of the ileocecal valve (ICV) and the colon.[2] Although parenteral nutrition (PN) and IVS are the mainstay of treatment, PN itself is associated with complications. Whenever possible, enteral feeding should be preferred because it is the most physiological and safest way to provide nutrition, so PN should be discontinued when sufficient intake and growth is achieved with oral and/or enteral feeding alone. However, even once full enteral nutrition has been achieved, some complications may persist or occur.

The physiological intestinal adaptation process promotes the villi to hypertrophy and the crypts to deepen. This process involves the secretion of several hormones, among which glucagon-like peptide-2 (GLP-2) is key, it acts as a stimulating growth factor for the mucosa of the small intestine,[3] increasing the absorptive capacity of the intestine after intestinal loss.

[Correction added on 30 July 2024, after first online publication: the affiliation has been revised for Lorenzo D'Antiga and Lorenzo Norsa.]

Since citrulline is a free amino acid produced almost exclusively by the enterocytes of the small intestine from glutamine and arginine it is widely used as a reliable marker of the functional mass of the small intestine even if its correlation with intestinal absorption is weaker.[4]

GLP-2 analogs such as teduglutide were designed to stimulate and increase the physiological process of intestinal adaptation to reduce PN needs.[5]

The treatment of patients with SBS was further strengthened by the European Medicines Agency's approval in 2016 of the use of teduglutide in children (aged 1 to 17 years) on PN support.[6]

Since then, some clinical studies and real-life experiences were published and proved the efficacy of teduglutide in lowering PN need for SBS children on PN.[7,8]

2 | CASE REPORT

We present a 13-year-old male patient with post-surgical SBS, type 2.

Born premature at 28 weeks gestational age with an adequate birthweight of 1.3 kg, he underwent resection of necrotic areas of the ileum and right-sided hemicolectomy with an ileocolonic anastomosis at 2 weeks of life due to necrotizing enterocolitis (NEC) and intestinal perforation. Four days later the newborn needed another surgery due to intestinal obstruction with further resection of a stenosis of the ileocolonic anastomosis as well as a left-sided hemicolectomy and cholecystectomy. As a result of those surgeries, he was left with a total length of 55 cm of small intestine; the absence of an ICV and the presence of a sigmoid colon.

During his long stay in neonatal intensive care unit his growth was sustained with PN until he was finally discharged at the age of 12 months on full oral feeding (extensively hydrolyzed cow's milk protein formulas 200 mL ×2 daily and complementary foods). Weight at discharge was 6.5 kg. Since discharge his homestay was characterized by good general condition and regular growth and weight around the 3rd percentile. The transit was characterized at first by frequent and poorly formed stools; later by a decrease in the number of stools to two to three partially formed per day testifying the process of physiological intestinal adaptation. He did not experience any other complications such as metabolic acidosis or electrolyte imbalance, or micronutrients deficiency (iron, vitamin D, or vitamin B12).

Follow-up was uneventful except for one intestinal subocclusive event which needed a readmission at the age of 3 years and which was resolved with evacuative enema and trans-anal irrigation.

After a partial loss to follow-up, he resumed a regular follow-up from the age of 10 years when he accessed our intestinal rehabilitation clinic for faltering weight growth (height: 134 cm [–1.10 *Z*-score], weight: 24.8 kg [–2.33 *Z*-score], body mass index (BMI): 13.4 kg/m^2 [–2.63 *Z*-score]) and significant abdominal distension. A full intestinal transit was performed which showed a significant ileal dilatation 75 mm. The stool transit was composed of 3 liquid stools/daily. He was first treated with intestinal decontamination with Metronidazole cycle every 3 months. A full dietetic workup revealed a caloric intake of 2000 kcal/day (80 kcal/kg/day) with a protein intake of 70 g/day (2.8 g/kg/day). Despite this significant caloric intake, the child showed a worsening of his nutritional status with a weight of 27.8 kg (–2.89 *Z*-score), a height of 143 cm (–1.31 *Z*-score) and a BMI of 13.2 kg/m^2 (–3.59 *Z*-score) at the end of the 2-year regular Intestinal Rehabilitation Center (IRC) follow-up. Furthermore, no improvement in pubertal stage was observed, reflected by Tanner stage that did nor advanced beyond 1.

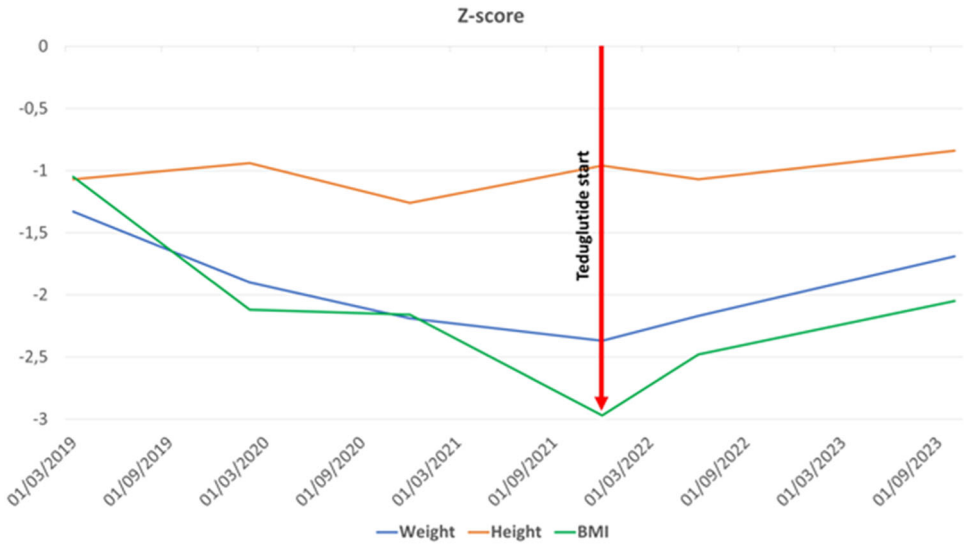

FIGURE 1 *Z*-score modification in height, weight, and body mass index before and after Tedugutide treatment.

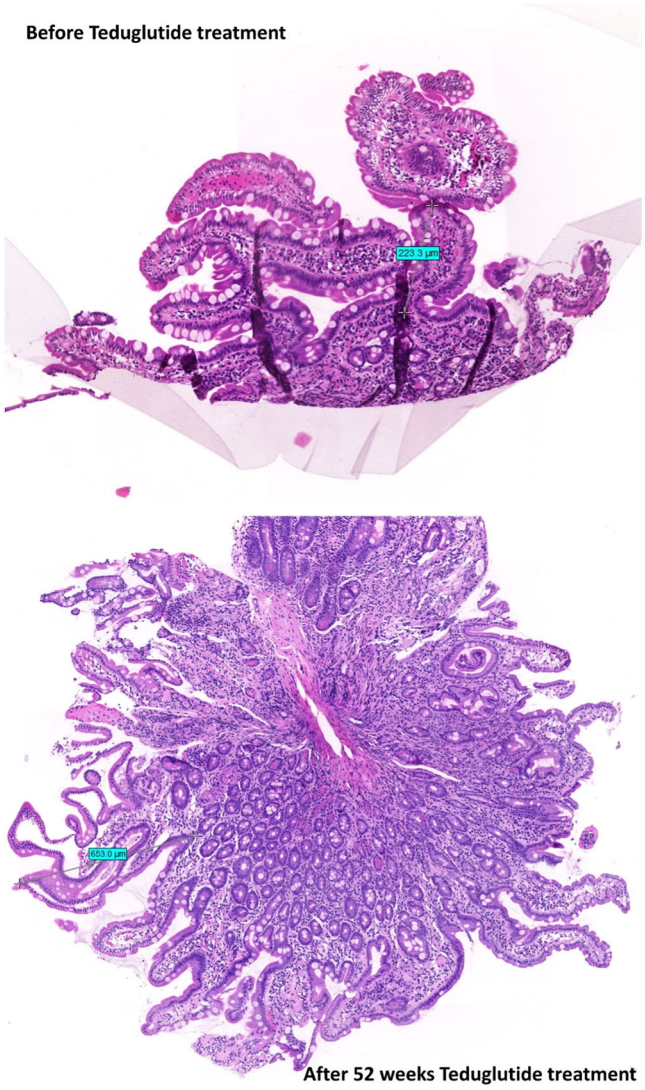

FIGURE 2 Duodenal biopsies before treatment displaying signs of chronic inflammation with a villous height of 223 µm. Duodenal after 52 weeks of teduglutide treatment shows a sign of chronic inflammation with normal villous architecture of 653 µm height.

After an endoscopic work up, which ruled out any peri anastomotic stricture, a multidisciplinary discussion by the intestinal rehabilitation team (gastroenterologist, pediatric surgeon, dietician psychologist, and social worker) was carried out with the three possible therapeutic options:

1. Resume PN support.
2. Work up for possible intestinal elongating surgery.
3. Hormonal treatment with GLP-2 analog.

Taking into consideration all pros and cons Teduglutide treatment was judged the best option and started at the age of 12 years at the standard dose of 0.05 mg/kg/with a subcutaneous daily injection.

After the first 6 months of treatment, we could appreciate a significant improvement in weight with a +2 kg increase and height +3 cm. and a change in transit characterized by 1–2 formed stools/daily.

Results after 18 months of treatment showed a further improvement with a weight of 38 kg (−1.75 *Z*-score) a height of 157 cm (−0.91 *Z*-score) and a BMI of 15.4 kg/m^2 (−2.08 *Z*-score) (Figure 1).

The oral energy intake during at last follow-up was 2500 kcal/day (65 kcal/kg) and the Tanner stage of 3.

Citrulline blood levels showed a sharp increase from 18 mmol/L before treatment to 44 mmol/L after 1 year of treatment.

According to teduglutide treatment protocol a follow-up endoscopy after 12 months was performed. Duodenal histology was compared with the one taken before treatment and showed an increase in villous height measurement from 223 µm before treatment to 653 µm after 1 year (Figure 2).

The increase in intestinal absorption was also confirmed by the disappearance of clinical abdominal distension; further corroborated by the improvement of ileal distension on the control gastrointestinal follow through.

No adverse events were described during the entire follow-up.

3 | DISCUSSION

We present a case of a child with SBS who gained enteral autonomy early in life but faced a progressive inability to gain weight and height, despite a significant hyperphagia, as soon as his energy requirements grew to prepare pubertal spurt.

After taking into consideration all the possible solutions to sustain his normal growth, the decision felt on teduglutide treatment which showed good acceptability, impressive improvement in growth and no adverse events after 1 year and a half of treatment.

This is the first case to date in which teduglutide treatment was initiated in a patient with SBS without PN dependency.

Enteral autonomy can be reached in as high as 89% of SBS children[8] at different timing, and can be affected by various prognostic factors.[9] In this case the length of the remaining bowel, the presence of the colon the NEC diagnosis, and the prematurity helped reaching a fast PN weaning.

During puberty there is a physiological increase in caloric need to promote the pubertal spurt.[10] This condition might bring in some SBS children precociously weaned off

PN to a condition described by the Necker IRC as “overloaded gut syndrome.”[11] Our patient falls completely into what was the definition of this condition. He was weaned early off PN and displaying significant compensatory hyperphagia with a caloric intake of 2000 kcal/daily for a calculated resting energy expenditure of 1080 which makes a ration of 185%.[12]

Teduglutide has demonstrated a good efficacy in promoting increase of intestinal absorption in SBS children both in clinical trial and in real-life experience.[6,7,13] Thus, the decision to use this treatment instead of PN resumption which would include a new central line placement and the exposure to all potential PN complications.[2]

Pubertal spurt and final height are not well studied in SBS children but a recent retrospective publication on SBS children weaned off PN support highlighted a height percentage of short stature in those children probably due to an insufficient prepuberal growth and pubertal spurt.[14]

The observed increase of height of small bowel villi and of depth of crypt support the positive response to teduglutide treatment,[15] together with the increase of serum citrulline following the treatment.[16]

We acknowledge that this case report has important limitations, first of all the fact that pubertal growth was assessed only throughout clinical evaluation and that we could not calculate the final target height for the patient since parents' height was unavailable.

4 | CONCLUSION

Teduglutide treatment might be a valuable alternative for SBS children weaned off PN facing a stop in their growth due to increase in caloric need for pubertal spurt. The treatment might represent a valid alternative to PN resumption with less complications and constraints. In this particular setting, teduglutide treatment discontinuation might be attempted when the final growth has been reached.

CONFLICT OF INTEREST STATEMENT

L. N. and L. D. A. received fees for consultation and advisory board from Takeda.

ETHICS STATEMENT

Informed parental/patient consent was obtained for publication of the case details.

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