International Journal of Surgery Case Reports 86 (2021) 106270

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

Bridging intestinal failure with Teduglutide – A case report

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ARTICLE INFO

Keywords:
Bridging intestinal failure
Short bowel syndrome
Intestinal failure
Teduglutide
GLP-2

ABSTRACT

Introduction and importance: Intestinal failure (IF) describes the state of a person's gastrointestinal absorption capabilities becoming unable to absorb fluids and nutrients needed to sustain normal physiology, leading to severe comorbidities and if left untreated, to death. IF is most commonly seen as a result of short bowel syndrome (SBS).

Teduglutide is a glucagon-like peptide 2 (GLP-2) analogue used in the treatment of patients with SBS and intestinal failure (IF) as a way to reduce the need for parenteral support. Teduglutide leads to the growth of intestinal mucosa by stimulating intestinal crypt cell growth and inhibiting enterocyte apoptosis. It is usually prescribed as a final treatment step after the diagnosis of SBS-IF is made.

Case presentation: In this case report we present a novel strategy for using teduglutide as a bridging therapy to intestinal reconstruction. The patient achieved enteral autonomy preoperatively, underwent surgery, and remained in enteral autonomy after intestinal reconstruction.

Clinical discussion: Teduglutide has been previously exclusively used as continuous therapy in SBS-IF, this is the first reported case of using teduglutide as bridging to intestinal reconstruction. The hypothesis of this approach was to achieve an adequate nutritional status for reconstruction without the disadvantages of parenteral support.

Conclusion: The controlled application of teduglutide can provide the benefits of preoperative nutritional optimization without the disadvantages of parenteral support and at the same time facilitate an earlier and easier intestinal reconstruction.

1. Background

Short bowel syndrome (SBS) is a heterogenic medical condition in which patients suffer from an impaired intestinal absorption due to either a loss of bowel after surgical resection or a loss of bowel function due to congenital defects or disease-related destruction of the bowel [1]. After surgery, depending on the resection site and the remaining bowel length, patients either suffer from intestinal insufficiency, or develop intestinal failure (SBS-IF). Patients with intestinal insufficiency are able to compensate for the loss of bowel either physiologically or with pharmacological or nutritional support, while for patients with SBS-IF parenteral support (PS) is vital [1]. The composition of PS differs inter-individually but generally consists of parenteral nutrition (PN), fluid support as well as micronutrient and electrolyte replenishment and has the treatment goal of preventing malnourishment. Studies have shown that surgical patients who are malnourished are at a greater risk of delayed recovery, have a higher hospital re-admission rate and higher rates of morbidity and mortality, suffer more severe complications and require more medications, and have a prolonged hospital stay [2–4]. It has also been shown that patients who have an optimized metabolic state before surgery have a decreased risk for complications, improved wound healing, and need a shorter time for the recovery of the bowel function and can, as a consequence, be discharged from hospital earlier [5].

While patients with SBS-IF are dependent on PS for survival and to prevent malnourishment, PS is associated with numerous adverse events such as central line associated blood stream infections (CLABSI), sepsis, thrombosis, and liver- or biliary disease, as well as a decrease of the patients' quality of life, associated with a long connection time to PS, social isolation, disturbed sleep and body image issues [6–8]. Therefore, finding ways to improve the structural and functional integrity of the remaining bowel to minimize PS is crucial for the long-term well-being of those patients.

Over the last few decades, several studies were able to demonstrate

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https://doi.org/10.1016/j.ijscr.2021.106270
Received 31 May 2021; Received in revised form 29 July 2021; Accepted 1 August 2021
Available online 3 August 2021
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that the glucagon-like peptide 2 (GLP-2) analogue teduglutide reduces the amount of PS needed in patients with SBS-IF and enables enteral autonomy for a small number of patients. Teduglutide is used daily by subcutaneous injection in a dose of 0.05 mg/kg and leads to the growth of intestinal mucosa by stimulating intestinal crypt cell growth and inhibiting enterocyte apoptosis, thereby leading to an increased intestinal surface. Common side effects of therapy include intestinal obstruction, biliary and pancreatic disease, fluid imbalance, and increased absorption of oral medications [1,9–11]. Teduglutide is used as a treatment for patients with SBS-IF, either after intestinal reconstruction or for patients who are ineligible for intestinal reconstruction.

To the best of the authors' knowledge, this case report is the first piece of published literature to report on the use of teduglutide in SBS-IF patients as bridging therapy to intestinal reconstruction. The reasoning behind this approach was twofold. In case enteral autonomy can be achieved with teduglutide treatment, patients would not suffer from any of the above-described disadvantages of being a malnourished surgical patient and at the same time, it would alleviate them from the disadvantages of parenteral nutrition. This case report has been constructed in line with the SCARE 2020 criteria [12].

2. Case report

In this case report, we present a 37-year-old male patient with Crohn's disease (CD), with no family history of inflammatory bowel disease, who first presented to our hospital 19 years after the initial diagnosis of CD. At this point, the patient already underwent multiple unsuccessful medical treatment attempts with corticosteroids, azathioprine, infliximab, and adalimumab, under all of which the patient's disease activity progressed. Finally, the patient was started on vedolizumab under which the patient's disease activity stabilized, however, full remission could not be achieved. In addition, multiple surgeries have been performed in an attempt to control the patient's disease. The patient underwent a right-sided hemicolectomy with an ileosigmoidostomy. Over the following years, multiple small bowel resections were performed, finally resulting in a terminal ileostomy. After an attempted intestinal reconstruction which was, however, complicated by an anastomotic leakage the patient received resections of the sigmoid colon, the terminal ileum as well as the small intestine and was left with a double-barrel jejunostomy and an ileostomy.

At the time of presentation, the patient had 80 cm of remaining functional small intestine length, a double-barrel jejunostomy, an ileostomy and an anorectal stump. Additionally, two small bowel enterocutaneous fistulas were present together with a remaining CD activity in the patient's rectum (see Fig. 1). The patient was severely malnourished, with a body mass index of 19 and qualitative malnourishment evident in the laboratory work-up.

During the first visit, the patient was examined by an experienced dietitian and surgeon. After taking the patient's history and completing a thorough clinical examination, it was concluded that this patient was eligible for intestinal re-construction and would benefit from a nutritional optimization before surgery. The possibility of using teduglutide to achieve enteral autonomy and thereby allowing the patient to gain the benefits of an optimized nutritional state without the disadvantages of PS was discussed with the patient, who consented. Therefore, off-label treatment with teduglutide was started one month after the initial presentation.

At the beginning of treatment, the patient received 1000 ml of PN and 6000 ml of intravenous fluids daily, had an oral fluid intake of 12000 ml per day, a urine output of 1700 ml per day, emptied his ostomy bag 15 times a day, had a fluid stool consistency and two disease-related sleep interruptions per night (see Fig. 2).

Once a month, the patient had a personal meeting with the treating dietitian and a surgeon. Additionally, phone or E-mail contacts between the dietitian and the patient were conducted at least once per week or more often if the patient suffered from an acute problem. Home care nurses familiarized the patient with the self-injection of teduglutide and showed him how to self-administer PS. Also, they collected data on the patient's physical progress which was discussed with the treating dietitian and surgeon.

The patient was very compliant, adhered exactly to the treatment recommendations and reported of no side effects of the treatment. Two months after the initiation of teduglutide the patient had completely discontinued PS and achieved enteral autonomy. He had gained 2.5 kg body weight (BW), his oral fluid intake had reduced from 12000 ml to 3950 ml per day, his urine output increased from 1700 ml to 2150 ml per day, the frequency of emptying his ostomy bag had decreased from 15 to 11 times per day, the consistency of his stool had increased and the frequency of disease-related sleep interruptions decreased from two interruptions to one per night. At this time the patient also underwent a bioelectrical impedance analysis (BIA) to determine body composition. The results of the BIA showed 9.63 kg of fat tissue, 25.62 kg of muscle tissue, and 37.35 l of water, which lies within the physiological range for a person of the patient's age, gender, and height. A laboratory workup was done which showed no signs of malnutrition.

Since the patient achieved enteral autonomy and good nutritional status, intestinal reconstruction was performed four months after teduglutide initiation. The patient received a complete adhesiolysis of the intestine and the double-barrel jejunostomy, as well as the enterocutane fistula were closed using a stapler, however, according to the wishes of the patient no rectum extirpation was performed, and the ileostomy remained (see Fig. 1). The surgery was performed by the department head of the colorectal surgery unit. Now, with two meters of functional small bowel, the patient remained in enteral autonomy after the discharge from the hospital. Contact with the treating dietitian is continued via telephone calls and email correspondence after discharge and the patient reported a further weight gain of 13 kg and a good clinical status.

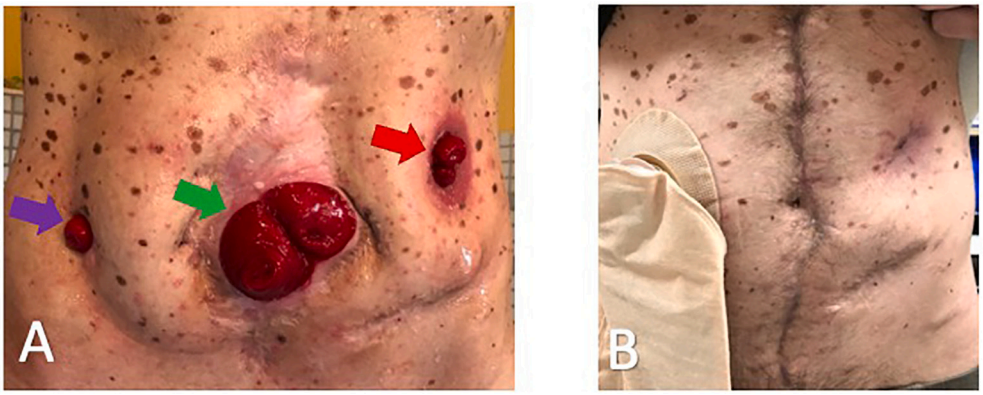
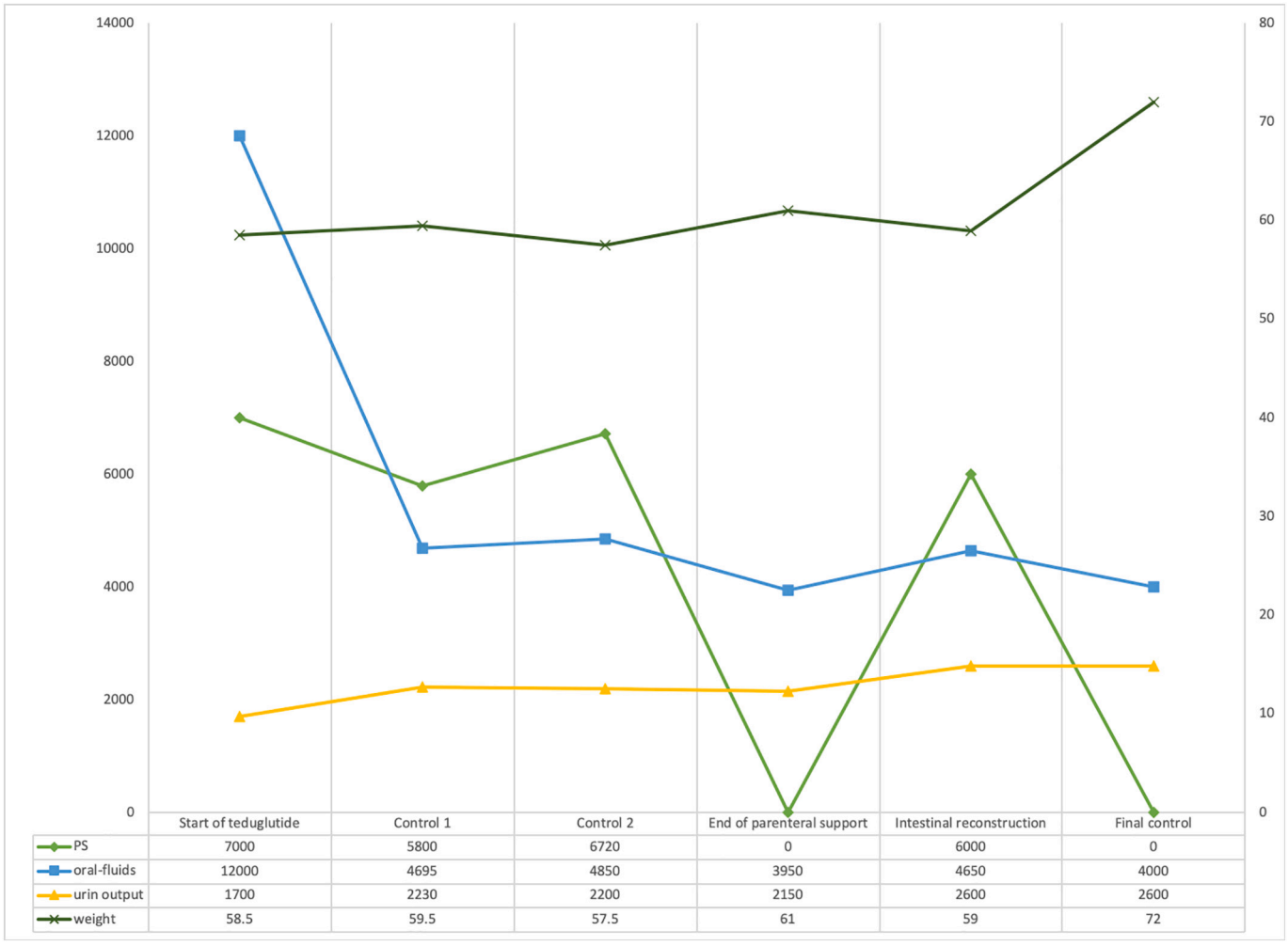


Fig. 1. Abdominal wall
(A) Preoperative. Red arrow indicating the double barrel jejunostomy, purple arrow indicating the ileostomy and green arrow indicating the two enteral fistulas showing hypertrophic mucosa. (B) Postoperative (3 months after surgery). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



	Start of teduglutide	Control 1	Control 2	End of parenteral support	Intestinal reconstruction	Final control
PS	7000	5800	6720	0	6000	0
oral-fluids	12000	4695	4850	3950	4650	4000
urin output	1700	2230	2200	2150	2600	2600
weight	58.5	59.5	57.5	61	59	72

Fig. 2. Overview of the amount of parenteral support, oral fluid intake, urinary output and body weight over the course of teduglutide therapy. Left y-axis indicating fluid amount in milliliters [ml]. Right y-axis indicating patient's body weight in kilogram [kg].

3. Patient's perspective

The patient, who was familiar with parenteral nutrition beforehand, was very satisfied with the results of his teduglutide treatment and the following surgery. The experimental character of the treatment timing was discussed in length with the patient prior to initiation and possible risks very discussed. According to our patient, the main advantage of this therapy approach was the freedom of not being dependent on parenteral support for many hours every day and the corresponding restrictions on activities of daily living.

4. Discussion

In this case report, we present a CD patient who previously underwent several intestinal resections leading to SBS-IF and was treated with a new treatment concept of using the GLP-2 analogue teduglutide as a bridging therapy prior intestinal reconstruction in order to achieve a good nutritional status that eliminates the disadvantages of PS.

Parenteral nutrition is associated with several adverse events, such as infection, liver disease, and thrombosis [7], whereas preoperative malnutrition is associated with an increased morbidity and mortality, more severe postoperative complications, and a prolonged hospital stay [2,3,5]. It is also known that surgical patients who receive enteral nutrition have an overall better postoperative outcome than patients who receive parenteral nutrition [13]. All of these factors combined leave physicians who are treating SBS-IF patients in a predicament. These patients are per definition reliant on parenteral nutrition which leaves them exposed to the possible adverse events described above. Therefore, we were trying to find a way to achieve a sufficient preoperative nutritional status without exposing our patients to the adverse events of PS.

Our approach to solving this predicament was to use teduglutide as a bridging therapy before intestinal reconstruction and to achieve enteral autonomy as quickly as possible before surgery, to ensure an adequate preoperative nutritional status without the need for parenteral support. It is important to note that teduglutide is generally used to reduce the amount of parenteral nutrition needed in SBS-IF patients, rather than to achieve enteral autonomy. In literature, the rate of enteral autonomy is generally described as low as 7% [9], 12% [14], 20% [10], 21% [11], and 33% [9]. However, the experience at our institution shows different results with most patients being able to achieve enteral autonomy. This is accomplished by providing tight-meshed support from a multidisciplinary team, not only in the clinic but also directly at the patient's home.

The generally low rates of enteral autonomy in SBS-IF patients treated with teduglutide also describe the most substantial limiting factor of this novel treatment approach. If enteral autonomy cannot be achieved with teduglutide therapy, the patient is still reliant on PS and would be exposed to possible adverse events. Nonetheless, it is also worth noting that using teduglutide in SBS-IF patients improves the nutritional status even if enteral autonomy cannot be achieved and would therefore still be beneficial to the patients' surgical outcome. In

addition, teduglutide is generally well-tolerated, and solely exposes patients to minimal treatment-related risks even if enteral autonomy cannot be achieved [15]. Another crucial factor to be considered for this novel treatment approach is the patient's preoperative anatomical and functional intestinal situation. If teduglutide is given as bridging therapy the patient's anatomical and functional intestinal situation has to show sufficient remaining bowel length and function that would make discontinuation of teduglutide possible. If discontinuation seems unlikely, teduglutide can still be used to improve intestinal resorption.

One limitation worth considering when using teduglutide are its high costs. In a cost-effectiveness study done by Raghu et al. [16] in 2019 teduglutide failed to meet a traditional cost-effectiveness threshold for PN reduction. However, it is important to note that this study used published data for their estimation and as discussed above, the rate of responders (reduction of parenteral support by >20%) and enteral autonomy in previously published data is reported to be very low, which is not the experience at our institution. It is also worth noting, that this study focused only on the reduction of parenteral nutrition, not the possibility of enteral autonomy. Nevertheless, teduglutide is an expensive drug, which complicates accessability and highlightens the importance of careful patient selection.

When the patient first presented to our institution, he had a bodyweight of 58.5 kg while receiving 1000 ml of parenteral nutrition and 3000 ml of intravenous fluids in addition to drinking 12000 ml of fluids and eating 8 meals per day. Two months after initiating teduglutide and using a tight-meshed multidisciplinary support plan, the patient was able to fully discontinue PN and intravenous fluids and reduce his oral fluid intake to 3950 ml per day, all while gaining 2.5 kg BW, therefore achieving enteral autonomy. This data shows that the patient weighed more after the discontinuation of parenteral support and was also able to reduce the amounts of fluids needed by increasing his intestinal absorption. Six months after the operation the patient's weight had increased by a total of 13.5 kg, reaching a bodyweight of 72 kg, proving that he was able to sustain enteral autonomy even after surgical intervention.

5. Conclusion

This is the first case report discussing teduglutide as bridging therapy for SBS-IF in patients who are awaiting intestinal reconstructive surgery. The rationale behind this approach was to offer the patient the benefits of being well-nourished before surgery without the side effects of PS. Our patient achieved enteral autonomy preoperatively, underwent surgery, and remained in enteral autonomy after intestinal reconstruction. This first patient sets a precedent for the use of teduglutide to achieve an adequate preoperative nutritional status without the need for PS in patients with SBS-IF awaiting surgery.

Sources of funding

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Guarantor

Prof. Anton Stift

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

The Ethics Committee of the Medical University of Vienna con- firms that the research described in this manuscript does not require the formal vote of its Ethics Committee.

Registration of research studies

Not applicable.

CRediT authorship contribution statement

Lukas Schlager, Johanna Gartner, Elisabeth Hütterer, Christopher Dawoud, Anton Stift, and Felix Harpain equally contributed to conception, design, acquisition and interpretation of data. All authors have revised the article and have approved of its final version.

Declaration of competing interest

None of the authors has any conflict of interest to declare regarding this article.

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