 **Teduglutide in short bowel syndrome patients: A way back to normal life?**

Felix Harpain¹  | Lukas Schlager¹ | Elisabeth Hütterer² | Christopher Dawoud¹ |
Sabine Kirchnawy¹  | Judith Stift³ | Pavla Krotka⁴ | Anton Stift MD¹

¹ Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria

² Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria

³ Department of Pathology, Medical University of Vienna, Vienna, Austria

⁴ Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria

Correspondence

Anton Stift, MD, Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria.

Email: anton.stift@meduniwien.ac.at

 This and other JPEN podcasts are available at <https://nutritioncare.org/podcasts>

Abstract

Background: The glucagon-like peptide 2 analogue teduglutide is an effective drug for the treatment of short bowel syndrome patients with intestinal failure (SBS-IF). This intestinotrophic peptide improves intestinal capacity for fluid and nutrient absorption through induction of mucosal growth and reduction of gastrointestinal motility. Clinical trials demonstrated the efficacy of teduglutide in reducing the need for parenteral support (PS). This study describes an SBS-IF patient population receiving teduglutide therapy in a specialized medical care setting.

Method: A retrospective analysis was performed using data of patients experiencing nonmalignant SBS-IF. They were treated with teduglutide in a multidisciplinary SBS-IF program at a single university medical center between June 2016 and June 2020.

Results: Thirteen patients under teduglutide treatment were included in the final analysis. Mean small bowel length was 82 ± 31 cm, with 77% of patients having their colon in continuity. Over a median follow-up of 107 weeks, all patients (13 of 13, 100%) responded to the therapy with a clinically significant reduction of PS volume. Mean PS reduction increased with therapy duration and ranged from -82.5% at week 24 ($n = 13$) to -100% in patients ($n = 5$) who were treated for 144 weeks. Enteral autonomy was achieved in 12 of 13 (92%) patients. Teduglutide therapy improved stool frequency and consistency, changed dietary habits, and reduced disease-associated sleep disruptions.

Conclusion: Integrating SBS-IF patients treated with teduglutide in a proactive and tight-meshed patient care program significantly improves the clinical outcome, leading to an increased proportion of patients reaching enteral autonomy.

KEYWORDS

enteral autonomy, glucagon-like peptide 2, intestinal failure, short bowel syndrome, teduglutide

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Journal of Parenteral and Enteral Nutrition* published by Wiley Periodicals LLC on behalf of American Society for Parenteral and Enteral Nutrition

CLINICAL RELEVANCY STATEMENT

Teduglutide is highly effective in reducing parenteral support in short bowel syndrome with intestinal failure (SBS-IF) patients. Patient integration into a multiprofessional team with a tight-meshed, patient-tailored approach increases the rate of enteral autonomy. Teduglutide significantly reduces the symptomatic burden in SBS-IF patients.

INTRODUCTION

Short bowel syndrome (SBS) is a heterogeneous medical condition in which patients experience impaired intestinal function because of structural or functional loss of the absorptive intestinal capacity as a result of surgical resection or disease-associated destruction of the bowel. Patients with SBS with intestinal failure (SBS-IF) are unable to compensate the compromised intestinal function, and they depend on parenteral support (PS) for survival.¹

The clinical presentation of SBS-IF is heterogeneous, with interindividual differences that may be attributed to differences in the anatomy of the remnant intestine.¹ The extent of PS (consisting of parenteral nutrition [PN] and fluid support) may differ significantly and depend on the length of the remaining small bowel, whether an ostomy is present, on the height of the ostomy, and on whether a remnant colon is in continuity.^{2,3}

Therapy regimens like dietary interventions, oral rehydration, or nutrition solutions and antidiarrheal and antisecretory agents focus on optimization of the functional capacity of the remnant bowel.^{2,4}

Glucagon-like peptide 2 (GLP-2) stimulates growth of the intestinal mucosa through stimulation of crypt cell growth and inhibition of enterocyte apoptosis⁵ and was therefore recently described as a critical factor in intestinal rehabilitation and growth.^{5,6} In addition, GLP-2 impedes gastric emptying and acid secretion,^{7,8} stimulates intestinal blood flow,⁹ and increases the intestinal barrier function.¹⁰

Teduglutide is a dipeptidyl-peptidase, degradation-resistant GLP-2 analogue.¹¹ Recent studies demonstrated that repeated administration enhances functional and structural capacity of the intestine.^{11,12} Jeppesen et al were able to show in a phase III placebo-controlled trial that 63% of patients receiving teduglutide were able to reduce PS volume by $\geq 20\%$ after 24 weeks.¹³ Since then, several studies have demonstrated the efficacy of teduglutide.¹⁴⁻¹⁹ Nevertheless, a significant discrepancy in success rates can be noted when comparing enteral autonomy rates ranging from 12% to 28%.^{14-16,20}

This heterogeneous patient population demands a patient-tailored therapeutic approach with a high amount of individual guidance through the treating physicians, dietitians, and nurses to maximize therapeutic response and minimize treatment or disease-related morbidity and mortality.²¹

Here, we are first to demonstrate that a patient-tailored treat-to-target concept with proactive and tight-meshed patient contact, with consequent and frequent treatment modifications through a multiprofessional team, leads to high response rates.

METHODS

The study protocol was performed according to the ethical guidelines of the Declaration of Helsinki 1975, as the ethics committee of the Medical University of Vienna approved this study (#1989/2020).

Patient characteristics

This retrospective study included all patients experiencing nonmalignant SBS-IF (type III IF according to the classification of Pironi et al²²) who were treated with teduglutide at the Medical University of Vienna between June 2016 and June 2020. All patients were treated by a multidisciplinary team consisting of visceral surgeons, gastroenterologists, and dietitians. Clinical data were systematically collected from the electronic patient chart system of the treating hospital and by a specialized homecare service provider (Healthcare, Austria: Tedu Reha Coach). All patients gave their informed consent for the treatment with teduglutide and received the approved standard dose of teduglutide (.05 milligrams per kilogram of body weight [mg/kg/BW]). The anatomical bowel situation of all patients after resection was intraoperatively characterized. Small bowel length was defined as remnant postduodenal length. Clinical data collection included the following variables: age (years), sex (male/female), weight (kilograms), body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), intravenous PN (ml/day), intravenous fluid (IVF) intake (ml/day), urinary output (ml/day), oral fluid intake (ml/day), stool consistency (liquid, liquid-mushy, mushy, firm, and constipation) and frequency (*n* per day), and sleep disruptions per night (*n* per day). In patients with a present ostomy, stool frequency was defined as number of times an ostomy bag was emptied (*n* per day). Variables were recorded before and regularly (individualized after each patient's clinical needs) after treatment initiation. Follow-up data (week >12) were defined as data obtained from the most current patient visit before, at, or after the indicated time point. Teduglutide treatment was not started simultaneously. The minimal required length of follow-up for inclusion into the final analysis was 24 weeks. Patients were integrated in a tight-meshed follow-up program, including daily or at least weekly patient contact (outpatient clinic visit, home care service provider, email, and phone contact) for the first 6 months of treatment and tailored to the patient's clinical needs after 6 months.

Adverse events (AEs) and serious AEs were routinely documented by the treating physician at our outpatient clinic during follow-up visits and by specialized home care providers during follow-up visits at home.

PS

PS included, per definition, either IVFs (fluid electrolytes or fluid electrolytes with vitamins and/or trace elements) or PN (any macronutrients and micronutrients admixture) or a combination of both. Before teduglutide treatment initiation, patients went through an optimization and stabilization period within routine medical care. During follow-up visits, PS adjustments were discussed among the interdisciplinary team and based on changes of clinical parameters, including BW and bioelectrical impedance analysis (BIA) results, oral fluid intake and urinary output, clinical symptoms of body fluid volume status, physical performance, and patient's subjective perception during activities of daily living (ADLs). PS modification was solely performed at our SBS center. Response to treatment was defined as a reduction of $\geq 20\%$ of daily PS volume from baseline. Enteral autonomy was defined as discontinuation of all periodic PS. The functional response analysis included the following time points: 2, 4, 8, 12, 16, 20, 24, 36, 48, 72, 96, 120, and 144 weeks (minimal requirement, $n > 5$).

Stool characteristics

Stool frequency per day and stool consistency were documented regularly by a specialized home care provider and consistency classified into five categories: liquid, liquid-mushy, mushy, firm, and constipation, in correlation to the Bristol Stool Form Scale (7, 6, 5, 4, and 2 and 1 combined).²³

Dietary habits

Meal frequency per day and meal serving size were documented by specialized home care providers. Serving size was classified into five categories: (1) $\frac{1}{4}$ serving, (2) $\frac{1}{2}$ serving, (3) $\frac{3}{4}$ serving, (4) 1 serving, and (5) > 1 serving. A serving was defined as the food arranged on one regular dinner plate.

Statistics

Statistical analysis was performed using SPSS statistical software package (IBM SPSS Statistics for Mac, Version 24.0). Descriptive statistics, such as mean, median, frequencies, and percentages, were used to present patient's characteristics. Categorical variables are presented as numbers, with percentages in brackets. Metric variables are expressed either as mean/SD (with normal distribution) or as median/range (without normal distribution). Missing values are reported as unknown. To assess the change in stool frequency and sleep disruptions at weeks 24 and 48, a two-tailed Wilcoxon signed rank test was used because the data were not normally distributed. Change in BMI over time was assessed by two-tailed, paired *t*-test. Normal distribution was verified using the Shapiro-Wilk test. A *P*-value of $< .05$ was considered statistically significant.

TABLE 1 Baseline patient characteristics

Included SBS-IF patients treated with teduglutide, n (%)	13 (100)
Female sex, n (%)	2 (15.4)
Age, years, mean \pm SD	50.9 \pm 9.9
BMI, mean \pm SD	19.2 \pm 3.6
Duration of intestinal failure to teduglutide start, months, mean \pm SD	23.0 \pm 22.9
Cause of SBS, n (%)	
Inflammatory bowel disease	8 (61.5)
Vascular disease	2 (15.4)
Surgical complications	3 (23.1)
Patients with colon in continuity, n (%)	10 (76.9)
No colon resection, n (%)	0 (0)
Partial colon resection, n (%)	7 (53.8)
Colostomy, n (%)	3 (23.1)
Remnant small bowel length, cm, mean \pm SD	73.3 \pm 29.2
Unknown, n (%)	1 (7.7)
Patients with small bowel enterostomy, n (%)	3 (23.1)
Duodenostomy, n (%)	0 (0)
Jejunostomy, n (%)	1 (7.7)
Ileostomy, n (%)	2 (15.4)
Remnant small bowel length, cm, mean \pm SD	106.7 \pm 25.2
Unknown, n (%)	0 (0)
Total parenteral volume, ml/day, mean \pm SD	3364.8 \pm 983.1
Total PN, ml/day, mean \pm SD	1403.3 \pm 687.2

Abbreviations: BMI, body mass index; SBS-IF, short bowel syndrome with intestinal failure; PN, parenteral nutrition.

RESULTS

Patient characteristics

In total, 28 SBS-IF (malignant + nonmalignant) patients were treated at a single university tertiary referral hospital in the abovementioned time period. Seventeen patients received teduglutide as treatment for their nonmalignant SBS-IF. Three patients were excluded from this study, as their follow-up was < 24 weeks. In addition, one patient had to be excluded from the final analysis because of patient noncompliance (the patient did not administer teduglutide according to prescription, skipping injections for indeterminate periods of time) so that administration of teduglutide on a regular basis could not be guaranteed. Therefore, 13 patients were included into the final analysis (2 [15.4%] women; mean age of 51 years) in total. All patients experiencing inflammatory bowel disease were diagnosed with Crohn's disease. One patient who experienced systemic scleroderma died during the study period because of respiratory failure. His data were included in the analysis, as he received teduglutide treatment for > 24 weeks. Patient baseline characteristics are presented in Table 1.

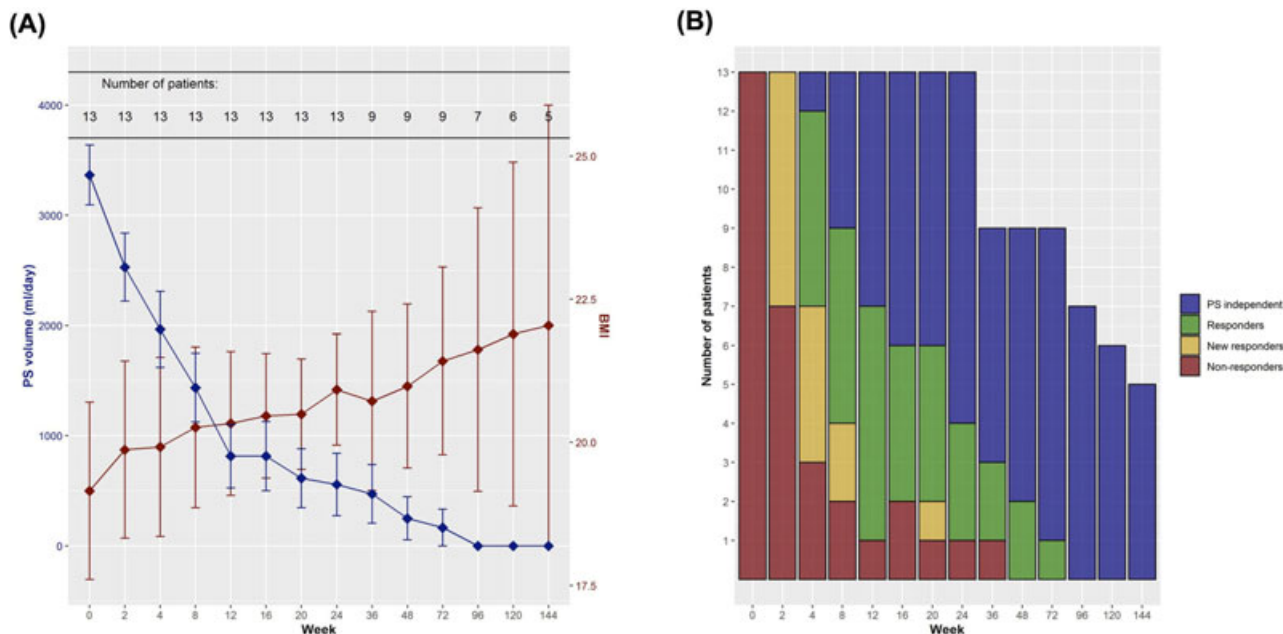


FIGURE 1 Effect of teduglutid treatment on PS requirements. (A) Mean (SE) reduction of PS volume and increase of mean (SE) BMI from baseline. (B) Distribution of responders over time. BMI, body mass index; PS, parenteral support

Functional response: PS requirements, oral fluid intake, and urinary output

Thirteen SBS-IF patients received teduglutid treatment for ≥24 weeks, with a median follow-up of 107 weeks, ranging from 26 to 205 weeks. At baseline, all patients were dependent on PS (PN + IVF), with only one patient being merely dependent on fluid and electrolyte substitution. No statistically significant difference in baseline PS volumes between patients with small bowel enterostomy and patients with colon in continuity was observed ($P = .232$). Twenty-four weeks after teduglutid therapy initiation 12 of 13 patients (92%) were classified as responders and 9 of 13 patients (69%) reached enteral autonomy with complete discontinuation of PS. Over the total length of follow-up, all 13 patients (100%) were classified as responders and the rate of patients who reached enteral autonomy increased to 12 of 13 patients (92%). The one patient remaining PS-dependent at the end of the study period is male, experienced a vascular event as the underlying cause of SBS-IF, and has a 30-cm remaining small bowel length, a colon (except for the cecum) in continuity, and received teduglutid therapy for 6 months. Functional response is presented in detail in Figures 1 and 2.

Symptomatic response: stool characteristics, dietary habits, and sleep disruption

Mean stool frequency per day at baseline was 23.9 per day and ranged from 10 to 60 per day. After 24 and 48 weeks, patients already demonstrated a significant reduction in stool frequency (−14.6 per day on mean [$P = .002$] and −17.2 per day on mean [$P = .009$], respectively). Besides, stool consistency increased from mostly liquid stools at base-

line to a mushy and/or firm stool consistency. To report the change in dietary habits and appetite under teduglutid therapy, meal frequency and size were recorded. Both parameters increased with treatment duration. To assess sleeping quality, patients documented disease-associated sleep disruptions. These interruptions ranged from 1 to 15 per night (mean 4.6) at baseline and significantly decreased over the follow-up period (−2.8 on mean at week 24 [$P = .002$] and −3.2 on mean at week 48 [$P = .014$]). See Figures 3–5 for symptomatic response data.

Nutrition status response: BMI, BIA, and serum albumin level

All patients were monitored regarding their nutrition status, with continuous observance of BW and blood parameters. Mean BMI at baseline was 19.1 and significantly increased in week 24 (+1.77 on mean; $P = .017$) and week 48 (+2.29 on mean; $P = .022$). Serum albumin levels remained within the reference range after 24 weeks, and no significant difference to baseline values was observed ($n = 10$, baseline: 38.6 g/L and week 24: 38.9 g/L; $P = .893$). BIA was not measured regularly, and data were available for only eight patients, which revealed a body composition within the physiological norm (mean fat mass index [FMI], male 3.65 and female 9.70; mean fat-free mass index [FFMI], male 17.48 and female 16.97).

AEs and SBS treatment-associated complications

At least one AE occurred in 9 of 13 of patients (69%). Most frequently reported AEs were of gastrointestinal origin, including nausea and

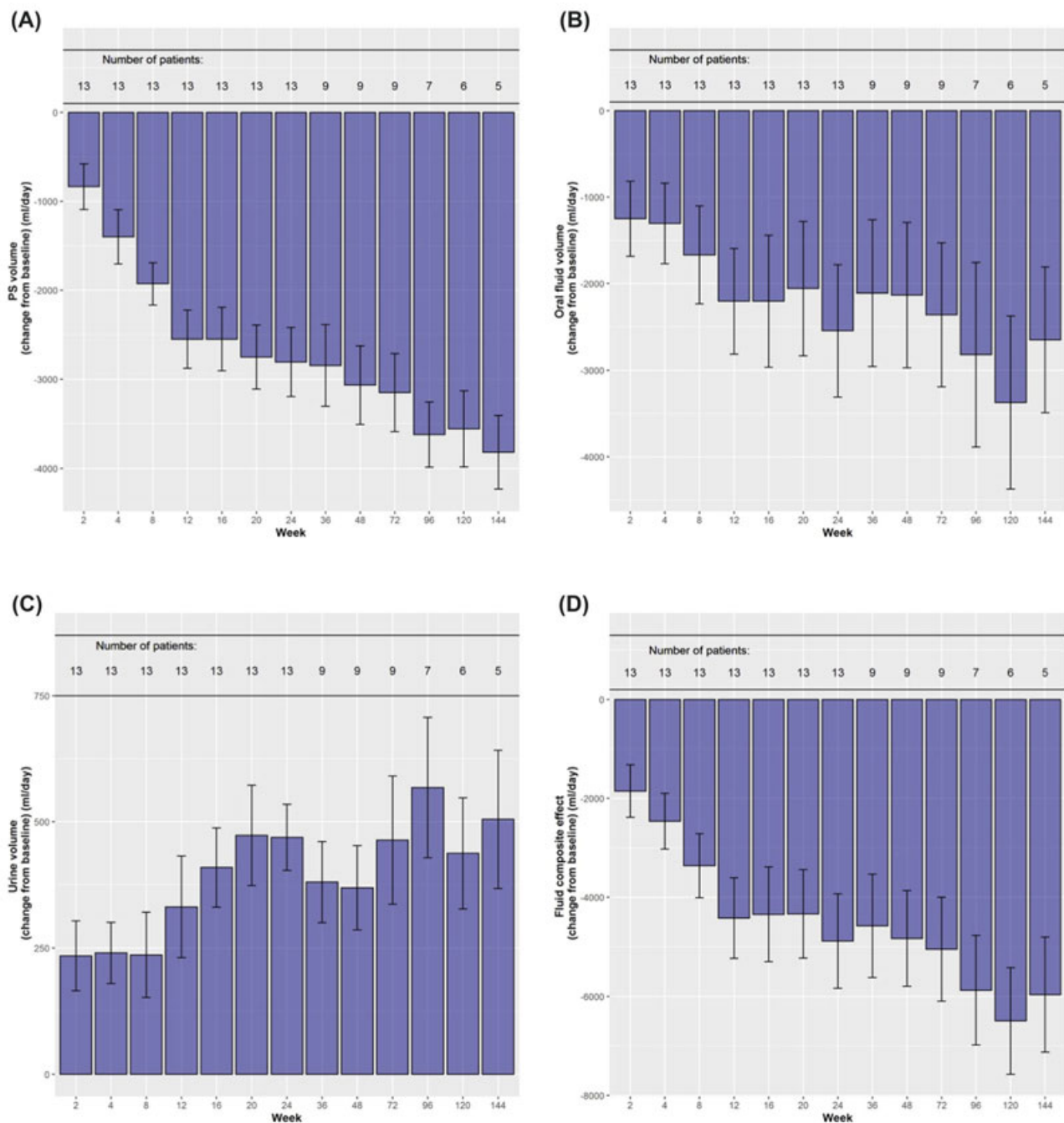


FIGURE 2 Summary of changes in (A) mean (SE) PS volume, (B) mean (SE) oral fluid volume, (C) mean (SE) urine volume, and (D) mean (SE) fluid composite effect from baseline. PS, parenteral support

vomiting (4 of 13, 31%), abdominalgia (3 of 13, 23%), fatigue (3 of 13, 23%), diarrhea (2 of 13, 15%), abdominal distension and bloating (1 of 13, 8%), and constipation (1 of 13, 8%). Other AEs included clinical signs of volume overload (eg, peripheral edema) (4 of 13, 31%), joint pain/muscle pain (2 of 13, 15%), vertigo (2 of 13, 15%), heavy sweating (2 of 13, 15%), headache (1 of 13, 8%), and upper respiratory tract infection (1 of 13, 8%). One patient experienced cholecystitis, which had to be treated with in-hospital antimicrobial therapy. No AE led to permanent discontinuation of teduglutide treatment. Nevertheless, temporary discontinuation or adjustments in dose, as well as injection

interval lengthening, had to be applied in five patients (38%). One death occurred during the study period (respiratory failure because of systemic scleroderma).

Central line-associated bloodstream infections (CLABSIs) with subsequent port catheter/peripherally inserted central catheter removal was documented in 92% of the patients, resulting in a CLABSI rate of 3.7 per 1000 catheter days. All patients included in the final analysis had undergone screening colonoscopy prior to teduglutide initiation and periodic follow-up colonoscopies. No polyps nor signs of colorectal tumorigenesis or carcinogenesis were observed.

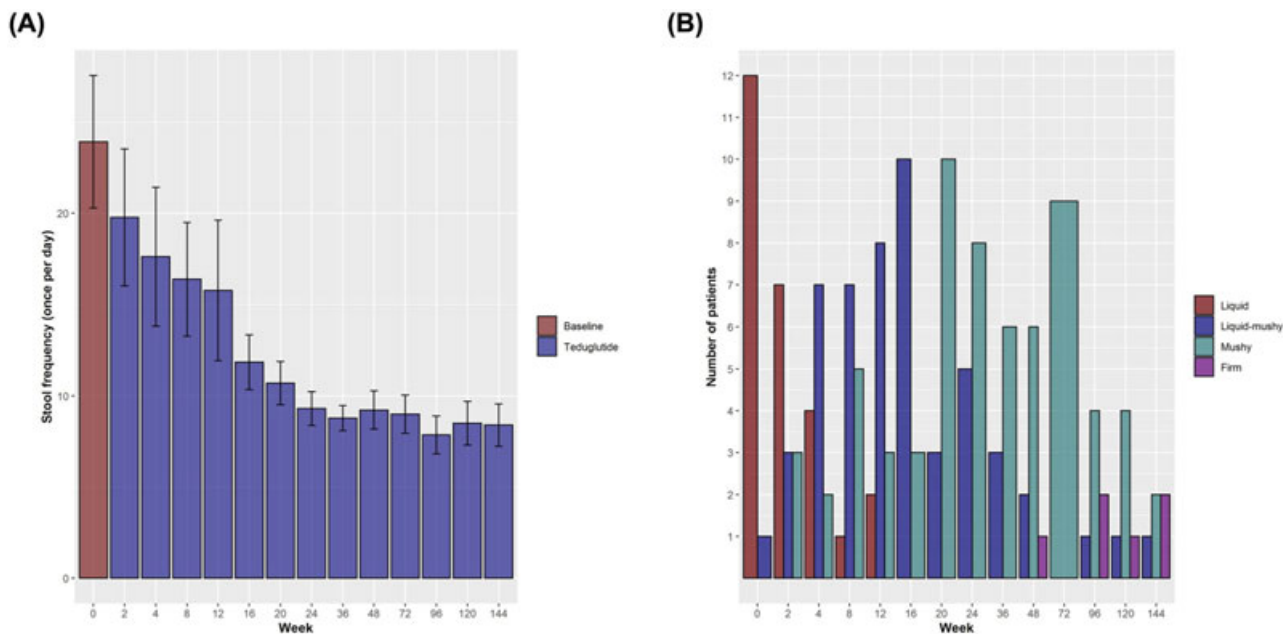


FIGURE 3 Effect of teduglutide treatment on stool characteristics. (A) Mean (SE) reduction of stool frequency from baseline. (B) Change of stool consistency from baseline

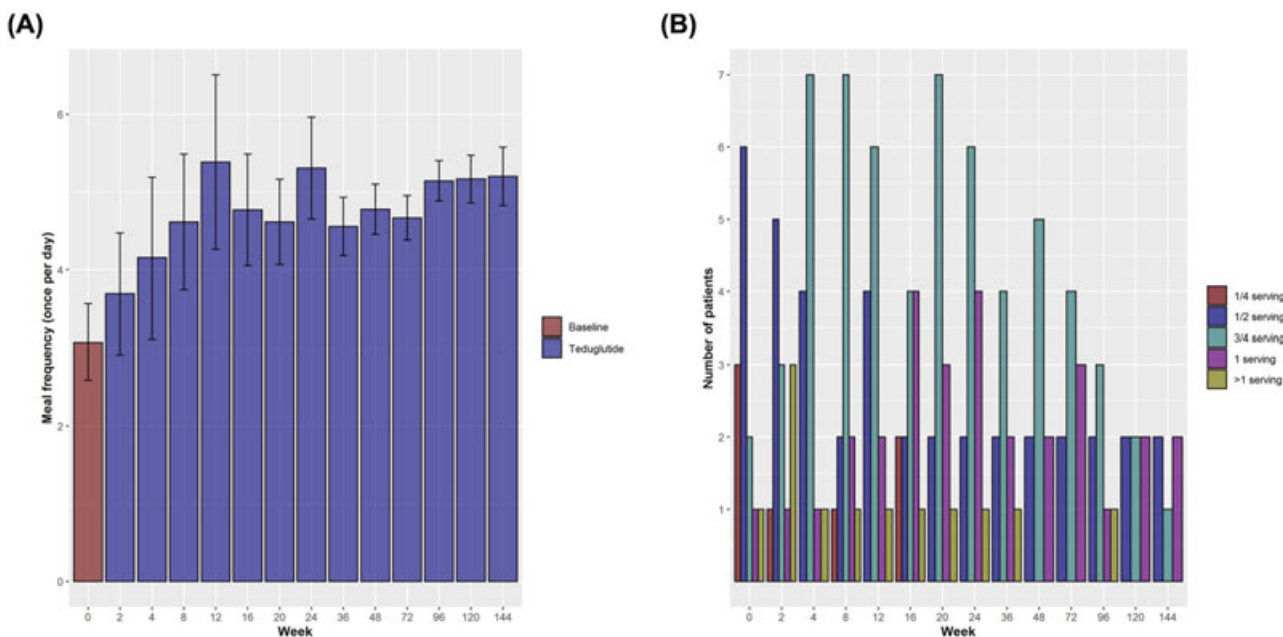


FIGURE 4 Effect of teduglutide treatment on dietary habits. (A) Mean (SE) increase of meal frequency from baseline. (B) Change of meal size from baseline

DISCUSSION

The results of this single-center analysis demonstrate the effectiveness of teduglutide in reducing PS dependency in SBS-IF patients in a “real-life” clinical setting. More importantly, the majority of patients were

able to reach enteral autonomy under teduglutide treatment with a treat-to-target concept.

Prospective controlled clinical trials,^{12,13} as well as observational cohort analyses,^{14,16,17} demonstrated the potential of teduglutide in reducing PS in SBS-IF patients by enhancing spontaneous intestinal

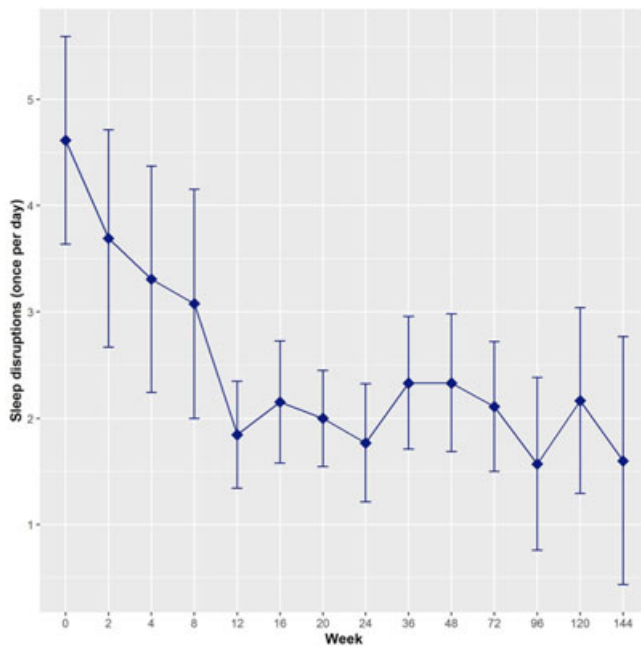


FIGURE 5 Mean (SE) sleep disruptions per night

rehabilitation through enhanced structural and functional adaptation of the intestinal resorptive capacity.¹¹ Enteral autonomy, meaning the complete discontinuation of PS, remains the primary therapy goal of teduglutide treatment in SBS-IF patients. Although several studies demonstrated that SBS-IF patients who were treated with teduglutide were able to reduce PS with varying levels of success, enteral autonomy was only reported in the minority of treated patients.^{20,24} Jeppesen et al were unable to report on patients reaching enteral autonomy after 24 weeks of teduglutide treatment in the original multicenter, randomized placebo-controlled “Study of Teduglutide Effectiveness in PN-Dependent SBS Subjects (STEPS).”¹³ In contrast, the 24-month open-label extension STEPS2 study by Schwartz et al describe 13 patients (15%) obtaining enteral autonomy (10 patients receiving teduglutide already in the STEPS1 trial and three patients who were either randomly assigned into the placebo group or not treated in the original STEPS trial).¹⁸ Outside controlled clinical trials, the rate of patients reaching enteral autonomy seems to be higher. Puello et al report on 29% of patients completely discontinuing PS after a median follow-up period of 3.2 years in a single-center cohort,¹⁴ whereas Joly et al demonstrate an enteral autonomy rate of 24% in a French multicenter observational study after 24 weeks of follow-up.¹⁵ Nevertheless, this leaves the majority of the patients dependent on PS.

The present study is the first to report on enteral autonomy in nearly all SBS-IF patients treated with teduglutide (92%), with a median follow-up of 107 weeks. Almost a quarter (23%) of patients in the presented cohort already reached enteral autonomy after 24 weeks of teduglutide treatment. The one patient in this cohort remaining dependent on PS was treated with teduglutide for 35 weeks at the end of the study period and may still achieve enteral autonomy.

A reduction of $\geq 20\%$ of the PS from baseline is considered a clinically beneficial threshold, and most published studies (the presented

included) define patients beyond this point as responders. It was suggested that the strict reduction protocols of the clinical trials hinder a fast reduction of PS. Jeppesen et al and their first phase III clinical trial in SBS-IF patients revealed a responder rate of 46% after 24 weeks (teduglutide dose 0.05 mg/kg/day).¹² With an adaptation of the weaning protocol, allowing a more aggressive PS volume reduction, namely from 10% to 30% of baseline PS volume at each study visit, Jeppesen et al were able to increase the responder rate to 63% in the treatment group of the subsequent phase III clinical trial.¹³ Furthermore, the high responder rate (30%) in patients receiving placebo even after a clinical optimization and stabilization period in the STEPS trial underlines the importance and the potential of physicians in their dedicated attempt to reduce the PS. Observational cohort analyses, which were not bound to any reduction regimens, revealed responder rates of up to 85% after 24 weeks.¹⁵ The results of the presented cohort analysis demonstrate a responder rate of 92% after 24 weeks of teduglutide treatment. The high percentage of “early” responders in this patient population emphasizes the effectiveness of teduglutide in improving spontaneous intestinal rehabilitation early after therapy initiation and underlines the importance of tight-meshed monitoring visits during this phase. Nevertheless, therapy response kept on improving significantly also after 24 weeks, with patients reaching enteral autonomy widely distributed over the first 72 weeks. This heterogeneous functional response demands a structured clinical follow-up program with a high amount of individual guidance.

The authors of this study believe that the embedding of this complex and heterogeneous patient population into a multiprofessional team with a tight-meshed, patient-tailored therapeutic approach that allows for a high amount of individual guidance through the treating physicians, dietitians, and nurses to maximize therapeutic response and minimize treatment or disease-related morbidity and mortality is the key factor for the here-reported high response rates. In addition, one experienced dietitian functioning as case manager and central patient contact as a way to manage high interindividual variability also proved to be effective and beneficial for therapy success. These thoughts go in line with results from a recent retrospective study, in which the survival of children experiencing IF was significantly improved with the establishment of a multiprofessional team.²⁵ Furthermore, our experience is congruent with the opinion of the French observational study of Joly et al,¹⁵ who highlighted the importance of dietetic optimization in the overall management of SBS-IF patients. The vast majority of our study population experienced Crohn’s disease as underlying SBS disorder, and complaints of gastrointestinal origin dominated the observed AEs, thereby further highlighting the need for dietetic consultations.

Small bowel length is described as crucial factor for long-term PS dependency in SBS-IF patients.^{26,27} Therefore, when interpreting the present results, it needs to be considered that, with a mean remnant small bowel length of 73 cm in ostomy patients and 90 cm in patients with bowel in continuity, our patient collective has a favorable anatomy for enteral autonomy. Nevertheless, small bowel length is comparable with the SBS-IF cohort of the available prospective randomized controlled trials.^{12,13} In addition, a mean duration of IF of <2 years allows the assumption that in some patients, the full

potential of spontaneous intestinal rehabilitation may not be exploited. We believe that a proactive and more aggressive dietetic adaptation of oral fluid and energy intake represents a crucial factor in enabling early and persistent teduglutide-induced reduction of PS volumes. The fast reduction in PN volumes, leading to PN-independency in >50% of patients after only 8 weeks and 92% after 72 weeks, is striking. Reducing the amount of administered PN may decrease the risk of developing an IF-associated liver disease.²⁸ In addition, the amount of administered parenteral energy depicts an independent risk factor for central-catheter infections.²⁹ Also, the application of PN, compared with IVF, is a time-consuming procedure, generating several hours of infusion time every day, thereby reducing the quality of life (QoL) in affected patients.^{30,31}

More importantly, more frequent central catheter manipulations may increase the risk of CLABSI. Although PS is a life-saving treatment in SBS-IF patients, morbidity and mortality are closely related to the central catheter and the PS composition.^{27,29,32,33} SBS-IF with home PN (HPN) dependency is associated with a decreased long-term survival, with nonmalignant SBS patients surviving 1, 5, and 10 years in 94%, 70%, and 52%, respectively.²⁶ Pironi et al describe a cohort of patients receiving HPN in which PN-related deaths increase with the duration of PN support.³⁴ The death rate attributable to PN-related AEs ranges from 9% to 33% with 50%–71% resulting from infections of the central venous catheter.^{27,35–37} In our study cohort, we observed a CLABSI rate of 3.7 per 1000 catheter days, with a median study follow-up period of 107 weeks. These numbers underline the importance of the therapy goal enteral autonomy in our treat-to-target strategy, which is in fact associated with a decrease of catheter use to zero.

Regarding the effect of teduglutide therapy on clinical symptoms and QoL, this study also reports on alterations in stool characteristics, dietary habits, and sleep disruptions. Patients with SBS who depend on PS manifest a significantly decreased QoL,³¹ which may be at least partly explained by disease-related disruptions of their ADLs and sleeping periods. Patients are connected to their PS up to 16 h per day,³⁸ restricting their mobility; nightly infusions exacerbate nocturnal urination; and a high stool frequency or large output stoma may cause frequent sleep disruptions.³⁹ Over the course of teduglutide treatment, stool frequency decreased and consistency improved, most likely because of the effect of teduglutide on intestinal wet weight resorption, as described by Jeppesen et al.⁶ Meal frequency and size increased as well, and patients were able to keep their dietary habits constant after an initial adaptation and stabilization period. In addition, mean sleep disruptions significantly decreased and were reduced by >50% after only 12 weeks of teduglutide treatment.

Nutrition status was monitored throughout the whole study period. Repetitive BW measures demonstrated significantly increasing BMIs with ongoing teduglutide treatment. Besides, serum albumin levels remained within physiological limits. No statistically significant changes were observed to week 24. BIA is an easy-to-use and cheap tool to assess a patient's body composition in a clinical setting. BIA measure was available for most but not all patients in the follow-up and revealed a physiologic body composition in terms of FMI and FFMI despite a continuous reduction in PS volumes and the subse-

quent necessary and radical adaptations of dietary habits. In addition, we observed a comparable high rate of fluid overload (31%) in our study cohort. We attributed this to the long study follow-up period, in which peripheral edema was observed in four patients at any time point. Nevertheless, this highlights the importance of tight-meshed clinical controls in this fragile patient population.

Concern has been raised about the potential of teduglutide to stimulate tumorigenesis in its role as an intestinotrophic growth factor. Although the available data from the follow-up of the STEPS study series reported a polyp surveillance detection rate within the range of the general population,⁴⁰ studies in azoxymethane⁴¹ and 1,2-dimethylhydrazine⁴² colon cancer rodent models treated with the protease-resistant GLP-2 analogue Gly²-GLP-2 observed increased rates of colonic neoplasms and dysplastic changes. All patients from this study received a baseline and regular surveillance colonoscopies. After a maximum follow-up of 247 weeks, no new adenoma formations were observed.

Most of the limitations of this study may be attributed to the retrospective nature. Nevertheless, retrospective cohort analyses seem feasible and necessary in studies examining rare diseases, as accumulation of scientific data seems difficult otherwise. This study acquired data only through observation, thereby increasing the risk for underreporting, as data records may not be entirely complete. The retrospective study design, in combination with the extraordinary study results, may raise the concern of a selection bias. This concern may further be asserted by the fact that the composition of the study population is rather unusual when compared with SBS-IF populations described in the literature: relatively young patients mostly experiencing Crohn's disease, with the majority of the patients having at least part of their colon in continuity (only three patients with a small bowel enterostomy). Although this may highlight the importance of intestinal reconstruction in SBS-IF patients, it also makes the comparability to other collectives of SBS-IF patients difficult. However, this analysis included all patients receiving teduglutide in the abovementioned time frame and institution, with no teduglutide patient being withheld from the analysis. Moreover, the small number of patients and the high interindividual heterogeneity of the patient population makes a generalization of the observed phenomenon difficult. Although the presented cohort features a relatively long follow-up, less than five patients received teduglutide over 3 years. Prospective clinical trials examining the effectiveness of teduglutide in an unrestricted clinical setting are needed to further verify our findings.

CONCLUSION

Teduglutide is highly effective in treating patients with SBS-IF. In addition to the results of previous studies that demonstrated significant reductions of the PS, this study provides evidence that the integration of this heterogeneous patient population into a multiprofessional team spearheaded by a dietitian enables enteral autonomy under teduglutide therapy in nearly all treated patients. Enteral autonomy, as the final goal of a treat-to-target strategy, seems necessary, as it results not only

in a decreased morbidity and mortality but also in improvement of QoL and may reduce the socioeconomic burden.

CONFLICT OF INTEREST

Felix Harpain reports a grant and lecture fee from Takeda, outside the submitted work. Elisabeth Hütterer and Anton Stift report lecture fees from Takeda, outside the submitted work. Lukas Schlager, Christopher Dawoud, Sabine Kirchnawy, Judith Stift, and Pavla Krotka have indicated they have no conflict of interests to disclose.

FUNDING INFORMATION

None declared.

AUTHOR CONTRIBUTIONS

Felix Harpain, Lukas Schlager, Elisabeth Hütterer, Christopher Dawoud, Sabine Kirchnawy, and Anton Stift contributed to the conception and design of the research; Felix Harpain, Lukas Schlager, Elisabeth Hütterer, Christopher Dawoud, Sabine Kirchnawy, Judith Stift, Pavla Krotka, and Anton Stift contributed to the acquisition, analysis, and interpretation of the data; and Felix Harpain drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

ORCID

Felix Harpain  <https://orcid.org/0000-0001-6589-5712>

Sabine Kirchnawy  <https://orcid.org/0000-0002-4507-1211>

REFERENCES

- Jeppesen PB. Spectrum of short bowel syndrome in adults: intestinal insufficiency to intestinal failure. *JPEN J Parenter Enteral Nutr.* 2014;38(1 Suppl):8S-13S.
- Jeppesen PB. Pharmacologic options for intestinal rehabilitation in patients with short bowel syndrome. *JPEN J Parenter Enteral Nutr.* 2014;38(1 Suppl):45S-52S.
- Jeppesen PB. Teduglutide, a novel glucagon-like peptide 2 analog, in the treatment of patients with short bowel syndrome. *Therap Adv Gastroenterol.* 2012;5(3):159-171.
- Jeppesen PB. New approaches to the treatments of short bowel syndrome-associated intestinal failure. *Curr Opin Gastroenterol.* 2014;30(2):182-188.
- Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci U S A.* 1996;93(15):7911-7916.
- Jeppesen PB, Hartmann B, Thulesen J, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. *Gastroenterology.* 2001;120(4):806-815.
- Wojdemann M, Wettergren A, Hartmann B, Holst JJ. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. *Scand J Gastroenterol.* 1998;33(8):828-832.
- Wojdemann M, Wettergren A, Hartmann B, Hilsted L, Holst JJ. Inhibition of sham feeding-stimulated human gastric acid secretion by glucagon-like peptide-2. *J Clin Endocrinol Metab.* 1999;84(7):2513-2517.
- Bremholm L, Hornum M, Andersen UB, Hartmann B, Holst JJ, Jeppesen PB. The effect of glucagon-like peptide-2 on mesenteric blood flow and cardiac parameters in end-jejunosomy short bowel patients. *Regul Pept.* 2011;168(1-3):32-38.
- Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut.* 2009;58(8):1091-1103.
- Jeppesen PB, Sanguinetti EL, Buchman A, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut.* 2005;54(9):1224-1231.
- Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut.* 2011;60(7):902-914.
- Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology.* 2012;143(6):1473-1481.e3.
- Puello F, Wall E, Herlitz J, Lozano ES, Semrad C, Micic D. Long-term outcomes with teduglutide from a single center. *JPEN J Parenter Enteral Nutr.* 2021;45(2):318-322.
- Joly F, Seguy D, Nuzzo A, et al. Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: A real-world French observational cohort study. *Clin Nutr.* 2020;39(9):2856-2862.
- Pevny S, Maasberg S, Rieger A, et al. Experience with teduglutide treatment for short bowel syndrome in clinical practice. *Clin Nutr.* 2019;38(4):1745-1755.
- Schoeler M, Klag T, Wendler J, et al. GLP-2 analog teduglutide significantly reduces need for parenteral nutrition and stool frequency in a real-life setting. *Therap Adv Gastroenterol.* 2018;11:1756284818793343.
- Schwartz LK, O'Keefe SJ, Fujioka K, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. *Clin Transl Gastroenterol.* 2016;7(2):e142.
- Seidner DL, Fujioka K, Boullata JI, Iyer K, Lee HM, Ziegler TR. Reduction of parenteral nutrition and hydration support and safety with long-term teduglutide treatment in patients with short bowel syndrome-associated intestinal failure: STEPS-3 study. *Nutr Clin Pract.* 2018;33(4):520-527.
- Iyer KR, Kunecki M, Boullata JI, et al. Independence from parenteral nutrition and intravenous fluid support during treatment with teduglutide among patients with intestinal failure associated with short bowel syndrome. *JPEN J Parenter Enteral Nutr.* 2017;41(6):946-951.
- Jeppesen PB, Gabe SM, Seidner DL, Lee HM, Olivier C. Factors associated with response to teduglutide in patients with short-bowel syndrome and intestinal failure. *Gastroenterology.* 2018;154(4):874-885.
- Pironi L, Arends J, Baxter J, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. *Clin Nutr.* 2015;34(2):171-180.
- Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32(9):920-924.
- Seidner DL, Gabe SM, Lee HM, Olivier C, Jeppesen PB. Enteral autonomy and days off parenteral support with teduglutide treatment for short bowel syndrome in the STEPS trials. *JPEN J Parenter Enteral Nutr.* 2020;44(4):697-702.
- Hess RA, Welch KB, Brown PI, Teitelbaum DH. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. *J Surg Res.* 2011;170(1):27-31.
- Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. *Clin Nutr.* 2013;32(3):368-374.
- Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology.* 1999;117(5):1043-1050.

28. Xu ZW, Li YS. Pathogenesis and treatment of parenteral nutrition-associated liver disease. *Hepatobiliary Pancreat Dis Int.* 2012;11(6):586-593.
29. Dissanaïke S, Shelton M, Warner K, O'Keefe GE. The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. *Crit Care.* 2007;11(5):R114.
30. Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. *Gut.* 1999;44(6):844-852.
31. Jeppesen PB, Pertkiewicz M, Forbes A, et al. Quality of life in patients with short bowel syndrome treated with the new glucagon-like peptide-2 analogue teduglutide—analyses from a randomised, placebo-controlled study. *Clin Nutr.* 2013;32(5):713-721.
32. Santarpia L, Alfonsi L, Tiseo D, et al. Central venous catheter infections and antibiotic therapy during long-term home parenteral nutrition: an 11-year follow-up study. *JPEN J Parenter Enteral Nutr.* 2010;34(3):254-262.
33. Gillanders L, Angstmann K, Ball P, et al. A prospective study of catheter-related complications in HPN patients. *Clin Nutr.* 2012;31(1):30-34.
34. Pironi L, Joly F, Forbes A, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. *Gut.* 2011;60(1):17-25.
35. Messing B, Lemann M, Landais P, et al. Prognosis of patients with nonmalignant chronic intestinal failure receiving long-term home parenteral nutrition. *Gastroenterology.* 1995;108(4):1005-1010.
36. Kelly DG, Tappenden KA, Winkler MF. Short bowel syndrome: highlights of patient management, quality of life, and survival. *JPEN J Parenter Enteral Nutr.* 2014;38(4):427-437.
37. Scolapio JS, Fleming CR, Kelly DG, Wick DM, Zinsmeister AR. Survival of home parenteral nutrition-treated patients: 20 years of experience at the MayoClinic. *Mayo Clin Proc.* 1999;74(3):217-222.
38. Carlsson E, Berglund B, Nordgren S. Living with an ostomy and short bowel syndrome: practical aspects and impact on daily life. *J Wound Ostomy Continence Nurs.* 2001;28(2):96-105.
39. Scolapio JS, Savoy AD, Kaplan J, Burger CD, Lin SC. Sleep patterns of cyclic parenteral nutrition, a pilot study: are there sleepless nights? *JPEN J Parenter Enteral Nutr.* 2002;26(3):214-217.
40. Armstrong D, Forbes A, Jeppesen PB, Lee HM, Nagy P, Seidner DL. Colon polyps in patients with short bowel syndrome before and after teduglutide: post hoc analysis of the STEPS study series. *Clin Nutr.* 2020;39(6):1774-1777.
41. Iakoubov R, Lauffer LM, Trivedi S, Kim YI, Brubaker PL. Carcinogenic effects of exogenous and endogenous glucagon-like peptide-2 in azoxymethane-treated mice. *Endocrinology.* 2009;150(9):4033-4043.
42. Thulesen J, Hartmann B, Hare KJ, et al. Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice. *Gut.* 2004;53(8):1145-1150.

How to cite this article: Harpain F, Schlager L, Hütterer E, et al. Teduglutide in short bowel syndrome patients – A way back to normal life? *J Parenter Enteral Nutr.* 2022;46:300–309. <https://doi.org/10.1002/jpen.2272>