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Original article

Real-world experience of Teduglutide use in adults with short bowel syndrome: A seven-year international multicenter survey☆

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SUMMARY

Background and aim: Teduglutide is a glucagon-like peptide-2 analogue used to promote intestinal rehabilitation and decrease the dependence from intravenous supplementation (IVS) in patients with short bowel syndrome and intestinal failure (SBS-IF). The aim of this study was to gain a better understanding of international real-world Teduglutide use since its launch.
Methods: Data from an international multicenter database for chronic IF were analysed. All the adult patients with SBS-IF included by centers that treated at least one patient with Teduglutide during the study period (2015–2022) were investigated. The baseline characteristics and the outcome of patients treated with Teduglutide (n.269) were compared to those of patients not receiving the drug (Controls, n.3081). The center experience was categorized based on the number of patients treated with Teduglutide: <10 or ≥10.
Results: Teduglutide cohort exhibited higher male prevalence, younger age, longer duration of HPN, higher percentage of SBS with jejunocolonic anastomosis, lower IVS volume, improved oral intake, and higher percentage of patients weaned from IVS. Controls showed higher percentages of patients deceased or lost to follow up. Centers with ≥10 patients treated with Teduglutide showed higher weaning rates and lower mortality rates.
Conclusions: This is the largest analysis of Teduglutide's real-world setting in SBS-IF. Clinicians preferentially selected for treatment patients with better prognostic indicators. Outcomes were significantly better in centers with higher Teduglutide treatment volumes, emphasizing the need for specialized referral centers to optimize care for SBS-IF patients.

1. Background

Intestinal failure (IF) is a highly disabling condition characterized by the "reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth" [1]. In patients who develop chronic IF (CIF), the IVS is provided at the patient's home by home parenteral nutrition (HPN) programs. In adults, short bowel syndrome (SBS) is the most common cause of CIF [1]. SBS is a rare condition associated with a residual functional small intestinal length less than 200 cm. SBS often results from extensive intestinal resection required for mesenteric ischemia, Crohn's disease or following surgical complications [1]. The incidence of SBS is estimated at about 5–10 patients per million population per year [2].

In patients with SBS and intestinal failure (termed 'SBS-IF'), the aim of medical treatment is intestinal rehabilitation aiming at maximizing residual intestinal absorptive capacity for oral nutrients and, ultimately, reducing or eliminating the need for IVS. In adult patients, intestinal rehabilitation programs based on the spontaneous post-operative intestinal adaptation process, dietary counselling, drugs to control stool losses and non-transplant surgical procedures allow complete HPN weaning in about one-half of cases 5-years after SBS-IF onset [3].

Over the past two decades, glucagon like peptide-2 (GLP-2) analogues have raised interest as potential disease-modifying therapies for SBS-IF. GLP-2 analogues enhance spontaneous post-resection intestinal adaptation, a process termed "hyper-adaptation" [4]. Teduglutide is the first GLP-2 analogue developed and approved for the treatment of SBS–IF. Other GLP-2 analogues are currently under investigation in clinical trials [5]. In randomized controlled trials (RCTs), GLP-2 analogue efficacy has been defined as the reduction in the weekly IVS volume of at least 20 % from baseline [6–9]. The 2-year, open-label Study of Teduglutide Effectiveness in Parenteral Nutrition Dependent SBS Subjects (STEPS)-2 demonstrated efficacy endpoint attainment in 65 % (57/88) of

patients on an intention-to-treat basis [9]. A reduction in the number of days per week of IVS was observed in 38 % of patients and 20 % achieved complete IVS cessation [9]. Notably, greater efficacy and HPN weaning rates, up to 85 % and 60 %, respectively, have subsequently been reported in real-life surveys [10–22]. The differences observed in the efficacy of Teduglutide noted between RCTs and real-life clinical practice raise a question as to whether patient selection differs between the two settings.

2. Aim

The aim of this study was to gain a better understanding of international real-world Teduglutide use since its launch. The data included in the international database for CIF of the European Society for Clinical Nutrition and Metabolism (ESPEN) were analyzed to evaluate the characteristics of patients with SBS-IF treated with Teduglutide during the seven years of the database collection, from 2015 to 2022.

3. Materials and methods

3.1. Study protocol and data collection

The ESPEN international multicenter survey for CIF is based on the retrospective analysis of data prospectively recorded during 12-month follow-up periods. The aim of the survey is to investigate the characteristics and factors associated with the outcome of adult patients on HPN for CIF due to non-malignant disease [23,24]. Participation of HPN/IF centers is voluntary and details regarding center enrolment have previously been published [23]. The study started on March 1st, 2015. HPN/IF centers were required to enroll all patients who were dependent on HPN for CIF. On March 1st of every subsequent year, participating centers recorded follow-up data for those patients already included in the database, as well as baseline data for all the new patients commencing HPN during the preceding 12 months. Data were collected in a structured questionnaire embedded in an Excel (Microsoft Co., 2013) database, termed “the CIF Action day” [23].

For each patient, the following data were collected at first inclusion in the database (baseline): age and gender; body weight and height; underlying disease and its benign or malignant nature; pathophysiological mechanism of CIF; HPN requirements (duration, number of days of infusion per week, type of parenteral nutrition admixture, IVS volume and energy for each day of infusion). The pathophysiological mechanisms of CIF were classified as SBS with end-jejunostomy (SBS-J), end-ileostomy (SBS-I), jejunocolic anastomosis (SBS-JC) or jejuno-ileal anastomosis and total colon in continuity (SBS-JIC), intestinal dysmotility (dysmotility), intestinal fistulas (fistulas), mechanical obstruction (obstruction) and extensive small bowel mucosal disease (mucosal disease). The severity of CIF was divided into eight categories, based on the type (fluid and electrolyte alone, FE; parenteral nutrition including macronutrients, PN) and volume of IVS, calculated as daily mean of the total volume infused per week (volume per day of infusion × number of infusions per week/7 (mL/day)): FE1 or PN1, ≤1000 mL; FE2 or PN2, 1001–2000 mL; FE3 or PN3, 2001–3000 mL; FE4 or PN4, >3000 mL [24]. At the end of each 12-month follow-up period, patient outcome was classified as still on HPN, weaned off HPN or deceased. Treatment with Teduglutide or any other intestinal growth factor was recorded from yearly follow-up data. The causes of death were grouped as HPN/IF-related, underlying disease-related and other causes (neither HPN/IF nor underlying disease-related). For the present study, the period of observation was March 1st, 2015 (baseline) to March 1st 2022 (end of follow-up) and the patient's outcome was censored at the last year of recording.

3.2. Patient inclusion criteria and duration of the survey for the present study

On March 1st 2022, the database included 15,247 patients on HPN for CIF. Exclusion criteria for the study were: malignant underlying disease; mechanism of CIF other than SBS; patients with SBS-IF weaned off HPN because of non-transplant surgery (NTS) or intestinal growth factors (IGF) other than Teduglutide; patients included in the database by centers that did not treat any SBS patients with Teduglutide; pediatric patients (age <18 years at baseline). Inclusion criteria were: adult patients with SBS-IF due to benign underlying disease included by centers that treated at least one patient with Teduglutide. Fig. 1 provides a detailed summary of the patients included in the study based on these criteria. Two cohorts of patients with SBS-IF meeting the inclusion and exclusion criteria were compared: 269 patients treated with Teduglutide and 3081 not treated with the drug. Four centers treated only pediatric patients with Teduglutide (Supplemental Table 1). The adult SBS-IF patients not treated with the drug by these centers were included in the analysis, comprising 64 non-treated patients (2.0 % of non-treated patients).

3.3. Statistical analysis

Continuous variables are reported as median and interquartile range (IQR) and analyzed by Mann–Whitney Test. Categorical variables are reported as absolute and relative frequencies. Continuous variables were also categorized into intervals. Pearson chi-square test, Fisher's exact test and linear-by-linear association test were used to analyze frequencies, where appropriate. Two-tailed p-values less than 0.05 were considered as statistically significant. The strength of the association between Teduglutide treatment and patients' outcomes was assessed using Cramer *V* for the chi-square analyses [25]. According to Cohen, Cramer *V* of 0.1, 0.3 and 0.5 indicate a small, medium and large effect size, respectively [26]. The analyses were performed using the IBM SSPS Statistics package for Windows, version 27 (BM Co., Armonk, NY, USA).

3.4. Ethical statement

The research was based on anonymized information extracted from patient records at the time of data collection. The study was conducted with full regard to confidentiality of the individual patient. Ethical committee approval was obtained by the individual HPN centers according to local regulations.

4. Results

During the 8 years of data collection, a total of 49 hospital centers from 19 countries enrolled the 3350 adult patients with SBS-IF included in the analysis of the present study, of which 269 treated with Teduglutide (Teduglutide) and 3081 not treated with the drug (Controls) (Table 1 and Supplemental Table 1). Three quarter of patients originated from European countries: Teduglutide 75.0 %, Controls 75.8 %.

4.1. Patient cohorts

The clinical characteristics at baseline (first year of enrolment in the survey) and the outcome status (last year of follow-up within the database) of patients with SBS-IF included in the analysis are reported in Table 2. The Teduglutide cohort comprised a higher

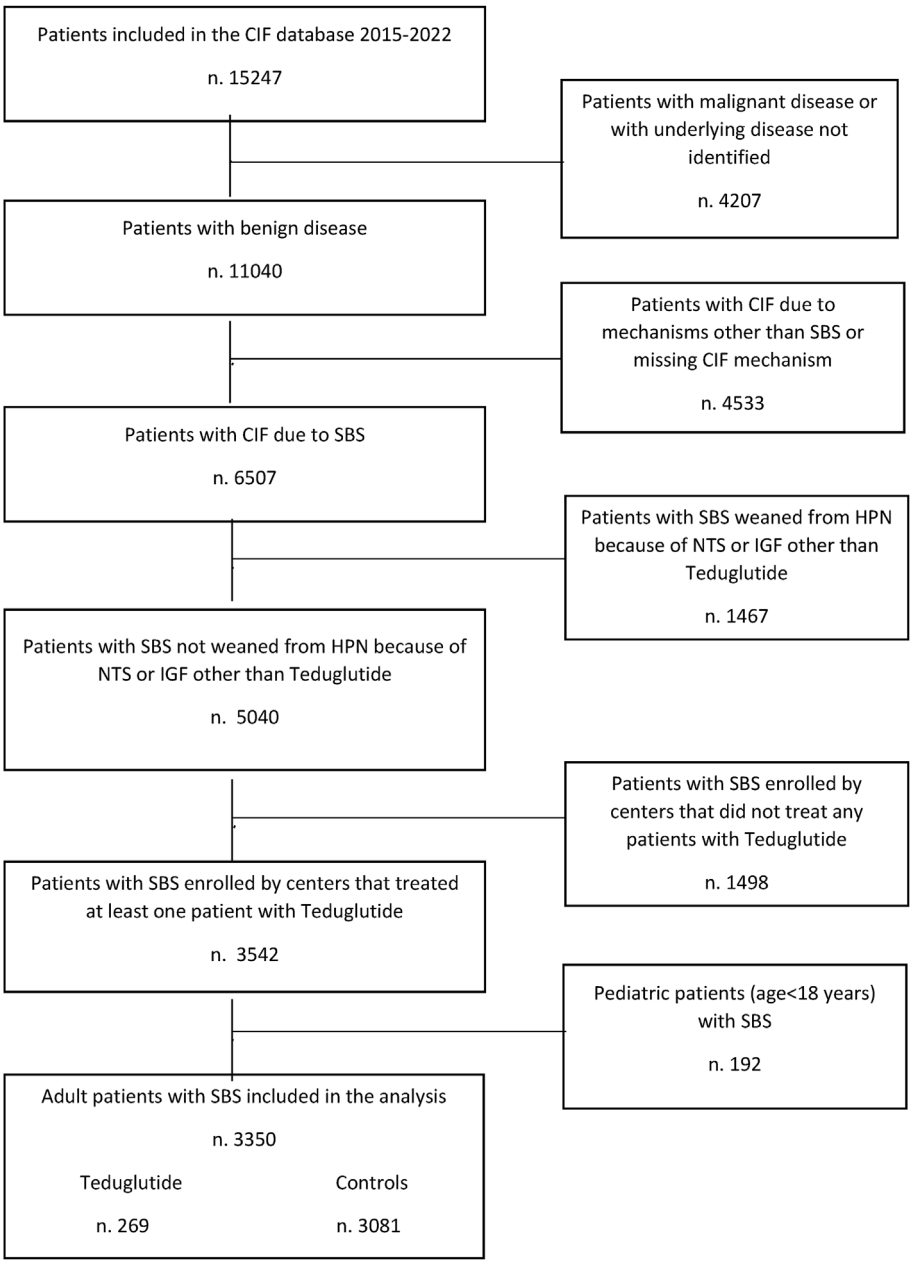

Fig. 1. Flow chart of patients with chronic intestinal failure (CIF) due to short bowel syndrome (SBS) included in the study, delineated according to Teduglutide treatment or not. (NTS, non-transplant surgery; IGF, intestinal growth factors; HPN, home parenteral nutrition).

percentage of males, and a higher percentage of patients with SBS-JC; patients were also younger age at starting HPN, had been on HPN for a longer duration; they also received lower volume and lower energy IVS, required less days of IVS per week, had less severe CIF, and required a higher percentage of customized IVS admixture. We also observed a higher percentage of patients on oral feeding with free food and beverages in the Teduglutide cohort. Concerning the underlying disease, the Teduglutide cohort had a numerically lower percentage of patients with radiation enteritis. In terms of anatomical status, the Control cohort comprised a higher percentage of patients with SBS-J and a lower proportion of patients with colon-in-continuity (CIC).

No difference was observed for BMI between the cohorts.

4.2. Patient outcome

Patient outcome significantly differed between the two cohorts (Table 2), with a small effect size (Cramer's $V = 0.1585$). The percentage of patients weaned from HPN was higher in the Teduglutide group, whereas the percentages of deceased or lost to follow up were higher in the Control group.

Table 3 compares the clinical characteristics and outcomes of patients treated with Teduglutide. Patients weaned off HPN within the Teduglutide-treated group were more likely to have the following characteristics: SBS-JC as the remnant GI anatomy, longer duration of HPN and lower IVS volume and energy in comparison to patients treated with Teduglutide but remaining on HPN. No

Table 1
Hospital centers and patients with short bowel syndrome and chronic intestinal failure included in the analysis, grouped by country of origin and whether or not patients were treated with Teduglutide.

Country	Centers	Controls		Teduglutide	
	n.	n.	%	n.	%
Argentina	2	65	2.1	17	6.3
Australia	4	61	2.0	12	4.5
Austria	1	6	0.2	14	5.2
Belgium	1	91	3.0	1	0.4
Brazil	1	15	0.5	1	0.4
Croatia	1	15	0.5	1	0.4
Denmark	1	132	4.3	1	0.4
France	7	727	23.6	88	32.7
Germany	2	75	2.4	25	9.3
Israel	2	66	2.1	4	1.5
Italy	10	602	19.5	37	13.8
Poland	2	263	8.5	10	3.7
Serbia	1	10	0.3	1	0.4
Slovenia	1	42	1.4	4	1.5
Spain	8	57	1.9	12	4.5
Sweden[a]	1	61	2.0	0	0
Switzerland	1	7	0.2	4	1.5
UK	1	248	8.0	5	1.5
USA	2	538	17.5	33	12.3
Total	49	3081	1	269	1

Patients enrolled by European countries: controls n.2336 (75.8 %); Teduglutide n.202 (75.0 %).
[a] This center was Included in the analysis because it enrolled one pediatric patient treated with Teduglutide.

difference was observed for BMI, age, underlying disease, or age of starting HPN. Concerning the oral intake, the proportion of patients taking free food and beverages was similar between patients remaining on HPN (90.2 %) compared to those weaned off HPN (97.1 %).

4.3. Patient characteristics and outcome according to the experience of the enrolling centers

The experience of the enrolling centers was categorized based on the number of patients treated with Teduglutide: <10 (Tedu<10) or ≥10 (Tedu≥10). Seven centers were tedu≥10 (range 10–44 patients) for a total of 1475 patients, 1326 Controls and 149 Teduglutide. Forty-two centers were Tedu<10, including a total of 1875 patients, 1755 Controls and 120 Teduglutide. Four out of the 7 Tedu≥10 centers were in the top 5 of total patients included in the study by single center, summarizing 1343 patients, that was 40.0 % of total patients included in the survey (Supplemental Table 1).

Table 4 describes the clinical characteristics at baseline and at end of follow-up of the Control and Teduglutide cohorts of patients, enrolled by the two categories of centers.

In both the Control and the Teduglutide cohorts, patient age was younger, the duration of HPN was shorter, the percentage of patients receiving the FE type of IVS and that of patients on free oral food and beverages were all higher in the Tedu≥10 centers. Furthermore, all patients treated with Teduglutide enrolled by the Tedu≥10 centers were on free oral food and beverages. No difference between Tedu<10 and Tedu≥10 was observed for the other patient characteristics, in both the Control and the Teduglutide-treated cohorts.

Concerning the outcome, in both the Control and the Teduglutide cohorts, the percentage of patients weaned off HPN was higher in the Tedu≥10 centers. In the Control cohort, the percentage of death was lower in the Tedu≥10 centers.

5. Discussion

This is the largest published cohort to date evaluating the use of a new treatment for SBS-IF in a real-life, international multicenter setting. The characteristics of adult patients with SBS-IF treated with Teduglutide were compared to those of patients who did not receive the treatment. The participating centers included all of their SBS-IF patients during a seven-year period.

Most of the previous real-life monocenter [10–15,21] and multicenter [16,17,20] surveys only described patients treated with the drug. Indeed, non-treated patients have been reported in one single center study [19], representing local expertise and attitude, and in the prospective, observational, multicenter SBS Registry committed by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to evaluate the risk of colorectal cancer in adult and pediatric patients with SBS-IF treated with Teduglutide. Patient enrolment criteria in this Registry differed from ours because participating centers were not requested to include all of their ongoing patients with SBS-IF and were asked to exclude patients who were on HPN for less than 6 months [22]. As in some previous surveys, in our cohort of patients treated with Teduglutide, we compared the characteristics of those who were weaned off HPN with those who were not. We also analyzed whether there was a different center approach to patient treatment, according to center experience, categorized by the number of patients treated with Teduglutide. The recommendations for delivering clinical care to people living with CIF have been extensively described within the ESPEN updated guidelines [1] and recent position paper [27]. However, it is important to recognize that there are major disparities across the world in access to high standard of care for patients with CIF and that HPN as well as teduglutide are not yet available in many countries.

The comparison of the characteristics of cohorts of SBS-IF patients treated and non-treated with Teduglutide suggests that the decision to treat may have been driven by 3 criteria: a) patients with a higher probability of weaning off HPN, b) younger patients with fewer comorbidities, which could facilitate treatment tolerance and monitoring, and c) patients with longer clinical course, less probability of further spontaneous improvement and secured monitoring compliance. Indeed, the cohort of patients treated with Teduglutide differed from the cohort of non-treated patients with a higher percentage of males, younger age, higher percentage of mesenteric ischemia and lower percentage of Crohn's disease as cause of intestinal resection, higher percentage of patients with jejuno-colic anastomosis, longer duration of HPN, lower dependence on IVS and higher percentage of those who were on free oral food. These data are in agreement with those of post-hoc analyses of RCTs [28] and with previous real-life studies [10]. Seidner et al. [28] analysed the characteristics of adults with SBS-IF enrolled in phase III Study of Teduglutide Effectiveness in Parenteral Nutrition Dependent SBS Subjects (STEPS) study [7] and the open-label extensions STEPS-2 [9] and STEPS-3 [29], that were associated with weaning from IVS and with the number of days off IVS per week. Patients who attained IVS independence tended to have lower baseline IVS volumes. Furthermore, SBS-IF with >50 % of CIC and non-inflammatory bowel disease etiology showed a trend for achieving greater numbers of days per week off IVS [28]. In their real-life study, Joly et al. [10] showed that the probability of weaning off HPN was greater in patients with SBS-IF with CIC and higher oral intake. Other two post hoc analyses of STEPS study investigated the characteristics of patients associated with a better

Table 2
Clinical characteristics at baseline (first year of enrolment in the survey) and outcome (at the last year of data inclusion), of adult patients with short bowel syndrome and chronic intestinal failure included in the analysis. Controls, patients not treated with Teduglutide. Teduglutide, patients treated with the drug.

	Controls	Teduglutide	P
Total patients, n.	3081	269	
Sex, patients n.	3077	269	0.002
Males	39.7 %	49.4 %	
Females	60.3 %	50.6 %	
Age (yr), patients n.	3074	269	
Median (IQR)	59.0 (23.6)	51.7 (23.4)	<0.001
Category			<0.001
18-29	7.3 %	13.0 %	
30-49	23.1 %	32.3 %	
50-69	43.2 %	42.4 %	
≥70	26.4 %	12.3 %	
BMI (kg/m^2), patients n.	2945	265	
Median (IQR)	21.5 (5.5)	21.5 (4.5)	0.710
Category			0.657
≤ 15.0	2.9 %	2.6 %	
15.1-18.5	17.8 %	12.1 %	
18.6-25.0	56.2 %	67.5 %	
25.1-30.0	16.2 %	14.0 %	
>30	7.0 %	3.8 %	
Underlying disease, patients n.	3076	268	<0.001[b]
Mesenteric ischemia	26.0 %	32.8 %	
Crohn's disease	23.2 %	25.0 %	
Surgical complications	14.0 %	8.6 %	
Radiation enteritis	6.9 %	1.1 %	
Dysmotility	4.1 %	2.9 %	
Volvulus	3.6 %	7.9 %	
Adhesions	3.2 %	3.0 %	
Trauma	1.8 %	6.7 %	
Others	17.2 %	12.0 %	
Type of SBS, patients n.	3081	269	<0.001
SBS-J	40.4 %	27.5 %	
SBS-I	21.9 %	14.5 %	
SBS-JC	25.8 %	46.5 %	
SBS-JIC	11.9 %	11.5 %	
Age at starting HPN (yr), patients n.	2172	216	
Median (IQR)	56.0 (26.0)	46.5 (27.7)	<0.001
Category			<0.001
<1	0.9 %	0.5 %	
1-5	0.0 %	0.9 %	
5-10	0.1 %	0.5 %	
10-18	1.2 %	3.7 %	
18-29	9.2 %	17.6 %	
30-49	26.4 %	34.3 %	
50-69	42.6 %	33.8 %	
≥70	19.4 %	8.8 %	
Duration of HPN (yr), patients n.	2886	260	
Median (IQR)	0.7 (2.3)	6.6 (7.6)	<0.001
Category			<0.001
≤1	63.0 %	40.0 %	
1.1-3	13.3 %	21.5 %	
3.1-10	15.5 %	24.2 %	
>10	8.2 %	14.2 %	
IVS volume (mL), patients n.	2987	252	
Weekly, Median (IQR)	12,292 (10,500)	9000 (9000)	<0.001
Daily, Median (IQR)	1756 (1500)	1285 (1285)	<0.001
IVS energy (kcal), patients n.	2989	254	
Weekly, Median (IQ)	7980 (6790)	5705 (6002)	<0.001
Daily, Median (IQ)	1140 (970)	815 (857)	<0.001
Days of IVS per week (n.), patients n.	2992	254	
Median (IQR)	7 (2)	5 (3)	<0.001
Category			<0.001
≤2	3.4 %	6.7 %	
3-4	18.5 %	30.0 %	
5-6	15.7 %	22.3 %	
7	62.3 %	40.7 %	
CIF severity, patients n.	2987	252	0.001
FE1	5.2 %	4.0 %	
FE2	2.7 %	2.8 %	
FE3	0.2 %	0	

(*continued on next page*)

Table 2 (*continued*)

	Controls	Teduglutide	P
FE4	0.2 %	0	
PN1	20.2 %	32.9 %	
PN2	36.0 %	33.3 %	
PN3	23.9 %	17.5 %	
PN4	11.7 %	9.5 %	
IVS admixture type, patients n.	2979	253	0.164
PA	18.8 %	13.4 %	
PAFE	17.8 %	17.0 %	
FE	9.1 %	8.3 %	
CA	44.3 %	51.4 %	
CAFE	9.9 %	9.9 %	
[a]**Type of oral feeding**, patients n.	1277	88	<0.001
Total fasting	5.6 %	0	
Only water	0.5 %	0	
Clear beverages	1.7 %	0	
Small amount of food & beverages	23.5 %	6.8 %	
Free food and beverages	68.7 %	93.2 %	
Year of enrollment, patients n.	3081	269	0.001[b]
2015	30.6 %	39.8 %	
2016	9.8 %	11.9 %	
2017	10.7 %	11.2 %	
2018	9.4 %	8.2 %	
2019	9.0 %	5.2 %	
2020	10.9 %	8.6 %	
2021	10.0 %	3.7 %	
2022	9.6 %	11.5 %	
Outcome, patients n.	3081	269	<0.001
Still on HPN	49.5 %	63.2 %	
Weaned off HPN	18.2 %	30.5 %	
Deceased	21.8 %	4.8 %	
Lost to follow up	10.5 %	1.5 %	

BMI, body mass index.
SBS, short bowel syndrome.
SBS-J, end-jejunostomy.
SBS-I, end-ileostomy.
SBS-JC, jejuno-colic anastomosis.
SBS-JIC, jejuno-ileal anastomosis and total colon in continuity.
HPN, home parenteral nutrition.
IVS, intravenous supplementation.
CIF, chronic intestinal failure.
CIF severity categories: type (Fluid and electrolyte alone, FE; parenteral nutrition including macronutrients, PN) and volume of the IVS, calculated as daily mean of the total volume infused per week (mL/day)):
FE1 or PN1, ≤1000.
FE2 or PN2, 1001–2000.
FE3 or PN3, 2001–3000.
FE4 or PN4, >3000.
IVS admixture type: PA, premixed admixture alone; PAFE, premixed admixture plus extra fluids and/or electrolytes; FE, fluids-electrolytes alone; CA, customized admixture alone; CAFÉ, customized admixture plus extra fluids and/or electrolytes.
[a] Type of oral feeding, this item was collected starting from 2016.
[b] As ≥1 cells have expected count less than 5, the Chi-squared approximation might be incorrect.

response to Teduglutide, described as reduction of IVS volume. Jeppesen et al. [30] showed that patients with higher baseline IVS volume requirements had the largest absolute IVS volume reduction. Chen et al. [31] observed that higher-response subpopulation were characterized by Crohn's disease etiology, absence of distal/terminal ileum or ileocecal valve, a lower likelihood of having CIC. Interestingly, the primary endpoint for treatment seems to differ between RCTs and clinical practice. In RCTs, the primary endpoint was the reduction of at least 20 % in IVS volume compared to baseline [6–9]. According to this goal, the best candidates would be patients with SBS-J with a high level of IVS dependence [30,31]. On the contrary, our observations would suggest that, in real-life, clinicians consider the probability of weaning off HPN a more important criterion when selecting patients for treatment. While for clinical approval RCTs, a measurable objective efficacy endpoint was the primary study goal, given the enormous resources required for GLP-2-analogue treatment, the higher probably of benefitting and of better long-term prognosis defined the target-population for treating centers. Furthermore, patient selection may also have been influenced by reimbursement issues, as no challenging on drug expenses would have been raised if patient weaned off HPN.

Further reasons for the observed differences between the treated and non-treated cohorts could relate to the presence of co-morbidities and the probability of better treatment tolerance, as well as the shorter duration of CIF. The non-treated cohort probably includes patients deemed unsuitable for treatment because of contraindications and/or of co-morbidities. Indeed, two single center studies that evaluated candidacy for Teduglutide amongst their SBS-IF patient cohorts reported that only 48 % [32] and 35.5 % [33] were eligible for treatment. On the basis of special warnings and precautions as well as contraindications for the drug, listed in the RCTs criteria and in the drug monographs, 34.2 % were non-

Table 3
Clinical characteristics at enrolment in the survey of the cohort of adult patient treated with Teduglutide, grouped according to the outcome, as still on HPN or weaned off HPN.

	Still on HPN	Weaned off HPN	P
Total patients, n.	**170**	**82**	
Sex, patients n.	169	82	0.501
Males	46.7 %	52.4 %	
Females	53.3 %	47.6 %	
Age (yr), patients n.	165	82	
Median (IQR)	50.8 (23.1)	51.8 (22.9)	0.996
Category			0.676
18-29	12.7 %	14.6 %	
30-49	34.5 %	28.0 %	
50-69	41.2 %	45.1 %	
≥70	11.5 %	12.2 %	
BMI (kg/m^2), patients n.	167	81	
Median (IQR)	21.2 (4.2)	21.7 (5.2)	0.143
Category			0.060[b]
≤ 15.0	1.8 %	2.5 %	
15.1-18.5	15.6 %	4.9 %	
18.6-25.0	67.7 %	70.4 %	
25.1-30.0	12.6 %	16.0 %	
>30	2.4 %	6.2 %	
Underlying disease, patients n.	169	81	0.700[b]
Mesenteric ischemia	33.1 %	28.0 %	
Crohn's disease	24.3 %	27.2 %	
Surgical complications	7.7 %	11.1 %	
Radiation enteritis	1.8 %	0	
Dysmotility	3.6 %	2.5 %	
Volvulus	8.9 %	6.2 %	
Adhesions	2.4 %	3.7 %	
Trauma	7.1 %	7.4 %	
Others	11.1 %	13.9 %	
Type of SBS, patients n.	169	82	0.024
SBS-J	29.6 %	19.5 %	
SBS-I	16.6 %	8.5 %	
SBS-JC	42.6 %	62.2 %	
SBS-JIC	11.2 %	9.8 %	
Age at starting HPN (yr), patients n	121	67	
Median (IQR)	44.0 (28.0)	47.0 (25.0)	0.621
Category			0.300[b]
<1	0.0 %	1.5 %	
1-5	1.7 %	0.0 %	
5.1–10	0.0 %	1.5 %	
10.1–18	2.5 %	3.0 %	
18.1–29	19.8 %	13.4 %	
30-49	34.7 %	37.3 %	
50-69	35.5 %	29.9 %	
≥70	5.8 %	13.4 %	
Duration of HPN (yr), patients n.	167	82	
Median (IQR)	6.6 (8.9)	6.6 (6.4)	0.576
Category			0.010
≤1	8.4 %	0	
1.1–3	19.8 %	18.3 %	
3.1–10	41.3 %	56.1 %	
>10	30.5 %	25.6 %	
IVS volume (mL), patients n.	168	67	
Weekly, Median (IQR)	10,250 (9400)	7500 (9360)	0.049
Daily, Median (IQR)	1464 (1342)	1071 (1337)	0.049
IVS energy (kcal), patients n.	168	69	
Weekly, Median (IQR)	6162 (5891)	4720 (6315)	0.039
Daily, Median (IQR)	880 (841)	674 (902)	0.039
Days of IVS per week, patients n.	168	69	
Median (IQR)	6 (3)	5 (3.7)	0.026
Category			0.012
≤2	4.1 %	14,7 %	
3-4	29.0 %	29.4 %	
5-6	21.9 %	26.5 %	
7	44.9 %	29.4 %	
CIF severity, patients n.	161	67	0.300[b]
FE1	1.9 %	7.5 %	
FE2	2.5 %	1.5 %	
PN1	33.5 %	32.8 %	
PN2	31.7 %	37.3 %	
PN3	18.6 %	16.4 %	
PN4	11.8 %	4.5 %	

(*continued on next page*)

Table 3 (*continued*)

	Still on HPN	Weaned off HPN	P
[a]**Type of oral feeding**, patients n.	51	34	0.395[b]
Small amount of food & beverages	9.8 %	2.9 %	
Free food and beverages	90.2 %	97.1 %	

BMI, body mass index.
SBS, short bowel syndrome.
SBS-J, end-jejunostomy.
SBS-I, end-ileostomy.
SBS-JC, jejuno-colic anastomosis.
SBS-JIC, jejuno-ileal anastomosis and total colon in continuity.
HPN, home parenteral nutrition.
IVS, intravenous supplementation.
CIF, chronic intestinal failure.
CIF severity categories: type (Fluid and electrolyte alone, FE; parenteral nutrition including macronutrients, PN) and volume of the IVS, calculated as daily mean of the total volume infused per week (mL/day)):
FE1 or PN1, ≤1000.
FE2 or PN2, 1001–2000.
FE3 or PN3, 2001–3000.
FE4 or PN4, >3000.
IVS admixture type: PA, premixed admixture alone; PAFE, premixed admixture plus extra fluids and/or electrolytes; FE, fluids-electrolytes alone; CA, customized admixture alone; CAFÉ, customized admixture plus extra fluids and/or electrolytes.
[a] Type of oral feeding, this item was collected starting from 2016.
[b] as ≥1 cells have expected count less than 5, the Chi-squared approximation might be incorrect.

eligible because of a contraindication (risk of digestive malignancy, recent history of any other cancer, or listing for intestinal transplantation) and 30.4 % were deemed eligible on a case-by-case basis because of warnings and precautions (other premalignant conditions, risk of intestinal obstruction, entero-cutaneous fistulas, or severe comorbidities) [33]. Interestingly, lower IVS dependency and higher oral intake were also characteristics of patients categorized as eligible for treatment [33]. Another criterion driving the clinician's decision could relate to the probability of patient tolerance to the treatment. Teduglutide could be particularly effective and with rapid onset in patients with SBS-J [30,31] with a greater risk of fluid retention. Patients with SBS-IF with CIC are essentially more IVS energy-dependent than fluid-dependent. In SBS-J patients, rapid improvement of fluid absorption due to Teduglutide requires close and frequent monitoring via face-to-face office visits to avoid fluid overload [34]. In real life, this could hamper the decision to offer the treatment to patients living far from the center and/or with poor compliance to monitoring. Finally, the non-treated cohort showed a shorter duration of CIF, perhaps suggesting that Teduglutide is not offered to such patients as they are still undergoing spontaneous intestinal adaptation [34].

SBS-IF is a rare condition. We know that, in general, reference centers play a pivotal role in the care of patients with rare diseases. Due to the low prevalence of these conditions, specialized expertise and resources are often concentrated within these centers. These institutions can provide comprehensive care, including diagnosis, treatment and ongoing management. As the number of patients under the care of a center was an accepted criterion to define center expertise for CIF [24,27], we chose the number of 10 patients treated with Teduglutide as a cut-off to define center expertise in treating SBS-IF with GLP-2 analogues. Four out of the 7 centers categorized as expert centers based on this criterion accounted for 40 % of total patients included in the survey. Patients included in the survey from the other 3 expert centers represented only 3.9 % of the total cohort. Indeed, there may be factors other than experience that could have driven the decision to treat patients with Teduglutide, such as national health system reimbursement and physician as well as patient attitude toward new treatments. However, significant differences were observed between the two categories of centers based on the number of patients treated with Teduglutide. In both the control and the Teduglutide cohorts, patient age was younger, the duration of HPN was shorter, the percentage of patients receiving the FE type of IVS was higher and the percentage of patients on free oral food and beverages was higher in the tedu≥10 centers. Furthermore, in the Teduglutide cohort, all the patients enrolled by the tedu≥10 centers were on free oral food and beverages. Interestingly, in both the control and the Teduglutide cohorts, the percentage of patients weaned off HPN was higher in patients enrolled by the tedu≥10 centers. Moreover, the percentage of deaths was lower in the tedu≥10 centers. Thus, it appears that outcomes, both in controls and those treated with Teduglutide, are more favorable in centers that treated more patients with Teduglutide. This suggests that these centers may have a multidisciplinary approach, perhaps more focused on global management, including diet, close monitoring and complication management. Furthermore, reference centers serve as hubs for research and education, contributing to the advancement of knowledge and the development of new therapies for rare diseases. The effect size calculation showed that the strength of the association between Teduglutide treatment and patients' outcomes was small in comparison to controls. While the reported differences between the characteristics of the treated and non-treated cohorts could account for an underestimation of the actual effect size of the treatment, the observed small effect size further supports the importance of managing Teduglutide treatment within expert centers. Notably, studies in adults and in children demonstrated the improvement of patient's quality of life [35] and the cost-effectiveness of the treatment [36,37] in carefully selected and appropriately managed SBS-IF patients. Centralizing patient care in high-volume and expert centers should therefore be a priority in order to achieve optimal cost-effectiveness for this treatment.

The large cohort of patients, the multicenter design of the survey, the completeness of patient enrollment by centers and the unrestricted criteria of patient inclusion are the strengths of this real-life study. The weakness of the study perhaps primarily relates to the aforementioned lack of characterization of patients within the control group, mainly concerning those co-morbidities that could have led clinicians to avoid treating patients with Teduglutide. Since the aim of this study was to understand how Teduglutide is prescribed in real life, the indication and prescribing methods

Table 4
Clinical characteristics at baseline (first year of enrolment in the survey) and outcome status (at last year of recorded follow up) of adult patients with SBS-CIF grouped according to the total number of patients treated with Teduglutide (Tedu) by participating centers: Tedu<10 or tedu≥10. Controls: cohort of SBS-CIF no treated with Teduglutide. Teduglutide: cohort of patients treated with Teduglutide.

	Controls			Teduglutide		
	Tedu<10	Tedu≥10	P	Tedu<10	Tedu≥10	P
Total patients, n.	1754	1327		120	149	
Sex, patients n.	1750	1327	0.392	120	149	0.624
Males	40.4 %	38.8 %		47.5 %	51.0 %	
Females	59.6 %	61.2 %		52.5 %	49.0 %	
Age (yr), patients n.	1750	1326		120	149	
Median (IQR)	61.0 (22,1)	56.4 (24.3)	<0.001	54.0 (26.1)	49.9 (22.4)	0.167
Category			<0.001			0.146
18-29	6.1 %	8.9 %		10.8 %	14.8 %	
30-49	20.2 %	26.9 %		30.0 %	34.2 %	
50-69	43.1 %	43.4 %		45.0 %	40.3 %	
≥70	30.6 %	20.8 %		14.2 %	10.7 %	
BMI (kg/m^2), patients n.	1709	1236		119	146	0.903
Median (IQR)	21.4 (5.6)	21.6 (5.3)	0.254	21.6 (4.8)	21.4 (4.4)	0.600
Category			0.221			
≤ 15.0	3.0 %	55.0 %		3.4 %	25.4 %	
15.1-18.5	18.4 %	16.9 %		15.1 %	9.6 %	
18.6-25.0	55.2 %	57.6 %		63.9 %	70.5 %	
25.1-30.0	17.6 %	14.2 %		13.4 %	14.4 %	
>30	5.9 %	8.5 %		4.2 %	3.4 %	
Underlying disease, patients n.	1750	1327		120	149	0.106[b]
Mesenteric ischemia	28.2 %	23.1 %		35.8 %	30.2 %	
Crohn's disease	21.1 %	25.9 %		23.3 %	26.2 %	
Surgical complications	17.7 %	9.3 %		11.7 %	6.0 %	
Radiation enteritis	7.0 %	6.7 %		0.8 %	1.3 %	
Dysmotility	2.2 %	6.7 %		1.6 %	4.7 %	
Volvulus	3.5 %	3.7 %		5.8 %	9.4 %	
Adhesions	3.4 %	2.9 %		1.7 %	4.0 %	
Trauma	1.8 %	1.7 %		9.2 %	4.7 %	
Others	85.1 %	20.0 %		10.1 %	13.5 %	
Type of SBS, patients n.	1754	1327	<0.001	120	149	0.400
SBS-J	44.5 %	35.0 %		26.7 %	28.2 %	
SBS-I	19.5 %	25.0 %		16.7 %	12.8 %	
SBS-JC	25.0 %	26.9 %		48.3 %	45.0 %	
SBS-JIC	11.0 %	13.1 %		8.3 %	14.1 %	
Age at starting HPN (yr), patients n	971	1201		80	136	
Median (IQR)	58.0 (25.0)	54.0 (25.0)	<0.001[b]	49.5 (29.5)	45.0 (26.0)	0.600
Category						
<1	0.8 %	0.9 %		0.0 %	0.7 %	
1-5	0	0.1 %		0	1.5 %	
5-10	0.2 %	0.1 %		0.0 %	0.7 %	
10-18	0.7 %	1.7 %		3.8 %	3.7 %	
18-29	9.0 %	9.4 %		18.8 %	16.9 %	
30-49	22.2 %	29.8 %		27.5 %	38.2 %	
50-69	43.5 %	42.0 %		40.0 %	30.1 %	
≥70	23.6 %	16.1 %		10.0 %	8.1 %	
Duration of HPN (yr), patients n.	1667	1209	<0.001	117	143	
Median (IQ)	0.8 (2.7)	0.6 (1.7)		6.8 (8.8)	6.3 (7.2)	0.039
Category			<0.001			0.107
≤1	60.4 %	66.9 %		35.0 %	44.1 %	
1.1−3	13.5 %	13.0 %		22.2 %	21.0 %	
3.1−10	17.4 %	12.9 %		25.6 %	23.1 %	
>10	8.9 %	7.3 %		17.1 %	23.1 %	
IVS volume (mL), patients n.	1746	1241		120	132	
Weekly, Median (IQR)	12,500 (10.300)	12,000 (10,500)	0.816	8800 (8875)	10,000 (10,075)	0.248
Daily, Median (IQR)	1.785 (1471)	1.714 (1500)	0.816	1257 (1267)	1428 (1439)	0.248
IVS energy (kcal), patients n.	1747	1242		120	134	
Weekly, Median (IQR)	7777 (6100)	8250 (7824)	0.010	5870 (5127)	5635 (6818)	0.879
Daily, Median (IQR)	1111 (871)	1178 (1117)	0.010	838 (732)	805 (973)	0.879
Days of IVS per week, patients n.	1751	1241		120	134	
Median (IQR)	7.0 (2)	7.0 (2)	0.515	5 (3)	5 (3)	0.662
Category			<0.001			0.758
≤2	2.77 %	4.3 %		8.3 %	5.3 %	
3-4	18.9 %	18.0 %		30.0 %	30.0 %	
5-6	17.0 %	13.8 %		20.8 %	24.0 %	
7	61.3 %	63.8 %		40.8 %	40.6 %	
CIF severity, patients n.	1746	1241	0.001[b]	120	132	0.040
FE1	4.0 %	6.8 %		0.8 %	6.8 %	
FE2	2.8 %	2.5 %		1.7 %	3.8 %	
FE3	0.2 %	0.2 %		0	0	
FE4	0.3 %	0.1 %		0	0	

(*continued on next page*)

Table 4 (*continued*)

	Controls			Teduglutide		
	Tedu<10	Tedu≥10	P	Tedu<10	Tedu≥10	P
PN1	20.6 %	19.7 %		40.0 %	26.5 %	
PN2	37.2 %	34.3 %		34.2 %	32.6 %	
PN3	24.7 %	22.7 %		15.8 %	18.9 %	
PN4	10.3 %	13.6 %		7.5 %	11.4 %	
IVS admixture type, patients n.	1739	1240	<0.001	119	134	0.020
PA	22.3 %	14.0 %		17.6 %	9.7 %	
PAFE	15.9 %	20.5 %		20.2 %	14.2 %	
FE	7.2 %	11.8 %		3.4 %	12.7 %	
CA	41.3 %	48.6 %		48.7 %	53.7 %	
CAFE	13.4 %	5.1 %		10.1 %	9.7 %	
[a]**Type of oral feeding**, patients n.	689	588	<0.001[b]	41	47	0.008
Total fasting	7.0 %	4.1 %		0.0 %	0.0 %	
Only water	0	1.0 %		0	0.0 %	
Clear beverages	1.3 %	2.2 %		0.0 %	0.0 %	
Small amount of food & beverages	33.1 %	12.2 %		14.6 %	0.0 %	
Free food and beverages	58.6 %	80.4 %		85.4 %	100.0 %	
Outcome, patients n.	1754	1327	<0.001	120	149	0.010
Still on HPN	54.3 %	43.1 %		73.3 %	55.0 %	
Weaned off HPN	13.4 %	24.6 %		21.7 %	37.6 %	
Deceased	26.1 %	16.2 %		3.3 %	6.0 %	
Lost to follow up	6.2 %	16.1 %		1.7 %	1.3 %	

SBS, short bowel syndrome.
SBS-J, end-jejunostomy.
SBS-I, end-ileostomy.
SBS-JC, jejuno-colic anastomosis.
SBS-JIC, jejuno-ileal anastomosis and total colon in continuity.
HPN, home parenteral nutrition.
IVS, intravenous supplementation.
CIF, chronic intestinal failure.
CIF severity categories: type (Fluid and electrolyte alone, FE; parenteral nutrition including macronutrients, PN) and volume of the IVS, calculated as daily mean of the total volume infused per week (mL/day)):
FE1 or PN1, ≤1000.
FE2 or PN2, 1001–2000.
FE3 or PN3, 2001–3000.
FE4 or PN4, >3000.
IVS admixture type: PA, premixed admixture alone; PAFE, premixed admixture plus extra fluids and/or electrolytes; FE, fluids-electrolytes alone; CA, customized admixture alone; CAFÉ, customized admixture plus extra fluids and/or electrolytes.
[a] Type of oral feeding, this item was collected starting from 2016.
[b] As ≥1 cells have expected count less than 5, the Chi-squared approximation might be incorrect.

were left to the prescribers. Some differences may be linked to habits, but also to regulatory constraints due to reimbursement procedures, which may differ from one country to another. Conducting prospective questionnaires to investigate the reasons behind a physician's decision for the use of Teduglutide may be helpful for future research.

6. Conclusions

Real-world data on Teduglutide treatment are crucial for understanding long-term clinical outcomes, as well as identifying the indications and characteristics of patients considered eligible for treatment. While Teduglutide has demonstrated efficacy in reducing dependence on IVS, clinicians are more likely to offer the treatment to patients with a high expected benefit, particularly those with a high probability of weaning off IVS and fewer comorbidities. It has been observed that medical centers treating a significant number of SBS-IF with Teduglutide, specifically more than 10, tend to demonstrate improved outcomes, not only for those patients receiving the medication but also for those who are not. The observation that centers with a higher volume of Teduglutide patients experience improved outcomes underscores the importance of developing and identifying reference centers for patients with SBS-IF. These centers can serve as models of excellence, providing high-quality care and driving advancements in the field.

Author contribution

LP devised the study protocol, collected the data, analyzed the results and drafted the manuscript. FJ devised the study protocol, analyzed the results and drafted the manuscript. GB and MZ collected the data, cured the data, performed the statistical analysis, cured the data presentation and reviewed the manuscript. The Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN discussed and approved the protocol study, discussed the results and reviewed the manuscript before submission. Coordinators of the participating centers collected the data and reviewed the manuscript upon submission. All authors approved the final version of the manuscript before submission.

Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI and AI-assisted technologies were not used in the writing process of this manuscript.

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Conflict of interest

FJ: Consulting fees for Takeda, Northsea therapeutics, VectivivBio, Hanmi; Payment or honoraria for attending meetings for Takeda, Northsea therapeutics, Baxter, Fresenius Kabi, Bbraun; Support for attending meetings for Takeda; Participation on a Data Safety Monitoring Board for Takeda, Ironwood.

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DS: none.

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MT: none.

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Appendix A. Supplementary data

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